Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 1:

CARDIOVASCULAR DISEASES IN THE UNITED STATES AND PREVENTION APPROACHES

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The large and long-term decline in mortality from the cardiovascular diseases accounted for almost 4 of the 5.6-year increase in life expectancy in the United States attained between 1965 and 1995.[1] The 55 percent decline in the age-corrected death rate for total cardiovascular disease between 1950 and 1996 indicates the extent to which these leading causes of death are subject to preventive and therapeutic measures. These diseases, however, still account for 41 percent of all deaths and are leading causes of morbidity and health care utilization. Control of these diseases should focus on prevention because of its inherent benefits, its apparent role in the mortality reductions, and its potential given the presence of modifiable risk factors in millions of Americans.

CARDIOVASCULAR DISEASES

Major Cause of Morbidity and Mortality

The most common cardiovascular diseases are hypertension and heart disease, but the basis for most cardiovascular diseases is atherosclerosis, which is almost universally present in U.S. adults and is manifest clinically as coronary heart disease (CHD), cerebrovascular disease (stroke), or peripheral arterial disease. The likelihood of developing one of these diseases is high, and they affect the health of nearly 59 million Americans.[2] In 1999, these diseases were projected to account for $178 billion in health care expenditures in the United States-2 percent of the gross domestic product (Fig. 1-1). These diseases also account for an estimated $108 billion in lost productivity due to illness and premature mortality. These expenditures and indirect costs are by far the largest for any diagnostic group.

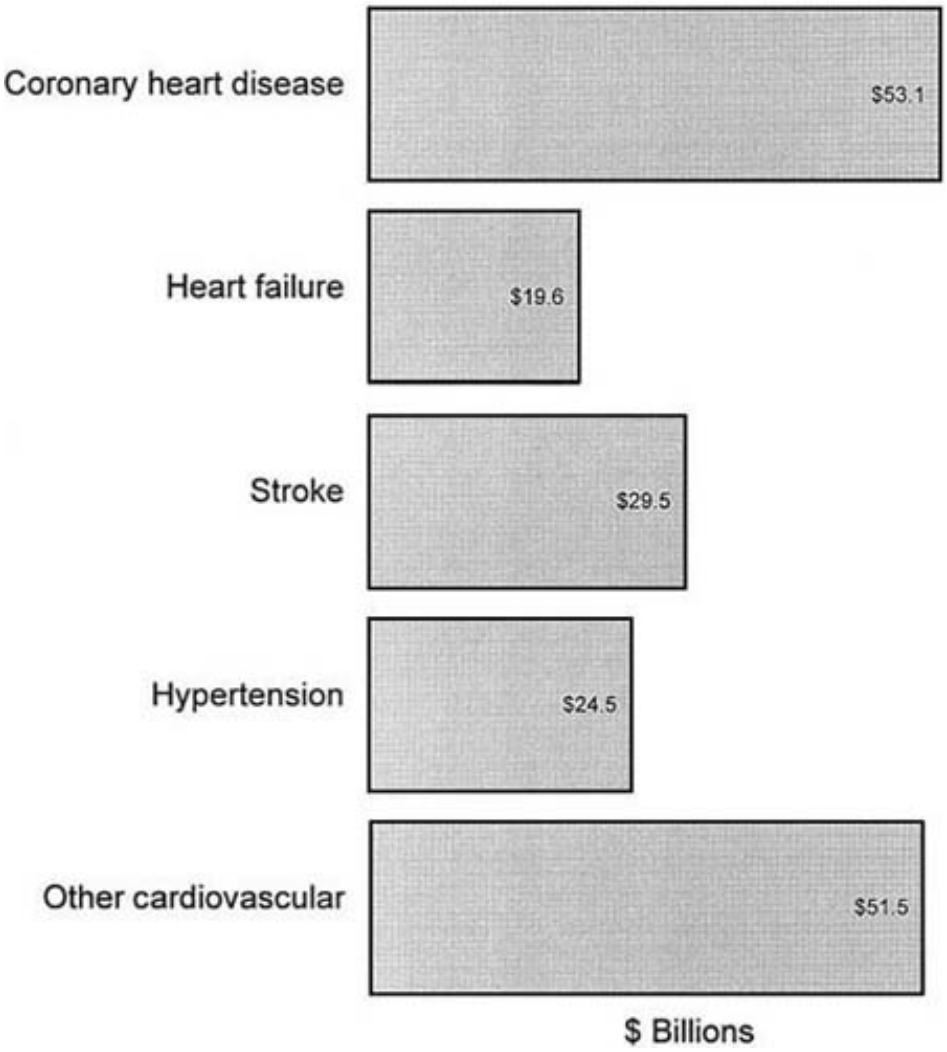

Figure 1-1: Health expenditures for cardiovascular diseases, United States, 1999 (includes expenditures for hospital, home, and nursing home care; physician and other professionals; and drugs). (From the American Heart Association and National Heart, Lung, and Blood Insitute.[2])

During the past 30 years, there have been major reductions in mortality rates for the various forms of cardiovascular disease (Fig. 1-2). Cardiovascular diseases, however, continue to be the most common threat to life and health. The lifetime risk of developing CHD after age 40 is 49 percent in men and 32 percent in women.[3] Even at age 70, the risk is 35 percent for men and 24 percent for women. CHD is the leading or second leading cause of death beginning at age 45 in men and in women.[4] An estimated 8 percent of the U.S. population, 20 million persons, have some form of heart disease.[5] About 50 million, 20 percent of the total population and one-fourth of the adult population, have hypertension, defined as a systolic blood pressure of 140 mmHg or greater, a diastolic blood pressure of 90 mmHg or greater, or normal blood pressure levels maintained by use of antihypertensive medication.[1,2] Thirty-two percent of persons with heart disease and 36 percent of those with stroke are limited in their usual activity by the condition.[6] Heart disease and hypertension, respectively, are the third and fourth most common chronic conditions causing limitation of activity.[1] Almost 60 percent of those with hypertension are under 65 years of age, and about 50 percent of persons with heart disease are under that age.[5] The prevalence and mortality from the cardiovascular diseases increase with decreasing levels of family income and education.[5,7] Between 1990 and 1992 in the United States, heart disease and hypertension accounted for an estimated 542 million days of restricted activity and 206 million bed days.[6] In 1997, there were an estimated 33 million days in short-stay hospitals, 60 million visits to physicians' offices, 5 million outpatient visits, and 616,000 patients receiving home health care (in

1996) for the cardiovascular diseases.[8-11]

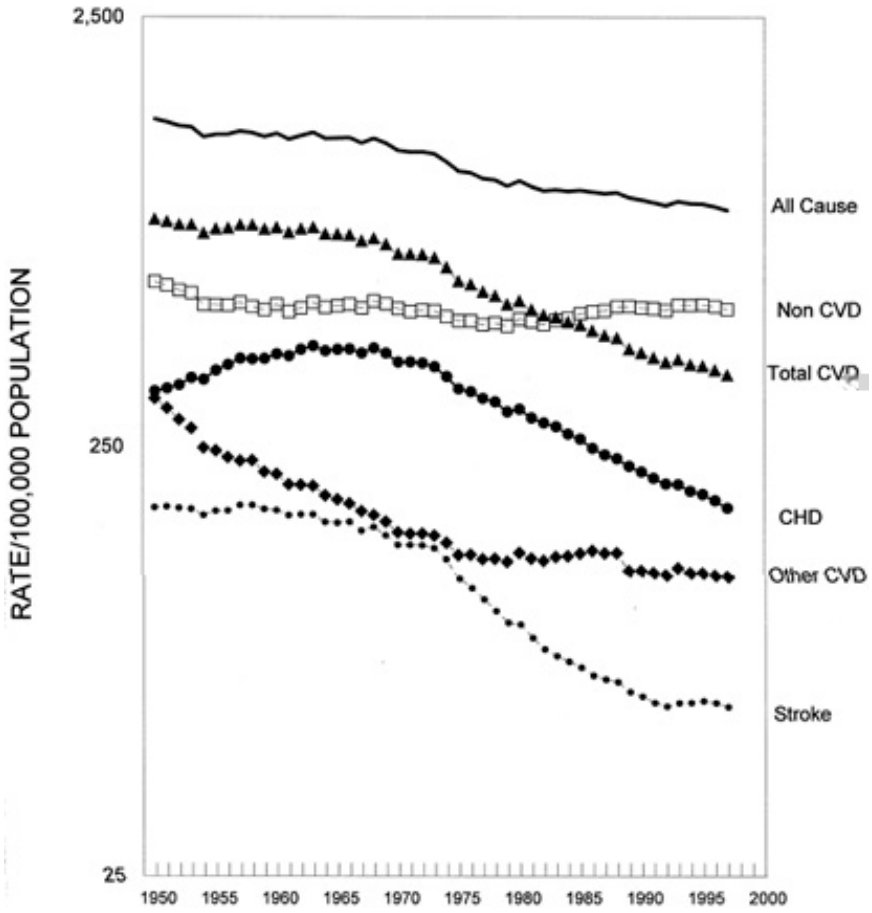

Figure 1-2: Age-adjusted death rates for selected causes of death; United States,1950-1997 (adjusted to U.S. population 2000) CVD, cardiovascular disease; CHD, coronary heart disease. (From *Vital Statistics of the United States*, National Center for Health Statistics.)

In 1997, cardiovascular diseases accounted for 41 percent of all deaths in the United States, a total of 952,000.[1] Largely because there are many more older women than older men in the U.S. population, the analogous percentage is higher in women (42 percent) than in men (39 percent), and the number of deaths from cardiovascular diseases is greater in women than in men.[4] Of all cardiovascular disease deaths, 36 percent occurred "prematurely," i.e., before 75 years of age. Atherosclerosis, when manifested as CHD, cerebrovascular disease, or peripheral arterial disease, accounted for 71 percent of all deaths from the cardiovascular diseases in 1997.[1] Heart disease is the leading cause of death in all racial groups.[4] Stroke ranks third highest in whites, blacks, and Asians in the U.S. population; fourth in Hispanics; and fifth in Native Americans.[12] Age-adjusted death rates for cardiovascular disease in 1997 were highest in black males, next highest in white males, and then followed by black females and white females.[2] Rates are not quite as high in Native Americans, Asian Americans, and Hispanic Americans.

Unfortunately, national incidence and case fatality data for the cardiovascular diseases do not exist. Data from the Framingham (Massachusetts) Heart Study, which began in 1948, and the Framingham Offspring Study provide reliable estimates for 44 years of follow-up of a defined population sample of men and women aged 35 to 94, the original cohort, and for 20 years of follow-up of their offspring. The average annual rates of first major cardiovascular events rose from 7 per 1000 men at ages 35 to 44 years to 68 per 1000 at ages 85 to 94 (Table 1-1). For

women, comparable rates are achieved 10 years later in life, with the gap narrowing with advancing age. CHD is the predominant cardiovascular event, comprising more than one-half of all such events in men and in women under age 75 (Table 1-2). The proportions of cardiovascular events due to CHD decline with age, as the proportions due to stroke and congestive heart failure (CHF) increase with age. Under age 75, there is a higher proportion of cardiovascular events due to CHD in men than in women and a higher proportion due to CHF in women than in men (see Tables 1-1 and 1-2).

Secular Trends

The trend in mortality from total cardiovascular disease has been downward since about 1940, with long-term declines for the three subgroups-rheumatic, cerebrovascular, and hypertensive diseases-and a decline for CHD since the mid-1960s.[1] The coronary decline antedates effective antithrombolytic and antihypertensive treatment. Prior to 1940, cardiovascular mortality increased and became the predominant cause of death because of control of infectious and parasitic diseases and an epidemic increase in fatal coronary attacks. Cardiovascular mortality declined just less than 1 percent per year in the 1950s and 1960s. The decline became more precipitous in the 1970s, with the rate falling 3 percent per year since then. For CHD, there has been more than a 58 percent decline in the age-adjusted death rate between the peak of mortality in 1963 and 1997; the current decline is 2 to 3 percent per year. For stroke, the rate of decline was 4 to 6 percent per year in the 1970s and early 1980s, but the decline slowed and has been less than 1 percent per year between 1990 and 1996.

The decline in cardiovascular mortality, including the steep rise and fall in CHD mortality, indicates that the major cause of mortality is controllable. Whether attributable more to beneficial changes in disease-promoting lifestyle or to better medical care of those already afflicted, it is clear that cardiovascular disease in most patients is not an inevitable burden of aging or genetic makeup. Although the causes of the decline in cardiovascular mortality are uncertain, the decline has been substantial, sustained, and real. The decline has coincided with increased efforts to achieve healthier living habits and with improvements in the ambient burden of cardiovascular risk factors.

Unfortunately, there are very few statistics on trends in morbidity, particularly incidence. Some, but not all, studies suggest that there have been declines in incidence and case fatality of CHD and stroke.[13,14] For myocardial infarction (MI), de- clines have been reported from most international sites in the MONICA (Monitoring Trends in Cardiovascular Diseases) studies.[15] This is important because reduction in mortality without a decline in the incidence rate would indicate that better medical care were responsible, whereas a reduction in both incidence and mortality would suggest that environmental influences and/or preventive measures have improved. If reduction in mortality continues, the size of the elderly population will continue to increase over and above increases due to demographic effects.

Risk Factors and Subclinical Disease

Observational studies in populations such as the Framingham Study have documented factors that increase the risk of cardiovascular diseases.[16,17] These include atherogenic attributes such as dyslipidemia, hypertension, glucose intolerance, and elevated fibrinogen; living habits that promote them; indicators of unstable lesions; and signs of compromised circulation, e.g., measures of subclinical arterial disease. Risk factors can be classified into the lipids, metabolic factors, hemostatic factors, blood pressure, and lifestyle factors. Some are modifiable. They promote cardiovascular disease in both sexes at all ages but with different strengths. Diabetes and high-density lipoprotein (HDL) cholesterol operate with greater power in women. Cigarette smoking is particularly influential in men, is noncumulative, and loses some of its adverse impact shortly

after quitting. Some risk factors, such as blood lipids, impaired glucose tolerance, uric acid, and fibrinogen, have smaller risk ratios in advanced age, but this lower relative risk is offset by a high absolute risk. In fact, most of the major risk factors remain relevant in the elderly. Obesity or weight gain promotes or aggravates all the atherogenic risk factors, and physical indolence worsens some of them and predisposes to cardiovascular events at all ages. Systolic blood pressure and isolated systolic hypertension are major risk factors at all ages in both sexes. The ratio of total to HDL cholesterol is used by many as a convenient lipid risk factor profile (see also Chap. 53).

Beyond age 65, women become nearly as vulnerable to cardiovascular mortality as men.[4] The predisposing modifiable risk factors for CHD, stroke, peripheral arterial disease, and cardiac failure are similar in the young and old in men and women.[16] An attenuated risk ratio for some risk factors at advanced age is offset by a greater incidence of cardiovascular disease. Consequently, the attributable risk and the potential benefit of treatment rise with age. In old age, average atherogenic total and low-density lipoprotein (LDL) cholesterol levels are considerably higher in women than in men. Cardiovascular risk profiles comprising the major risk factors predict CHD as efficiently in the elderly as in the young. This, and the fact that the decline in cardiovascular mortality has included the elderly, suggests the potential for intervention.

Evidence from the Framingham Study suggests that the presence of certain risk factors in women can attenuate their advantage in cardiovascular risk over that in men. The male-female gap in incidence closes with advancing age. After menopause, risk escalates two- to threefold, with more infarction and sudden death. A high total to HDL cholesterol ratio of 7.5 or greater virtually eliminates the female advantage. Diabetes has twice the relative impact on risk in women, almost canceling the female advantage. Electrocardiographic evidence of left ventricular hypertrophy has a greater relative impact on risk in women. The residual effect of triglycerides after consideration of HDL cholesterol appears to be greater in women than in men.

The major modifiable risk factors that contribute powerfully to cardiovascular disease are highly prevalent in the population. Trends in their prevalence and differences in their impact on the various atherosclerotic sequelae are noteworthy. Despite 30 years of appreciable decline in the percentage of persons who smoke cigarettes, one-fourth of adults, 49 million, still smoke.[2] Despite declining trends in mean total serum cholesterol level, more than 50 percent of American adults, 98 million, have blood cholesterol levels of 200 mg/dL or greater, and of these, 39 million have levels of 240 mg/dL or greater. Fifty million have hypertension, but fortunately, treatment and control of this condition improved considerably since the early 1970s.[1,2] Not improving is obesity. One-third of adults, 106 million, are overweight, defined as a body mass index greater than 25 kg/m2. An estimated 10 million persons are at increased risk of cardiovascular disease because they have diabetes.[2] Another highly prevalent risk factor is sedentary lifestyle. It plays a role in the prevalence of overweight, dyslipidemia, and hypertension and, thus, cardiovascular disease. There also are persons under 18 years of age who have one or more modifiable risk factors.[1,12]

More recent additions to the list of risk factors include homocystinemia. In the general population, 29 percent have deficient enough vitamin B intake to elevate homocystine to more than 14 μmol/L.[18] Inadequate intake of vitamins B_{12} and B_6 and folate account for 67 percent of the elevated homocystine encountered in the general population. An estimated 25 percent of the population have Lp(a) lipoprotein cholesterol values greater than 20 mg/dL.[19] Small, dense LDL (pattern B) occurs in 11.1 percent of the population and in 50 percent of patients with CHD.[20] Fibrinogen greater than 300 mg/dL occurs in 30 percent of the population. Other novel risk factors are leukocyte count, estrogen deficiency, factor VII, endogenous tissue plasminogen activator, plasminogen activator inhibitor type 1, D-dimer, C-reactive protein, and possibly *Chlamydia pneumoniae*.[16,17]

Very early asymptomatic cardiovascular disease can be diagnosed by noninvasive testing, such as magnetic resonance imaging (MRI) and computed tomographic (CT) scanning. Well-established clinical indicators include left ventricular hypertrophy, audible vascular bruits, a positive exercise electrocardiogram (ECG), absent arterial pulses in the limbs and neck, regional wall motion abnormality on the echocardiogram, reduced ankle-arm blood pressure ratio, sonographic evidence of carotid wall thickness, reduced left ventricular ejection fraction, and presence of coronary calcium.

No individual risk factor is essential or sufficient in the causation of cardiovascular disease; causation is multifactorial. Indeed, the risk posed by one factor is generally enhanced in the presence of another. Thus multivariate risk factor assessment gives the most useful measure of the joint effect of the risk factors.[16] Multivariate analyses help provide a better understanding of the pathogenesis of the disease and guidelines for prevention. Based on the absolute, relative, and attributable risks imposed by the various risk factors, the older concepts of *normal* have evolved to optimal values associated with long-term freedom from disease. As a consequence, acceptable blood pressures, blood glucose levels, and lipid values have been revised downward.[16] Multifactorial risk functions based on the Framingham Study data, composed of the major identified risk factors, have been shown to predict the rate of occurrence of coronary disease in a variety of U.S. population samples, suggesting that much of the cardiovascular disease in the population is attributable to these factors[21] (see also Chap. 41).

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CORONARY HEART DISEASE

CHD kills and disables people in their most productive years and in 1999 was estimated to account for $53 billion in medical care costs and $47 billion in indirect economic costs.[2] Each year there are more hospitalizations for CHD than for any broad diagnostic group, with the exceptions of births, all respiratory diseases, all digestive diseases, and all injuries.[8]

Prevalence

In the United States, an estimated 12 million people have CHD, about one-half of whom have acute MI and half have angina pectoris.[2] For men, prevalence of MI is 1 percent at ages 35 to 44 years and 16 percent at age 75 and over (Fig. 1-3). In women, the prevalence is less than 1 percent at ages 35 to 44 years and 13 percent at age 75 and over.

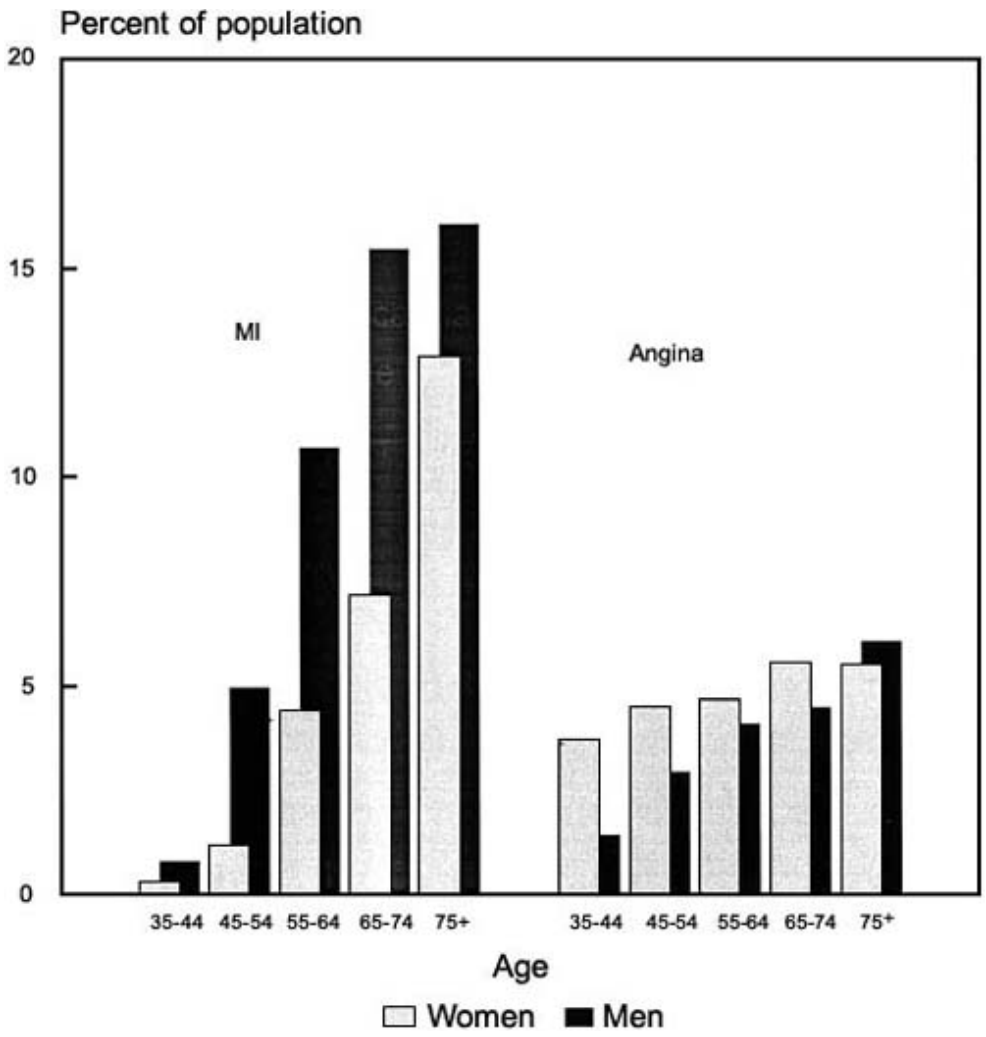

Figure 1-3: Prevalence of MI and angina pectoris by age and sex, United States, 1988-1994 (self-reported myocardial infarction and Rose angina from health interviews). MI, myocardial infarction. (From the

National Health and Nutrition Examination Survey, 1988-1994, National Center for Health Statistics.)

Incidence

In the United States, CHD causes about 650,000 new heart attacks each year and 450,000 recurrent attacks.[2] The incidence in women lags behind that in men by 10 years for total CHD and by 20 years for more serious clinical manifestations such as MI and sudden death (Tables 1-1 and 1-3). Male predominance is least striking for uncomplicated angina pectoris. The first coronary presentation for women is more likely to be angina, whereas in men it is more likely to be MI (Table 1-4). In men, more angina occurs after MI than before. Only 20 percent of coronary attacks are preceded by long-standing angina; the percentage is lower if the infarction is silent or unrecognized. In premenopausal women, serious manifestations of CHD such as infarction or sudden death are relatively rare. The incidence and severity of CHD increase with age in both sexes (see Table 1-3 and Table 1-4). There seems to be a more precipitous increase for women after menopause, with CHD rates in postmenopausal women two to three times those of women the same age who remain premenopausal.[21] This applies whether the menopause is natural or surgical and, in the latter case, whether or not the ovaries are removed. The sex ratio in incidence narrows progressively with advancing age.

Unrecognized MIs are common in the Framingham Study, numbering at least one in three infarctions (Fig. 1-4). Half the unrecognized infarctions are silent, and the rest are atypical so that neither the patient nor the physician entertains the possibility.[22] More than half these persons eventually develop some overt clinical manifestations of CHD and hence come under medical care. Angina is less frequent in individuals with unrecognized MI than in those with recognized symptomatic MI, either before or after the infarction occurs. Despite the apparent mild nature of unrecognized MI, t risk of subsequent mortality is nearly the same as in patients with recognized infarction. Diabetic men and hypertensive persons of both sexes are particularly susceptible to silent or unrecognized MIs.

Prognosis

In patients who survive the acute stage of an MI, the morbidity and mortality range from 1.5 to 15 times that of the general population, depending on the person's sex and clinical outcome (Table 1-5). The rates of occurrence of reinfarction, sudden death, angina pectoris, cardiac failure, and stroke are all substantial. The relative and absolute risks of these events are as great in women as in men after MI. Within 6 years following a recognized MI, 18 percent of men and 35 percent of women have a recurrent infarction, and 27 percent of men and 14 percent of women develop angina. About 22 percent of men and 46 percent of women are disabled with cardiac failure; 8 percent of men and 11 percent of women will have a stroke. Sudden death will be experienced by 7 percent of men and 6 percent of women. The prognosis is nearly as bad, sometimes worse, following an unrecognized MI (see Table 1-5).

Table 1-5: Six-Year Prognosis Following Myocardial Infarction: Framingham Study, 44-Year Follow-Up of Cohort and 20-Year Follow-Up of Offspring[a]

	MEN		WOMEN	
	Percent	Risk Ratio[b]	Percent	Risk Ratio[b]
Recognized				
Death	37	2.5	60	5.1
Sudden death	7	2.2	6	4.4
Myocardial infarction	18	2.2	35	9.6

Angina pectoris	27	4.1	14	2.3
Cardiac failure	22	5.4	46	15.4
Stroke/TIA	8	2.4	11	3.1
Unrecognized				
Death	46	2.5	34	2.4
Sudden death	5	1.7	2	2.1
Myocardial infarction	19	2.0	18	3.6
Angina pectoris	11	1.6	17	3.2
Cardiac failure	27	5.8	21	6.2
Stroke/TIA	13	3.5	7	1.5

[a]Surviving 30 days.[b]Standardized morbidity and mortality ratios (times 0.01).
SOURCE: The Framingham Study.

Mortality

CHD is the leading single cause of death in adults in the United States, accounting for 1 in 5 deaths.[4] In 1997, there were 466,000 coronary deaths. Mortality from this disease increases with age, but CHD is also a prominent cause of death in adults at the peak of their productive lives. Heart disease is the leading cause of death in men and women in every racial or ethnic group except Asian-American females.[2] The CHD death rate is almost three times higher in men than in women at ages 25 to 34, but this ratio declines to 1.6 by ages 75 to 84. The coronary death rate is more than 50 percent higher in blacks than in whites at ages 25 to 34, and this difference disappears by age 75. CHD mortality is not as high among the Hispanic population as it is among blacks and whites.

In a substantial number of CHD deaths, the progression from inapparent clinical disease to death is swift. Much of the premature mortality from CHD comes with little warning in a population prone to this disease. Sudden, unexpected, out-of-hospital coronary deaths that occur too rapidly to allow arrival alive at the hospital account for one-half of all coronary fatali- ties. The proportion of coronary deaths that are sudden deaths is lower in women than in men and lower in elderly men than in the young (Fig. 1-5). The percentage of sudden coronary deaths that occur without prior CHD, however, is much greater in women than in men (Fig. 1-6). In 50 percent of men and 63 percent of women who died suddenly, there was no prior overt evidence of coronary disease (see also Chap. 36).

There is a higher risk of death in patients with a prior coronary attack, yet most CHD deaths arise from the population who are still free of symptomatic CHD.[23] Hence primary prevention ultimately appears to offer more to society than secondary prevention. After MI, sudden death occurs at four to six times the rate in the general population. The first year following a recognized MI is especially dangerous, with 25 percent of men and 38 percent of women succumbing (Fig. 1-7). Long-term survival following unrecognized MI is only slightly better than for recognized MIs, and survival is better for women than for men (

Table 1-6). In men under age 65 with uncomplicated angina pectoris, the survival picture is nearly the same as it is for recognized MI and is much worse than the survival in women (see also Chap. 38).

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HYPERTENSION

Hypertension, present in 50 million Americans, is one of the most powerful contributors to cardiovascular morbidity and mortality: the 600,000 annual cases of stroke, 1.1 million annual heart attacks, 400,000 annual new cases of CHF, and most of the nearly 1 million annual deaths from cardiovascular and kidney diseases.[2,4]

Prevalence

In a 1988-1994 national survey of persons aged 20 to 74 years, the prevalence of hypertension, i.e., systolic blood pressure of 140 mmHg or greater or diastolic blood pressure of 90 mmHg or greater or on antihypertensive medication, was 24 per- cent in white men, 19 percent in white women, 35 percent in black men, and 34 percent in black women.[24] Prevalence in- creases with age and is highest among blacks and the elderly (Fig. 1-8). Isolated systolic hypertension is a common and distinctly hazardous condition in the elderly. There is evidence from the Systemic Hypertension in the Elderly Program (SHEP) and the Syst-Eur trial that treatment of this form of hypertension in the elderly is distinctly efficacious not only against stroke but also against coronary disease.[25,26] Persons with hypertension face serious excess risks of cardiovascular sequelae, and since much of this excess risk is attributable to mild hypertension, there is need for intervention through preventive lifestyle modification, if not through drug treatment. Because of the higher prevalence of milder hypertension, almost 60 percent of the excess mortality attributable to hypertension comes from this blood pressure range. The risks of cardiovascular sequelae are proportional to the blood pressure level at any age and in both sexes and are increased whether the elevation is systolic or diastolic. Approximately one-half of persons who suffer a first heart attack and two-thirds who suffer a first stroke have blood pressures greater than 160/95 mmHg.

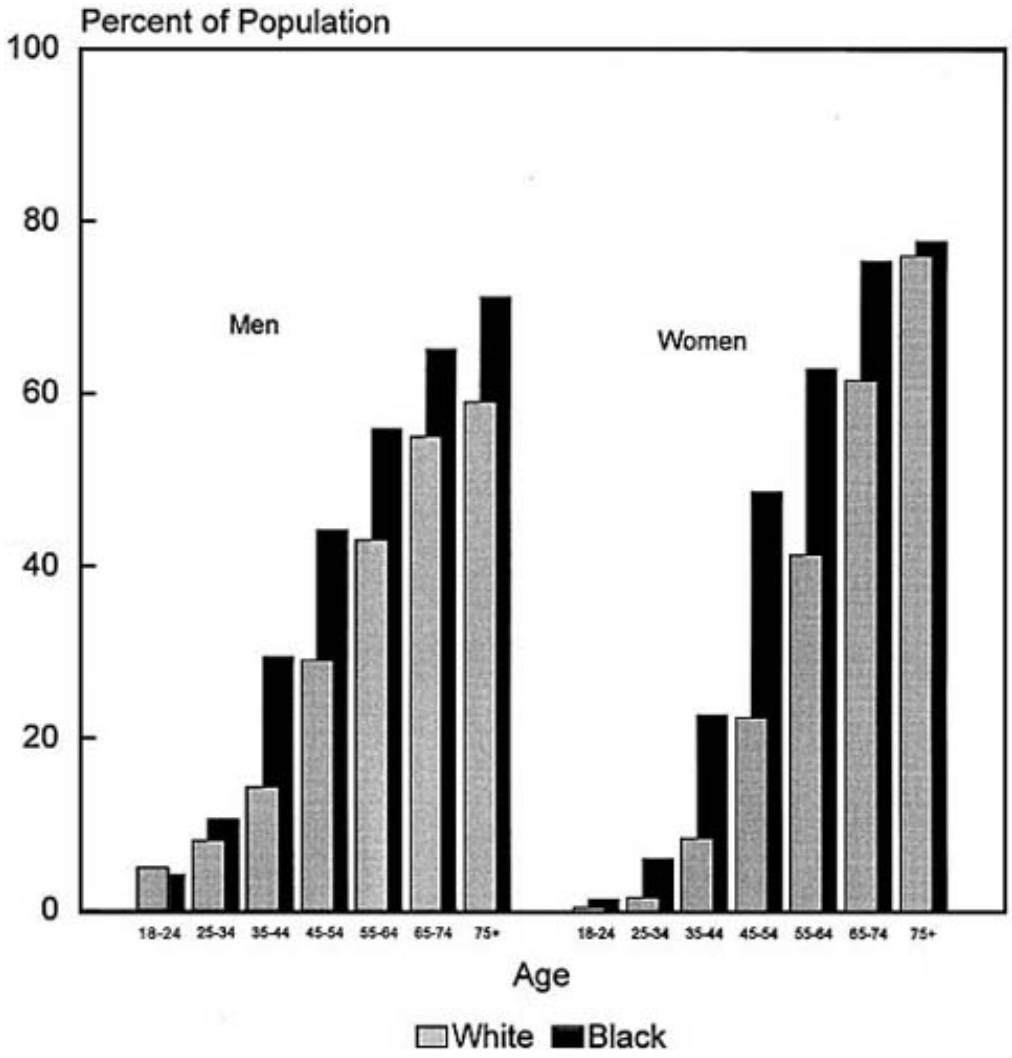

Figure 1-8: Prevalence of hypertension by age, race, and sex; United States, 1988-1994 (hypertension: 140/90 mmHg or greater or on antihypertensive medication). (From the National Health and Nutrition Examination Survey, National Center for Health Statistics.)

Although there is a rise in blood pressure with age in both sexes, in most affluent populations this is not universal, and it does not imply that blood pressure inevitably must rise with age or that in those whose pressures do rise it reflects a normal aging process. In the United States, there is about a 20 mmHg systolic and 10 mmHg diastolic rise in mean pressures from age 30 to age 64. Systolic pressures continue to rise in women into their eighties and in men into their seventies. Diastolic pressures level off earlier and in men decline beyond age 55. The pressures start lower in young-adult women and rise more steeply in middle age (50 and over), and they equal those of men in their fifties and then progressively exceed those of men in later life; this crossover is observed for both systolic and diastolic pressures. In some populations in the world, blood pressure does not rise with age.

For the following discussion, *hypertension* means that a patient has blood pressure of 160/95 mmHg or greater or is on antihypertensive medication; *under control* means that a patient is on antihypertensive medication and has blood pressure of less than 160/95 mmHg. Between the periods 1971-1972 and 1988-1994, there have been large improvements in the percentage of hypertensive patients who (1) are aware of their hypertension (from 51-88 percent), (2) are on antihypertensive medication (from 36-79 percent), and (3) are under control (from 16-65 percent).[1] Although an improving trend is also seen at the 140/90 mmHg and greater level of control, using this definition, 46 percent still do not have medication prescribed for their hypertension.[2]

Incidence

Longitudinal observation of blood pressures as people age reveals a different pattern than cross-sectional prevalence data. The reason for this difference is obscure. Diastolic pressures are essentially parallel in both sexes, with women's pressures consistently below those of men at all ages. In women, systolic pressures are initially lower than in men but subsequently rise more steeply with age. They converge at age0 with those of men but never exceed them. With advancing age in both genders, a progressive and disproportionate rise in systolic pressure occurs that is presumed to result from loss of arterial elasticity. Blacks have higher blood pressures than whites in most Western cultures.

Determinants

While genetic susceptibility plays a large role in hypertension, this may be only permissive, requiring one or more environmental cofactors such as salt intake, alcohol, or weight gain to bring on hypertension. Of all the identifiable determinants of hypertension, weight gain and adiposity, particularly abdominal in distribution, seem to be predominant. New underlying causes of hypertension are discovered every decade, but the causes of the vast majority of cases remain undetermined. Of the identifiable causes, chronic renal diseases, renovascular disease, and oral contraceptives head the list. Routine search for underlying causes not suggested by signs or symptoms is usually unrewarding and often counterproductive. Recent research suggests that insulin resistance occurring in association with obesity may play a fundamental role [27] (see also Chaps. 41 and 56).

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STROKE

Prevalence

Two percent of the U.S. adult population, 4.4 million people, have cerebrovascular disease (stroke).[2] More than 1 million of these individuals are limited in their usual activity.[6] Prevalence rises from 2 percent in men at 45 to 54 years to 12.5 percent for men aged 75 and over and from 1 to 10.7 percent in the respective age groups in women (Fig. 1-9). In the Framingham Study, the most common variety of complete stroke is atherothrombotic brain infarction, which accounts for 61 percent of all strokes (excluding transient ischemic attacks).[28] Next most common are cerebral embolus (24 percent), intracerebral hemorrhage, and subarachnoid hemorrhage. Intracerebral hemorrhage apparently has declined most in recent years (see also Chap. 98).

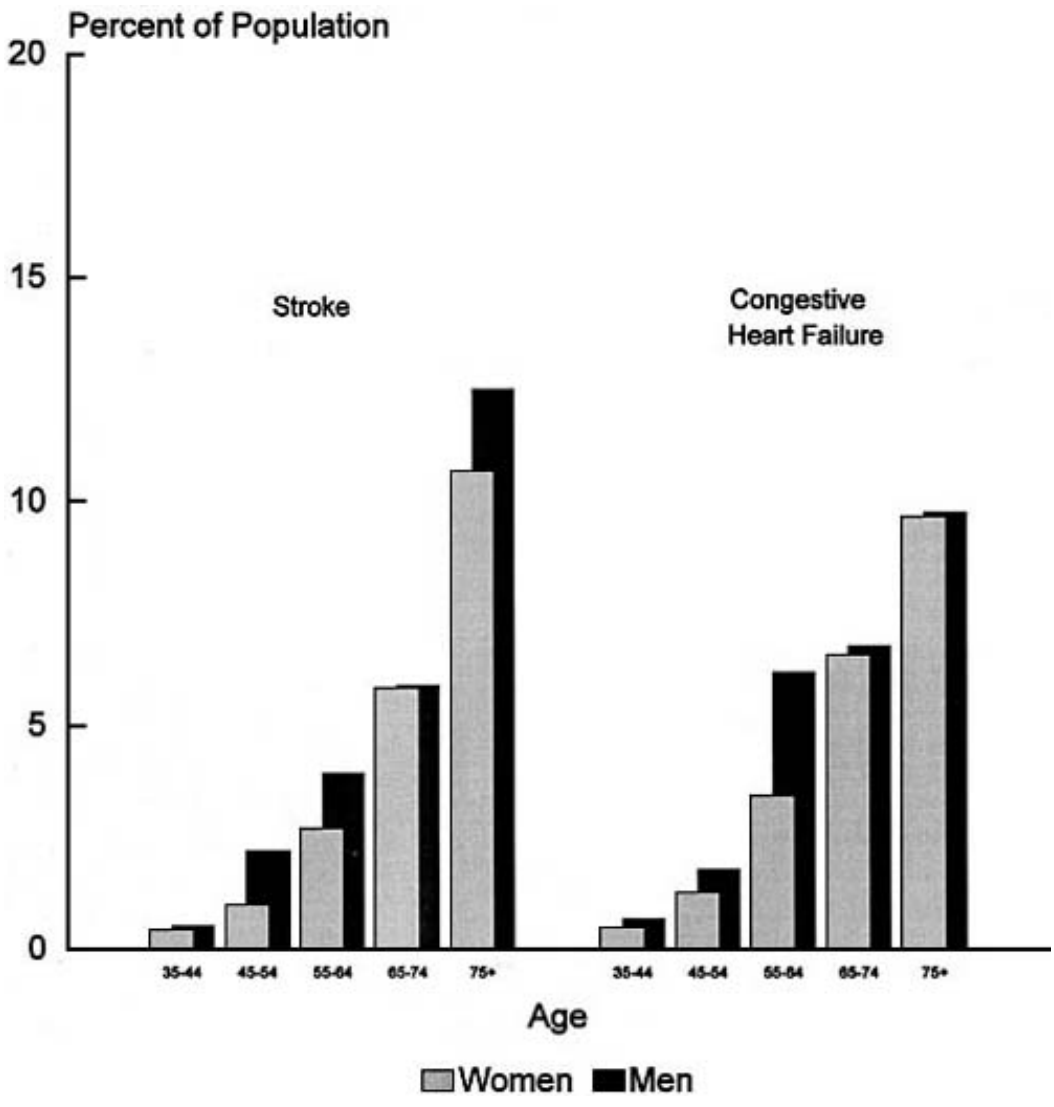

Figure 1-9: Prevalence of stroke and CHF by age and sex, United States, 1988-1994 (self-reported stroke and congestive heart failure from health interviews). (From the National Health and Nutrition Examination Survey, National Center for Health Statistics.)

Incidence and Disability

In the Framingham Study, the chance of having a stroke before age 70 was 5 percent for both sexes.[28] Annual incidence in the Atherosclerosis Risk in Communities Study was 5.3 per 1000 persons at risk in black men aged 45 to 64 years, 4.0 in black women, 2.0 in white men, and 1.5 in white women.[29] Of the incident events, 83 percent were ischemic strokes, 10 percent were hemorrhagic, and 7 percent were subarachnoid hemorrhage. Among the 54 percent classified as definite thrombotic brain infarctions, 38 percent were classified as lacunar, more than twice as many in blacks as in whites. The time course of functional recovery is strongly related to initial stoke severity.[30] Of survivors of an initial event, 50 to 70 percent return to functional independence, but 15 to 30 percent become permanently dependent. Institutional care is required by 20 percent at 3 months after onset.[31]

Stroke attacks have become less severe in recent years, but prevention is essential for dealing effectively with the problem of stroke because of the irreversibility of established ischemic brain damage and the neurologic deficit it induces. The underlying cerebrovascular disease is not a necessary consequence of aging. Modifiable contributing factors offer the possibility of prevention in identified stroke candidates. Stroke prevention requires early and sustained treatment of persons with hypertension, cardiac disorders (especially atrial fibrillation), and transient cerebral ischemic attacks.

Mortality

Cerebrovascular disease, the third leading cause of death, was responsible for 207,000 deaths in the United States in 1974, but by 1997, the number had declined to 160,000.[4,12] This decline is remarkable because the population of older persons increased substantially during that time. The age-adjusted death rate declined by more than 50 percent over this period, but the decline appears to have almost ended in the 1990s.[1] This disease still accounts for 7 percent of all deaths, and 44,000 of them occur in individuals younger than 75 years of age. Under age 65, the mortality rate is three times greater in blacks than in whites, largely as a result of the higher prevalence and increased severity of hypertension in the former. The proportion of strokes that result in death within 1 year is about 22 percent in men and 25 percent in women, less if the stroke occurs before age 65 (see Fig. 1-7). For men or women under age 65, however, only 50 percent survive past 8 years (see Table 1-6; see also Chap. 98).

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HEART FAILURE

Heart failure is the end stage of cardiac disease after the myocardium has used all its reserve and compensatory mechanisms. Once overt signs appear, half of patients die within 5 years despite medical management.[32] Heart failure is most often a consequence of hypertension, CHD, valve deformity, diabetes, or cardiomyopathy. The various etiologies tend to coexist. CHD, frequently accompanied by hypertension, is responsible in more than 50 percent of cases and has been increasing in prevalence among new cases of heart failure. Left ventricular hypertrophy, hypertension, and valvular diseases are diminishing determinants. The risk of cardiac failure is increased two- to sixfold with CHD, angina conferring half the risk compared with MI. The dominant cause continues to be hypertension, which precedes failure in 75 percent of patients.

An estimated 4.8 million Americans have CHF.[2] The prevalence increases with age to exceed 10 percent after age 60 (see Fig. 1-9). Each year there are an estimated 400,000 new cases.[2] In 1997, there were 43,000 deaths nominally classified to heart failure as the underlying cause and about another 200,000 where heart failure was listed on the death certificates as a secondary cause. The death rate increased in most years between 1968 and 1997. The rate of hospitalizations for heart failure increased between three and four times between 1970 and 1997 in patients aged 45 to 64 and 65 and over.[2,8] In 1997, heart failure was the first-listed discharge diagnosis in 957,000 hospital discharges and a secondary diagnosis in another 2.1 million discharges.[8] Twenty percent of all hospital discharges of patients aged 65 and over had heart failure as a primary or secondary diagnosis. The percentage of CHF patients who died in hospitals, however, decreased from 11.3 percent in 1981 to 5.0 percent in 1996.[1] Visits to physicians' offices for CHF increased from 1.7 million in 1980 to 3.2 million in 1995. The prevalence is similar in men and women, but it is higher in blacks than whites. It increased substantially as measured in national surveys in 1976-1980 and 1988-1994 (see also Chaps. 23 and 41).

Based on the Framingham Study, heart failure is equally frequent in men and women, and the annual occurrence approaches 10 per 1000 population after 65 years of age (see Table 1-1). Survival following the diagnosis of heart failure is worse in men than in women, but even in women fewer than 15 percent survive much longer than 8 to 12 years (see Table 1-6). The prognosis is not much better than for most forms of cancer. The 1-year fatality rate for heart failure is high, with one in five patients dying. Sudden death is a common mode of exitus, occurring at six to nine times the general population rate. With an increasing geriatric population, heart failure is a formidable problem.

There is little indication that the declines in death rates from heart disease in general and from CHD in particular in the United States have been accompanied by an improvement in the incidence of heart failure.[33] This cannot be readily explained. Some postulate that improved survival of patients with angina, MI, and hypertensive heart disease may result in an increased prevalence of chronic heart disease and ultimately heart failure. Data from the Framingham Study indicate very little improvement to date in the ominous outlook following the onset of CHF. The median survival of 652 incident cases of CHF was only 1.7 years in men and 3.2 years in women,[33] and the overall survival rates at 5 years were only 25 percent for men and 38 percent for women. The mortality increased with age in both sexes. If one adjusts for age, no significant

changes in the prognosis of CHF are evident over the past four decades despite improvements in treatment. Advances in treatment of hypertension, myocardial ischemia, and valvular heart disease have not resulted in dramatic improvements in survival once heart failure ensues.

Despite the availability of potent glycosides, diuretics, and antihypertensive agents, heart failure continues at a high incidence.[34] Because of the high attributable risk of hypertension and CHD, their prevention and effective treatment would appear to be required to make a significant impact on the incidence of congestive heart failure.

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IDIOPATHIC CARDIOMYOPATHY

Reliable estimates of the prevalence and incidence of idiopathic dilated (congestive) and hypertrophic cardiomyopathies are unavailable because of their comparatively uncommon occurrence in the general population. The National Center for Health Sta- tistics data from 1996 assigned 27,501 deaths to cardiomyopathy, hypertrophic cardiomyopathy accounting for only 1 percent.[4,35] Alcoholic heart muscle disease (cardiomyopathy) appears to account for 8 percent of deaths due to cardiomyopathy. This condition appears to be 2.5 times as frequent in blacks as in whites. Mortality from cardiomyopathy was highest in older persons, men, and blacks. Death rates rose sharply in the 1970s and 1980s but for reasons that are unclear. This apparent increase could be an artifact of changes in diagnostic criteria and death certification practices. In 1997, cardiomyopathy was the primary diagnosis for 39,000 hospitalizations and 261,000 days of hospital care, but 443,000 hospitalizations had cardiomyopathy listed as a secondary diagnosis[8] (see also Chaps. 72 and 73).

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ARRHYTHMIAS

Arrhythmias are a major cause of morbidity in heart failure and rheumatic heart disease and are a contributor to half the mortality from CHD. Many such victims die suddenly, without warning. Together with heart failure, arrhythmias are often the final common pathways of terminal heart disease. Estimates of morbidity and mortality are difficult to obtain. There is good evidence, however, that atrial fibrillation is the most common of the serious arrhythmias and is responsible for substantial morbidity and mortality in the general population.[36] Although the true frequency of arrhythmias is not known, in 1997 there were an estimated 3.5 million hospital discharges with arrhythmias as the primary (635,000) or secondary diagnosis, with two-thirds being due to atrial fibrillation.[8] Between 1982 and 1995, the rate of hospitalization for atrial fibrillation about doubled.[1] In 1995, there were an estimated 3.3 million visits to physicians' offices for arrhythmias, more than due to the cerebrovascular diseases.

The Framingham Study reported estimates for atrial fibrillation. In that population, prevalence rose from 0.5 percent at ages 50 to 59 years to almost 9 percent at ages 80 to 89 years.[36] Between 1968 and 1989, age-adjusted prevalence tripled in men but did not change appreciably in women. These trends are unexplained. Incidence also doubles with each successive age decade, to reach almost 5 percent per year at ages 85 to 94 years.

Most cases of atrial fibrillation evolved following development of overt cardiovascular disease. Heart failure, MI, and valvular heart disease were the most powerful precursors, with the relative risks as much as sixfold. Hypertensive cardiovascular disease was the most common prior cardiovascular disease, largely because of its great frequency in the general population. Impaired glucose tolerance was the other major risk factor predisposing substantially to atrial fibrillation.

Atrial fibrillation is associated with increased risks of cardiovascular morbidity and mortality. After adjusting for various factors, there was a three- to fivefold increased risk of stroke, the chief hazard of atrial fibrillation. Atrial fibrillation decreases survival and is associated with a near doubling of the risk of mortality, after adjusting for associated cardiovascular conditions (see Chap. 27).

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RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Rheumatic fever is a prominent cause of serious valvular heart disease. Acute rheumatic fever and subsequent rheumatic heart disease remain important cardiovascular problems in the tropical and subtropical developing countries of South America, Africa, the Middle East, and Asia, and there have been outbreaks in the United States in recent years.[37] Although preventable, rheumatic fever occurs more frequently because of overcrowding, the deceptive self-limited nature of symptoms in streptococcal pharyngitis, and the mild and often clinically inapparent nature of streptococcal infections. The availability of penicillin to treat these infections, living conditions that are less crowded than formerly, and evolution of different strains of *Streptococcus* have made rheumatic fever uncommon in the United States, although the incidence remains high in subgroups such as blacks, Puerto Ricans, Mexican Americans, and Native Americans (see Chap. 62). Because this disease has not been eradicated in this country, there is a need to define its incidence and prevalence more accurately as well as those of the infective endocarditis that may follow in order to pinpoint those at risk (see also Chap. 82).

An estimated 1.8 million persons have rheumatic heart disease in the United States, more than 6 per 1000 persons.[2] About 15 percent of these persons are limited in activity because of the resulting chronic carditis.[6] There is no national estimate of annual incidence. A study in Tennessee reported a range from 0.5 to 1.88 new cases per 100,000 school-aged children in 1977-1981, with the lowest rates in the affluent suburbs.[37] Occurrence tends to be concentrated in the lower socioeconomic subgroups, perhaps due to factors of nutrition, hygiene, and access to medical care. Rheumatic fever is rare before age 3, occurring most frequently between 5 and 15 years of age, when streptococcal infections are most frequent. During epidemics of streptococcal pharyngitis, the rheumatic fever attack rate may be 3 percent, whereas in endemic situations it is usually only 0.3 percent (see also Chap. 62).

With the decline in rheumatic fever in the United States, its clinical manifestations also have moderated so that carditis is detected in fewer than 20 percent of acutely affected patients.[38] The annual mortality has declined to about 5000 deaths per year. Because the cardiac sequelae of rheumatic fever are still seen in adults and adequate treatment can reduce attacks by 90 percent, rheumatic fever and rheumatic heart disease remain the two most preventable serious cardiovascular disorders. It seems clear that at least part of the decline in rheumatic fever was due to prompt antistreptococcal treatment by physicians. The decline in rheumatic fever, however, appears to have antedated the advent of antistreptococcal agents. We are currently unable to explain the reasons for the decline in rheumatic fever definitely, possibly because we do not fully understand its etiologic factors (see Chap. 62).

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OTHER VALVULAR DISEASE

In the two decades since mitral valve prolapse was described, the syndrome was thought to be a frequently diagnosed valvular deformity, more common in women. This assessment was based on studies that had patient selection bias and diagnostic criteria that were less specific than those used today. In a community population study, with false-positive results, false-negative results, and selection bias greatly minimized, the picture looks quite different.[39] The Framingham Study reports that prevalence is no more than 1 to 2 percent, no more common in women than in men, and diagnosis of associated cardiovascular sequelae is low. This assessment also has its limitations. Study results are based on a white population only, confidence limits around the prevalence estimates are large, results are subject to a survival bias, and patients with mitral valve prolapse that resulted in sudden death may not have been included in the cohort. The major importance of mitral valve prolapse may be the threat of endocarditis, which must be rare, and arrhythmias, which may be common (see Chap. 65).

Little information is available on the prevalence of valvular heart disease in the general population. Most prevalence estimates come from surgical studies and small numbers of patients referred for diagnosis. The Framingham Study has estimated prevalence of mitral, tricuspid, and aortic regurgitation in their population sample using color Doppler echocardiography routinely obtained on all participants.[40] Some degree of mitral and tricuspid regurgitation was seen in 19 and 15 percent of men and 19 and 18 percent of women, respectively. Aortic regurgitation was found in 13 percent of men and 8.5 percent of women.

Rheumatic heart disease is no longer the most frequent cause of valve disease. Mitral valve prolapse and degeneration of congenital aortic valve lesions are now the most common causes.[41] Aortic stenosis also may result from atherosclerotic degeneration of the valve in diabetes with dyslipidemia. It is the most common valve lesion in the elderly having valve replacement.[42] Aortic root or annular dilatation is responsible for most aortic regurgitation, of which 40 to 60 percent is of unknown cause.

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CONGENITAL HEART DISEASE

About one million persons in the United States have congenital cardiovascular disease, and each year an estimated 32,000 babies, about 8 per 1000 live births, are born with this disease.[2,43] Of the new cases, 8 to 13 percent have atrial sepal defects, 6 to 11 percent have patent ductus arteriosus, and 20 to 25 percent have ventricular sepal defects. The prevalence of congenital heart disease at birth as determined during the infant's brief stay in the hospital is likely to be underestimated, and recognition of specific lesions may be inaccurate.[44] Most data are deficient for a diagnosis after the first week of life. Prevalence data based on autopsy findings are unreliable because they reflect a fraction of the deaths and relate only to fatal lesions. Most information comes from retrospective studies based extensively on referral practices.

Structural abnormalities of the heart or intrathoracic great vessels seem to affect 8 to 10 of every 1000 infants born alive in the United States. If bicuspid aortic valves and mitral valve prolapse manifested later in life are included, the rate may well exceed 1 percent of live births. About 1 newborn per 1000 live births has a cardiac birth defect that cannot be managed medically or surgically. Most infants who previously would have died now survive to adult life because of improved treatment, but 5 to 6 of these infants per 1000 live births require frequent medical or surgical attention shortly after birth or later in childhood.

Except for the recent unexplained twofold increase in ventricular sepal defects and the threefold increase in patent ductus arteriosus, the incidence of most congenital heart diseases has remained stable. Rubella vaccine has reduced rubella-caused congenital heart disease, and congenital heart defects associated with Down's syndrome are less common because older women are having fewer babies. Pregnancies may be terminated if prenatal screening reveals Down's syndrome. Preventive strategies are impeded by lack of knowledge of the cause of most congenital heart disease, although it is known that alcohol, trimethadione, and lithium can cause cardiac defects. The majority of congenital heart disease may involve complex genetic-environmental interactions that remain to be elucidated (see Chaps. 69 and 70).

About 75 of each 1000 live births in the United States are premature, with the infants weighing less than 2500 g.[12] Almost half of premature infants weighing less than 1750 g will maintain patency of their ductus arteriosus, possibly because their immature lungs do not properly metabolize prostaglandins that cause the ductus to remain open.[45] The growing number of teratogens identified appears to account for only 5 percent of all human malformations, and single mutant genes are said to be responsible for only 3 percent of cases.

In 1997, deaths in infancy from congenital cardiovascular disease occurred at the rate of 0.5 per 1000 live births, about one-half the rate that occurred in 1980.[8] The 1-year fatality rate among the estimated 32,000 new cases at birth each year was about 6.5 percent in 1997. About 25 percent of infants with congenital heart disease have a malformation incompatible with life beyond the first year; possibly half of these can be treated surgically to improve the quality of life, if not to produce a cure. About 2.5 per 1000 live-born infants require specialized services for diagnosis and treatment of congenital heart disease shortly after birth, and another 2.5 per 1000 will need these resources later in childhood.

With the exception of bicuspid aortic valve in older patients, ventricular septal defect is the most common variety, accounting for 30 percent of congenital heart disease. Some 75 percent of congenital heart disease in infants and children is encompassed by seven defects: ventricular sepal defect, pulmonary stenosis, patent ductus arteriosus, tetralogy of Fallot, aortic stenosis, coarctation of the aorta, and transposition of the great arteries. There is an excess of birth defects in blacks. The rate among siblings is 17 per 1000 compared with 2.6 per 1000 in the general population (see Chap. 70).

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PULMONARY THROMBOEMBOLISM

More than 95 percent of pulmonary emboli arise from deep venous thrombi in the legs (above the knee); the remainder arise from the right cardiac chambers or other veins. The majority of deaths occur suddenly and can be avoided only by prophylaxis. Patients who survive to reach the hospital for medical treatment generally have a good outlook, with little morbidity and resolution of the emboli.

Estimates of mortality from pulmonary embolism vary depending on the source and accuracy of data. Pulmonary emboli are probably directly responsible for 50,000 deaths annually in the United States. If untreated, recurrent episodes are frequent, and more than 25 percent will be fatal. More than 60 percent of fatalities occur within 1 hour of onset; hence pulmonary embolism is likely to be confused with sudden coronary death. It is estimated that pulmonary embolism is grossly underdiagnosed, since only 10 to 30 percent of autopsied cases with evidence of embolism had an antemortem diagnosis.[46]

Among the U.S. population, the age-adjusted death rate for pulmonary embolism decreased 33 percent between 1979 and 1997.[4] The decline was greater in whites than in blacks and greater in men than in women. The rate of hospital discharges with a primary or secondary diagnosis of pulmonary embolism declined 38 percent from 7 per 10,000 population in 1979 to 4.3 in 1997.[8] Death rates and hospital rates for pulmonary embolism increase with age and are higher in men than in women and in blacks than in whites.[4] It was listed on 115,000 hospital records in 1997.[8] The incidence is even more uncertain. Only 10 percent of cases occur in normal persons without predisposing factors such as chronic cardiopulmonary and malignant disease, estrogen therapy, orthopedic trauma, immobilization, operative procedures, obesity, pregnancy, or blood dyscrasias. The elderly are more vulnerable.

Postoperative pulmonary emboli alone produce 4000 to 8000 deaths annually.[47] It is a major cause of death postpartum and in patients hospitalized for orthopedic conditions. Evidence from Britain suggests that the annual mortality from pulmonary embolism has been increasing for several decades despite anticoagulant drugs. More than 5 million persons over age 45 undergo major surgery each year in the United States; 1 or 2 of each 1000 will die postoperatively from pulmonary embolism. The recent advent of low-dose heparin prophylaxis may reduce this risk substantially (see Chap. 60).

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PREVENTIVE IMPLICATIONS FOR THE 21ST CENTURY

Examination of the incidence, prevalence, mortality, natural history, and risk factors of cardiovascular disease suggests the greatest benefits will be from a preventive approach. Further innovations in diagnosis and treatment for cardiovascular disease undoubtedly will improve the outlook of patients surviving the initial attack, but this can have only a limited impact because of the high initial mortality. When the heart or brain is infarcted, no therapy can be expected to restore full function. If the initial presentation is sudden death, therapy is unavailing. A preventive approach involving correction of predisposing factors in advance of the overt clinical expression of the disease can be expected to have a greater impact. To date, application of preventive measures of proven efficacy has been suboptimal.[48] Their application in the next century, even for the growing elderly population, has immense potential for primary and secondary prevention. Evidence is accumulating that medical therapy (vigorous risk-factor control) may be at least as effective as surgical or invasive revascularization in preventing recurrence of MI, progression of angina to MI, and premature CHD mortality. The potential benefits for primary prevention of MI by modification of risk factors has been demonstrated by a meta-analysis and reviews of the larger and more rigorous epidemiologic studies.[49] A multifactorial approach to risk reduction offers the best opportunity for saving patients at high risk and preventing the development of high-risk status in the first place.[50]

CHD often strikes without warning: One in five coronary attacks presents as sudden death, and two-thirds of the deaths occur in the community too precipitously to be brought under medical attention. While some strokes may give warning by transient ischemic attacks, most do not. Even when they do, intervention at that stage does not necessarily avoid a permanently damaging stroke or prolong life. Heart valves damaged by degenerative and rheumatic heart disease and infective endocarditis can be repaired surgically or replaced by prosthetic appliances; this approach often requires potentially dangerous anticoagulants to prevent emboli, and valve failure and hemolysis are distressingly common. Although such patients live longer, more comfortable lives than formerly, their survival does not approach that of patients with rheumatic fever who have been kept from progressing to severe valve damage by antibiotic prophylaxis against recurrent disease. Hypertension that pro-gresses to target-organ involvement is less manageable than if vigorously treated prior to such manifestations. The first sign of target-organ involvement is often a stroke, MI, or sudden death. Half of such events occur before evidence of organ involvement is discovered on routine biennial examination. In some respects, the occurrence of symptoms more properly may be regarded as a medical failure rather than as the initial indication for treatment (see Chap. 58).

A major impact on cardiovascular morbidity and mortality in the 21st century should derive from the practice of preventive medicine, from public health measures to alter lifestyle to one more favorable to cardiovascular health, and from health education to inform people of what they must do to protect their cardiovascular health. Recent expansion and improvements in these measures have occurred, conceivably contributing significantly to the 36 percent decline in cardiovascular mortality during the past two decades, which is responsible for most of the decline in overall mortality.[2]

The epidemiologic and clinical trial evidence of the cardiovascular diseases in the 20th century

has set the stage for opportunities in the next century to direct research and public health activities that can substantially reduce the risk and impact of cardiovascular disease. Foremost among those opportunities is implementation of comprehensive preventive programs of government regulation, health education, and preventive medicine designed to control the major identified cardiovascular risk factors. This includes exploring further the underlying basis for clustering of atherogenic risk factors and the prevalence and impact of insulin resistance, promoting cardiovascular risk profiles to more efficiently target high-risk cardiovascular disease candidates for preventive measures, and finding better ways to implement preventive measures against obesity, insulin resistance, and cigarette smoking. The potential is large if physicians can be induced to more aggressively implement the proven measures recommended to prevent cardiovascular disease.

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Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 2:

FUNCTIONAL ANATOMY OF THE HEART

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BACKGROUND

The study of the heart and great vessels has come a long way since the days of Andreas Vesalius, the great 16th-century anatomist who recognized the impact of anatomy on the practice of medicine.[1] During the European Renaissance, the tomographic approach to the study of cardiac anatomy became popular because of its artistic-based correlations. This is vividly depicted in the drawings of Leonardo da Vinci[2] (Fig. 2-1), who was called the first comparative anatomist since Aristotle. During the ensuing nearly four hundred years, however, interest in cardiac anatomy was very sporadic and limited to a few zealous and pioneering physicians, anatomists, and artists.

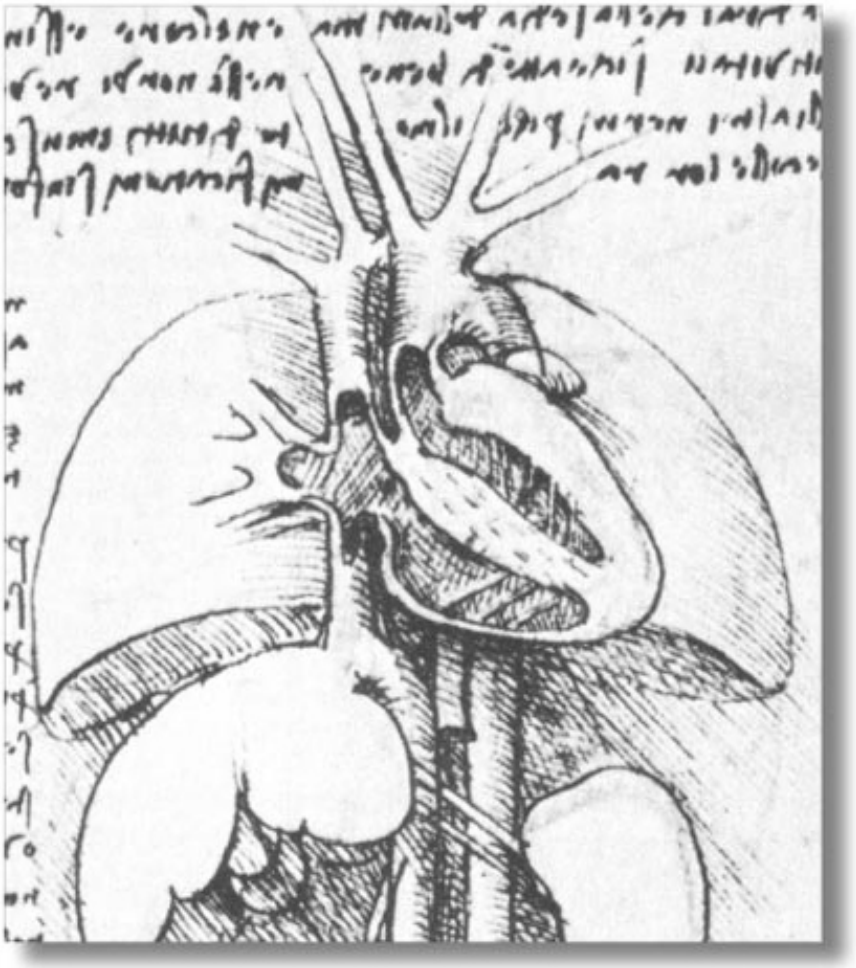


Figure 2-1: Four-chamber tomographic section of the heart as illustrated by Leonardo da Vinci. Note the thin-walled right ventricle and thick-walled left ventricle and detailed anatomic

connections. (From O'Malley and Saunders,[2] with permission.)

The 19th century ushered in the era of anatomic dissection for the study of physiologic and pathophysiologic processes. Virchow in 1885 described the *inflow-outflow method of cardiac dissection* that followed the direction of blood flow.[3] It was quick and simple and became the dissection method of choice. The works of Virchow and Osler paved the way to understanding the pathophysiologic basis of such diseases as pulmonary embolism, endocarditis, and heart failure.[4] Renewed interest in the study of cardiac anatomy and pathology was facilitated by the rise in autopsy rates in Europe and North America during the first half of the 20th century.[5] Herrick described the clinical features of coronary thrombosis.[5] Later, Blumgart, Schlesinger, and Zoll advanced our understanding of coronary artery disease through elegant clinicopathologic correlations.[5]

These achievements notwithstanding, however, they were limited to postmortem examinations. The advent of cardiac surgery in the 1950s, followed by coronary angiography, was a major impetus for promoting the study of in vivo clinicopathologic anatomic correlations. While cardiac surgeons were quick to appreciate the importance of having a detailed understanding of cardiac anatomy, clinical cardiologists were more interested in pathophysiology. However, with the introduction of noninvasive imaging techniques [echocardiography, computed tomography (CT), magnetic resonance imaging (MRI), and single-photon-emission computed tomography (SPECT)] over the past two decades, the perception of cardiac anatomy and pathophysiology radically changed for all of medicine in general and cardiology in particular.

With increasing use of tomographic techniques in the diagnosis and management of cardiovascular diseases, there has been a corresponding decrease in the use of autopsy for anatomic correlations. The reasons for this decrease are complex and controversial and include an increased confidence in technology, lack of reimbursement for the cost of autopsy, and rescinding the mandate for autopsies for hospital accreditation.[4] Nonetheless, autopsy still uncovers unexpected processes in about 15 percent of cases and is an invaluable tool for quality assurance programs.

Today, at the beginning of the 21st century, there is a resurgence in the clinicopathologic correlative approach to cardiovascular morphology. In particular, the tomographic presentation of cardiac structure, which had remained dormant for over a century, has become relevant because the diagnostic techniques used today are tomographic in nature.[6] The specialties associated with cardiovascular diseases have been quick to embrace these newer anatomic presentations. Echocardiography was brought into the operating room, and with the advent of transesophageal echocardiography, the cardiologist became an indispensable member of the surgical team.[7,8] Because of increasingly more sophisticated cardiac surgical techniques, coupled with closer interaction between the cardiac surgeon and the noninvasive cardiologist, there has been a growing demand for precise diagnostic tools with greater spatial and temporal resolution to guide the planning of surgical procedures and, therefore, to ensure their success.[7,8]

The interest in cardiac anatomy among cardiologists is by no means limited to those involved in imaging the heart. Over the past few years, there has been an explosion of interest in anatomically guided electrophysiologic mapping and ablation techniques, which are increasingly guided by intracardiac ultrasound.[9-13] It has thus become feasible to accurately pinpoint the anatomic location of the source of many arrhythmias[9-13] (Figs. 2-2 and 2-3). By providing the electrophysiologist with a real-time visual "road map," the "search and destroy" mission during an ablation procedure will be made much easier and results, as well as complications, recognized immediately.[9-13] By providing a new window to the heart, real-time anatomic-electrophysiologic correlations also may help to enhance our understanding of the mechanisms of propagation of various arrhythmias.

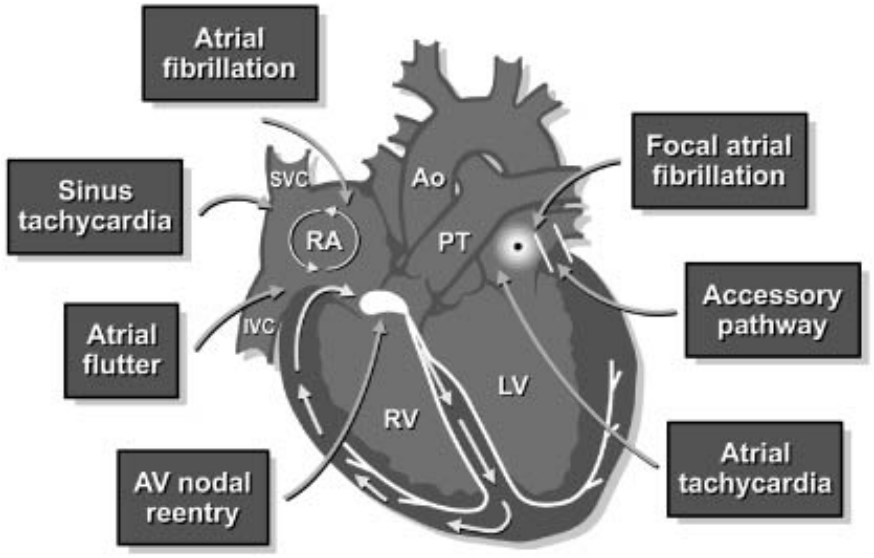


Figure 2-2: Anatomic considerations in the treatment of supraventricular arrhythmias. AV, atrioventricular; Ao, ascending aorta; IVC, inferior vena cava; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; SVC, superior vena cava. (Courtesy of Dr. Douglas L Packer, Mayo Clinic, Rochester, Minnesota.)

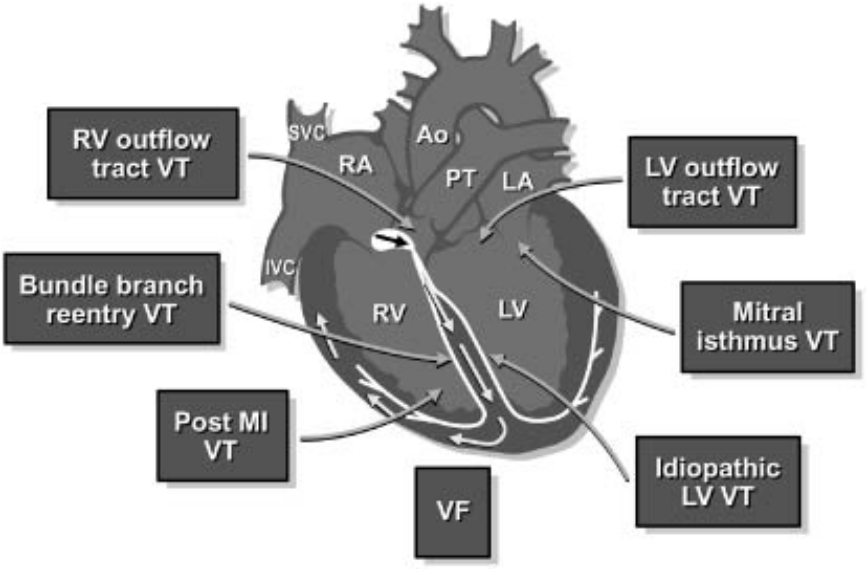


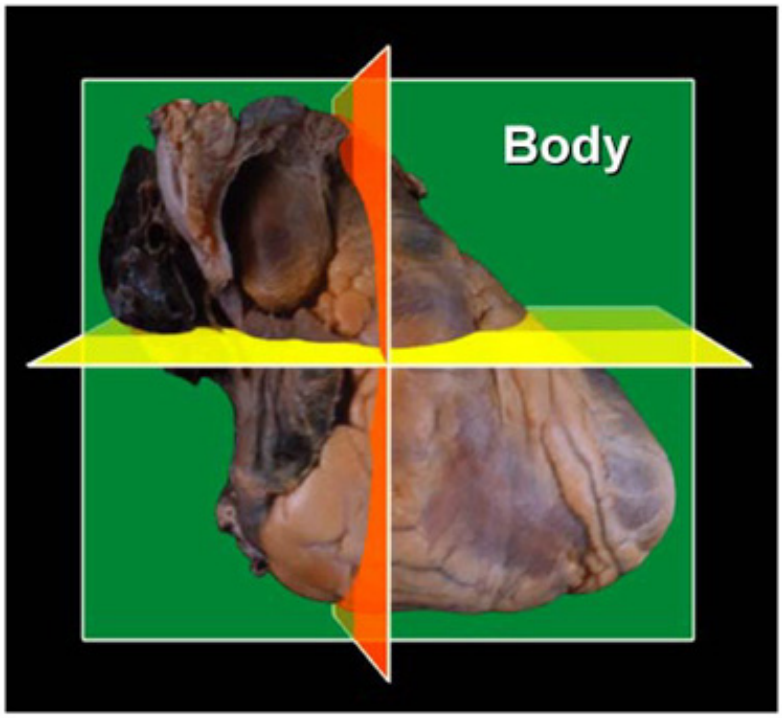
Figure 2-3: Anatomic considerations in the treatment of ventricular arrhythmias. LV, left ventricle; LA, left atrium; MI, myocardial infarction; VT, ventricular tachycardia; VF, ventricular fibrillation; other abbreviations as in Fig 2-2. (Courtesy of Dr. Douglas L Packer, Mayo Clinic, Rochester, Minnesota.)

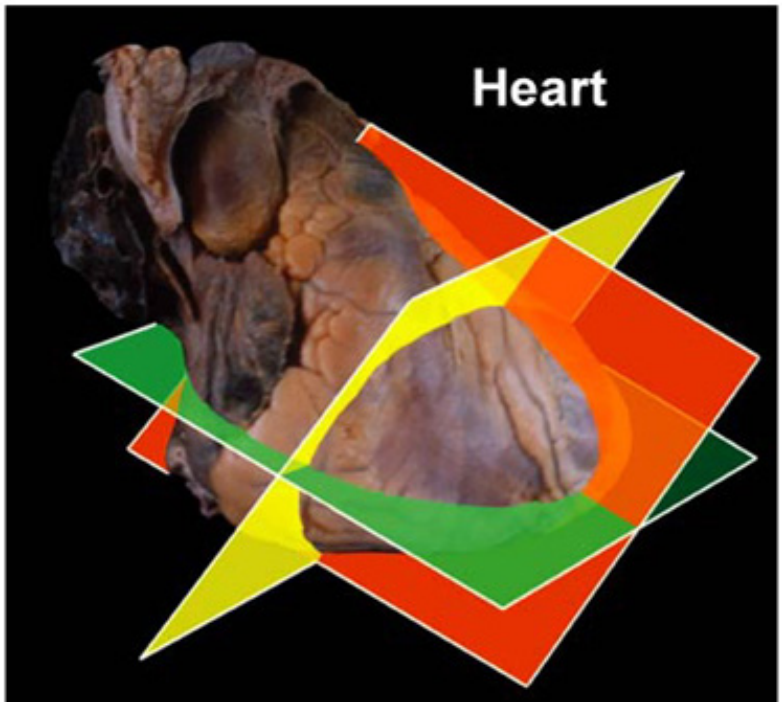
In this technologically driven era, a *new* appreciation of cardiac anatomy has emerged as the cornerstone for clinical cardiology. The purpose of this chapter is to describe the anatomy of the heart by principally using the tomographic format prevalent in current CT, MRI, and echocardiography, with special emphasis and focus on clinically relevant anatomic details. We will make only a passing note of the next generation of imaging techniques. The intent is to emphasize the important anatomic features of various cardiovascular disease processes relative to

diagnosis and management.

Orientation of the Heart Within the Thorax

The body may be viewed in three standard anatomic planes: (1) frontal (coronal), (2) horizontal (transverse), and (3) sagittal that are orthogonal to one another.[6,7] However, the three primary planes of the heart [short axis (transverse), four-chamber (frontal), and long-axis (sagittal)] do not correspond to the standard anatomic planes of the body[6,7] (Fig. 2-4, Plate 1). *Incorrect photographic or artistic orientation of surgical or autopsy specimens of the heart, presented out of context, can result in the display of two-dimensional images in nonanatomic positions and actually contribute to misconceptions regarding the position of the heart within the thorax*[6] (Fig. 2-5, Plate 2).





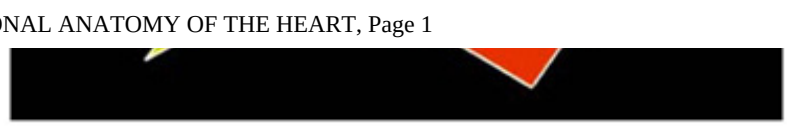


Figure 2-4: (Plate 1) The three primary planes of the body (*left*) and heart (*right*). Note that the planes of the body are aligned with vertical midline structures, such as the esophagus. In contrast, the major axis of the heart is oriented obliquely. Thus the heart's long and short axes do not lie in the same plane as the body's long and short axes. The body planes cut the heart obliquely and not in its primary planes. Conversely, the heart's primary planes cut the body obliquely.

Thus, first, when describing the orientation of a specific organ such as the heart, one must take into account both the position of the heart and the position of adjacent structures such as the thoracic aorta and esophagus. When interpreting two-dimensional images, clinicians must avoid making correlations that yield impossible anatomy[6] (Fig. 2-6). Accurate anatomic diagnoses require close interdisciplinary interactions between cardiovascular pathologists, clinicians, radiologists, anesthesiologists, and surgeons and emphasize a critical need for teamwork and a "common language" when describing cardiac anatomy and pathology.

Methods Used to Study Cardiac Anatomy

The two conventional approaches to the study of cardiac anatomy that have stood the test of time are (1) the inflow-outflow method (Fig. 2-7) and (2) the tomographic ventricular slice method[3,6] (Fig. 2-8, Plate 3). Although the inflow-outflow method readily demonstrates disease processes in a given cardiac chamber or valve, it does not allow simultaneous visualization of the effects of that process on contiguous structures.[6] Furthermore, the inflow-outflow method does not correspond well to clinical tomographic imaging modalities except possibly cavitary angiography.[6] With the ventricular slice technique (see Fig. 2-8), the ventricles are "bread sliced" perpendicular to the plane of the ventricular septum. This technique is ideal for the evaluation of ischemic heart disease but may need to be carried basally, well beyond the papillary muscle tips.[6]

NEXT

Chapter 2: FUNCTIONAL ANATOMY OF THE HEART

TOMOGRAPHIC METHOD

Renaissance anatomists such as da Vinci used the *tomographic approach* principally because of its *artistic correlations*.[2] Modern anatomists and pathologists have resorted to this method because it correlates with conventional diagnostic tomographic-anatomic techniques. With this method, cardiac dissection involves bisecting the heart into two pieces using a single plane of section.[6] Anatomy contained within the depth of each section fosters a perception of three-dimensional anatomy. Commonly used planes bisect the heart perpendicular to the base-apex axis (*short-axis "transverse" views*) (Fig. 2-9, Plate 4) or parallel to it (*long-axis and four-chamber "frontal" views*)[6] (Fig. 2-10, Plate 5). Planes that bisect the heart parallel to the conventional body planes (frontal **"coronal", transverse "short-axis", and sagittal "long-axis" views**) (Fig. 2-11, Plate 6) replicate *body tomography*.[6,14]

The *short-axis tomographic planes*[6,7] of the heart (Fig. 2-12) are similar to the ventricular slice method but differ in two important respects. The "bread slicing" of the heart is continued to the base of the heart and great vessels, and the slices are oriented as though the heart were being viewed from the apex toward the base rather than in the opposite direction, as has been the case with the ventricular slice technique. Photographs should correspond with diagnostic tomographic scans.

The *long-axis and four-chamber planes* are orthogonal to the short-axis planes. The four-chamber planes of cardiac dissection (Fig. 2-13) involve sectioning the heart along both lateral walls, from apex to base, such that both ventricles and both atria are included in the plane of section.[6,7] The long-axis two-chamber method (Fig. 2-14) involves bisecting the heart from the left ventricular apex through the mitral orifice and into the left atrium.[6,7] The long-axis plane can cut through both the left ventricular inflow tract (including the left atrium and mitral valve) and the left ventricular outflow tract (including the ventricular septum, anterior mitral leaflet, and ascending aorta) (Fig. 2-15). This plane also cuts obliquely through the right ventricular outflow tract.[6,7]

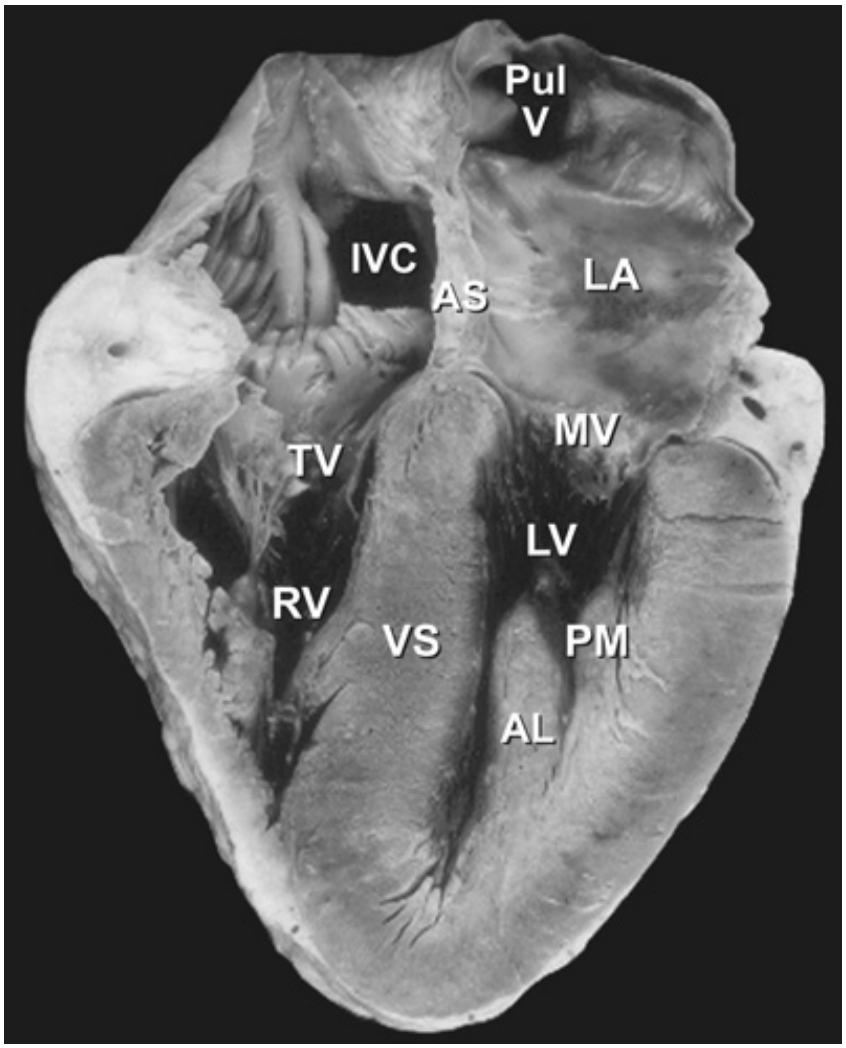
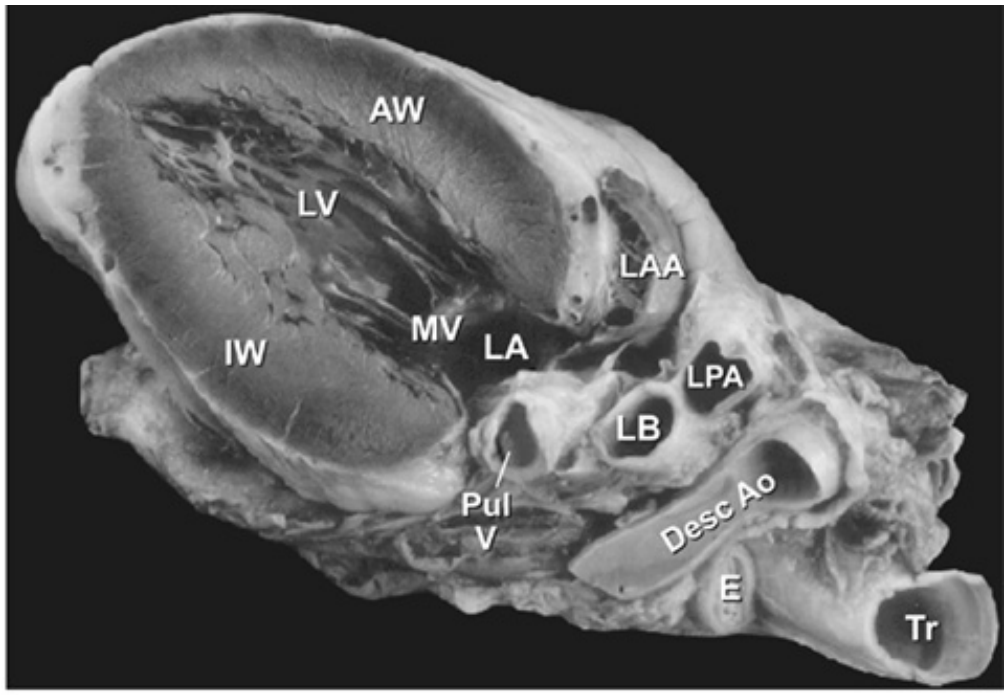


Figure 2-13: Tomographic cardiac dissection along the heart's primary fourchamber plane. The heart is viewed as though one were looking from the anterosuperior surface toward the posteroinferior surface. In the floor of the right atrium is the orifice of the inferior vena cava (IVC). The pulmonary veins (PulV) enter the posterior aspect of the left atrium. AL, anterolateral mitral papillary muscle; AS, atrial septum; LA, left atrium; LV, left ventricle; MV, mitral valve; PM, posteromedial mitral papillary muscle; RV, right ventricle; TV, tricuspid valve; VS, ventricular septum.



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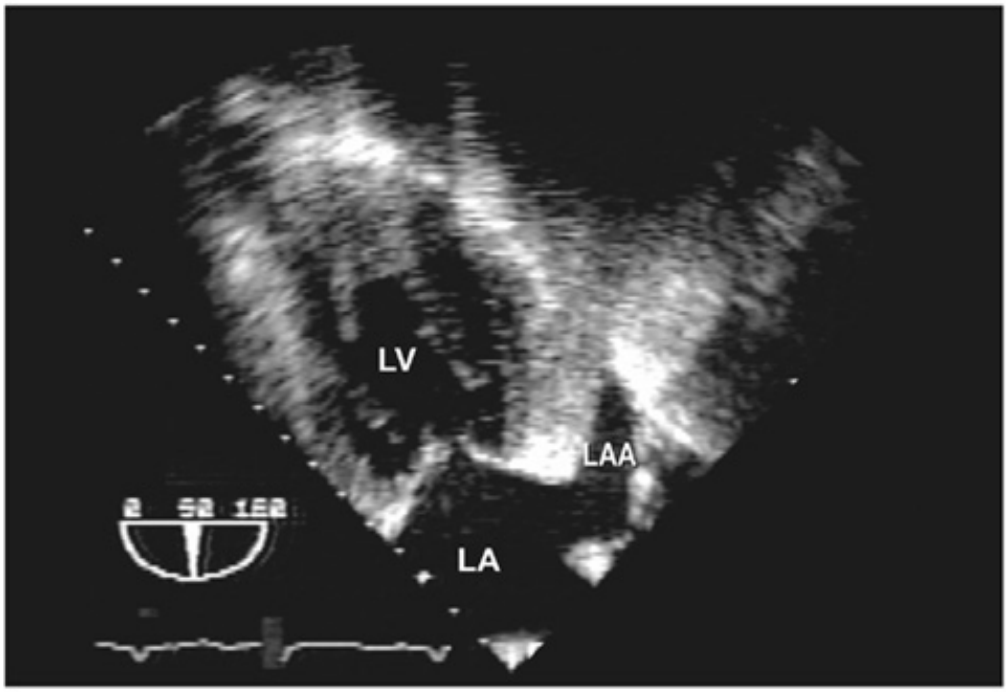


B

Figure 2-14: Tomographic cardiac dissection along the heart's primary long-axis plane. *A.* Tomographic section showing the left ventricle and left atrium. The mitral valve is also well demonstrated. The left atrial appendage is located anteriorly. The specimen is viewed as though one were looking from the tip of the left scapula toward the right nipple. *B.* Analogous two-chamber transesophageal view. AW, anterior wall; **Desc** Ao, **descending thoracic aorta;** E, **esophagus;** IW, **inferior wall**; LA, **left atrium;** LAA, **left atrial appendage;** LB, **left bronchus;** LPA, **left pulmonary artery;** LV, **left ventricle;** MV, **mitral valve;** PulV, pulmonary vein; Tr, trachea.

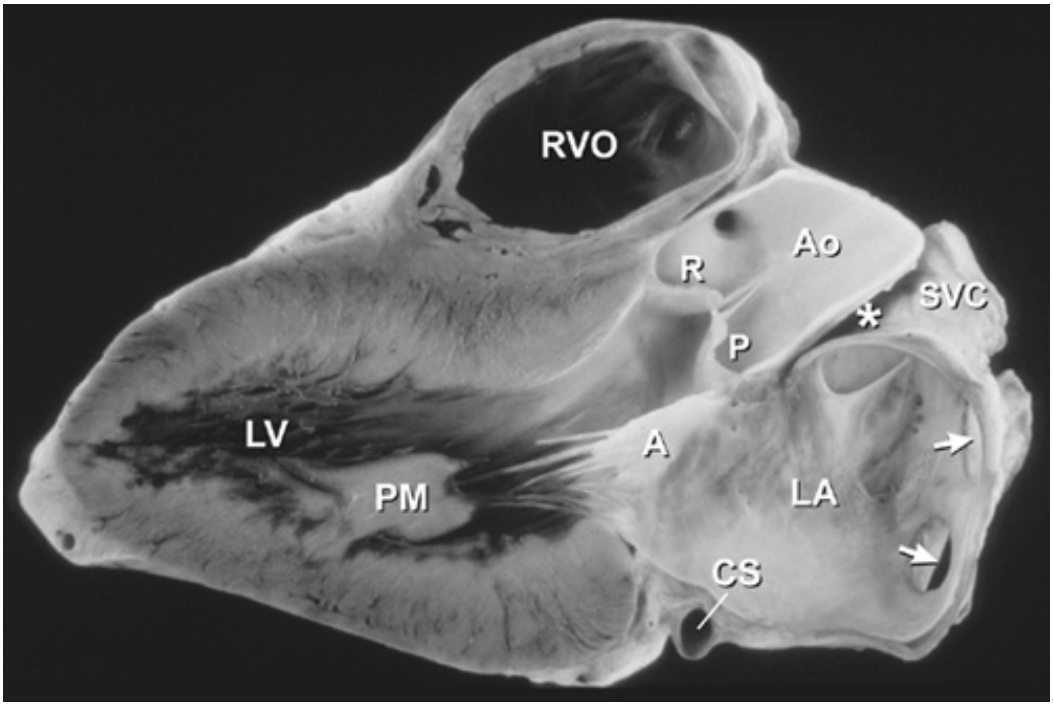
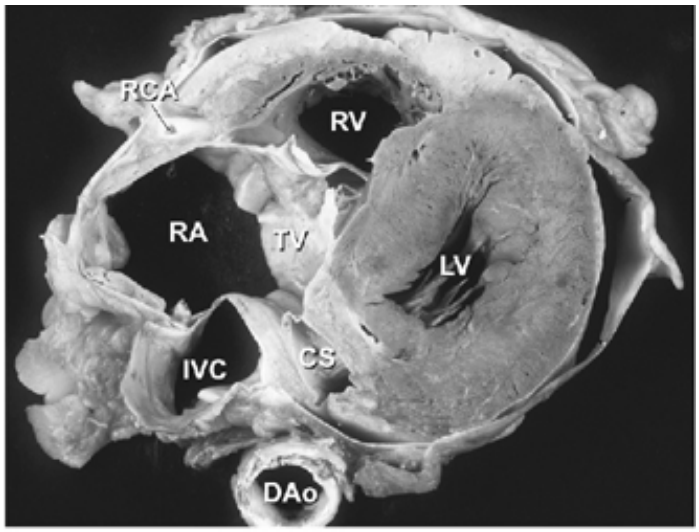


Figure 2-15: Left ventricular long-axis method of tomographic cardiac dissection (looking from left flank toward the midsternum). Continuity between mitral and aortic valves is clearly seen. The oblique sinus (*) abuts the wall of the left atrium. A, anterior mitral leaflet; Ao, ascending aorta; CS, coronary sinus; LA, left atrium; LV, left ventricle; P, posterior aortic cusp; PM, posteromedial mitral papillary muscle; R, right aortic cusp; RVO , right ventricular outflow; SVC, superior vena cava; arrows point to the right upper and lower pulmonary veins.

These three tomographic planes of the heart have been particularly useful in echocardiography. Serial sections within each plane produce a collage of anatomic slices (Fig. 2-16, Plate 7) that can be used for three-dimensional reconstruction, which is beyond the scope of this chapter. The tomographic planes of section can be tailored to the different imaging modalities. *Thus echocardiography and* SPECT *generally employ the primary planes of the* heart. *In contrast,* CT *and* MRI *use the primary planes of the* body. *The parasagittal or oblique planes of the body serve radionuclide angiography and left ventriculography.*[6] When the tomographic examination is not configured to the primary planes of the heart but rather to the planes of the body, the terms *short, long,* and *frontal* can be misleading (Figs. 2-17 and 2-18).



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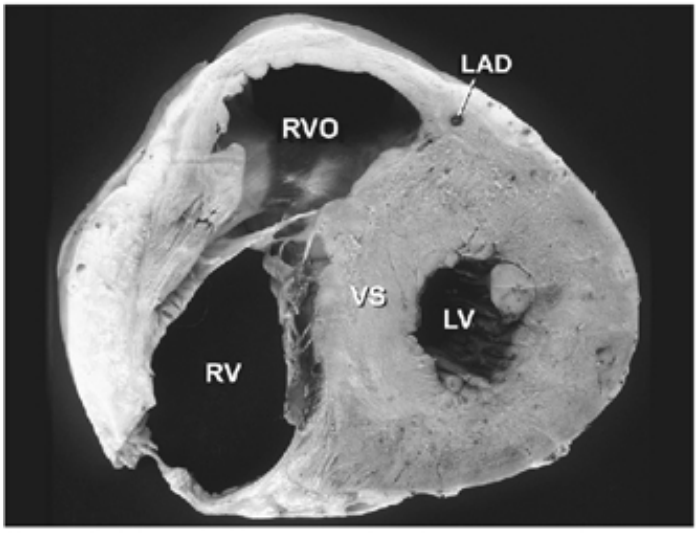

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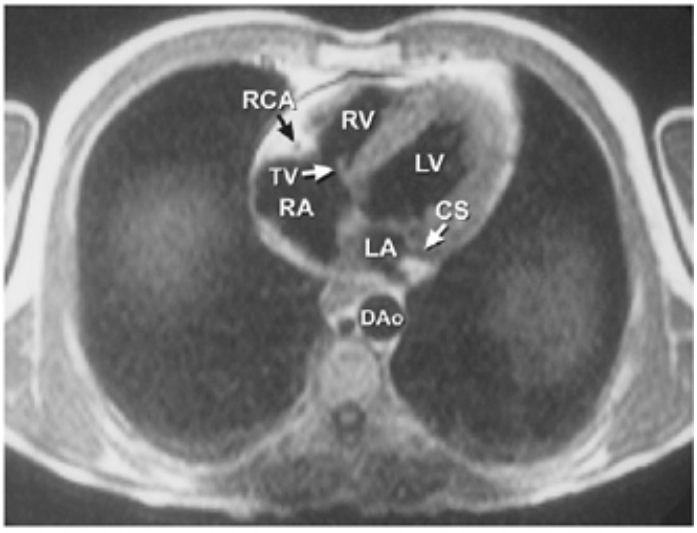

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Figure 2-17: Tomographic sections of the heart in the transverse (*A*) and frontal (*B*) planes of the body. A tomographic section in the transverse plane of the body (*A*) results in a four-chamber view of the heart. *A* tomographic section along the frontal plane of the body (*B*) results in an oblique short-axis view of the heart. *C*. MRI image corresponding to *A*. CS, coronary sinus; DAo, descending thoracic aorta; IVC, inferior vena cava; LA, left atrium; LAD, left anterior descending

coronary artery; LV, left ventricle; RA, right atrium; RCA, right coronary artery; RV, right ventricle; RVO, right ventricular outflow; TV, tricuspid valve; VS, ventricular septum.

Pathologic lesions in both congenital and acquired heart diseases often involve contiguous chambers, valves, or vessels. The tomographic method is the optimal technique for demonstrating intracardiac relationships and is ideal for any disease that involves several cardiac chambers. The proliferation of noninvasive tomographic imaging techniques makes this method particularly ideal for clinicopathologic correlations.

Limitations of tomographic dissection can be overcome by photography, computer imagery, and interestingly, the use of glue. After each tomographic section has been produced and photographed, the bisected specimens can be glued back together using any cyanoacrylate glue such as Krazy **Glue or Superglue** and resectioned along a different tomographic plane.[6] A step-by-step photographic documentation is necessary, since once the specimen has been glued and recut, the preceding tomographic plane of section will be available only in the photograph and not in the actual specimen.

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Chapter 2: FUNCTIONAL ANATOMY OF THE HEART

CORRELATIVE ANATOMY

This section in this chapter is an illustrated review of applied cardiac anatomy. The clinical significance of the anatomy described is highlighted in italics.

Pericardium

The fibrous (parietal) pericardium is a resilient sac that envelops the heart and attaches onto the great vessels.[15] Almost the entire ascending aorta and main pulmonary artery and portions of both venae cavae and all four pulmonary veins are intrapericardial (Fig. 2-19). *These are important anatomic landmarks to remember when evaluating diseases of the pericardium. Given the intrapericardial location of the ascending aorta, diseases such as localized aortic wall hematoma, aortic dissection, or aortic rupture can produce a rapidly fatal hemopericardium. Because the sac is collagenous, with little elastic tissue, it cannot stretch acutely. In patients with total anomalous pulmonary venous connection, the confluence of pulmonary veins is intrapericardial. In contrast, the right and left pulmonary arteries and ductal artery (ductus arteriosus) are extrapericardial structures.*[16]

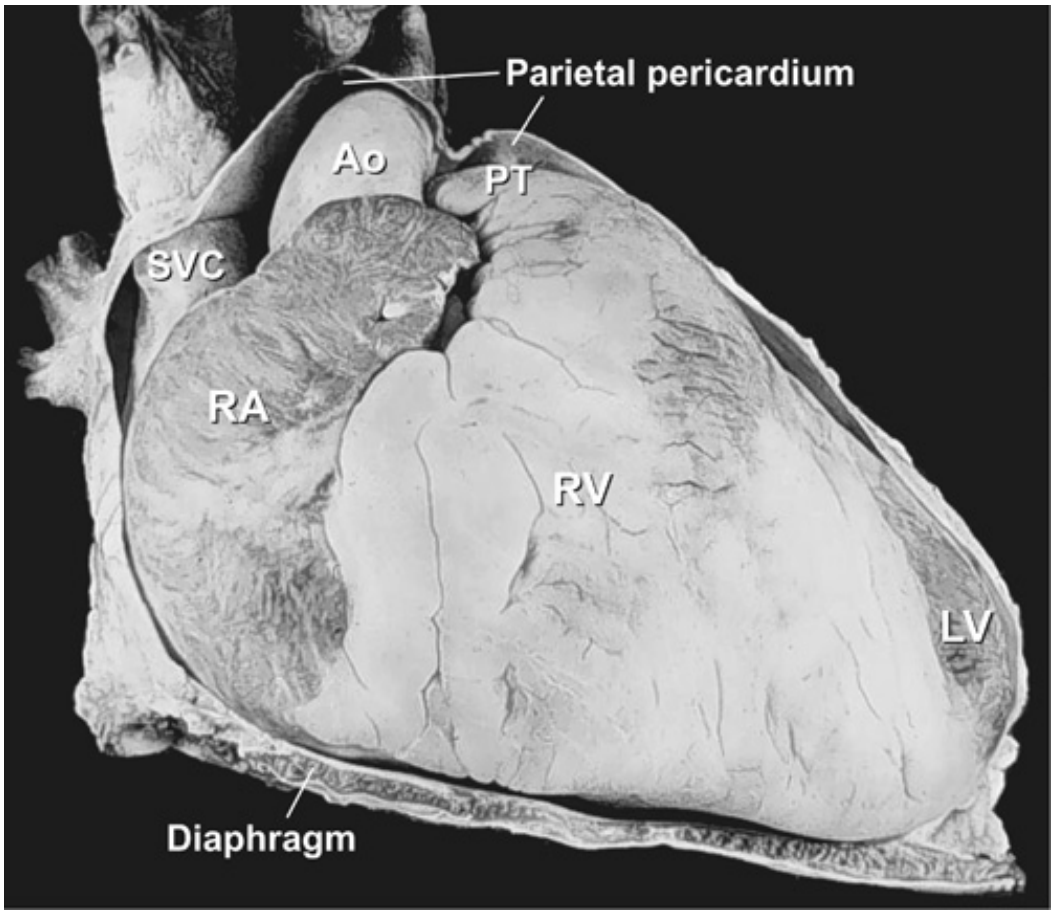


Figure 2-19: Anterior view of the heart. The anterior portion of the parietal pericardium has been

removed, exposing the intrapericardial portions of the superior vena cava (SVC), ascending aorta (Ao), and pulmonary trunk (PT). LV, left ventricle; RA, right atrium; RV, right ventricle.

The serous pericardium forms the delicate inner lining of the fibrous pericardium as well as the outer lining of the heart and great vessels (visceral pericardium). Over the heart, it is referred to as the epicardium, and it contains the epicardial coronary arteries and veins, autonomic nerves, lymphatics, and a variable amount of adipose tissue. The junctions between the visceral and parietal pericardium lie along the great vessels and form the pericardial reflections. The reflections along the pulmonary veins and vena cavae are continuous and form a posterior midline cul-de-sac known as the *oblique sinus*. Behind the great arteries, the *transverse sinus* forms a tunnel-like passageway (Fig. 2-20). *After open-heart surgery, localized accumulation of blood within the oblique sinus can produce isolated left atrial tamponade.*[16] *Similarly, a hematoma adjacent to the low-pressure right atrium can cause isolated right atrial tamponade*. With increasing age and with obesity, fat can accumulate within the parietal pericardium and epicardium.[16] *When imaging the heart, it is important not to misinterpret fat as an abnormal structure or a tumor*.

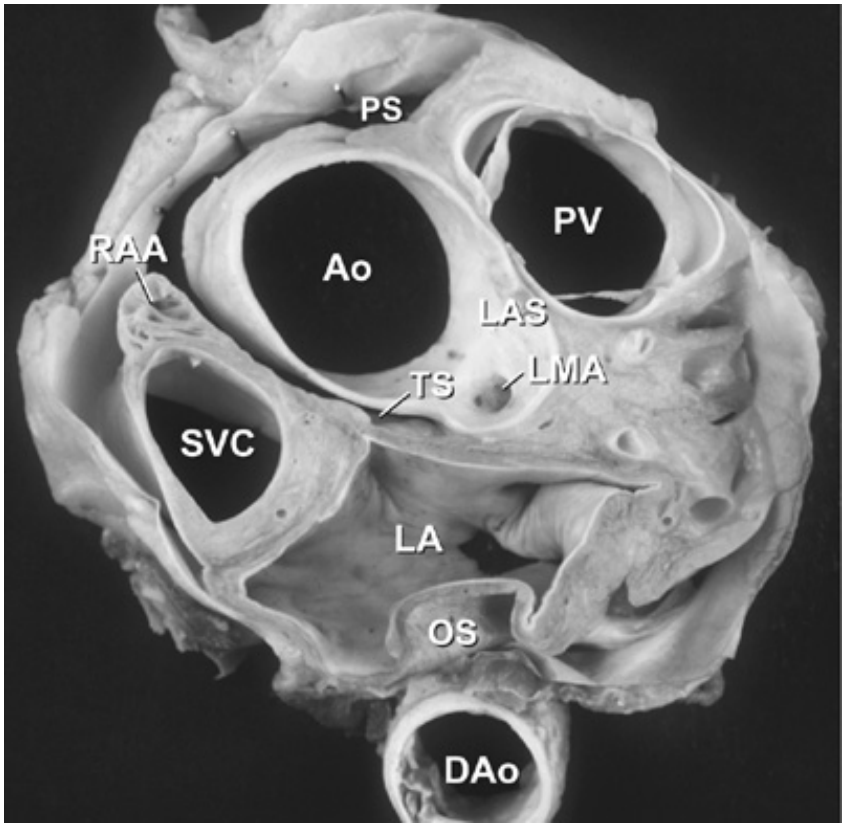


Figure 2-20: Tomographic section in the short-axis plane of the body, looking from apex toward the base, showing the oblique (OS) and transverse (TS) pericardial sinuses. Ao, ascending aorta; DAo, descending thoracic aorta; LA, left atrium; LAS, left aortic sinus; LMA, left main coronary artery: PS, pericardial sac; PV, pulmonary valve; RAA, right atrial appendage; SVC, superior vena cava.

Cardiac Skeleton

The four cardiac valves are anchored to their annuli, or valve rings. These fibrous rings, at the base of the heart, join to form the fibrous skeleton of the heart[16] (Fig. 2-21). The centrally located aortic valve forms the cornerstone of the cardiac skeleton, and its fibrous extensions abut each of the other three valves. The cardiac skeleton contains not only the four valve annuli but

also the membranous septum and the aortic intervalvular, right, and left fibrous trines. The fibrous trigones form the anatomic substrate for direct mitral-aortic continuity[16] (Figs. 2-21, Plate 8, and 2-22). The intervalvular fibrosa also forms part of the floor of the transverse sinus (see Figs. 2-22 and 2-33). *In patients with infective endocarditis of the mitral or aortic valves, the infection may burrow through the intervalvular fibrosa and produce fistulas betwn the left ventricle and the adjacent left atrium, ascending aorta, or transverse sinus.*[17]

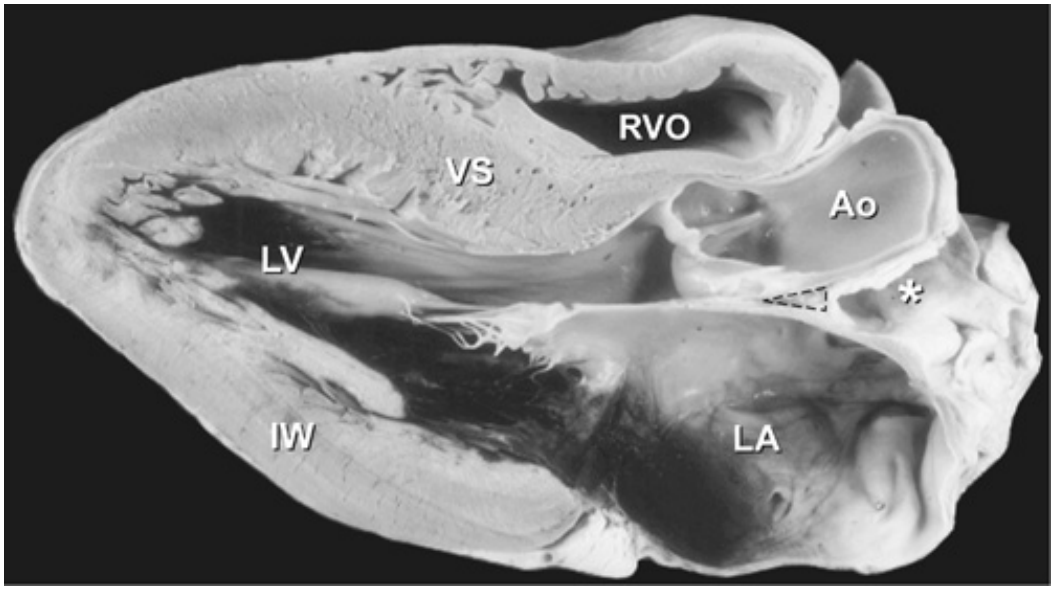


Figure 2-22: Long-axis section of the left ventricle. The intervalvular fibrosa (dashed triangle) lies between the anterior mitral leaflet and the posterior cusp of the aortic valve and abuts the floor of the transverse pericardial sinus (*). Ao, ascending aorta; IW, inferior wall; LA, left atrium; LV, left ventricle; RVO, right ventricular outflow; VS, ventricular septum.

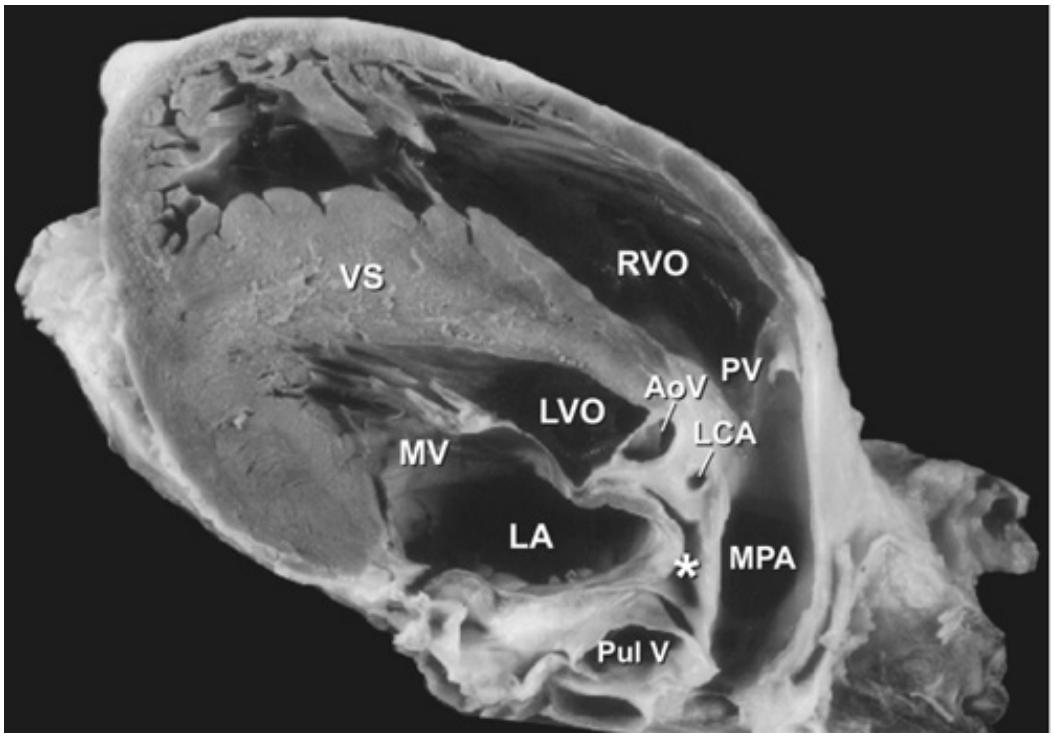


Figure 2-33: Long-axis view of the right ventricular outflow (RVO) tract showing the pulmonary valve (PV) and main pulmonary artery (MPA). AoV, aortic valve; LA, left atrium; LCA, left coronary artery; LVO, left ventricular outflow; MV, mitral valve; PulV, pulmonary vein; VS, ventricular septum; *, transverse sinus.

The right fibrous trigone, also known as the *central fibrous body*, welds together the aortic, mitral, and tricuspid valves and forms the largest and strongest component of the cardiac skeleton. It is through the right fibrous trigone that the atrioventricular (His) bundle passes. Otherwise, the fibrous cardiac skeleton serves to electrically isolate the atria from the ventricles. *Diseases or surgical alterations of one valve may affect the shape or angulation of adjacent valves (e.g., aortic valve replacement causing severe mitral regurgitation) and may affect the nearby coronary arteries or conduction tissue*.[17]

Tricuspid Valve

The tricuspid valve is comprised of five components (i.e., annulus, leaflets, commissures, chordae tendineae, and papillary muscles). The anterior tricuspid leaflet is the largest and most mobile and forms an intracavitary curtain that partially separates the inflow and outflow tracts of the right ventricle (Fig. 2-23). The posterior leaflet is usually the smallest. The septal leaflet is the least mobile because of its many direct chordal attachments to the ventricular septum. A distensible fibroadipose annulus is unique to the tricuspid valve.[17] Consequently, dilatation of the right ventricle commonly produces circumferential tricuspid annular dilatation that results in variable degrees of tricuspid valve regurgitation.[16]

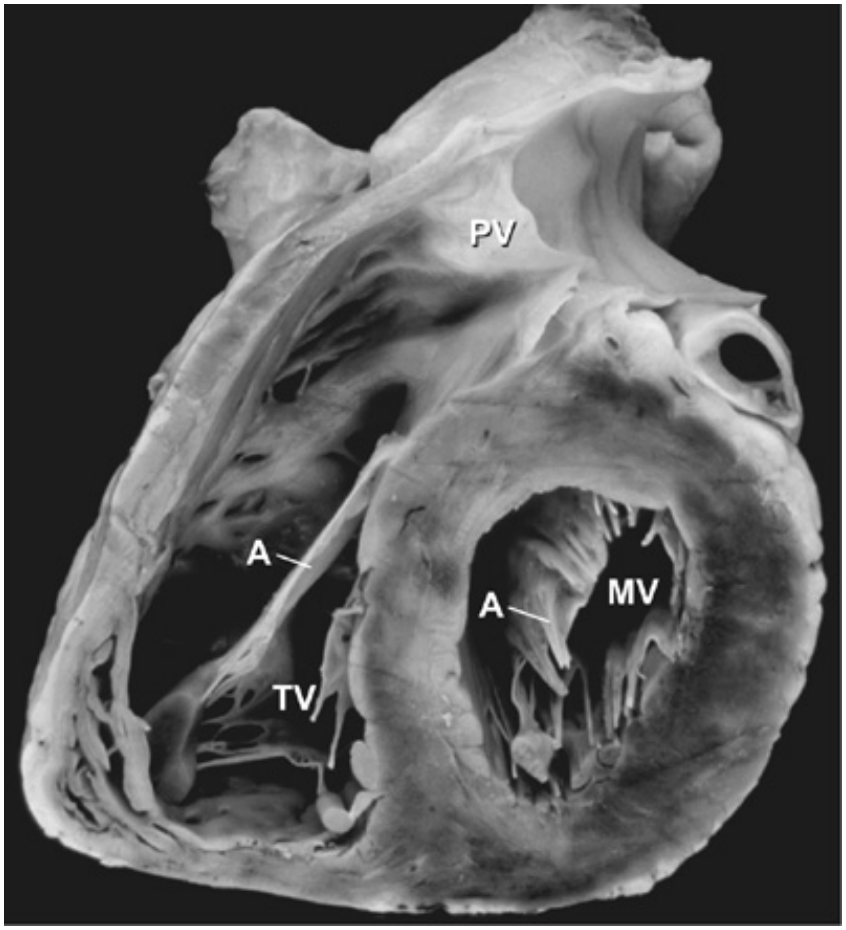


Figure 2-23: This oblique short-axis view of the heart shows the triangular-shaped tricuspid orifice (TV) and the elliptical mitral orifice (MV) at midleaflet level. The anterior tricuspid and anterior mitral leaflets (A) separate the inflow and outflow tracts of the right and left ventricles, respectively, and are parallel to one another. PV, pulmonary valve.

Mitral Valve

The mitral apparatus is comprised of the same five components as the tricuspid valve. Competent mitral valve function is a complex process that requires the proper interaction of all components, as well as adequate left atrial and left ventricular function. *Abnormalities of the mitral valve apparatus may involve any of these components or combinations thereof. The pattern of pathologic involvement often determines the feasibility of mitral valve repair (surgical or percutaneous)*.[18] The mitral valve annulus forms a complete fibrous ring that is firmly anchored along the circumference of the anterior leaflet by the tough fibrous skeleton of the heart[17] (see Fig. 2-21). Therefore, dilatation of the mitral valve annulus primarily affects the posterior leaflet. *All current operative mitral repair techniques are based on this principle of asymmetric annular dilatation. Mitral valve annuloplasty reduces the mitral valve inlet area by reducing the circumference of the posterior leaflet.*[17] *This is the rationale for using a partial posterior annuloplasty ring*.

Unlike the other cardiac valves, the mitral valve has only two leaflets. The anterior leaflet is large and semicircular, and it partially separates the ventricular inflow and outflow tracts (see Fig. 2-23). However, unlike its right-sided counterpart, it also forms part of the outflow tract. *In patients with hypertrophic obstructive cardiomyopathy, the anterior mitral leaflet may be drawn toward the basal anterior septum because of the Venturi effect, resulting in midsystolic outflow obstruction and mitral regurgitation*.[16] The posterior mitral leaflet is rectangular and usually is divided into three scallops. The middle scallop is the largest of the three in more than 90 percent of normal hearts. Occasionally, however, either the anterolateral or the posteromedial scallop is larger, and rarely there are accessory scallops[15,17] (Fig. 2-24, Plate 9). *Posterior mitral leaflet prolapse usually involves the middle scallop and may be associated with chordal rupture*. Both mitral leaflets are normally similar in area. The anterior leaflet is twice the height of the posterior leaflet but has half its annular length.[17] With advanced age, the mitral leaflets thicken somewhat, particularly along their closing edges.[15]

The commissures are cleftlike splits in the leaflet tissue that represent the sites of separation of the leaflets (Figs. 2-25 and 2-26*A*). Beneath the two mitral commissures lie the anterolateral and posteromedial papillary muscles, which arise from the left ventricular free wall (see Figs. 2-18*B* and 2-25). Commissural chords arise from each papillary muscle and extend in a fanlike array to insert into the free edge of both leaflets adjacent to the commissures (major commissures)[17] (see Figs. 2-24 and 2-26*A*, Plate 10) or into two adjacent scallops of the posterior leaflet (minor commissures) (see Figs. 2-24 and 2-25). *In contrast to congenital clefts, a true commissure is always associated with an underlying papillary muscle and an intervening array of chordae tendineae*.[17] The attachments of commissural chords precisely demarcate the commissure. *Because the commissural chords are seldom elongated, they serve as accurate reference points for determining the proper closing plane for the leaflets during surgical repair*.

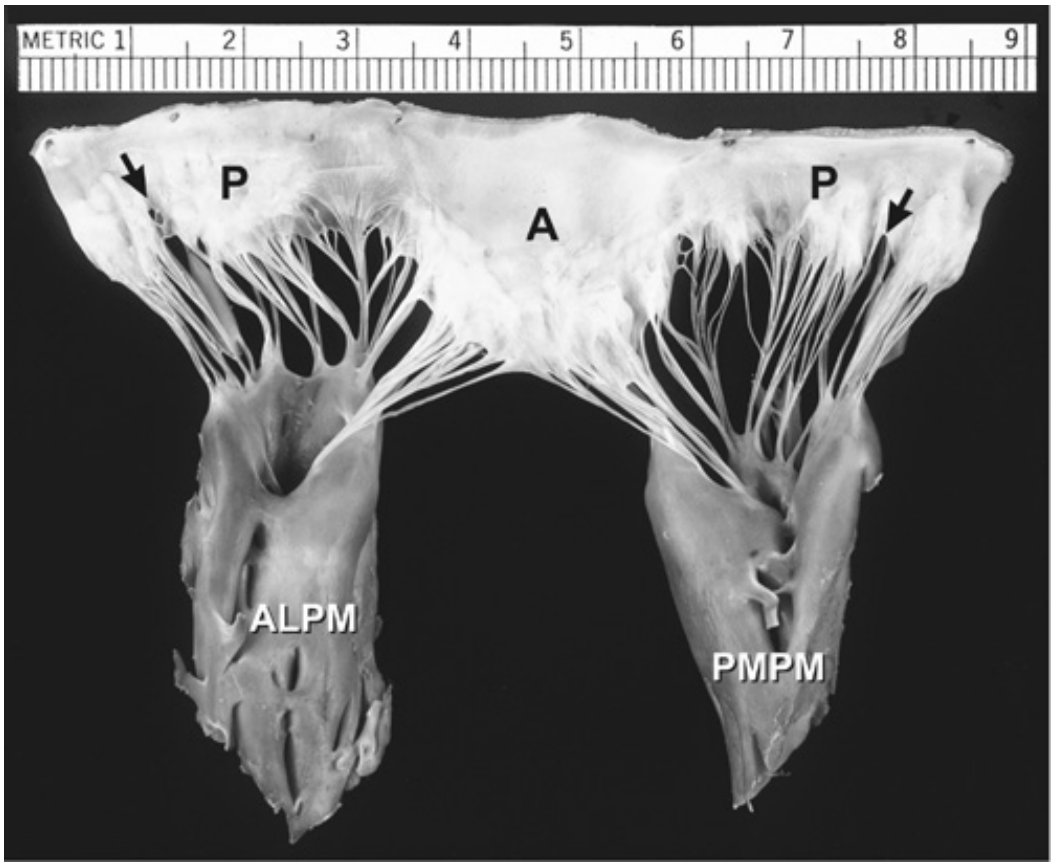


Figure 2-25: Gross anatomy of the mitral valve and papillary muscle-chordal apparatus, as demonstrated in an excised and unfolded valve. Each commissure overlies a papillary muscle. Arrows point to minor commissures. A, anterior leaflet; ALPM, anterolateral papillary muscle; P, posterior leaflet; PMPM, posteromedial papillary muscle.

The anterolateral papillary muscle is commonly single and usually has a dual blood supply from the left coronary circulation.[16] In contrast, the posteromedial papillary muscle usually has multiple heads and is most commonly supplied only by the right coronary artery.[16] Small left atrial branches supply the most basal aspects of the mitral leaflets.[17]

Papillary muscle contraction pulls the two leaflets toward one another and thereby promotes valve closure. The line of closure for either mitral leaflet is not its free edge but an ill-defined junction between a thin, clear zone and a thicker, rough zone[17] (see Fig. 2-26, Plate 10). The major chordae supporting a leaflet insert into its free edge and rough zone. The chordae tendineae anchor and support the leaflets and, by doing so, prevent leaflet prolapse during ventricular systole. Two particularly prominent rough zone chords, referred to as *strut chordae*, insert along each half of the ventricular surface of the anterior mitral leaflet and provide additional leaflet support.[17] They may contain cardiac muscle and tend to calcify with age. Unlike the tricuspid valve, the normal mitral leaflets have no chordal insertions into the ventricular septum.[16]

The functional orifice of the mitral valve is defined by its narrowest diastolic cross-sectional area. This may be at the annulus when there is extensive annular calcification or close to the papillary muscle tips in patients with rheumatic mitral stenosis.

Mitral valve prolapse is characterized by thickened and redundant leaflets, annular dilatation (with or without calcium), and thickened and elongated chordae tendineae (with or without rupture). Prolapse of the posterior leaflet occurs more frequently than that of the anterior leaflet. Rheumatic involvement of the mitral valve causes chordal shortening and thickening without annular dilatation. Rheumatic mitral stenosis is produced by chordal and commissural fusion,

often with calcification, whereas rheumatic mitral insufficiency results from scar retraction of leaflets and chords.[15] *Chronic postinfarction mitral regurgitation is associated with left ventricular dilatation and scarring of a papillary muscle and its subjacent ventricular free wall. Acute postinfarction mitral regurgitation may be associated with partial or complete rupture of a papillary muscle, usually the posteromedial one.*

Anatomically important structures during mitral valve surgery include the left circumflex coronary artery, which courses within the left atrioventricular groove near the anterolateral commissure, and the coronary sinus, which courses within the left atrioventricular groove adjacent to the annulus of the posterior mitral leaflet[17] (see Fig. 2-21A).

Aortic Valve

The aortic valve, like the pulmonary valve, is comprised of three components (i.e., annulus, cusps, and commissures). In contrast to the mitral and tricuspid valves, the two semilunar valves have no tensor apparatus (i.e., chordae tendineae or papillary muscles). The commissures form tall, peaked spaces between the attachments of adjacent cusps (Figs. 2-27 and 2-28) and attain the level of the aortic sinotubular junction, the ridge that separates the sinus and tubular portions of the ascending aorta (originally described by Leonardo da Vinci as the "suprortic ridge")[15] (see Fig. 2-28). The functional aortic valve orifice may be at the sinotubular junction or proximal to it.[17]

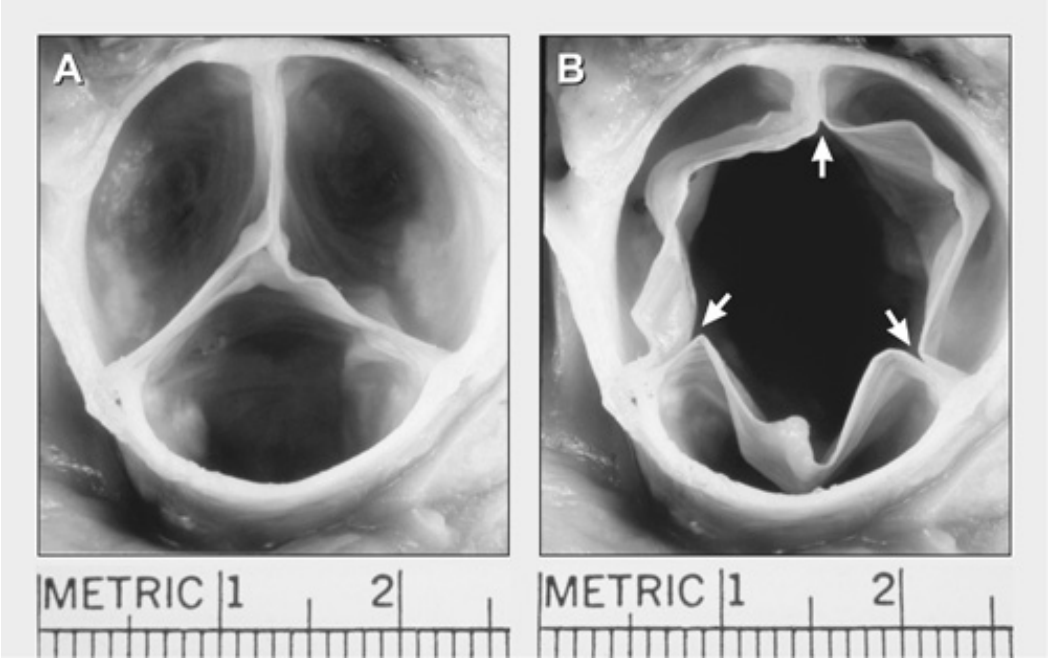


Figure 2-27: Each cusp of a semilunar valve is pocket-shaped. The aortic valve is viewed from above in simulated closed (*A*) and open (*B*) positions, showing the three commissures (arrows). Note that the length of the closing edge exceeds the straight-line distance between the commissures.

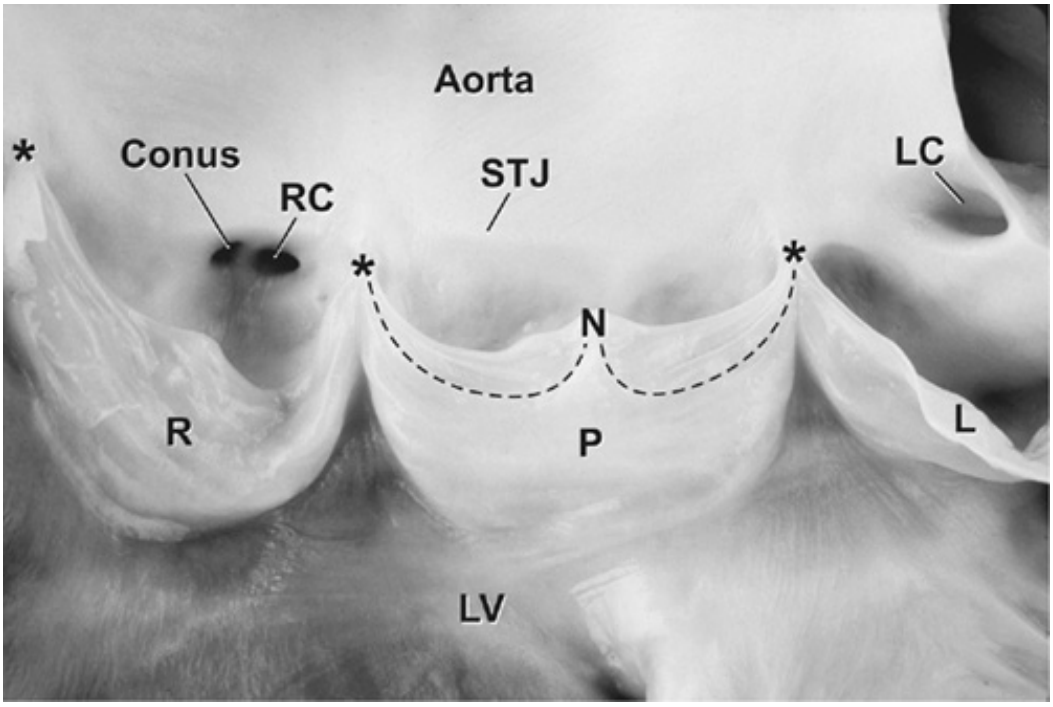


Figure 2-28: An opened aortic valve shows the right (R), left (L), and posterior (P) cusps. The dashed line marks the closing edge. Between the free and closing edges of each cusp are two lunular areas, representing the surfaces of apposition between adjacent cusps during valve closure. The commissures (*) attain the level of the aortic sinotubular junction (STJ). Conus, conus coronary ostium; LC, left coronary ostium; LV, left ventricle; N, nodule of Arantius; RC, right coronary ostium.

The three half-moon-shaped (semilunar) aortic cusps form pocket-like tissue flaps that are avascular. In only about 10 percent of hearts are they truly equal in size. In two-thirds of hearts, either the right or posterior cusp is larger than the other two.[17] Just below the free edge of each cusp is a ridgelike closing edge (see Fig. 2-28). At the center of each cusp the closing edge meets the free edge and forms a small fibrous mound, the *nodule of Arantius*[15] (see Fig. 2-28). Between the free and closing edges, to each side of the nodule, are two crescent-shaped areas known as the *lunulas* that represent the sites of cusp apposition during valve closure.[15] Lunular fenestrations, near the commissures, are common and increase in size and incidence with age[15] (Fig. 2-29). However, owing to their position distal to the closing edge, they rarely produce valvular incompetence.[17] When viewed from above, the linear distance along the closing edge of a cusp is much greater than the straight-line distance between its two commissures[15] (see Fig. 2-27). This extra length of cusp tissue is necessary for nonstenotic opening and nonregurgitant closure of the valve.[15] Normally, the diameter of the aortic annulus at the hinge points of the aortic valve is about equal to the diameter of the ascending aorta at the sinotubular junction.[8]

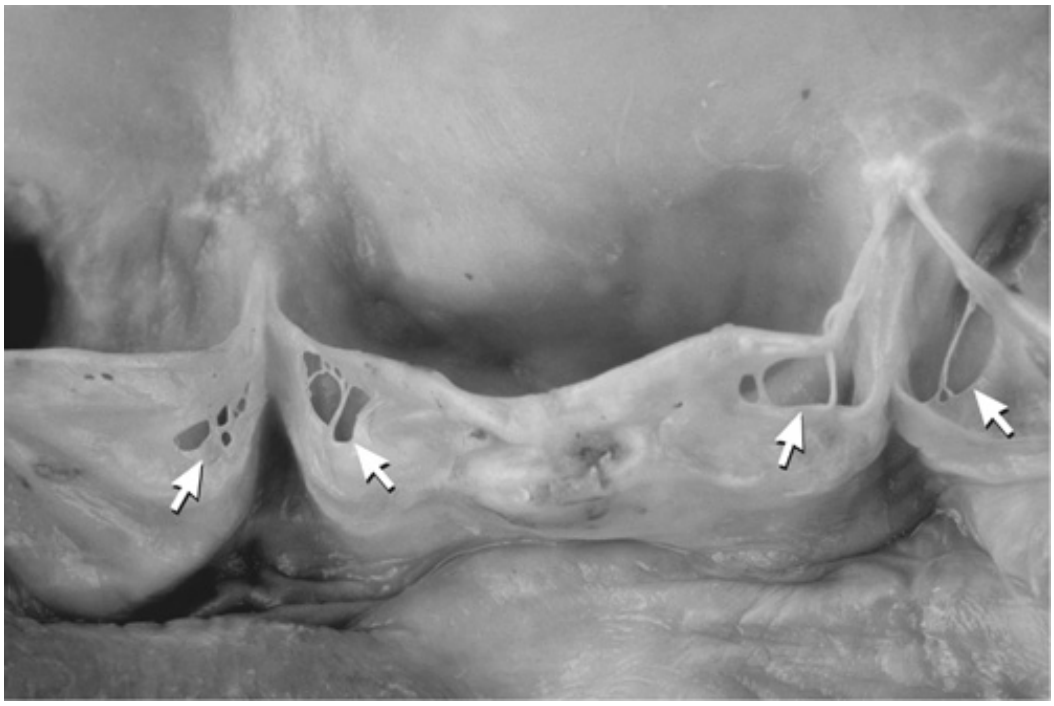


Figure 2-29: Aortic cusp fenestrations (arrows) occurring in the lunular regions near the commissures. This is a common age-related degenerative finding and normally accounts for little or no aortic valve regurgitation.

These are important anatomic details in patients undergoing aortic valve repair. In hearts from adults with bicuspid valves and other congenital aortic valve disease, the annular diameter is usually enlarged. In contrast, patients with normal aortic cusps and central aortic regurgitation show enlargement at the level of the sinotubular junction.[7]

A prebypass intraoperative transesophageal long-axis view of the left ventricular outflow tract is used to measure the aortic valve annular diameter prior to replacement by a homograft. By doing so, precious bypass time is saved while the homograft is being prepared.[8] *Disease processes that produce commissural fusion such as rheumatic valvulitis or which decrease cusp mobility such as fibrosis or calcification may lead to aortic stenosis.*[15] *In contrast, those disorders which decrease cusp size such as rheumatic valvulitis or which cause aortic root dilatation may lead to aortic regurgitation.*[15] *Combinations of these processes may produce combined stenosis and regurgitation.*

The commissure between the right and posterior aortic cusps overlies the membranous septum (Fig. 2-30) and contacts the commissure between the anterior and septal leaflets of the tricuspid valve (see Fig. 2-40). The commissure between the right and left aortic cusps contacts its corresponding pulmonary commissure and overlies the infundibular septum (see Fig. 2-12D). The intervalvular fibrosa, at the commissure between the left and posterior aortic cusps, fuses the aortic valve to the anterior mitral leaflet.[15,17]

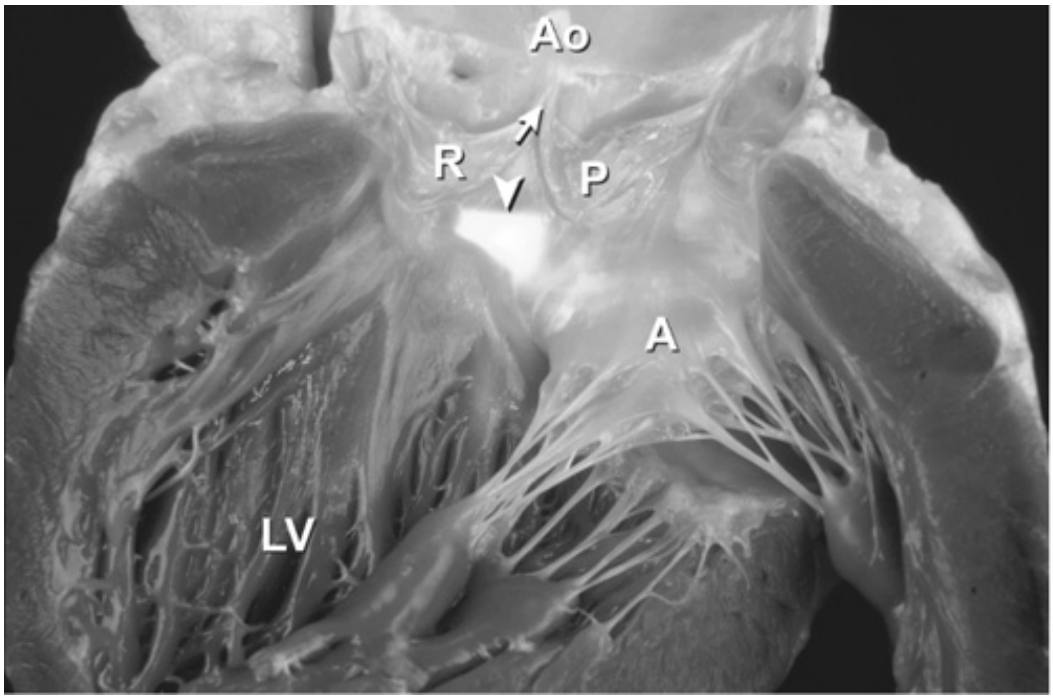


Figure 2-30: The commissure between the right and posterior aortic cusps (arrow) overlies the transilluminated membranous septum (arrowhead). A, anterior mitral leaflet; Ao, ascending aorta; LV, left ventricle; P, posterior aortic cusp; R, right aortic cusp.

During aortic valve replacement, the anterior mitral leaflet, left bundle branch, or coronary ostia may be injured inadvertently.[17] *Annular abscesses due to infective endocarditis involving the aortic valve may burrow into adjacent structures and thereby produce endocarditis of the other valves, conduction disturbances with septal involvement, aortoatrial, aortopulmonary artery, or aortoventricular fistulas, pericarditis, or fatal hemopericardium.*[15]

Pulmonary Valve

The pulmonary valve is virtually identical in design to the aortic valve.[17] The pulmonary artery sinuses are partially embedded within the muscle bundles of the right ventricular infundibulum, particularly adjacent to the right and left sinuses.[16,19] *In pulmonary valve atresia with an intact ventricular septum, hypertrophy of the muscle bundles and the narrow right ventricular outflow tract accentuate this relationship.*[19] Also, unlike the aortic valve, which is continuous with the mitral valve, the pulmonary and tricuspid valves are separated by infundibular muscle.[17]

Age-Related Valve Changes

Several age-related changes in the cardiac valves may have clinical significance.[20] In normal hearts, the thickness of the aortic and mitral leaflets increases progressively with each decade, particularly along their closure margins.[20] Probably the most common clinical manifestation of these changes is aortic valve sclerosis, characterized by valve thickening without hemodynamic dysfunction.[20] However, age-related degenerative calcification of an otherwise normal-appearing tricuspid aortic valve may result in progressive aortic stenosis.[20]

Age-related thickening along the nodule of Arantius and closing edges may be associated with the formation of whisker-like projections called *Lambl's excrescences*. These fine fibrous-like strands also can develop on the mitral valve.[17] *They are readily detected by echocardiography and have been associated with cardioembolic stroke.*[21] *Larger clusters, having the appearance of a sea anemone, are considered to be either neoplastic or reactive and are known as* papillary

fibroelastomas.[22]

The circumferences of all four cardiac valves increase with age in normal hearts. This is particularly evident in the semilunar valves.[20] Age-related annular dilatation of the aortic valve can result in aortic regurgitation.[20] Mitral annular calcification is rare before age 70 but is present in 40 percent of women over age 90.[20] Mitral annular calcification almost invariably only involves the posterior leaflet and forms a C-shaped ring of annular and subannular calcium.[17] *Mitral annular calcification may impede subannular ventricular contraction, thereby resulting in mitral regurgitation. Because of the proximity of the posteromedial commissure to the atrioventricular (His) bundle, mitral annular calcification may be associated with atrioventricular block.*[20] *With the increasing size of the aging population, degenerative calcific aortic disease is increasing in frequency*.[20]

Cardiac Grooves, Crux, and Margins

The atrioventricular groove encircles the heart and defines its base. It separates the atria from the ventricles (Fig. 2-31). The two ventricles are separated by the anterior and posterior (inferior) interventricular grooves, which define the plane of the ventricular septum (see Figs. 2-5*A* and 2-31).

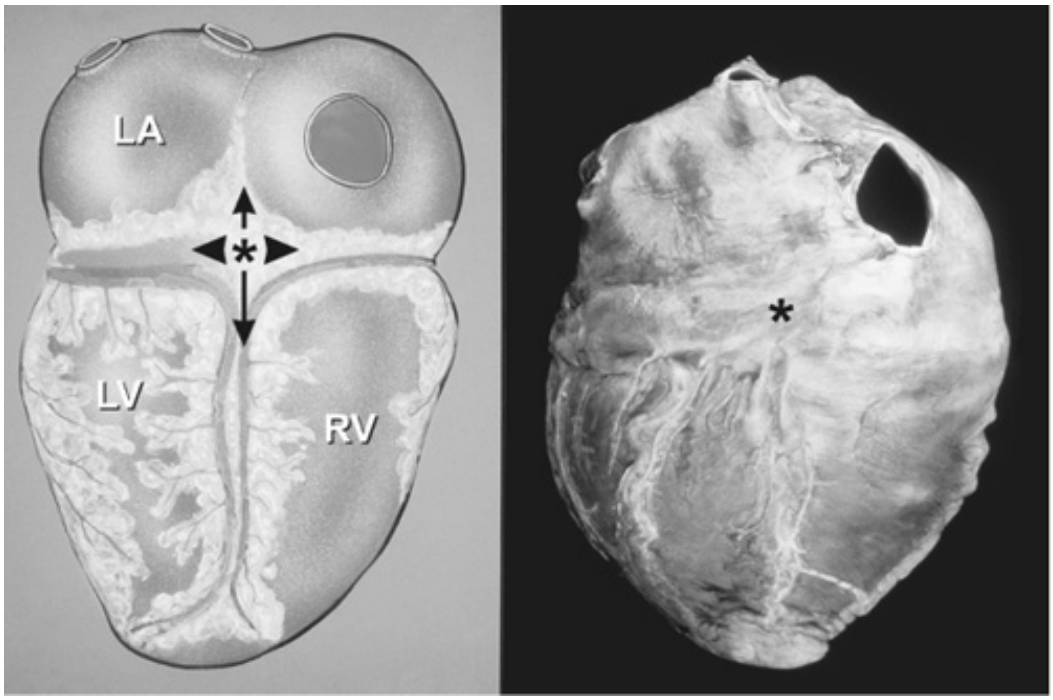


Figure 2-31: View of the diaphragmatic aspect of the heart shows the intersection of the atrioventricular (arrowheads), posterior interventricular (long arrow), and interatrial (small arrow) grooves at the external cardiac crux (*). (*Left*) Diagram. (*Right*) Cardiac specimen. LA, left atrium; LV, left ventricle; RV, right ventricle.

With age, fat tends to accumulate in increasing amounts in the epicardium, particularly in the atrioventricular grooves.[20,23] *Increased epicardial fat deposits may be associated with increased risk of cardiac rupture after acute transmural myocardial infarction*.[23] Excess fat in the atrial septum is called *lipomatous hypertrophy* and may result in a thickness that exceeds that of the ventricular septum. Fat in the right ventricular free wall is difficult to detect accurately clinically; its excess accumulation may be associated with increasing age, obesity, or arrhythmogenic right

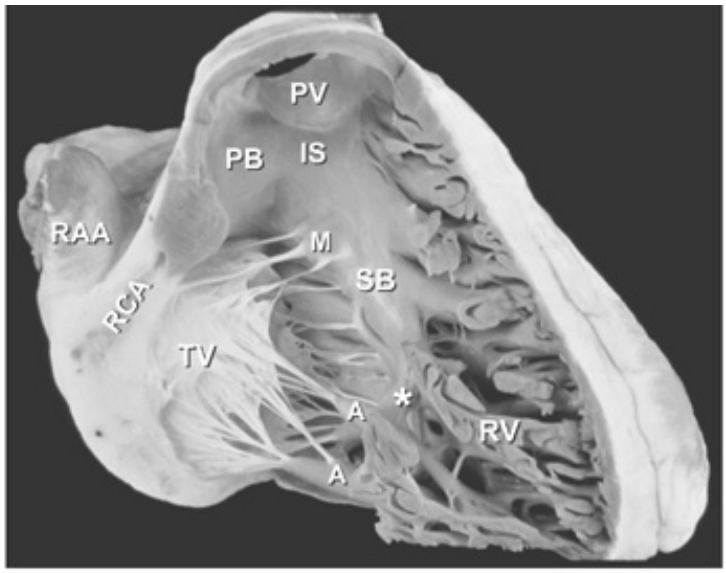
ventricular cardiomyopathy.[24]

Along the surface of the heart, the right and circumflex coronary arteries travel in the right and left atrioventricular grooves, respectively, and the left anterior and posterior descending coronary arteries course along the anterior and posterior (or inferior) interventricular grooves, respectively (see Figs. 2-5*A* and 2-31). The external cardiac crux is the cross-shaped intersection between the atrioventricular, posterior interventricular, and interatrial grooves (see Fig. 2-31). Its internal counterpart (the internal crux) is the posterior intersection between the mitral and tricuspid annuli and the atrial and ventricular septa (see Figs. 2-16*B* and 2-34, Plate 11).

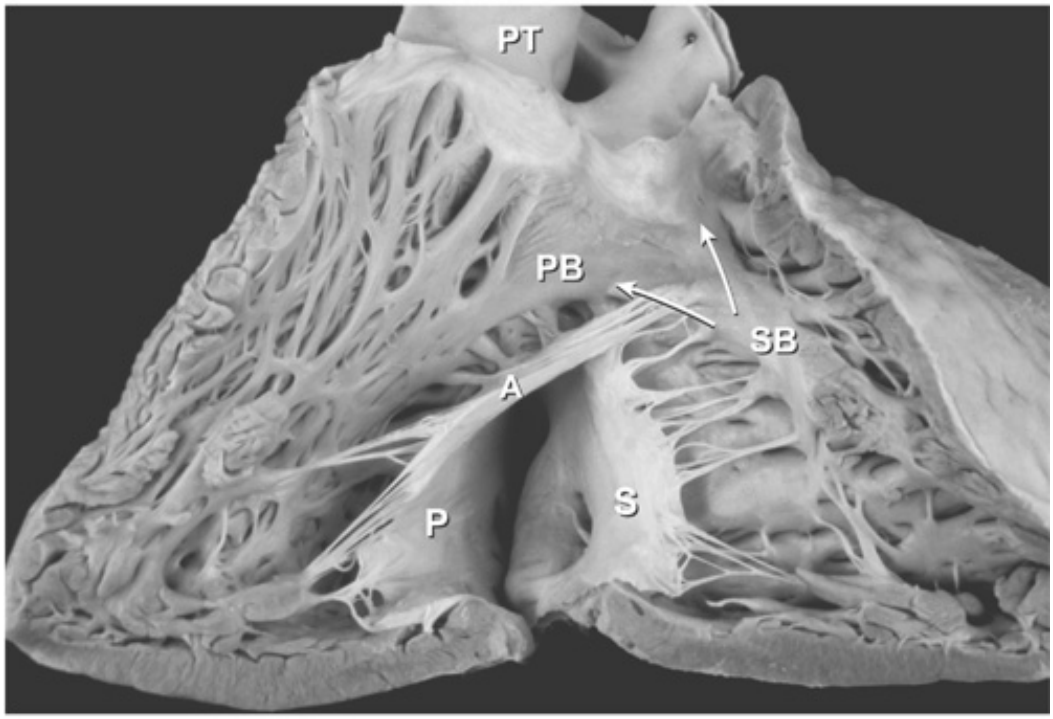
The junction between the anterior and inferior free walls of the right ventricle forms a sharp angle known as the *acute margin*. The rounded lateral wall of the left ventricle forms the *obtuse margin*.[15]

Right Ventricle

The right ventricle is a right-anterior structure. It is comprised of an inlet and trabecular and outflow segments[15] (Fig. 2-32). The inlet component extends from the tricuspid annulus to the insertions of the papillary muscles. An apical trabecular zone extends inferiorly beyond the attachments of the papillary muscles toward the ventricular apex and about halfway along the anterior wall.[15] *This muscular meshwork is the site of insertion of transvenous ventricular pacemaker electrodes. During right ventricular endomyocardial biopsy, tissue generally is obtained from the trabeculated apex. Disruption of a portion of the tricuspid support apparatus is a potential complication of right-sided heart instrumentation (e.g., right ventricular endomyocardial biopsy).*[17] The outflow portion, also known as the conus (meaning "cone") or *infundibulum* (meaning "funnel"), is a smooth-walled muscular subpulmonary channel[15,17] (see Fig. 2-32).



A



B

Figure 2-32: Right ventricle. *A*. The right ventricular free wall has been removed to show the archlike crista supraventricularis, which consists of the parietal band (PB), infundibular septum (IS), and septal band (SB). The moderator band (*) joins the septal band to the anterior tricuspid papillary muscle (*A*). The anteroapical portion of the chamber is heavily trabeculated. M, medial tricuspid papillary muscle; PV, pulmonary valve; RAA, right atrial appendage; RCA, right coronary artery; TV, tricuspid valve. *B*. The right ventricle has been opened by the inflow-outflow method to show the parietal band (PB) separating the tricuspid and pulmonary valves, as well as the two upper limbs (arrows) of e septal band (SB). *A*, anterior leaflet of the tricuspid valve; P, posterior leaflet of the tricuspid valve; PT, pulmonary trunk; S, septal leaflet of the tricuspid valve; other abbreviations as in *A*.

A prominent arch-shaped muscular ridge known as the *crista supraventricularis* separates the tricuspid and pulmonary valves. It is made up of three components (i.e., parietal band, infundibular septum, and septal band) that may appear as distinct structures or may merge

together[15,17] (see Fig. 2-32). The parietal band is a free-wall structure, whereas the adjacent infundibular septum is intracardiac and separates the two ventricular outflow tracts beneath the right and left cusps of both semilunar valves[15,17] (Figs. 2-12D and 2-33). The septal band forms a Y-shaped muscle, the two upper limbs of which cradle the infundibular septum. From this branching point of the septal band emanates the medial tricuspid papillary muscle[15,17] (see Fig. 2-32). The moderator band forms an intracavitary muscle that connects the septal band with the anterior tricuspid papillary muscle (see Fig. 2-32*A*).

Left Ventricle

The left ventricle, like the right ventricle, is made of an inlet portion comprised of the mitral valve apparatus, a subaortic outflow portion, and a finely trabeculated apical zone.[17] The left ventricular free wall is normally thickest toward the base and thinnest toward the apex, where it averages only 1 to 2 mm in thickness, even in hypertrophied hearts.[17] Structurally, the left and right ventricles differ considerably.[15,17] Normally, the left ventricular free-wall and septal thicknesses are three times the thickness of the right ventricular free wall. The mitral and aortic valves share fibrous continuity, whereas the parietal band separates the tricuspid and pulmonary valves. Whereas the mitral valve has an elliptical orifice and no septal attachments, the tricuspid valve has a triangular orifice and numerous direct septal attachments (see Fig. 2-23). The right ventricular apex is much more trabeculated than its counterpart on the left (see Figs. 2-9*B* and 2-18*C*). *The distinctive differences in apical trabeculations persist even in markedly hypertrophied or dilated hearts*.[17]

The annular attachment of the septal leaflet of the tricuspid valve inserts more apically than that of the anterior mitral leaflet, allowing distinction between the right and left ventricles by four-chamber imaging (Fig. 2-34). *Exceptions include partial atrioventricular septal defects and double-inlet ventricles in which the two valve annuli are at the same level. Ebstein's anomaly is characterized by exaggeration of apical displacement of the septal and posterior tricuspid leaflets resulting in an atrialized portion of the right ventricular chamber*.[16,17] *Morphologic differentiation of the right and left ventricles is particularly important in congenital heart disease*. The morphologic tricuspid valve virtually always connects to a morphologic right ventricle, whereas the morphologic mitral valve connects to a morphologic left ventricle.[15,16] Because of the rightward bulging of the ventricular septum, the left ventricular chamber appears circular in cross section, whereas the right ventricular chamber has a crescentic appearance (see Fig. 2-23). Tomographic segmental left ventricular anatomy will be reviewed in the section on coronary arteries.

Left ventricular false tendons, also referred to as *pseudotendons* or *bands*,[25] are discrete, thin, cordlike fibromuscular structures that connect two walls, the two papillary muscles, or a papillary muscle to a wall, usually the ventricular septum (Fig. 2-35). However, false tendons, as the name implies, are not attached to the mitral leaflets. *Chordal attachments between the mitral leaflets and the ventricular septum are abnormal and are usually associated with atrioventricular septal defects or straddling atrioventricular valves*.[16] False tendons are common anatomic variants of the normal left ventricle, occurring in 50 percent of hearts, and may become calcified with age (Fig. 2-36, Plate 12). They are more frequently observed in men, but their incidence does not appear to be age-related.[25] *It has been suggested that they may be the cause of innocent systolic musical murmurs*.[25] *Although they are readily detectable by echocardiography, they may be misinterpreted by the inexperienced sonographer as pathologic structures such as ruptured chords, mural thrombi, or vegetations*.[17,25]

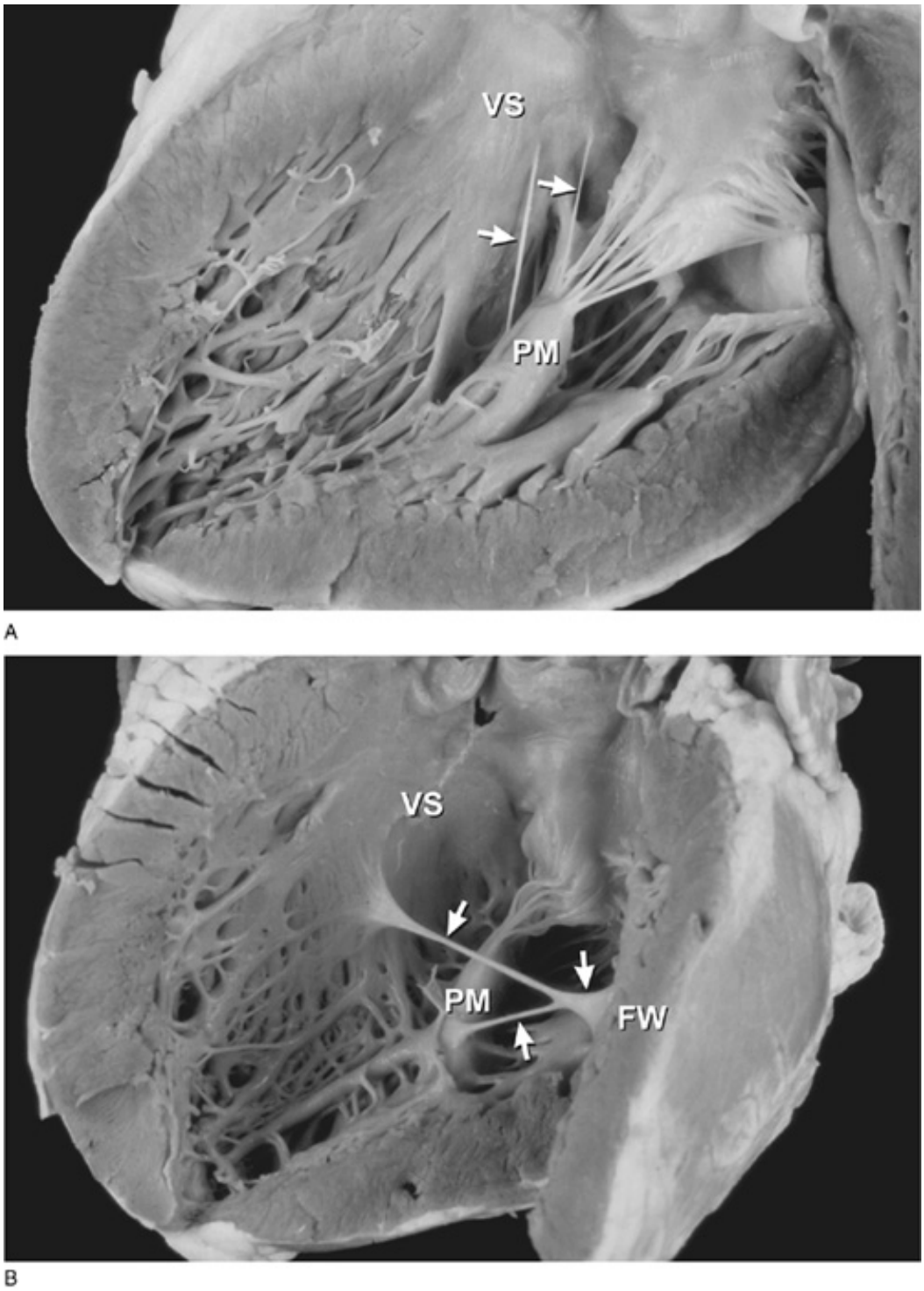


Figure 2-35: Various locations of left ventricular false tendons. *A.* Two false tendons (arrows) from posteromedial mitral papillary muscle (PM) to ventricular septum (VS), representing the most common location. *B.* Complex branching false tendon (arrows) with origin from the left ventricular free wall (FW) and insertions into the ventricular septum (VS) and base of posteromedial mitral papillary muscle (PM).

Prominent left ventricular trabeculations[26] are another common anatomic normal variant that may be an even greater source of misinterpretation by two-dimensional echocardiography in patients with suspected mural thrombus. They are defined as discrete, thick muscle bundles that generally connect the free wall to the septum (Fig. 2-37). Less common attachments include papillary muscle to the septum, septum to septum, or free wall to free wall. *In noncompaction of the left ventricular myocardium,*[27,28] *also known as* **spongy myocardium**, *there is persistence of multiple*

prominent ventricular trabeculations and deep intertrabecular recesses caused by arrest in the normal in utero process of myocardial compaction. The associated clinical manifestations and age at onset of symptoms (i.e., typically a dilated cardiomyopathy) are highly variable.

Figure 2-37: Prominent left ventricular trabeculations. Multiple large muscle bundles extend from the anterior free wall to the septum (probes). A single muscle bundle extends from the posteromedial mitral papillary muscle to the posterior septum (probe with white arrow), and one bundle extends from one portion of the posterior septum to another (probe with black arrow). Such trabeculations become even more prominent in noncompaction of the left ventricular myocardium.

Ventricular Septum

The ventricular septum is a complex intracardiac partition that can be considered to comprise four parts: inlet, trabecular, membranous, and infundibular. The plane of the infundibular portion (see Figs. 2-12*D* and 2-33) is different from that of the three other portions. *This anatomic relationship is important in many forms of congenital heart disease in which the infundibular septum is dissociated from the remainder of the ventricular septum (e.g., malalignment forms of ventricular septal defects in tetralogy of Fallot and in double-outlet right ventricle).*[15-17]

The ventricular septum also may be divided into muscular and membranous portions[15-17] (Figs. 2-38, Plate 13, and 2-39). The membranous septum lies beneath the right and posterior (noncoronary) aortic cusps (see Fig. 2-30) and contacts the mitral and tricuspid annuli (Fig. 2-40, Plate 14). The membranous septum in conjunction with the right fibrous trigone with which it is continuous fuses the commissure between the right and posterior aortic cusps to the commissure between the anterior and septal tricuspid leaflets (see Fig. 2-21*B*). *The majority of clinically significant ventricular septal defects involve the membranous septum.*[17] Owing to normal angulation between the infundibular septum and remaining ventricular septum, the septal surface follows the course of an inverted S (moving from apex to aortic valve). The basal half of the ventricular septum is smooth-walled, while the apical half is characterized by numerous small and irregularly arranged **trabeculations**.[15-17]

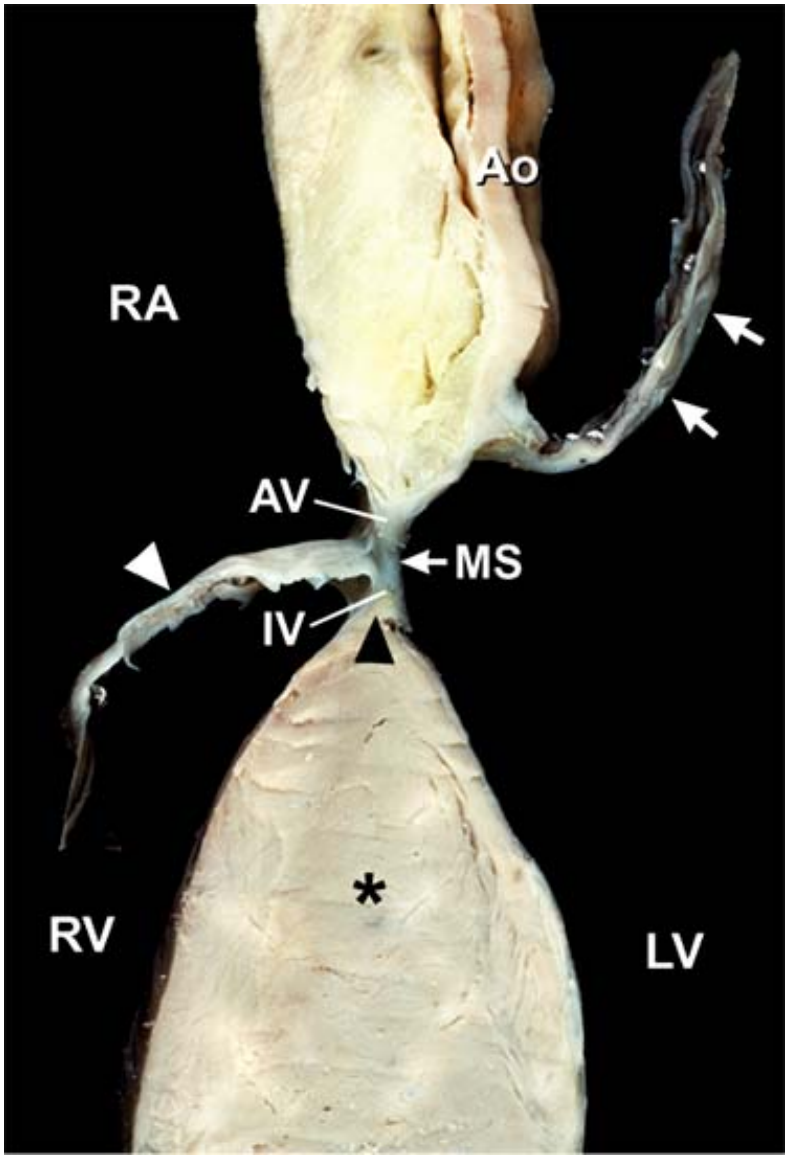


Figure 2-38: (Plate 13) Four-chamber tomographic slice through the aortic root (Ao) and aortic valve (arrows) showing the small membranous (MS) and large muscular (*) portion of the ventricular septum. The membranous septum is divided into atrioventricular (AV) and interventricular (IV) components by the septal tricuspid leaflet (white arrowhead). Black arrowhead points to the expected location of the AV (His) bundle. LV, left ventricle; RA, right atrium; RV, right ventricle.

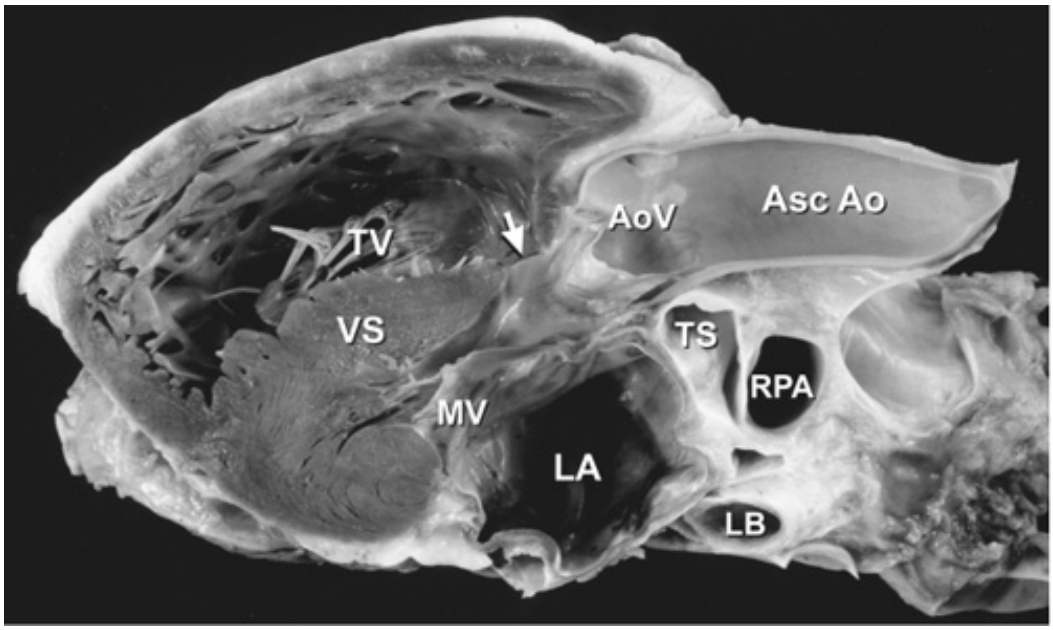


Figure 2-39: Tomographic section of the heart along a long-axis plane of the body. The aortic root lies in this plane. The left ventricle and aortic valve are cut obliquely. The membranous ventricular septum (arrow) lies beneath the right and posterior aortic cusps. AoV, aortic valve; Asc Ao, ascending aorta; LA, left atrium; LB, left bronchus; MV, mitral valve; RPA, right pulmonary artery; TS, transverse sinus; TV, tricuspid valve; VS, muscular ventricular septum.

Clinically relevant age-related anatomic changes include a disproportionate increase in ventricular septal thickness regardless of gender and in the absence of a history of hypertension.[20] This is associated with an appreciable increase in the ratio of ventricular septal to left ventricular free-**wall thickness** often exceeding 1.3 in patients older than **age** 60[20] (Fig. 2-41, Plate 15). This may be due in part to accentuation of the sigmoid shape of the basal septum[15,20] (Fig. 2-42). *Age-related ventricular septal angulation may have clinical importance because it may mimic certain features of hypertrophic cardiomyopathy,*[15,20] *particularly if complicated by the indiscriminate use of diuretics or afterload-reducing agents.*

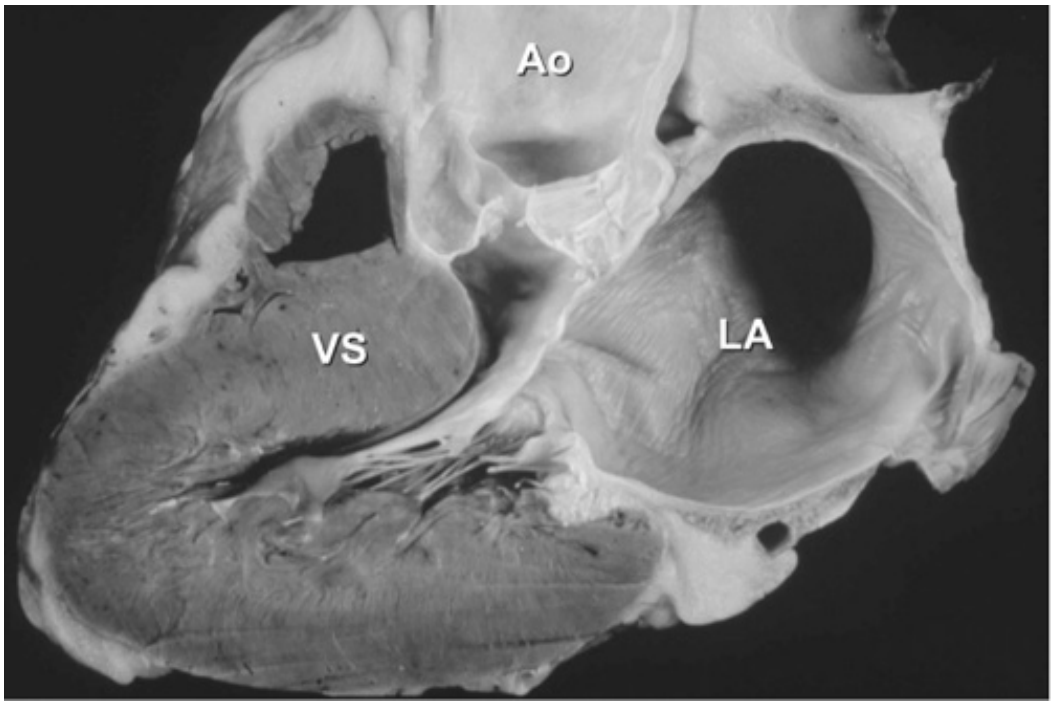


Figure 2-42: Age-related changes in the left-sided cardiac structures. Normal heart from an 84-year-old man demonstrates shortening of the base-to-apex (long-axis) dimension, decreased internal left ventricular dimension, aortic root dilatation, left atrial enlargement, and sigmoid-shaped septum. (Compare with Fig. 2-15 from an 18-year-old man.) Ao, ascending aorta; LA, left atrium; VS, ventricular septum.

Atrial Septum

When viewed from its right aspect, the atrial septum is comprised of interatrial and atrioventricular regions[16,17] (see Fig. 2-34). The interatrial portion is characterized by the fossa ovalis, which is the anatomic hallmark of a morphologic right atrium (Fig. 2-43*A*). Its outer muscular rim is a horseshoe-shaped limbus, and its central depression is the valve of the fossa ovalis[16,17] (see Fig. 2-43*A*). The potential interatrial passageway between the limbus and the valve (which is patent throughout fetal life) is the foramen ovale (Figs. 2-43*B* and 2-44). When viewed from the left atrium, the atrial septum is entirely interatrial, since the atrioventricular component lies below the mitral annulus, between the left ventricle and right atrium. Likewise, the limbus of the fossa ovalis is completely covered by its opaque valve and is not directly visible from the left atrium.[15]

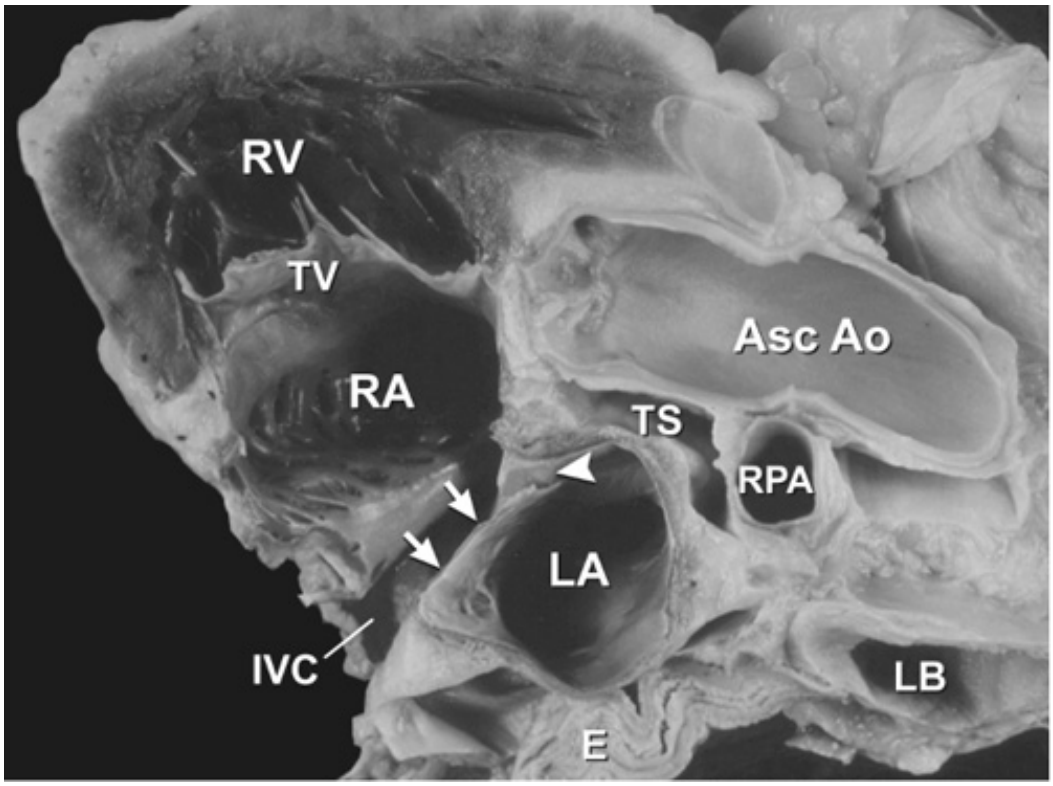


Figure 2-44: Tomographic section of the heart along a long-axis of the body. The valve of the fossa ovalis (arrows) and a patent foramen ovale (arrowhead) are seen in this view. Asc Ao, ascending aorta; E, esophagus; IVC, inferior vena cava; LA, left atrium; LB, left bronchus; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; TS, transverse sinus; TV, tricuspid valve.

The foramen ovale is anatomically closed in about two-thirds of adults, but in the remaining one-third it remains patent and, therefore, a potential source for shunts and paradoxical embolism. Stretching of the atrial septum, when the atria are markedly dilated, can transform a patent foramen ovale into an acquired atrial septal defect. The posterior aortic sinus abuts against the interatrial septum (see Fig. 2-12*D*). *During transseptal procedures, care must be taken to stay within the confines of the valve of the fossa ovalis in order to avoid perforation of an aortic sinus.*[16] *Echocardiography may help guide transseptal puncture during balloon mitral valvuloplasty or closure of an atrial septal defect with an occluder device.*[13] *Fenestrations of the valve of the fossa ovalis are the most common cause of congenital atrial septal defects. Redundant valve tissue may form an aneurysm of the valve of the fossa ovalis.*

The atrioventricular (AV) portion of the atrial septum is made of major muscular and minor membranous components and separates the right atrium from the left ventricle[16,17] (see Figs. 2-34 and 2-38). *This explains why there is a potential for left-ventricular-to-right-atrial shunts.*[16,17] *The AV septum corresponds roughly to the triangle of Koch, an important anatomic surgical landmark because it contains the AV node and proximal portion of the AV (His) bundle. Thus, during tricuspid annuloplasty procedures and patch closures of membranous ventricular septal defects, care must be taken to avoid injury to the conduction system.*[16,17] The muscular component of the AV septum is interposed between the membranous septum anteriorly and the internal cardiac crux posteriorly.

When defects occur in the muscular atrioventricular septum, the mitral annulus usually drops to the same level as the tricuspid annulus, so the defect becomes primarily interatrial (primum atrial septal defect), and the AV conduction tissues are displaced inferiorly. Lipomatous hypertrophy of the atrial septum is characterized by excessive accumulation of adipose tissue within the limbus of

the fossa ovalis but always sparing the valve of the fossa[7,15-17] (Fig. 2-45, Plate 16). Lipomatous hypertrophy of the atrial septum occurs commonly but not exclusively in older and obese persons.[15-17] *Although readily detected by echocardiography, it may be misinterpreted as a thrombus or tumor*.[7]

Right Atrium

A prominent internal muscle ridge, the crista terminalis (Fig. 2-46), separates the right atrial free wall into a smooth-walled posterior region that receives the venae cavae and coronary sinus and a muscular anterior region that is lined by parallel pectinate muscles and from which the right atrial appendage emanates.[15-17] *Pectinatus* is Latin for "comb," and the pectinate muscles and crista terminalis resemble the teeth and backbone of a comb, respectively.[17] The right atrial appendage abuts the right aortic sinus and overlies the proximal right coronary artery (see Fig. 2-52). *The right atrial free wall is paper thin between pectinate muscles and therefore can be perforated easily by stiff catheters*.[15-17]

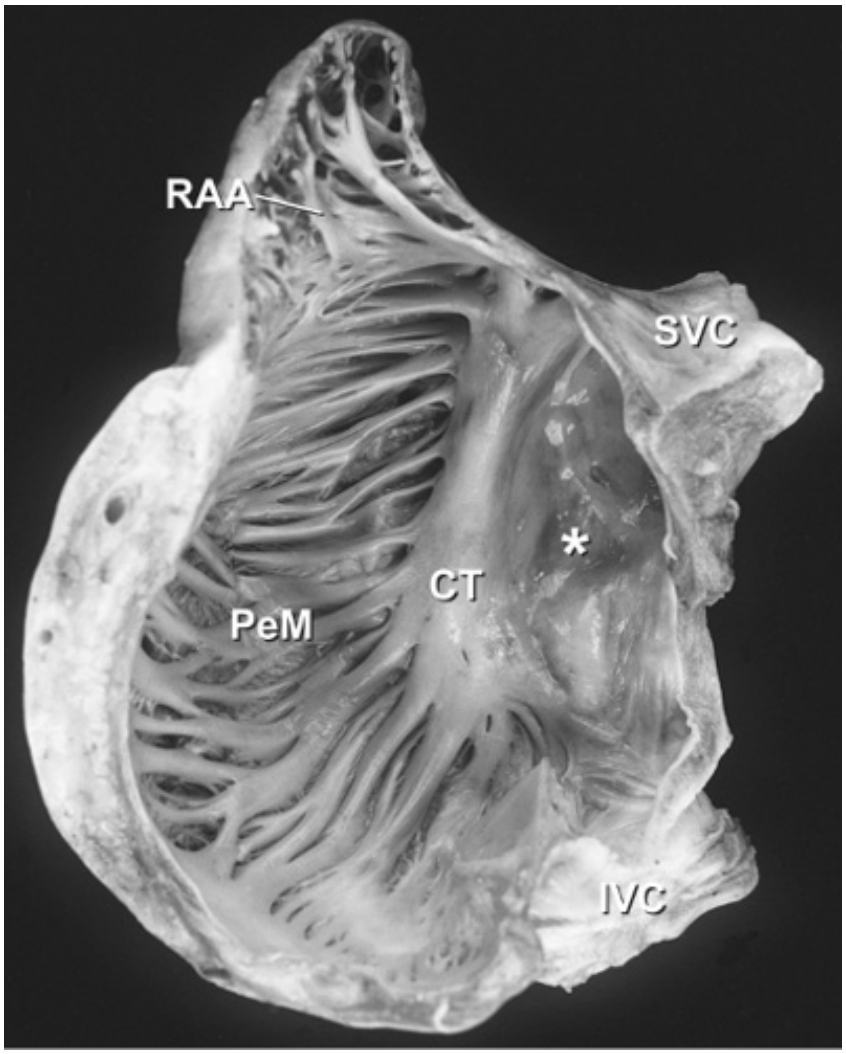


Figure 2-46: Right atrial free wall showing separation of the posterior smooth-walled (*) portion from the anterior muscular portion with its pectinate muscles (PeM) and right atrial appendage (RAA) by the crista terminalis (CT). IVC, inferior vena cava; SVC, superior vena cava.

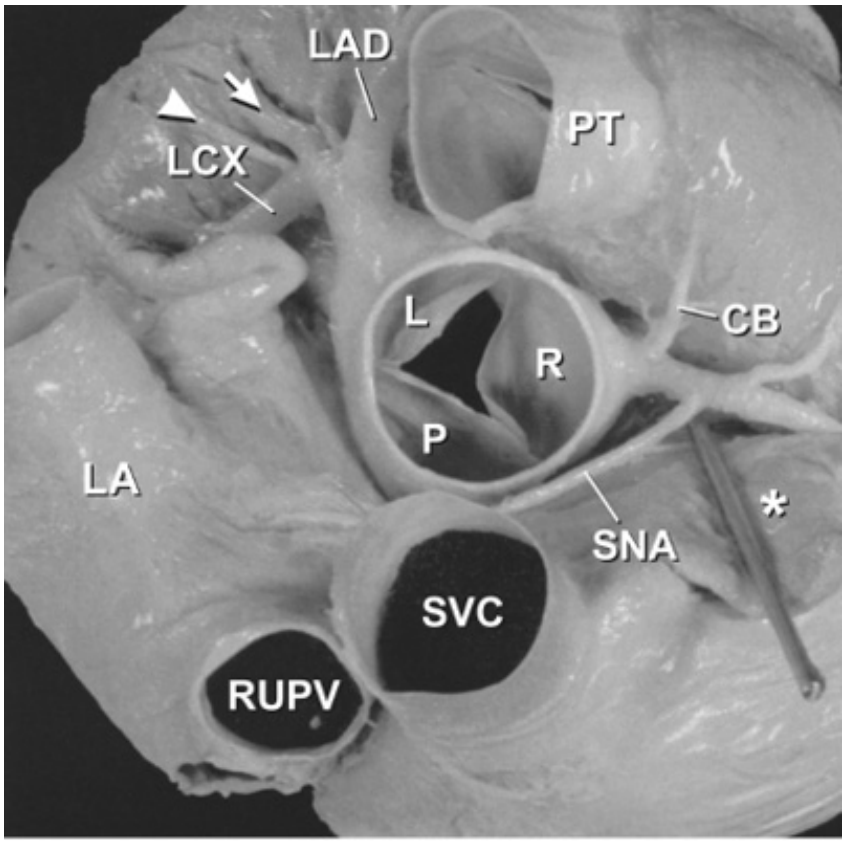


Figure 2-52: The right coronary artery gives rise to the conus branch (CB). A rod retracts the right atrial appendage (*) to disclose the sinus node artery (SNA). Arrow points to an intermediate left coronary artery; arrowhead points to a circumflex marginal branch. L, left aortic cusp; LA, left atrium; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; P, posterior aortic cusp; PT, pulmonary trunk; R, right aortic cusp; RUPV, right upper pulmonary vein; SVC, superior vena cava. (From McAlpine,[30] with permission.)

Inferior vena caval blood flow is directed by the eustachian valve toward the foramen ovale, and superior vena caval blood is directed toward the tricuspid valve[15] (Fig. 2-47, Plate 17). *Thus transseptal cardiac catheterization is more easily accomplished via the inferior vena cava, whereas instrumentation of the right ventricular apex (e.g., endomyocardial biopsy, placement of ventricular pacemaker lead) is more easily accomplished via the superior vena cava.*[15]

Left Atrium

The pulmonary vein orifices lie on the posterolateral (left pulmonary veins) and posteromedial (right pulmonary veins) aspects of the left atrial cavity. The left and right upper pulmonary veins are directed anterosuperiorly, whereas the lower veins enter the left atrium nearly perpendicular to the posterior atrial wall[15-17] (Figs. 2-15 and 2-48). *Left atrial muscle extends some distance within the pulmonary veins. The resultant cuff of muscle acts as a sphincter during atrial systole and may be the source of focal atrial fibrillation that is amenable to catheter ablation*[9-13] (see Fig. 2-2).

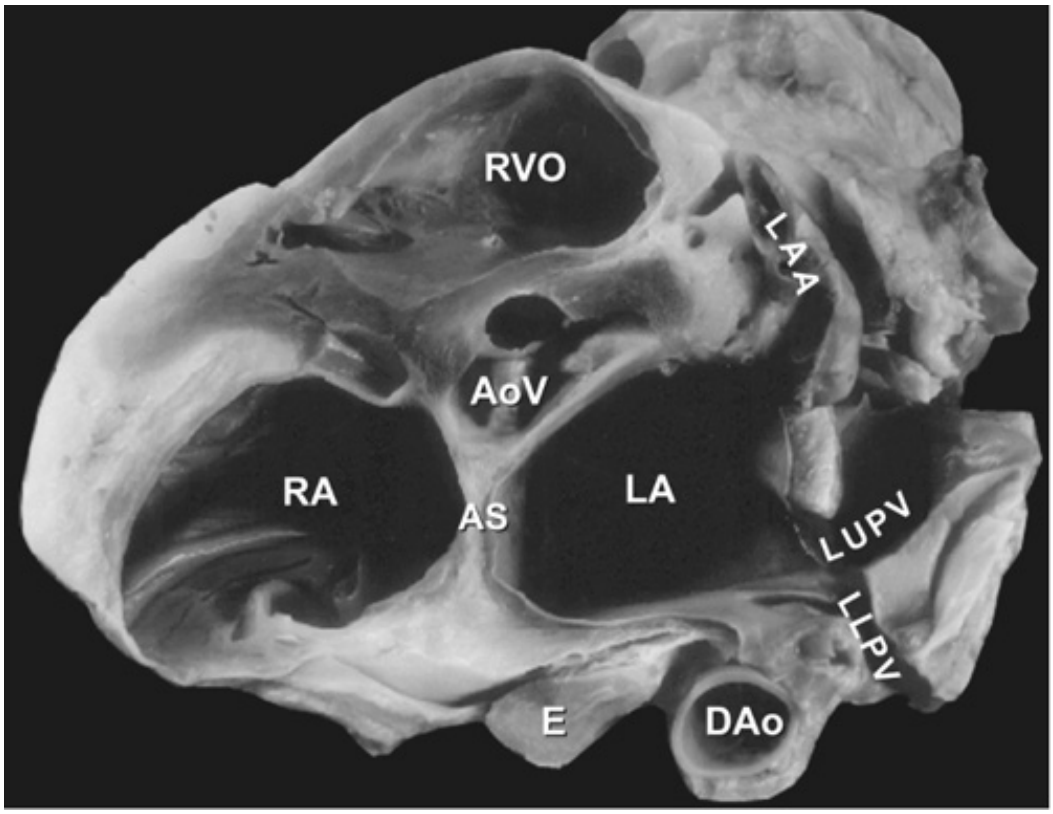


Figure 2-48: Oblique, short-axis cut at the base of the heart. The esophagus (E) is posterior and adjacent to the left atrium (LA) and adjacent to the descending thoracic aorta (DAo). The left upper pulmonary (LUPV) and left lower pulmonary vein (LLPV) are clearly seen. The right ventricular outflow tract (RVO) is anterior. AS, atrial septum; AoV, aortic valve; LA, left atrium; LAA, left atrial appendage; RA, right atrium.

The atrial appendage arises anterolaterally and lies in the left atrioventricular groove atop the proximal portion of the left circumflex coronary artery and, in some individuals, the left main coronary artery[16] (see Figs. 2-21*A* and 2-48). The left atrial appendage is smaller, more tortuous, and less pyramidal than its right atrial counterpart.[15-17] At least 80 percent are multilobed (up to four lobes, but the most frequent finding is two lobes)[29] (Fig. 2-49, Plate 18). There are also age- and sex-related differences in the dimensions of the appendage.[20] *With increasing use of transesophageal echocardiography to search for a cardiac source of embolism and to guide cardioversion and percutanous balloon valvuloplasty procedures, a thorough appreciation of the variations in normal left atrial appendage morphology has become important because a thrombus may be missed if all lobes in the appendage are not visualized.* In contrast to the right atrial free wall, the left has no crista terminalis and no pectinate muscles outside its appendage.[15-17]

The coronary sinus travels along the posterior wall of the left atrium within the left atrioventricular groove (see Fig. 2-21*A*). *In patients with persistent left superior vena cava, which most commonly drains into a dilated coronary sinus, the left-sided cava courses between the left atrial appendage and the left upper pulmonary vein.*[17] *The venous structure can be misinterpreted as the descending thoracic aorta, a mass, or a pathologic cavity.*

The esophagus and descending thoracic aorta are in contact with the posterior left atrial wall (see Figs. 2-20 and 2-48). *Accordingly, esophageal carcinomas may compress, infiltrate, or perforate the left atrium, and descending thoracic aortic aneurysms may compress this chamber.*[15] *A large hiatal hernia also can abut against the left atrium and resemble a mass.*

The marked increase in the incidence of atrial fibrillation from the fourth to the ninth decades of life may be due in part to the age-associated dilatation of the left atrium.[20]

Coronary Arteries and Veins

A detailed description of the spectrum of coronary artery anatomy including the many variations in the number and size of branches and course of the different arteries is beyond the scope of this chapter. The interested reader is referred to the elegant anatomic work by McAlpine published almost 25 years ago.[30] The focus of the discussion that will follow, therefore, is to introduce the reader to the clinically relevant anatomy of the coronary circulation, with special emphasis on tomographic analysis of regional blood flow.

From the right and left aortic sinuses arise the right and left coronary arteries, respectively, and their ostia normally originate about two-thirds the distance from the aortic annulus to the sinotubular junction and about midway between theaortic commissures[15-17] (Figs. 2-28 and 2-50, Plate 19). Whereas the right coronary artery arises nearly perpendicularly from the aorta, the left arises at an acute angle[15] (Fig. 2-51). Rarely, the anterior descending and circumflex arteries arise separately from a double-barrel left coronary ostium.[15-17] *Ostial stenosis most commonly results from atherosclerosis and degenerative calcification of the aortic sinotubular junction, which often overlies the right aortic sinus.*[17] *Less often it is due to aortic dissection or to aortitis associated with syphilis or ankylosing spondylitis. Stenosis of the right coronary ostium is much more frequent than that of the left. Iatrogenic ostial injury may complicate coronary angiography, intraoperative coronary perfusion, or aortic valve replacement.*[15-17] *Atherosclerosis or thrombosis of the most proximal portion of either coronary artery may mimic true ostial stenosis.*

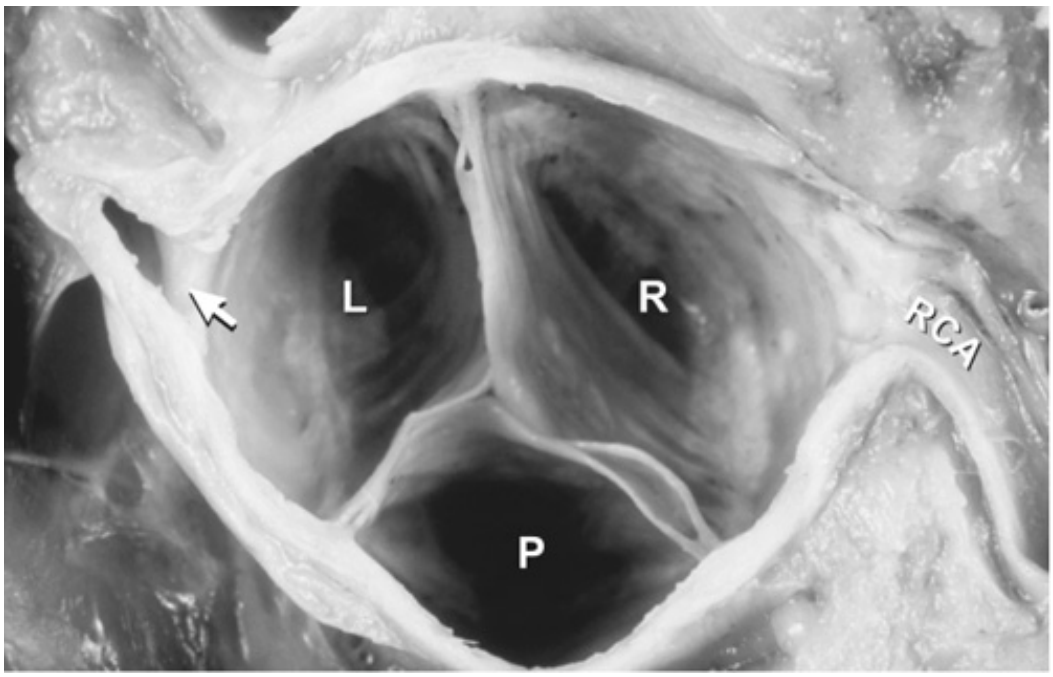


Figure 2-51: Differences in angulation at the origins of the right (RCA) and left main (arrow) coronary arteries. L, left aortic cusp; P, posterior aortic cusp; R, right aortic cusp.

The right coronary artery is embedded in adipose tissue throughout its course within the right atrioventricular groove. *Tricuspid annuloplasty or replacement may be complicated by injury to the right coronary artery.*[17] In 50 to 60 percent of persons, its first branch is the conus artery (Fig.

2-52), which supplies the right ventricular outflow tract and forms an important collateral anastomosis (circle of Vieussens), just below the pulmonary valve, with an analogous branch from the left anterior descending coronary artery.[15-17] In about a third of patients, the conus artery arises independently from the aorta[17] (see Fig. 2-28). The infundibular septum is supplied by the descending septal artery, which usually originates from the proximal right or conus coronary artery.[15-17] Among the numerous marginal branches of the right coronary artery that supply the remainder of the right ventricular free wall, the largest branch travels along the acute margin from base to apex[15-17] (see Fig. 2-50). In at least 70 percent of human hearts, the posterior descending artery arises from the distal right coronary artery (see Fig. 2-50). The posterior descending and distal posterolateral branches of a dominant right coronary artery supply the basal and middle inferior wall, basal (inlet) inferior septum, right bundle branch, AV node, AV (His) bundle, posterior portion of the left bundle branch, and posteromedial mitral papillary muscle.[17]

The left main coronary artery travels for a very short distance along the epicardium between the pulmonary trunk and left atrium (see Figs 2-50 and 2-52). It then divides into anterior descending and circumflex arteries (see Figs. 2-50 and 2-52). An intermediate artery also may arise at this division, thus forming a trifurcation rather than a bifurcation, and follows the course of a circumflex marginal branch[15-17] (see Fig. 2-52).

The left anterior descending coronary artery (LAD) courses within the epicardial fat of the anterior interventricular groove, wraps around the cardiac apex, and travels a variable distance along the inferior interventricular groove toward the cardiac base. Its septal perforating branches supply the anterior septum and apical septum. The first septal perforating branch supplies the AV (His) bundle and proximal left bundle branch[17] (Fig. 2-53, Plate 20). *In patients with symptomatic hypertrophic obstructive cardiomyopathy, nonsurgical septal reduction by percutaneous transluminal occlusion of septal branches of the* LAD *is a new therapeutic approach aimed at reducing the outflow gradient.*[31] *The long-term effects of this procedure are currently unknown.* The epicardial diagonal branches of the LAD supply the anterior left ventricular free wall, part of the anterolateral mitral papillary muscle, and the medial one-third of the anterior right ventricular free wall.[15-17] Although short segments of the LAD may travel within the myocardium (covered by a so-called myocardial bridge) (Fig. 2-54), the resulting systolic luminal narrowing is probably benign in the vast majority of people.[17] *However, whereas the prevalence of myocardial bridging is only 0.5 to 1.6 percent in the general population, it is reported to be 28 percent in children and 30 to 50 percent in adults with hypertrophic cardiomyopathy.*[32] *More important, myocardial bridging appears to be associated with a poor prognosis (higher incidence of myocardial ischemia and sudden death) in patients with hypertrophic cardiomyopathy regardless of age.*[32]

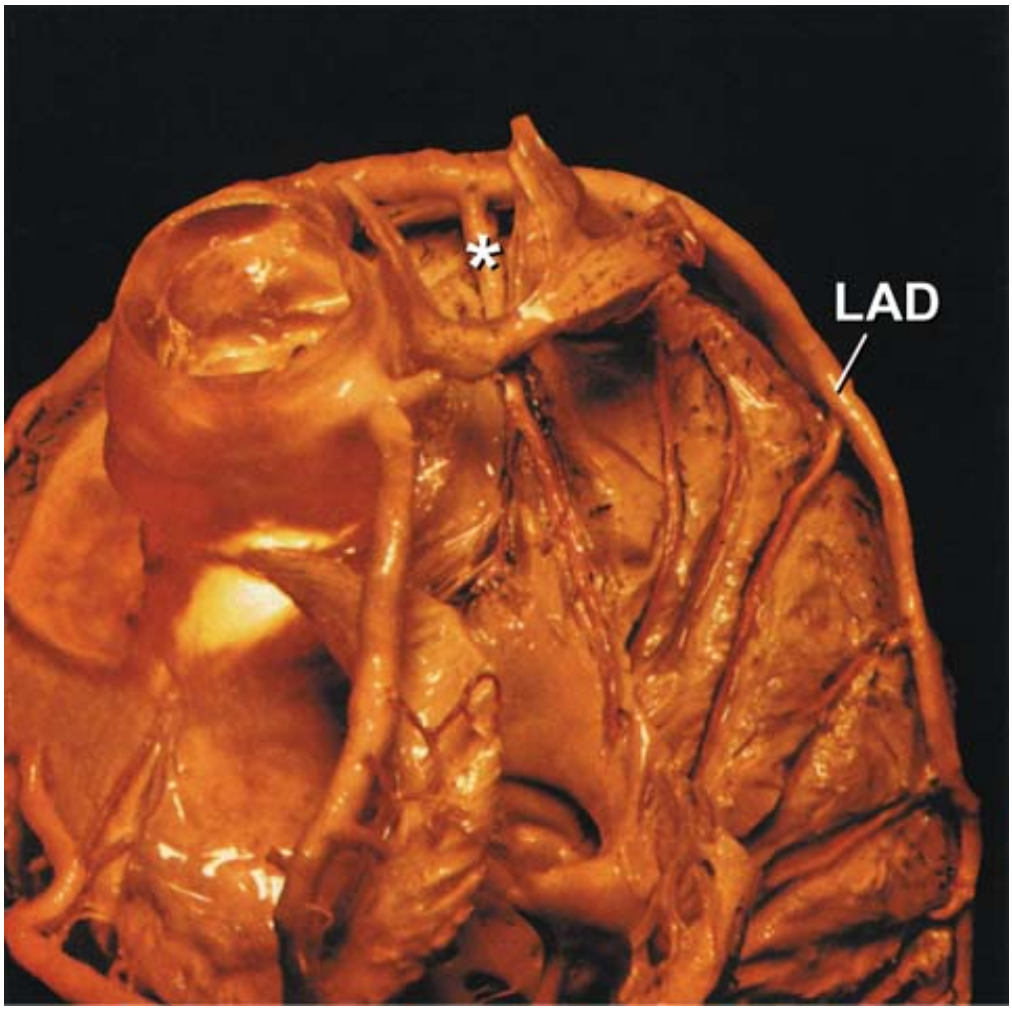


Figure 2-53: (Plate 20) Septal branches of the left anterior descending coronary artery (LAD); * points to the first septal perforator. (From McAlpine,[30] with permission.)

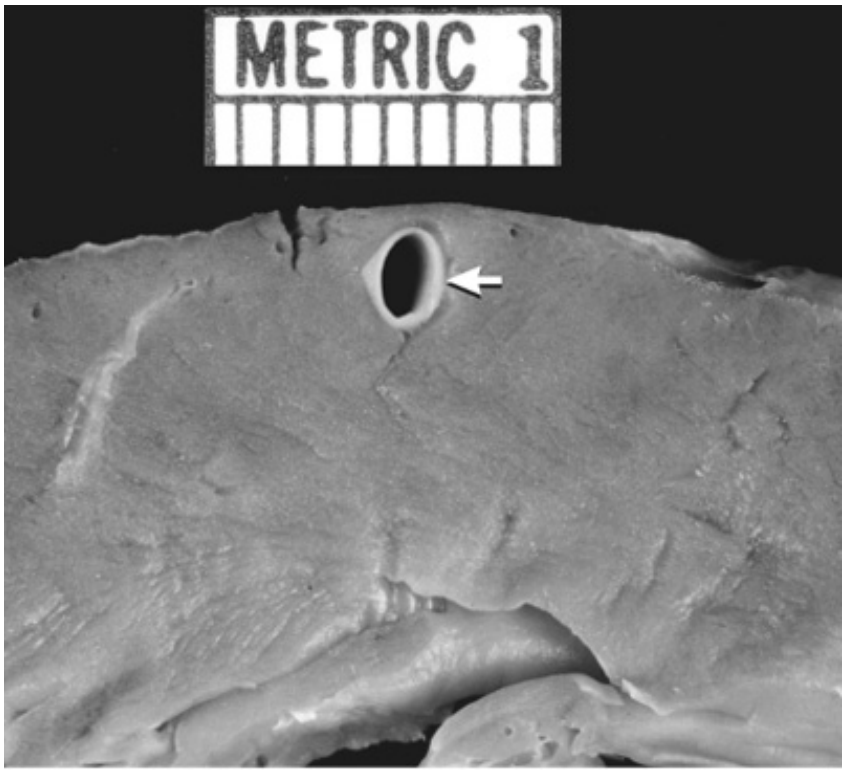


Figure 2-54: Intramyocardial course of the left anterior descending coronary artery (arrow).

The left circumflex coronary artery courses within the adipose tissue of the left atrioventricular groove (see Fig. 2-21*A*) and commonly terminates just beyond its large obtuse marginal branch (see Fig. 2-50). It supplies the lateral left ventricular free wall and a portion of the anterolateral mitral papillary muscle.[15-17]

Along the inferior surface of the heart, the length of the right coronary artery varies inversely with that of the circumflex artery. The artery that crosses the cardiac crux and gives rise to the posterior descending branch represents the dominant coronary artery. Dominance is right in 70 percent of human hearts, left in 10 percent, and shared in 20 percent.[15-17] *In patients with a congenitally bicuspid aortic valve, the incidence of left coronary dominance is 25 to 30 percent.*[17]

The coronary venous circulation is comprised of coronary sinus, cardiac veins, and thebesian venous systems[15-17] (Fig. 2-55, Plate 21). The great cardiac vein travels in the anterior interventricular groove beside the left anterior descending coronary artery and in the left atrioventricular groove beside the left circumflex artery.[15-17] The great cardiac vein and other cardiac veins, such as the left posterior and middle cardiac veins, drain into the coronary sinus, which courses along the posteroinferior aspect of the left atrioventricular groove and empties into the right atrium[15-17] (see Fig. 2-21*A*). The ostium of the coronary sinus is guarded by a crescent-shaped valvular remnant, the thebesian valve. Rarely, the coronary sinus drains directly into the left atrium.[17]

During cardiac operations, cardioplegic solution may be administered retrogradely into the coronary sinus. In patients with the Wolff-Parkinson-White preexitation syndrome and left-sided bypass tracts, the ablation catheter during electrophysiologic studies can be positioned within the coronary sinus and great cardiac vein adjacent to the mitral valve ring in order to localize the aberrant conduction pathway.[17] *The coronary veins, via the coronary sinus, provide access to percutaneous epicardial mapping and pacing of the ventricles and ablation of subepicardial arrhythmogenic foci*[33] (Fig. 2-56, Plate 22). *Some patients with ischemic cardiomyopathy may be poor candidates for conventional revascularization procedures (e.g., coronary artery bypass graft*

surgery or angioplasty) because their epicardial coronary arteries are diffusely diseased. Since in virtually all people the coronary veins run parallel to the entire course of coronary arteries, alternative percutaneous revascularization methods that use the coronary veins as a bypass conduit for coronary arterial flow are being explored.[34-36] *Myocardial revascularization is achieved by either connecting the coronary artery proximal and distal to a stenosis to its companion coronary vein (similar to a conventional bypass graft) or by retroperfusion through the venous microvasculature if the artery and vein are only connected proximal to the stenosis. Coronary veins, unlike saphenous veins, are not removed, thus preserving their adventitia and blood supply.*[34-36]

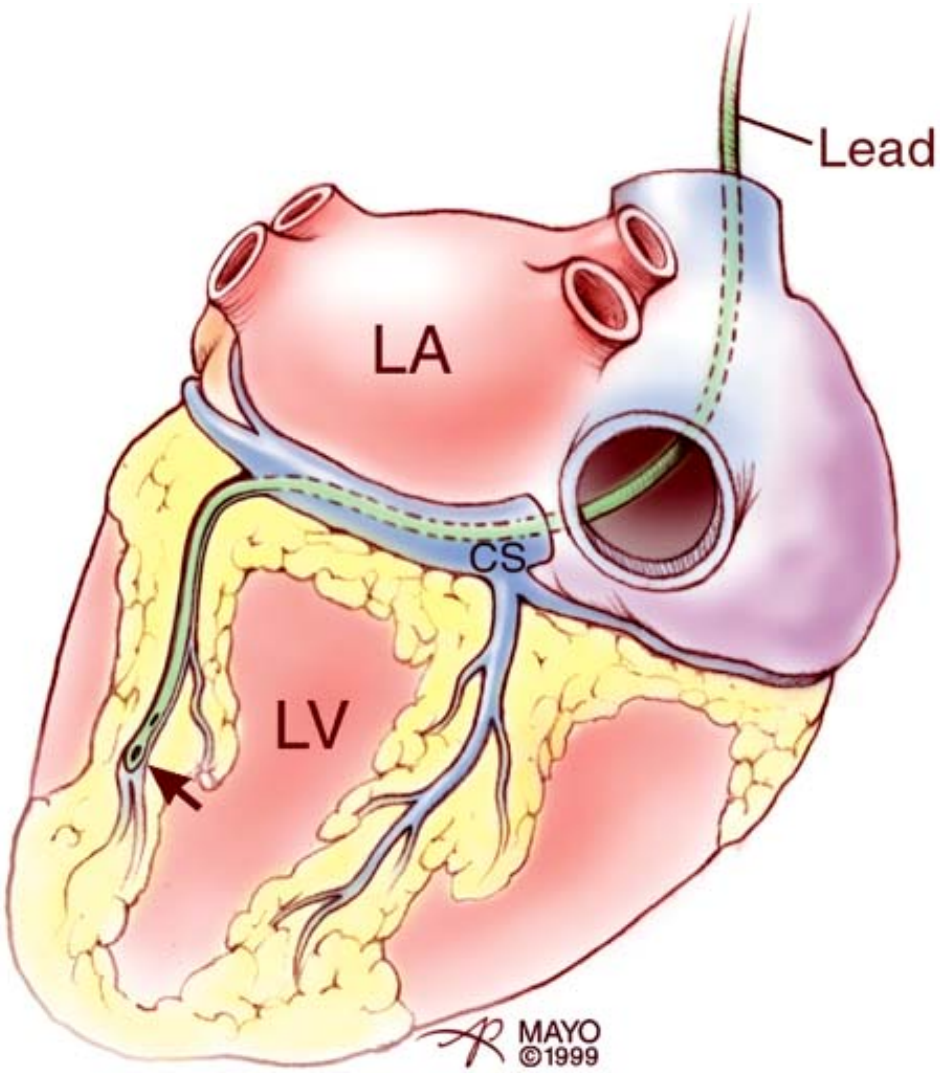
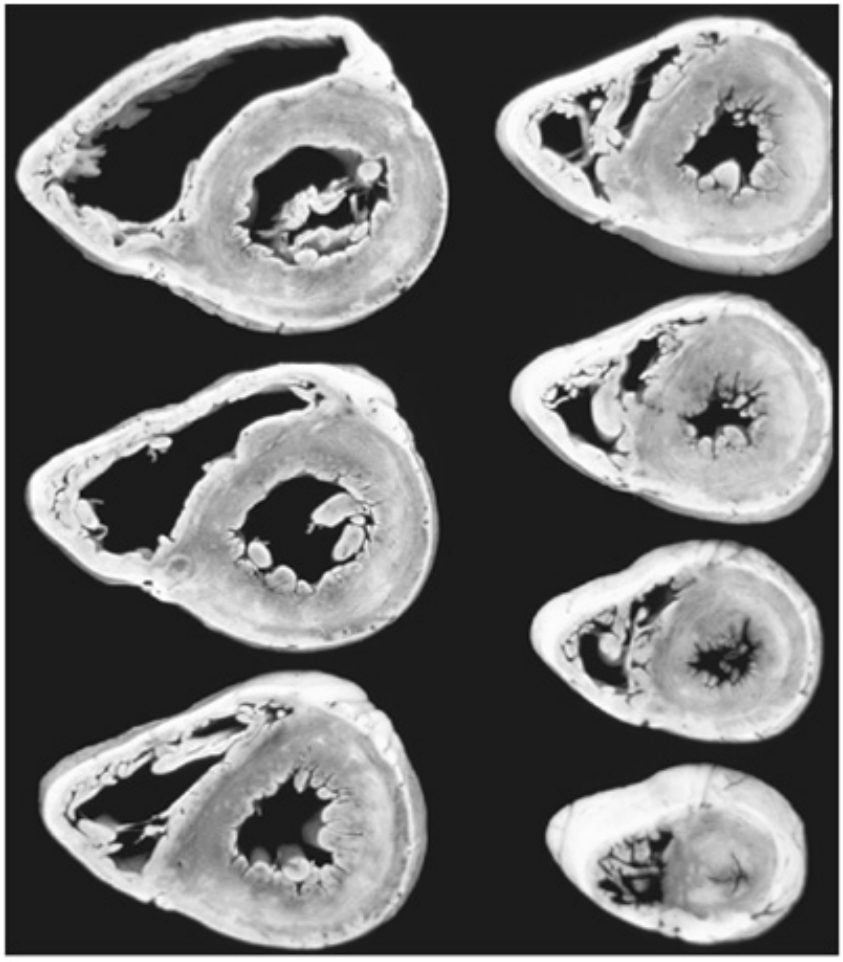


Figure 2-56: (Plate 22) Schematic diagram shows placement of the tip of a pacing/mapping catheter within a coronary vein (arrow) via the coronary sinus (CS). LA, left atrium; LV, left ventricle.

Coronary artery disease is associated with regional abnormalities in ventricular structure and function. Because analysis of segmental myocardial perfusion or contractility is the cornerstone of tomographic imaging techniques [stress echocardiography, SPECT imaging, positron emission tomography (PET), and MRI], for clinicopathologic correlations (Fig. 2-57), a combination tomographic and segmental approach to coronary artery anatomy is recommended.[17,37,38] Ventricular mass is made of the left and right ventricular free walls and the partitioning

ventricular septum. Three levels (i.e., basal, midventricular, and apical) are used to divide the base-apex length of the left ventricle into thirds (Fig. 2-58). The basal third includes that portion between the mitral annulus and the tips of the papillary muscles. The midventricular third is from the papillary muscle to the most apical insertion point of these muscles into the left ventricular free wall. The apical third includes the remainder of the ventricle, from the insertion of the papillary muscles to the left ventricular apex. A similar approach can be applied to the right ventricle.[15-17,37] The ventricular septum can be divided into anteroseptal, septal, and inferoseptal segments, and the left ventricular free wall is divided into anterior, lateral, and inferior segments at the basal and midventricular levels (see Fig. 2-58). The left ventricular apical level consists of four segments (i.e., septum, inferior, lateral, and anterior) (see Fig. 2-58).



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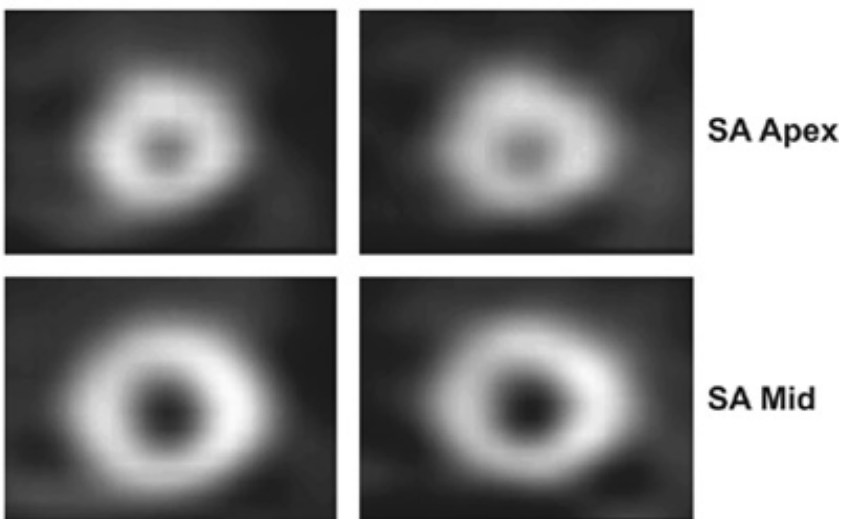

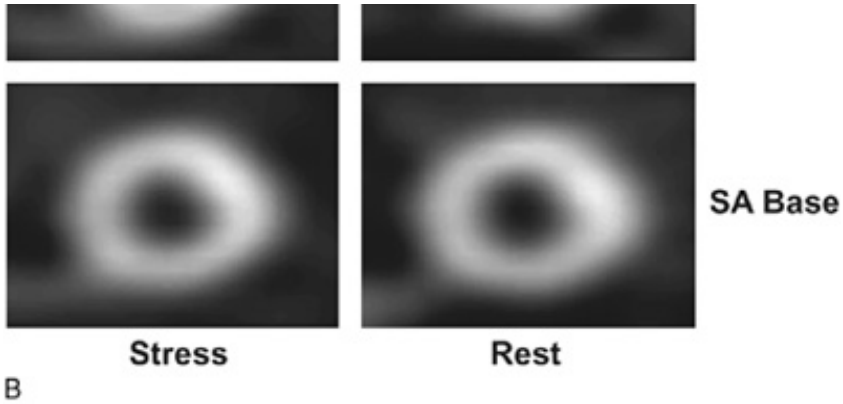

Figure 2-57: Short-axis views. A. Collage of anatomic sections obtained by "bread slicing" the heart in its short-axis plane, corresponding to the tomographic sections obtained by echocardiography and SPECT imaging, viewed from the apex toward the base of the heart. B. Comparable sestamibi SPECT images of the left ventricle showing normal myocardial perfusion at rest and with exercise. SA, short axis.

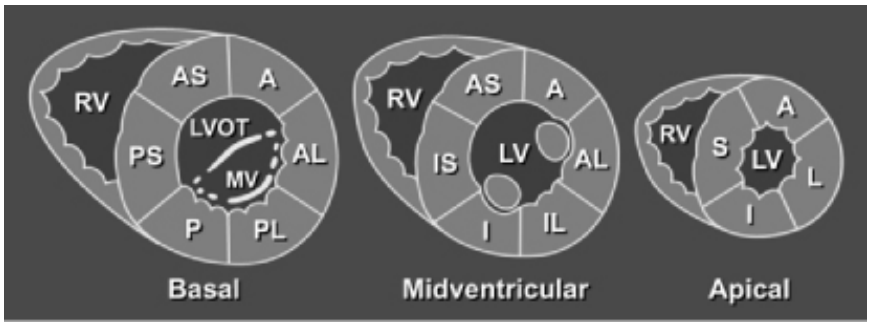

Figure 2-58: Schematic diagram of the three levels of short-axis tomographic views used in echocardiography for 16-segment wall motion analysis. A, anterior; AL, anterolateral; AS, anterior ventricular septum; I, inferior; IL, inferolateral; IS, inferior ventricular septum; L, lateral; LV, left ventricle; LVOT, left ventricular outflow tract; P, posterior; PL, posterolateral; PS, posterior ventricular septum; RV, right ventricle; S, septum. The most basal segment of the inferior wall is the anatomically true posterior segment. At this level, the adjacent ventricular septum is commonly referred to as either the *basal posterior septum* or the *basal inferior septum* and the adjacent lateral wall as either the *basal posterolateral wall* or the *basal inferolateral wall*.

This regional approach is not arbitrary and has been verified by studies of normal, dilated, and hypertrophied hearts. According to this system, there are 16 left ventricular segments that can be evaluated for regional abnormalities. This regional approach also can be used to assess transmural infarct size, because the percentage of left ventricular mass contributed by any particular region is not altered in any significant manner by symmetric hypertrophy or dilatation.[17]

Regional Coronary Artery Supply

The ventricular regions described tend to correlate well with common patterns of coronary arterial distribution[15-17] (Figs. 2-59 and 2-60, Plate 23). Any specific epicardial coronary artery generally will supply a certain cluster of regions. For example, in a typical right-dominant system, the left anterior descending coronary artery would supply the midventricular and basal segments of the anterior and anterolateral walls and anterior septum and all apical segments. The left circumflex artery would supply the midventricular and basal inferolateral segments, and the right coronary artery would supply the midventricular and basal inferior wall and inferior septum (see

Fig. 2-60). However, because the patterns of coronary distribution are so highly variable, these correlations between coronary blood flow and regional anatomy are not precise. For example, a hyperdominant right coronary artery may supply the apex, and a large, obtuse marginal branch of the circumflex artery may supply the anterolateral or inferior wall. Also, any given myocardial region may, in some people, receive its blood supply from the branches of two independent major epicardial arteries.[15-17] In old age, the coronary arteries become dilated and tortuous (Fig. 2-61).

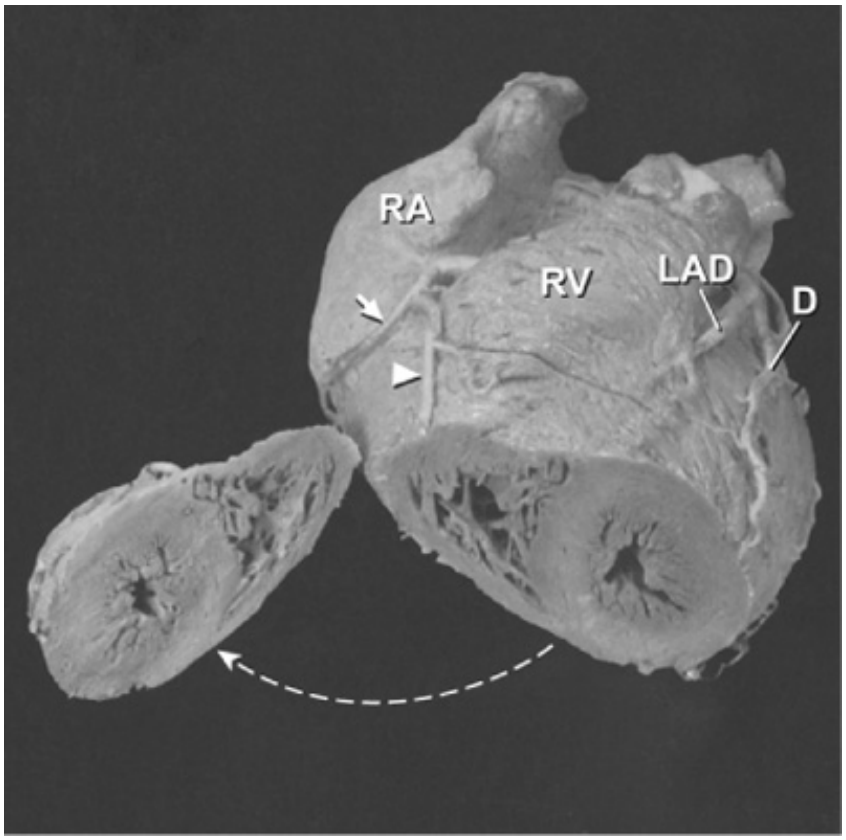

Figure 2-59: Regional coronary flow, with a short-axis slice of the heart. A large diagonal branch (**D**) of the left anterior descending coronary artery (LAD) supplies the lateral wall, and an acute marginal branch (arrowhead) of the right coronary artery (arrow) supplies the anterior right ventricular free wall. The distal segment of the LAD is intramural. RA, right atrium; RV, right ventricle. (From McAlpine,[30] with permission.)

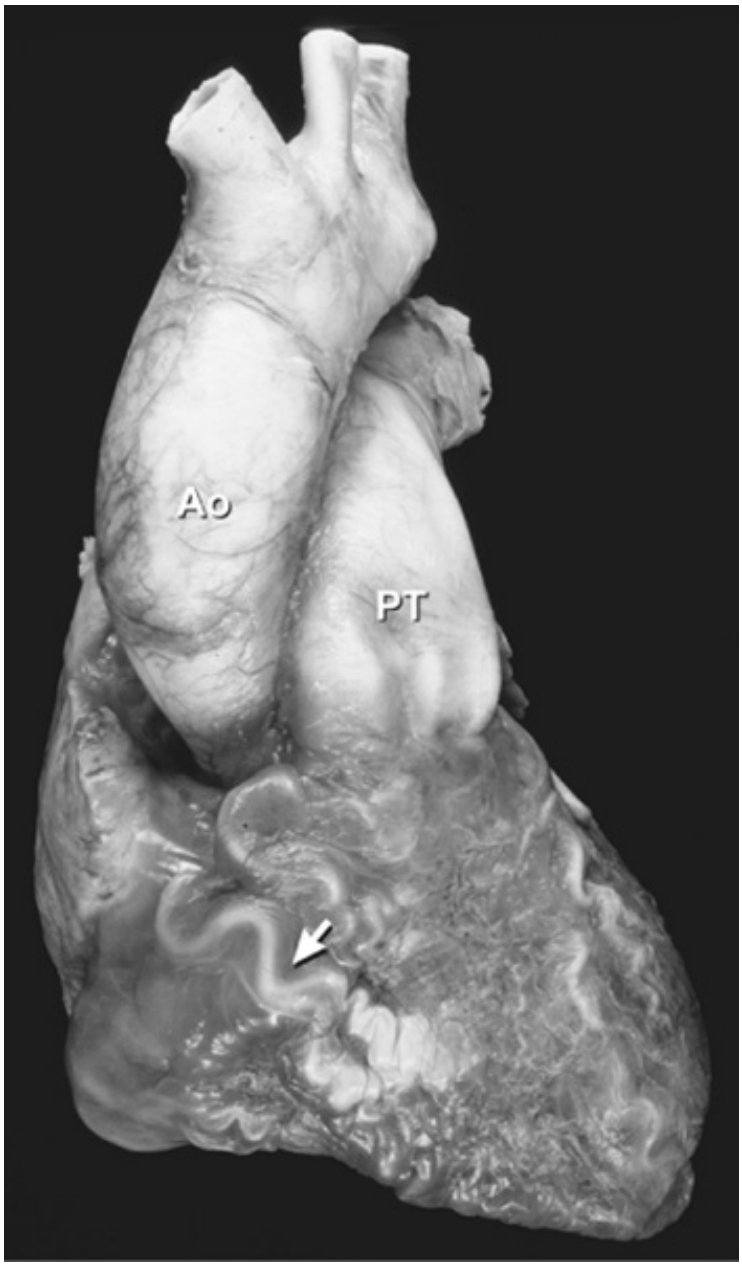

Figure 2-61: Tortuous coronary arteries (arrow) typically seen in the elderly with nondilated hearts. Ao, ascending aorta; PT, pulmonary trunk.

Coronary Collaterals and Microcirculation

Collateral channels provide communication between the major coronary arteries and their branches.[17] If stenosis of an epicardial coronary artery produces a pressure gradient across such a vessel, the collateral channel may dilate with time and provide a bypass avenue for blood flow beyond the obstruction. Such functional collaterals may develop between the terminal extensions of two coronary arteries, between the side branches of two arteries, between branches of the same artery, or within the same branch (via the vasa vasorum). These are most common in the ventricular septum (between septal perforators of the anterior and posterior descending arteries), in the ventricular apex (between anterior descending septal perforators), in the anterior right ventricular free wall (between anterior descending and right or conus arteries), in the anterolateral left ventricular free wall (between anterior descending diagonals and circumflex marginals), at the cardiac crux, and along the atrial surfaces (between the right and left circumflex arteries).[17]

The intramural coronary vessels form the microcirculation. There are age-related variations in the

pattern of distribution of the coronary microcirculation.[39] *Angina-like chest pain in some patients with angiographically normal epicardial coronary arteries (i.e., syndrome X, or microvascular angina) may be secondary to abnormal vasodilator reserve or vasoconstriction of the coronary microcirculation.*[40] *Abnormal flow reserve of the coronary microcirculation is seen in both dilated and hypertrophied hearts. In the latter, structural changes in the coronary arterioles can be found on histologic examination of the myocardium.*[41-43] *In patients with symptomatic hypertrophic cardiomyopathy without angiographic evidence of epicardial coronary artery disease, myocardial tissue obtained during surgical myectomy may show smaller than normal coronary arteriolar lumina.*[43] *Postmortem analysis of hearts with hypertrophic cardiomyopathy also has revealed coronary arterioles with abnormally thick walls.*[43] *With contrast echocardiography, it may be possible to noninvasively visualize intramyocardial arterioles and study coronary flow reserve.*[44] *Demonstration of an intact microvascular circulation in akinetic myocardium following acute myocardial infarction, using PET or SPECT imaging or contrast echocardiography, is evidence of viability of the affected segment.*[44] *The creation of intramyocardial channels with CO_2 laser transmyocardial revascularization has been associated with augmentation of collateral flow to ischemic myocardium through angiogenesis.*[45]

Cardiac Lymphatics

The myocardial lymphatics drain toward the epicardial surface, where they merge to form the right and left lymphatic channels, which travel in retrograde fashion with their respective coronary arteries. These two lymphatic channels travel along the ascending aorta and merge before draining into a pretracheal lymph node beneath the aortic arch. This single lymphatic channel then travels through a cardiac lymph node, between the superior vena cava and innominate artery, and finally empties into the right lymphatic duct. Metastatic tumor obstruction of epicardial lymphatics can produce a pericardial effusion.[15-17]

Great Vessels

The subclavian and internal jugular veins merge bilaterally to form the right and left innominate veins (Fig. 2-62). Valves in the subclavian and internal jugular veins, near their junctions with the innominate veins, are important anatomic structures that help maintain unidirectional antegrade blood flow not only in the normal state but also in the setting of elevated right-sided heart filling pressures.[46] Subclavian and internal jugular venous valves are absent in 2 and 6 percent of people, respectively, and venous valves may be damaged by catheter-induced trauma or by age.[46] *Absent or malfunctioning valves may interfere with the success of closed-chest cardiopulmonary resuscitation and contribute to the development of brain edema during such a procedure.*[46]

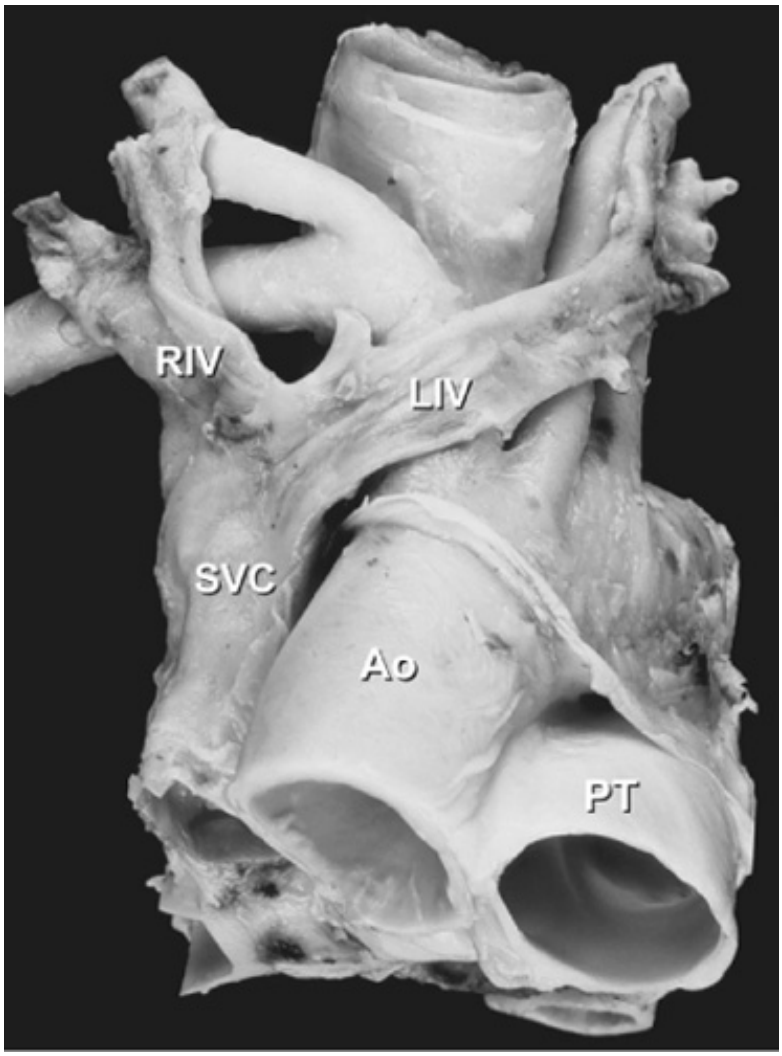

Figure 2-62: The longer left (LIV) and shorter right (**RIV**) innominate veins normally join to form the right superior vena cava (SVC). Ao, ascending aorta; PT, pulmonary trunk.

The left innominate vein is two to three times the length of its right-sided counterpart. It travels anteriorly to the aortic arch along the right anterolateral border of the ascending aorta, where it joins the shorter right innominate vein to form the superior vena cava[15-17] (see Fig. 2-62). *Transesophageal echocardiographic imaging of the upper ascending aorta may show a double lumen (i.e., aorta and adjacent innominate vein) that can be misinterpreted as aortic dissection by an inexperienced echocardiographer.*[7]

The superior vena cava lies anterior to the right pulmonary artery (Fig. 2-63) and receives the azygos vein posteriorly before draining into the superior aspect of the right atrium, just posterior to the atrial appendage[15-17] (see Figs. 2-46, 2-47, and 2-63). *The vein of Marshall forms the terminal connection between a persistent left superior vena cava and the coronary sinus. Its vestigial remnant in normal adults is the ligament of Marshall* (Fig 2-64, Plate 24). *Both vein and ligament are a potential source of arrhythmias*. The ostium of the inferior vena cava is guarded by a crescent-shaped, often fenestrated flap of tissue, the eustachian valve[15-17] (see Fig. 2-16*A*), that is readily seen by echocardiography. Although generally small, the eustachian valve may become so large that it can produce a double-chambered right atrium.[16] Also, when either the eustachian or thebesian valve is large and fenestrated, it is referred to as a *Chiari net*.[15-17] *By echocardiography, a Chiari net may be misinterpreted as a mass*.

The thoracic aorta arises at the level of the aortic valve and is divided into three segments:

ascending aorta, aortic arch, and descending thoracic aorta (Fig. 2-65). The ascending aorta consists of sinus and tubular portions, which are demarcated by the sinotubular junction (Figs. 2-28 and 2-66). *This is the site at which supravalvular aortic stenosis is often most severe*.[15-17]

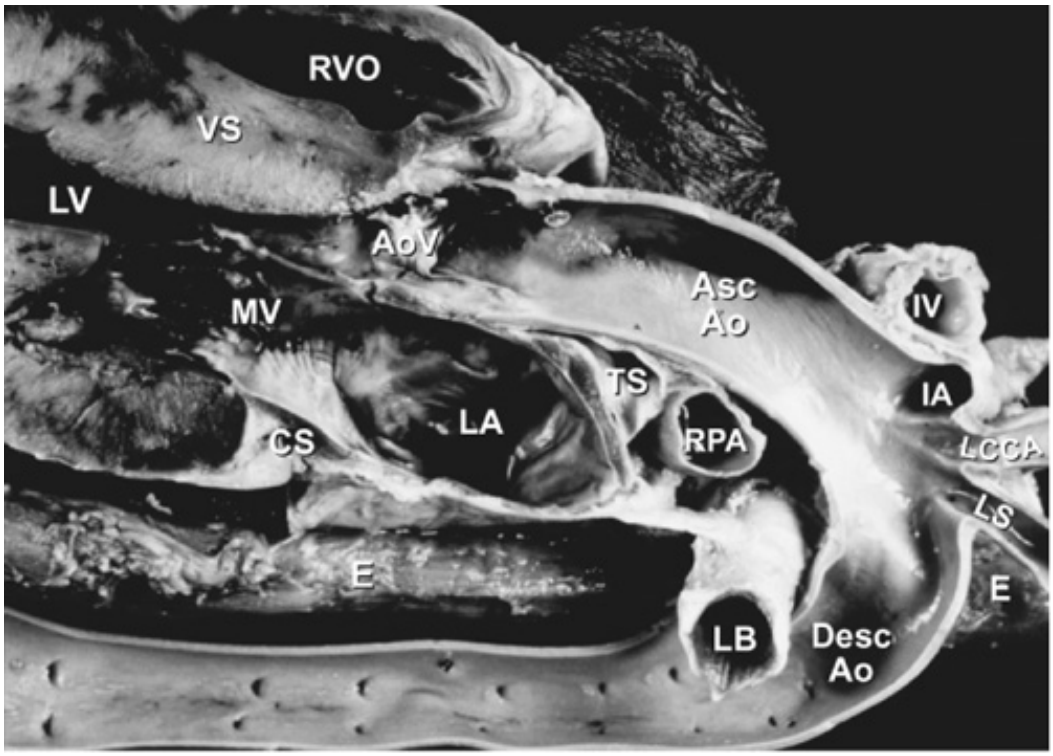

Figure 2-65: Thoracic aorta. The entire thoracic aorta has been cut in a tomographic manner. The aortic arch travels over the left bronchus and the right pulmonary artery. Asc Ao, ascending aorta; AoV, aortic valve; CS, coronary sinus; Desc Ao, descending thoracic aorta; E, esophagus; IA, innominate artery; IV, innominate vein; LA, left atrium; LB, left bronchus; LCCA, left common carotid artery; LS, left subclavian artery; LV, left ventricle; MV, mitral valve; RPA, right pulmonary artery; RVO, right ventricular outflow; TS, transverse sinus; VS, ventricular septum.

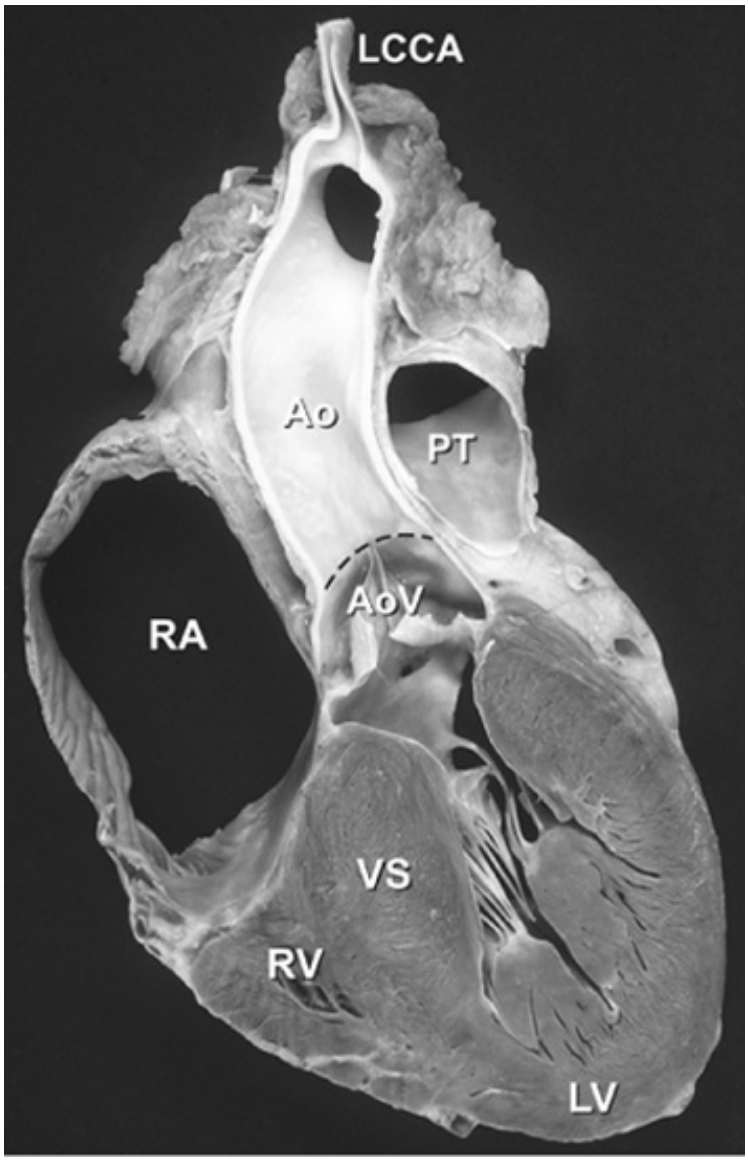

Figure 2-66: Tomographic section of the heart in the frontal plane of the body showing the aortic sinotubular junction (dashed line). Ao, ascending aorta; AoV, aortic valve; LCCA, left common carotid artery; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; LV, left ventricle; VS, ventricular septum.

Behind the aortic valve cusps are three outpouchings, or sinuses (of Valsalva). The right aortic sinus abuts against the ventricular septum and right ventricular parietal band and is covered in part by the right atrial appendage (see Figs. 2-30 and 2-52). In contrast, the left aortic sinus rests against the anterior left ventricular free wall and a portion of the anterior mitral leaflet, abuts the left atrial free wall, and is covered in part by the pulmonary trunk and left atrial appendage (see Figs. 2-20 and 2-21*A*). The posterior (noncoronary) aortic sinus overlies the ventricular septum and a part of the anterior mitral leaflet, forms part of the transverse sinus, abuts the atrial septum, and indents both atrial free walls[15-17] (see Figs. 2-12*D* and 2-22). *Rupture of the right and posterior aortic sinuses of Valsalva may result in a communication with the right ventricular outflow tract or right atrium, whereas rupture of the left aortic sinus of Valsalva leads to a communication with the left atrium or left ventricular outflow tract. Annuloaortic ectasia is associated with hypertension, aortic medial degeneration, and advanced age and may produce aortic regurgitation, ascending aortic aneurysm, or aortic dissection.*[15-17]

The aortic arch gives rise to the innominate, left common carotid, and left subclavian arteries in

that order (see Fig. 2-65). In about 10 percent of people, the innominate and left common carotid arteries share a common ostium, and in 5 percent of people, the left vertebral artery arises directly from the aortic arch, between the left common carotid and left subclavian arteries.[17] The ligamentum arteriosum (ductal artery ligament) represents the vestigial remnant of the fetal ductal artery, which when patent connects the proximal left pulmonary artery to the undersurface of the aortic arch.[17] *Most coarctations occur just distal to the left subclavian artery* (see Fig. 2-69). *When thoracic aortic dissection does not involve the ascending aorta (Debakey type III and Stanford type B), the intimal tear is commonly near the ligamentum arteriosum or the ostium of the left subclavian artery*.[17] *Nonpenetrating deceleration chest trauma, as may occur in motor vehicle accidents, commonly involves the aorta in the region between the aortic arch and descending thoracic aorta and may be associated with aortic transection or pseudoaneurysm formation*.[17]

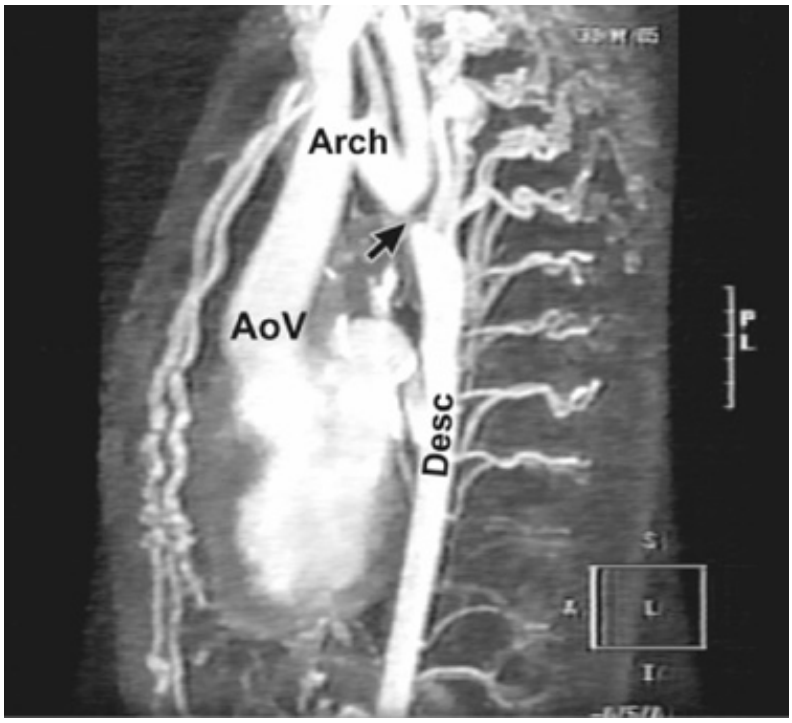

Figure 2-69: Real-time three-dimensional CT reconstruction of the thoracic aorta in a patient with coarctation (arrow) distal to the left subclavian artery. AoV, aortic valve. Desc, descending thoracic aorta.

The descending thoracic aorta lies adjacent to the left atrium, esophagus, and vertebral column. The pulmonary trunk (or main pulmonary artery) emanates from the right ventricle and travels to the left of the ascending aorta. As it bifurcates, the left pulmonary artery courses over the left bronchus, whereas the right pulmonary artery travels beneath the aortic arch and behind the superior vena cava (see Figs. 2-11*A* and 2-63). Thus the *left* bronchus and the *right* pulmonary artery normally travel beneath the aortic arch.

Cardiac Conduction System

The cardiac conduction system consists of the sinus node, internodal tracts, AV node, AV (His) bundle, and right and left bundle branches[15-17] (Fig. 2-67, Plate 25). The sinus node is located sub-epicardially in the terminal groove, close to the junction between the superior vena cava and right atrium. The sinus node artery arises from the right coronary artery in 55 percent of

people. Its course may place it in contact with the base of the right atrial appendage and the superior vena cava-right atrial junction (see Fig. 2-52). When the sinus node artery arises from the left circumflex artery (45 percent), it may course close to the left atrial appendage. *During such surgical operations as the Mustard and Fontan procedures, the sinus node and its artery are susceptible to injury*.[16,17]

By light microscopy, there are no morphologically distinct conduction pathways between the sinus and AV nodes.[17] However, electrophysiologic studies support the concept of functional preferential pathways that travel along the crista terminalis and atrial septum including the limbus but not the valve of the fossa ovalis.[17] *Internodal conduction disturbances therefore are not expected as a result of transseptal procedures. With the Mustard operation for complete transposition of the great arteries, there may be severe disturbance of internodal conduction because the entire septum is resected, and the surgical atriotomy may disrupt the crista terminalis*.[17] *Lipomatous hypertrophy of the atrial septum may interfere with internodal conduction and induce a variety of atrial arrhythmias. Ventricular preexcitation is most commonly associated with aberrant bypass tracts that span the annulus of the tricuspid or mitral valve* (see Fig. 2-2).

The AV node, in contrast to the sinus node, is a sub*endo*cardial structure that is located within the triangle of Koch[15-17] (Fig. 2-68, Plate 26). The triangle of Koch is bordered by the coronary sinus ostium posteroinferiorly and the septal tricuspid annulus anteriorly. *Because of its right atrial location near the tricuspid annulus, the AV node is susceptible to injury during tricuspid annuloplasty and during plication procedures for Ebstein's anomaly*.[15-17]

The AV (His) bundle arises from the distal portion of the AV node and travels along the ventricular septum adjacent to the membranous septum[15-17] (see Fig. 2-68). *The AV conduction tissue is generally remote from the defect in the outlet, inlet, and muscular forms of ventricular septal defect but travels along the inferior margin of a membranous ventricular septal defect*. The AV bundle travels through the central fibrous body (right fibrous trigone) and therefore is closely related to the annuli of the aortic, mitral, and tricuspid valves. *Thus, during operative procedures involving these valves or a membranous ventricular septal defect, care must be taken to avoid injury to the His bundle. Whereas in normal hearts the AV bundle courses along the posteroinferior rim of the membranous septum, it courses along the anterosuperior rim of the membranous septum in hearts with AV discordance*. The AV bundle receives a dual blood supply from the AV nodal artery and the first septal perforator of the left anterior descending coronary artery.[17]

The right bundle branch emanates from the distal portion of the AV bundle and forms a cordlike structure that travels along the septal and moderator bands toward the anterior tricuspid papillary muscle (see Fig. 2-67). In contrast, the left bundle branch represents a broad fenestrated sheet of subendocardial conduction fibers that spread along the septal surface of the left ventricle[15-17] (see Fig. 2-67). The right and left bundle branches receive dual blood supply from the septal perforators of the left anterior descending coronary artery and posterior descending coronary arteries.[17] Left ventricular pseudotendons may contain conduction tissue from the left bundle branch.[17] *Following right ventriculotomy for reconstruction of the right ventricular outflow tract, the ECG shows a pattern of right bundle-branch block even though the right bundle is not disrupted*.[16]

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NEW DEVELOPMENTS AND FUTURE CHALLENGES

The future holds promise for an integrated multidimensional approach to the study of cardiac anatomy that incorporates static three-dimensional data, the elements of time (the fourth dimension) and motion, and physiologic (pressure and perfusion) and metabolic parameters.[47-49] Until recently, the geometric fusion of anatomy and function was not possible without physically invading the body. With the currently available imaging techniques, multidimensional anatomy and physiology are mentally reassembled from the sequential tomographic images using echocardiography, MRI or CT, or multiple scintigraphy, as with SPECT imaging.[47] With the advances made in medical technology propelled by the rapid developments in computer technology, digital imaging, and data-storage techniques, it has become possible to electronically perform virtual dissection and reconstruction of the heart and cardiovascular system[47-49] (Fig. 2-69). Furthermore, multidimensional imaging allows continued study of any human organ of interest because of the ability to permanently store anatomic images and physiologic features for retrieval, comparison for change, and ultimately, physical replication.[47-49]

The potential realization of virtual anatomy notwithstanding, standardization of the various tomographic approaches to image acquisition in a manner that conforms with anatomic correctness remains a major challenge that has to be overcome if multidimensional cardiac imaging is to become a clinical reality. There is current progress in this direction. Real-time three-dimensional reconstruction of the heart using identical CT and two-dimensional tomographic sectioning of the heart is now possible. Virtual vivisection may soon become reality. It will allow virtual surgery (dry runs prior to the actual operation) and dissection of the heart into its various functional components, be it anatomic, physiologic, or metabolic, either separately or in various combinations. Because of these advances in multimedia technology, the centuries-old great divide between physiologists and anatomists has been relegated to the history books.

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ANATOMY NOT ADDRESSED AND QUANTUM COMPUTING

Fine-detailed anatomy such as that of the conduction system and microvasculature is not available to the usual anatomic dissection. Additionally, tissue histology or molecular biologic assessment is not obtained routinely by the dissectionist. At the other end of the spectrum, three-dimensional gross anatomic dissection of contiguous structures is also normally not available. How does metastatic cancer throughout the system relate to a primary tumor in the gut?

These and other desirable anatomic and histologic dissections await the future of increasing computer technology. Both pathologic and living tissues someday will be dissected and analyzed not by destructive cutting but by digital imagery. Today's computers have introduced the information era. Information has become a commodity expanding our ability to access useful data. Within the next two decades, however, we will have evolved to the quantum era where all that has been discussed in this chapter plus gross and microscopic anatomy will be possible within an electronic environment. Reality will be broken down into its base parts or characteristics and then re-formatted relative to the desired information. Gross anatomy, physiology, tissue characteristics, and even histopathology can be dissected and presented as a quantifiable geometric image.

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Figure 2-10: (Plate 5) Bisected cardiac specimen in the four-chamber view parallel to the base-apex axis of the heart. (*Left*) The bisected specimen has been partially opened to show the relative relationship of the bisected halves. (*Right*) The two components of the bisected specimen are opened completely. Note the positions of the pulmonary veins posteriorly and the positions of the atrial appendages at the atrioventricular groove. AL, anterolateral papillary muscle; AS, atrial septum; IVC, **inferior vena cava**; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; PM, posteromedial papillary muscle; PulV, pulmonary vein; RA, right atrium; RAA, right atrial appendage; RV, right ventricle; TV, tricuspid valve; VS, ventricular septum.

Figure 2-11: Tomographic cardiac dissection along the body primary planes. *A*,*B*. Transverse sections (looking from head toward feet) at the level of the great vessels (*A*) or the cardiac chambers (*B*). The aortic arch travels over the left bronchus and the right pulmonary artery. *C*,*D*. Frontal sections (looking from anterior to posterior) through both ventricles (*C*) or left ventricle and right atrium (*D*). *E*,*F*. **Parasagittal sections looking from right** (*E*) **to left** (*F*). Ao, **ascending aorta;** CS, coronary sinus; E, **esophagus;** IA, innominate artery; IVC, **inferior vena cava;** LA, **left atrium;** LAA, **left atrial appendage;** LB, left bronchus; LCX, left circumflex **coronary artery;** LIV, left innominate vein; LLPV, left lower pulmonary vein; LPA, left pulmonary artery; LUPV, left upper pulmonary vein; LSA, left subclavian artery; LV, **left ventricle;** MS, membranous ventricular septum; MV, **mitral valve;** PS, pericardial sac; PT, **pulmonary trunk;** PV, pulmonary valve; RA, **right atrium;** RAA, **right atrial appendage;** RPA, right pulmonary artery; RUPV, right upper pulmonary vein; RV, **right ventricle**; RVO, right ventricular outflow; SVC, **superior vena cava;** TV, **tricuspid valve.**

Figure 2-12: *A*-*D*. Tomographic cardiac dissections along the heart's primary short-axis plane. This method of tomographic dissection shows the crescentic right ventricle (RV) and circular left ventricle (LV). The atrioventricular valves are sectioned at the level of their papillary muscles (in *A*), chordae tendineae (in *B*), atrioventricular valve leaflets (in *C*), and their annuli and the semilunar valves (in *D*). The infundibulum septum (IS) separates the pulmonary and aortic valves. The atrial septum (AS) separates the tricuspid and mitral valves and abuts the posterior (noncoronary) cusp of the aortic valve. LA, left atrium; MV, mitral valve; RA, right atrium; RVO, right ventricular outflow; TV, tricuspid valve.

Figure 2-13: Tomographic cardiac dissection along the heart's primary fourchamber plane. The heart is viewed as though one were looking from the anterosuperior surface toward the posteroinferior surface. In the floor of the right atrium is the orifice of the inferior vena cava (IVC). The pulmonary veins (PulV) enter the posterior aspect of the left atrium. AL, anterolateral mitral papillary muscle; AS, atrial septum; LA, left atrium; LV, left ventricle; MV, mitral valve; PM, posteromedial mitral papillary muscle; RV, right ventricle; TV, tricuspid valve; VS, ventricular septum.

Figure 2-14: Tomographic cardiac dissection along the heart's primary long-axis plane. *A*. Tomographic section showing the left ventricle and left atrium. The mitral valve is also well demonstrated. The left atrial appendage is located anteriorly. The specimen is viewed as though one were looking from the tip of the left scapula toward the right nipple. *B*. Analogous two-chamber transesophageal view. AW, anterior wall; **Desc** Ao, **descending thoracic aorta;** E, **esophagus;** IW, **inferior wall**; LA, **left atrium;** LAA, **left atrial appendage;** LB, **left bronchus;** LPA, **left pulmonary artery;** LV, **left ventricle;** MV, **mitral valve;** PulV, pulmonary vein; Tr, trachea.

Figure 2-15: Left ventricular long-axis method of tomographic cardiac dissection (looking from left flank toward the midsternum). Continuity between mitral and aortic valves is clearly seen. The oblique sinus (*) abuts the wall of the left atrium. A, anterior mitral leaflet; Ao, ascending aorta; CS, coronary sinus; LA, left atrium; LV, left ventricle; P, posterior aortic cusp; PM, posteromedial mitral papillary muscle; R, right aortic cusp; RVO , right ventricular outflow; SVC, superior vena cava; arrows point to the right upper and lower pulmonary veins.

Figure 2-16: Collage of four-chamber tomographic sections cutting from inferior wall to anterosuperior wall showing coronary sinus (*A*), internal cardiac crux (*) (*B*), and aortic valve (*C*). Ao, ascending aorta; CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; arrow in *A* points to a fenestrated eustachian valve.

Figure 2-17: Tomographic sections of the heart in the transverse (*A*) and frontal (*B*) planes of the body. A tomographic section in the transverse plane of the body (*A*) results in a four-chamber view of the heart. *A* tomographic section along the frontal plane of the body (*B*) results in an oblique short-axis view of the heart. *C*. MRI image corresponding to *A*. CS, coronary sinus; DAo, descending thoracic aorta; IVC, inferior vena cava; LA, left atrium; LAD, left anterior descending coronary artery; LV, left ventricle; RA, right atrium; RCA, right coronary artery; RV, right ventricle; RVO, right ventricular outflow; TV, tricuspid valve; VS, ventricular septum.

Figure 2-18: Oblique methods of tomographic cardiac dissection. *A, B.* Right anterior oblique sections, viewed from the right, are taken parallel to the ventricular and atrial septa, may include the right side of the heart (*A*) or the left side of the heart (*B*), and are similar to the two-chamber tomographic sections. *C,D.* Left anterior oblique sections, viewed from the apex toward the base, may be taken at various levels and are similar to the short-axis tomographic sections. Ao, aorta; CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; PT, pulmonary trunk; PV, pulmonary valve; RA, right atrium; RV, right ventricle; RVO, right ventricular outflow; SVC, superior vena cava; TV, tricuspid valve.

Figure 2-19: Anterior view of the heart. The anterior portion of the parietal pericardium has been removed, exposing the intrapericardial portions of the superior vena cava (SVC), ascending aorta (Ao), and pulmonary trunk (PT). LV, left ventricle; RA, right atrium; RV, right ventricle.

Figure 2-20: Tomographic section in the short-axis plane of the body, looking from apex toward the base, showing the oblique (OS) and transverse (TS) pericardial sinuses. Ao, ascending aorta; DAo, descending thoracic aorta; LA, left atrium; LAS, left aortic sinus; LMA, left main coronary artery: PS, pericardial sac; PV, pulmonary valve; RAA, right atrial appendage; SVC, superior vena cava.

Figure 2-21: (Plate 8) Base of heart. *A.* Section through the base of the heart, looking from base toward apex, with the atria and great arteries removed, shows all four cardiac valves. *B.* A comparable schematic diagram of the fibrous cardiac skeleton. The centrally located aortic valve forms the cornerstone of the cardiac skeleton. Its fibrous extensions anchor and support the other three valves. *A*, anterior; AoV, aortic valve; AV, atrioventricular; CS, coronary sinus; IV, interventricular; L, left; LCX, left circumflex coronary artery; MV, mitral valve; P, posterior; PV, pulmonary valve; R, right; RCA, right coronary artery; S, septal; TV, tricuspid valve.

Figure 2-22: Long-axis section of the left ventricle. The intervalvular fibrosa (dashed triangle) lies between the anterior mitral leaflet and the posterior cusp of the aortic valve and abuts the floor of the transverse pericardial sinus (*). Ao, ascending aorta; IW, inferior wall; LA, left atrium; LV, left ventricle; RVO, right ventricular outflow; VS, ventricular septum.

Figure 2-23: This oblique short-axis view of the heart shows the triangular-shaped tricuspid orifice (TV) and the elliptical mitral orifice (MV) at midleaflet level. The anterior tricuspid and anterior mitral leaflets (A) separate the inflow and outflow tracts of the right and left ventricles, respectively, and are parallel to one another. PV, pulmonary valve.

Figure 2-24: (Plate 9) Mitral valve, viewed from left atrial aspect. Minor commissures (*) divide the posterior leaflet into four scallops (arrows). A, anterior; C, major commissures; P, posterior.

Figure 2-59: Regional coronary flow, with a short-axis slice of the heart. A large diagonal branch (**D**) of the left anterior descending coronary artery (LAD) supplies the lateral wall, and an acute marginal branch (arrowhead) of the right coronary artery (arrow) supplies the anterior right ventricular free wall. The distal segment of the LAD is intramural. RA, right atrium; RV, right ventricle. (From McAlpine,[30] with permission.)

Figure 2-60: (Plate 23) Coronary distribution using a 16-segment model. **D**, diagonal branch of the left anterior descending coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMA, left main coronary artery; OM, obtuse marginal branch of the circumflex coronary artery; PD, posterior descending coronary artery; RCA, right coronary artery; RM, right marginal branch; other abbreviations as in Fig 2-58.

Figure 2-61: Tortuous coronary arteries (arrow) typically seen in the elderly with nondilated hearts. Ao, ascending aorta; PT, pulmonary trunk.

Figure 2-62: The longer left (LIV) and shorter right (**RIV**) innominate veins normally join to form the right superior vena cava (SVC). Ao, ascending aorta; PT, pulmonary trunk.

Figure 2-63: Long-axis view of the superior vena cava (SVC) and inferior vena cava (IVC). The specimen is viewed from the left looking toward the free wall of the right atrium. The right atrium (RA) and its appendage (RAA) are anterior. This is a commonly used tomographic plane in transesophageal echocardiography. AS, atrial septum; LA, left atrium; LB, left bronchus; RPA, right pulmonary artery.

Figure 2-64: (Plate 24) Schematic diagrams showing the ligament/vein of Marshall in normal hearts (*left*) and persistent left superior vena cava (LSVC) (*right*). CS, coronary sinus; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; RA, right atrium; RSVC, right superior vena cava.

Figure 2-65: Thoracic aorta. The entire thoracic aorta has been cut in a tomographic manner. The aortic arch travels over the left bronchus and the right pulmonary artery. Asc Ao, ascending aorta; AoV, aortic valve; CS, coronary sinus; Desc Ao, descending thoracic aorta; E, esophagus; IA, innominate artery; IV, innominate vein; LA, left atrium; LB, left bronchus; LCCA, left common carotid artery; LS, left subclavian artery; LV, left ventricle; MV, mitral valve; RPA, right pulmonary artery; RVO, right ventricular outflow; TS, transverse sinus; VS, ventricular septum.

Figure 2-66: Tomographic section of the heart in the frontal plane of the body showing the aortic sinotubular junction (dashed line). Ao, ascending aorta; AoV, aortic valve; LCCA, left common carotid artery; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; LV, left ventricle; VS, ventricular septum.

Figure 2-67: (Plate 25) Schematic diagram of the cardiac conduction system. (*Left*) The right side of the heart showing the sinus node, atrioventricular (AV) node, AV (His) bundle, and right bundle branch. (*Right*) The left side of the heart showing incomplete anatomic separation of the left bundle into antero and posterior fascicles. Ao, ascending aorta; AV, atrioventricular; CS, coronary sinus; CT, crista terminalis; FO, fossa ovalis; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary valve; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

Figure 2-68: (Plate 26) The atrioventricular node (AVN) lies within the triangle of Koch (dashed triangle), and the AV (His) bundle (AVB) travels through the tricuspid annulus to rest along the summit of the ventricular septum. CS, coronary sinus; FO, fossa ovalis; IVC, inferior vena cava; S, septal leaflet of the tricuspid valve; SVC, superior vena cava.

Figure 2-69: Real-time three-dimensional CT reconstruction of the thoracic aorta in a patient with coarctation (arrow) distal to the left subclavian artery. AoV, aortic valve. Desc, descending thoracic aorta.

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PREVIOUS

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Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 3:

NORMAL PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

Authors: Martin M. LeWinter, George Osol

The cardiovascular system functions to deliver oxygen, nutrients, and other essential molecules to the tissues and carry waste products (e.g., carbon dioxide, metabolic end products) to the organs responsible for their elimination (i.e., lungs, liver, kidney). To accomplish these functions, a system with two separate circulations in series has evolved. The pulmonary circulation is a low-resistance, high-capacitance vascular bed specialized for bidirectional gas exchange with the environment. The systemic circulation consists of multiple, relatively high resistance vascular beds specialized for the delivery of oxygen and nutrients to tissues and extraction of carbon dioxide and metabolic waste products. Blood is a solvent that dissolves and transports the substances required for and produced by metabolic processes. It travels sequentially through the two circulations and is pumped by two highly adapted pumps in series. The latter are combined in one organ, the heart, that is under coordinated local and neurohumoral control. Each side of the heart is composed of two chambers, a thin-walled atrium that accepts venous blood from its respective circulation and also has a booster pump function and a thicker-walled ventricle that pumps the blood to its respective circulation.

A key aspect of the cardiovascular system is that it must function under a wide variety of demands. Thus, during the stress of exercise, the amount of blood pumped, the *cardiac output* (CO), must increase fourfold or more.[1,2] Extremes of temperature (e.g., during exercise) require that the cardiovascular system function to maximize heat loss or conservation. Beat-to-beat variations in loading of the heart related to normal functions such as respiration require exquisitely fine tuning of the stroke volume (SV) produced by each side of the heart. Moreover, the system has little or no room for error; even a slight, sustained mismatch of left- and right-sided SV would result in a catastrophe. This chapter reviews the cellular and organ-level cardiac and vascular mechanisms nature has devised to accomplish these tasks.

CARDIAC FUNCTION

The Cardiac Cycle

As a departure point, we begin this section by considering the sequence of events that occur at the organ level during the course of a single heartbeat, or cardiac cycle (Fig. 3-1, Plate 27). Before mechanical activity begins, an electric signal is delivered to the myocardium (see Chaps. 11 and 23). Electrical signaling is accomplished by specialized conduction system tissue that controls heart rate (HR) by responding to a variety of influences (especially sympathetic and parasympathetic stimulation), provides a normal sequence of activation of the heart chambers that in turn maximizes efficient contraction and filling, and at the cellular level, initiates the biochemical processes that underlie contraction. With respect to HR, conduction system cells have the general property of undergoing spontaneous electrical depolarization and thereby functioning as pacemakers that control the rate of beating. The sinus node, located in the right atrium (RA) near the superior vena caval junction, is the component of the conduction system that has the fastest rate of spontaneous depolarization and therefore provides normal control of HR. It is under the direct influence of the autonomic nervous and neuroendocrine systems, which modulate beat-to-beat and longer-term variations in HR.

At the body surface, activity of the specialized conduction system and spread of the electric impulse is represented by the electrocardiogram (ECG), which is caused by electrical potential differences generated by the heart (see Chap. 11). At the cellular level, electrical excitation consists of transmission of a membrane-based depolarizing and then repolarizing current called the *action potential* (AP) that is propagated through the cardiac chambers via the specialized conduction system, ultimately reaching

individual atrial and ventricular myocytes.

The electric signal (AP) begins in the sinoatrial node and then traverses specialized conduction tissue in both atria, spreading to atrial myocytes and causing atrial contraction (the P wave of the ECG). The atrial conduction system tissue then converges at the atrioventricular node region, consisting of the atrioventricular node itself and the more distal His bundle. These structures are located in the junctional tissue where interatrial and interventricular septa meet. The atrioventricular node is an area of relatively slow conduction that is responsible for most of the normal delay between atrial and ventricular contraction (the PR interval of the ECG). A properly timed delay maximizes the booster pump function of the atria and also protects the ventricles from excessively rapid stimulation. From the His bundle, electrical excitation spreads through large, intraventricular fascicles, the left and right bundles. The left bundle branches into two smaller branches, the left anterior and posterior fascicles. Both bundle-branch systems then ramify within the ventricular myocardium. The smallest branches of the specialized conduction tissue are Purkinje system fibers. The electric signal is transmitted from the Purkinje fibers to individual ventricular myocytes, which contract following a series of cellular events described below. Depolarization of ventricular myocardium accounts for the QRS complex of the ECG. Within the myocardium, the AP spreads from myocyte to myocyte through specialized structures called *intercalated disks,* which contain low-resistance gap junctions across which current flows preferentially. The left ventricle (LV), most massive of the cardiac chambers, is the largest source of electrical potential differences. Electrical activation of the LV begins in the interventricular septum, spreads toward the anteroapical region, and reaches the posterobasal portion last. Activation of the right ventricle (RV) begins slightly after the LV.

This pattern of normal electrical activation causes a coordinated sequence of contraction and relaxation of the cardiac chambers, resulting in ejection of blood by the ventricles into the aorta and pulmonary artery (PA), followed by relaxation and filling. The fact that interference with the normal electrical activation sequence almost always adversely affects cardiac function is strong evidence that normal activation is also the most efficient.

By convention, the mechanical cycle (see Fig. 3-1) is considered to begin at ventricular end diastole (ED), the instant just before systole, when the ventricles begin to actively generate tension as signaled by a sudden, rapid rise in intraventricular pressure. Soon after ventricular systolic pressure begins to rise, it exceeds atrial pressure, at which time the mitral and tricuspid valves close. Ventricular pressures then continue to rise rapidly until aortic (Ao) and PA pressures are exceeded, resulting in opening of the Ao and pulmonic valves and onset of the period of *ejection* of blood into the systemic and pulmonary circulations. Between mitral/tricuspid valve closure and Ao/pulmonic valve opening, ventricular volume is constant. This phase of the cycle is termed *isovolumic* or *isovolumetric contraction*. As ejection proceeds, ventricular and Ao/PA pressures rise and then fall together. The Ao and pulmonic valves close, and ejection ends when ventricular pressure falls below Ao and PA pressure. This event is signaled by the *dicrotic notch* of the respective arterial pressures. In the LV, a period then ensues during which pressure continues to fall rapidly until it drops below left atrial (LA) pressure, when the mitral valve opens. Since Ao and mitral valves are closed during this period, volume is constant, and it is termed *isovolumic* or *isovolumetric relaxation*. Although pulmonic valve closure and tricuspid valve opening are shown as separated significantly in time in Fig. 3-1, the point at which RV pressure falls below PA pressure is actually so low (slightly above the point at which it falls below RA pressure) that the RV isovolumic relaxation period is almost nonexistent.[3]

The time when ventricular pressure falls below atrial pressure signals the onset of the *ventricular filling period*. (There is disagreement as to the best conceptual definition of the *onset of diastole*. One is that contraction and relaxation should be viewed as linked events. Diastole therefore does not begin until relaxation is complete. As will be seen, ventricular filling begins *before* relaxation ends. A second is that diastole begins when ventricular filling commences. A third is that diastole begins when the ventricular myocardium begins to relax, i.e., at about the time ventricular systolic pressure begins to fall. Each definition has merit, and there is no need to take sides in the debate.) Immediately after the atrioventricular (AV) valves open, there is rapid inflow of blood into the ventricles. The latter is caused by an AV pressure gradient (typically several millimeters of mercury) that develops immediately after the AV pressure crossover (Fig. 3-2). Ventricular pressure normally declines by at least several millimeters of mercury immediately after the onset of filling and then rises rapidly after reaching its minimum value. Following

this initial *rapid filling phase*, ventricular pressure plateaus, the AV gradient diminishes markedly, and filling slows and actually may come to a complete halt (*diastasis*). Slow filling is immediately succeeded by the final filling event, contraction of the atria, which results in a second increase in the AV gradient and injection of an additional bolus of blood into the ventricle. The increase in pressure caused by atrial contraction is the *a wave*. Because of its brief duration, it has relatively little effect on *mean* atrial pressure. Thus normal atrial pump function augments ventricular filling with little risk of an excessive increase in atrial pressure and attendant circulatory congestion. With a normal PR interval, ventricular contraction begins during atrial relaxation.

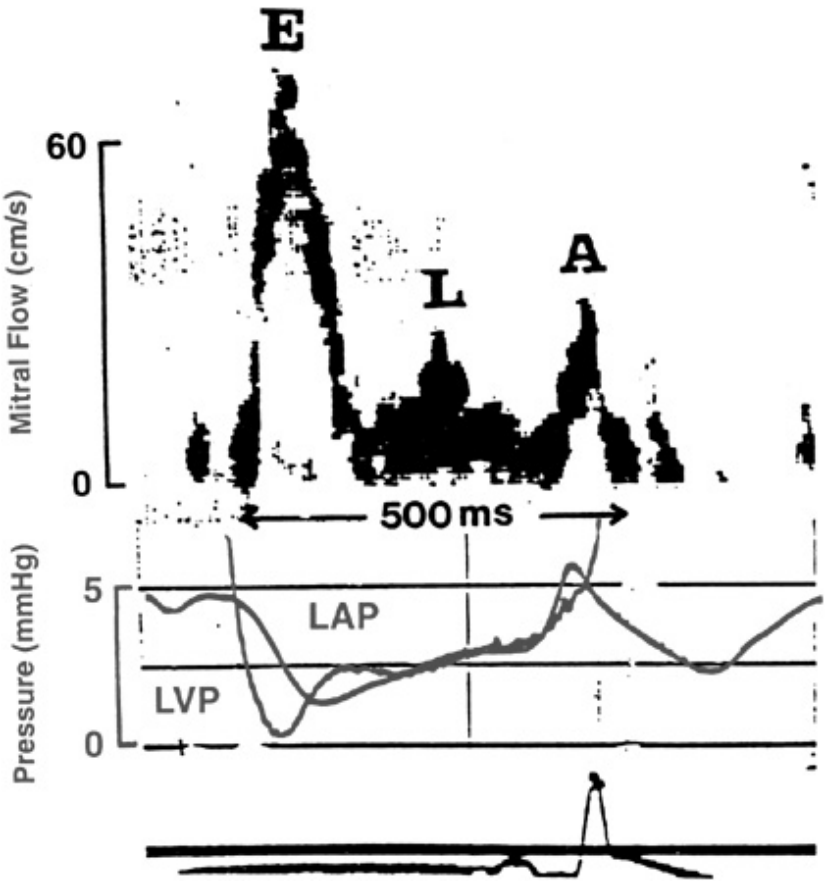


Figure 3-2: Mitral flow recorded with a Doppler probe in the mitral annulus and simultaneous LA (LAP) and LV (LVP) pressures in a dog. Note initial gradient immediately after LV pressure crosses LA pressure. As shown here, when recorded with high-fidelity manometers, this is typically followed by a brief reversal of the gradient and then, following the slow-filling phase, by atrial contraction and a second increase in the gradient. Note rapid, early transmitral mitral flow (E wave) and smaller contribution of atrial contraction (A wave). The record also reveals a middiastolic increase in flow (L wave) that is occasionally observed. (From Yellin EL, Nikolic SD. Diastolic suction and the dynamics of LV filling. In: Gaasch WH, LeWinter MM, eds. *LV Diastolic Dysfunction and Heart Failure*. Philadelphia: Lea & Febiger, 1994:92. Reproduced with permission of the publisher.)

Ventricular volume changes as a function of time are similar on the right and the left sides, except for the virtual absence of isovolumic relaxation on the right (see Fig. 3-1). Systolic pressure waveforms, of course, differ. The thick-walled LV generates a much higher pressure than the RV, reflecting the high-resistance systemic vascular bed. Pressure waveforms during filling are qualitatively similar in both ventricles but normally on the order of a few to as many as 7 to 8 mmHg higher in the left, reflecting the less distensible, thicker-walled LV chamber. Table 3-1 is a listing of hemodynamic values in normal adult human subjects.

Table 3-1: Hemodynamic Values in Normal Recumbent Adults

Measurement	Range	Mean
Cardiac index, liters/min per m^2	2.8-4.2	3.4
SV, mL/beat	30-65	47
Arteriovenous oxygen difference, mL per liter of blood	30-48	38
Intravascular pressure,[a] mmHg		
Brachial artery		
Systolic	90-140	-
Diastolic	60-90	-
Mean	70-105	85
LV		
Systolic	90-140	-
ED	5-12	-
LA or PA wedge		
Mean	5-12	-
PA		
Systolic	15-28	-
Diastolic	5-16	-
Mean	10-22	16
RV		
Systolic	15-28	-
ED	0-8	-
RA		
Mean	0-8	-
LV volume index (mL/m^2)		
ED	50-90	-
ES	15-25	-
Resistance, $dyn \cdot s/cm^5$		
Total systemic	900-1400	1150
Systemic arteriolar	600-900	850
Total pulmonary	150-250	200
Pulmonary arteriolar	45-120	70

[a]Baseline for pressure measurements one-half of anteroposterior chest diameter. 1 mmHg = 133.332; Pa = 0.133 kPa.

LA and RA pressure waveforms are also similar (see Figs. 3-1 and 3-2). Mean LA pressure is normally higher than RA pressure (upper limit of mean RA pressure is ~7 mmHg; LA, ~12 mmHg). The positive *a* wave resulting from atrial contraction is followed by a decline in pressure (the *x* descent) as the atria relax, during which time ventricular contraction begins. There is often an additional small positive wave, the *c wave*, superimposed on the *x* descent. Following the ventricular-atrial pressure crossover at the beginning of ventricular systole, atrial pressure initially continues to decline as atrial relaxation continues but then rises progressively during ventricular ejection, reaching a peak at time of the ventricular-atrial pressure crossover signaling the onset of AV valve opening and ventricular filling. This second positive atrial wave is the *v* wave, caused by passive filling of the atria while the AV valves are closed. Normally, the *a* wave is larger than the *v* wave in the RA, with the reverse in the LA. The *v* wave is followed by a second pressure decline, the *y* descent, that begins with AV valve opening and is more gradual than the simultaneous decline in ventricular pressure occurring at the onset of filling (see Fig. 3-2).

The most important beat-to-beat variation in loading of the cardiac chambers is caused by normal respiration. The inspiratory decrease in intrathoracic pressure causes a substantial *increase* in venous return to the right side of the heart and pooling of blood in the pulmonary circulation in association with a small decrease in venous return to the left side of the heart. As a result of the relative changes in left- and right-side heart filling during inspiration, RV SV increases in relation to LV SV. This prolongs RV ejection time and delays pulmonic valve closure, accounting for the inspiratory increase in splitting of the second heart sound (see Chap. 10).

The Cellular Basis of Cardiac Contraction

Cardiomyocytes may be considered to consist of three systems: (1) a sarcolemmal excitation system that participates in spread of the AP and functions as a switch initiating the intracellular events giving rise to contraction, (2) an intracellular excitation-contraction coupling (ECC) system that amplifies and converts the electric excitation signal to a chemical signal that, in turn, activates the (3) contractile system, a molecular motor based on formation of chemical crossbridges between two proteins, actin and myosin (Fig. 3-3).

EXCITATION SYSTEM

This system is also discussed in Chap. 23. The cellular AP consists of a transient, local transsarcolemmal depolarizing current that raises the transmembrane potential from its normal resting value of negative 80 to 90 mV to slightly positive values, followed by a depolarizing current that returns the potential to its resting value[4-6] (Fig. 3-4). The AP is initiated within the specialized conduction tissue and is propagated to individual myocytes. It results from a series of coordinated changes in the conductance of specific ionic species through variably gated sarcolemmal channels. The earliest and largest component of membrane depolarization is caused by a rapid, inward Na current. The resting potential is established and maintained by the transsarcolemmal Na-K-ATPase, which uses energy from ATP hydrolysis to pump Na ions out of the cytoplasm.

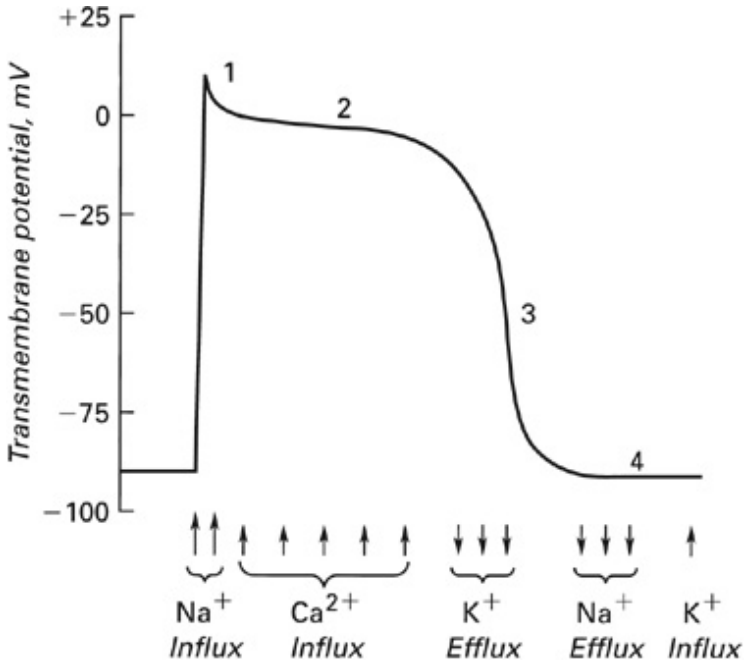


Figure 3-4: Phases of cellular AP and major associated currents in ventricular myocyte. Initial phase zero spike (not labeled) and overshoot (1) is caused by rapid inward Na current, the plateau phase (2) by slow inward Ca current through L-type Ca channels, and repolarization (phase 3) by outward K current. Phase 4 resting potential (Na efflux, K influx) is maintained by the Na-K-ATPase. Na-Ca exchanger is mainly responsible for Ca extrusion. In specialized conduction system tissue, there is spontaneous depolarization during phase 4 until the voltage resulting in opening of the Na channel is reached.

With respect to initiation of contraction, the most important component of the AP is a relatively *slow, inward Ca current* through voltage-sensitive, L-type (for long-lasting) Ca channels[5,7,8] (Ca^{2+} influx in Fig. 3-4). These channels open, and the current begins when transmembrane potential reaches -35 to -20 mV and, because of its slow kinetics, continues well after the Na current has ceased. The Ca current is mainly responsible for the AP plateau phase. It ceases when L-type channels become inactivated, and regenerative currents (mainly K efflux) begin the repolarization process. L-type channels, also termed *dihydropyridine (DHP)receptors,* are concentrated in invaginations of the sarcolemma called the *transverse-tubule system,* in close proximity to sarcoplasmic reticulum membrane-associated *ryanodine receptor* (RyR) Ca release channels (discussed below).

The AP results in a net movement of Ca ions into and a net movement of Na ions out of the cytoplasm. Ionic balance is restored mainly by another sarcolemmal ion-transport mechanism, the *Na-Ca exchanger*.[7,9-11] The exchanger is a shuttle that moves one Ca ion out of the cell against its concentration gradient while using energy from the Na gradient to move one Na ion into the cell. The exchanger also can function in so-called reverse mode, moving a Ca ion into the cytoplasm and a Na ion out.[9-11] Normally, the reverse mode does not contribute significantly to inward movement of Ca ions.

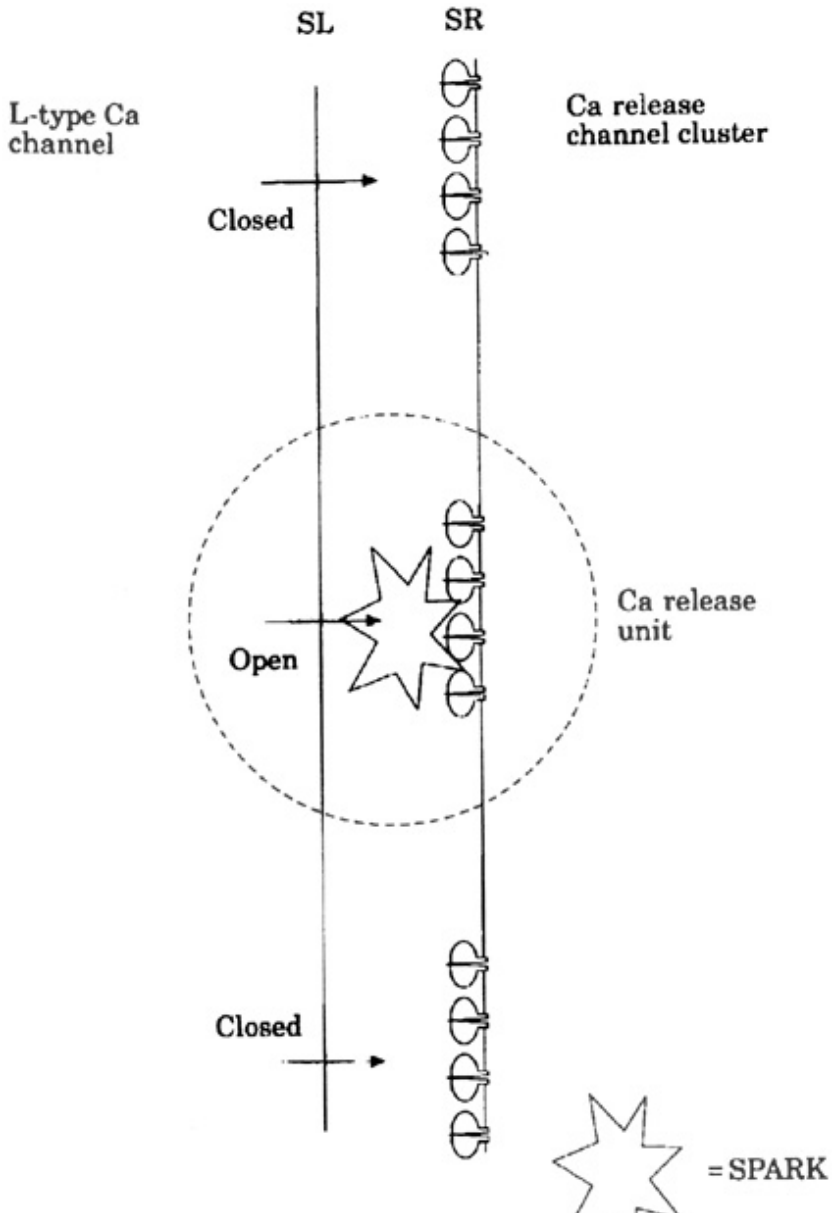
EXCITATION-CONTRACTION COUPLING SYSTEM

ECC is accomplished by the *sarcotubular system,* an arrangement of specialized sarcolemmal and intracellular membranes that functions to control and amplify the ability of the AP to switch the activity of the contractile system on and off. It does so by creating electrochemical signals between the sarcolemma and intracellular organelles; these signals occur much more rapidly than would be possible by simple diffusion of the signaling molecule (in this case, Ca ions).

The sarcotubular system consists of two main components, transverse or T-tubules and the sacroplasmic reticulum (SR)[7,12,13] (see Fig. 3-3). T-tubules are transverse invaginations of the sarcolemma that are concentrated at the Z line of the sarcomere (see below). The SR is a longitudinally oriented system of intracellular membranous sacs and tubules consisting of collar-like structures encircling the contractile

filaments at 1- to 2-μm spacings and forming repeating closed compartments that extend along the length of each myofibril from cross striation to cross striation. At the end of each collar is a bulge (*cistern*) that closely abuts a T-tubule, creating a *dyad* or sometimes a *triad* structure. The gap between the cistern and nearby T-tubule is bridged by structures called *feet*.

The SR contains a large store of Ca ions that are released into the cytoplasm as a result of a process termed *Ca-induced Ca release* (CICR)[7,8,14-21] that takes place within or near the dyad. At any point in time, the bulk of Ca ions within the SR is associated with binding proteins, for example, calsequestrin. The details of CICR have been illuminated by Ca "spark" studies employing Ca concentration-sensitive bioluminescent intracellular dyes in conjunction with confocal microscopy[17-21] (Fig. 3-5). As indicated earlier, DHP receptor Ca channels are concentrated in the T-tubule region forming the dyad. The adjacent SR membranes in the dyad contain Ca release channels (RyRs)[7,8,16,25] that bridge the cisternal membrane near the foot proteins of the dyad. When the AP depolarizes the cell membrane in the dyad region, the voltage-sensitive DHP receptor channel gate opens, allowing movement of Ca from the extracellular space across the sarcolemma into the gap region of the dyad. Nearby RyR channels are activated (opened) by the local rise in Ca concentration in the dyad,[7,25] resulting in very rapid release of much larger amounts of Ca ions from the SR cisternae into the cytoplasm (causing the intracellular Ca "spike" or transient[26] detectable with bioluminescent dyes) (Fig. 3-6). This large amount of Ca ions in turn activates the contractile system (see below).



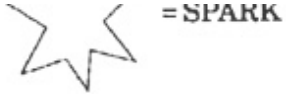


Figure 3-5: Schematic of Ca-induced Ca release from SR resulting in a Ca "spark." Opening of sarcolemmal (SL) L-type Ca channel results in movement of a relatively small amount of Ca ions into the cell. The latter causes opening of a number of nearby RyR channels (Ca release unit) with local release of a large amount of Ca ions from the SR and appearance of a "spark," as bioluminescent dye responds to change in local Ca concentration. (From Williams.[8] Reproduced with permission of the publisher.)

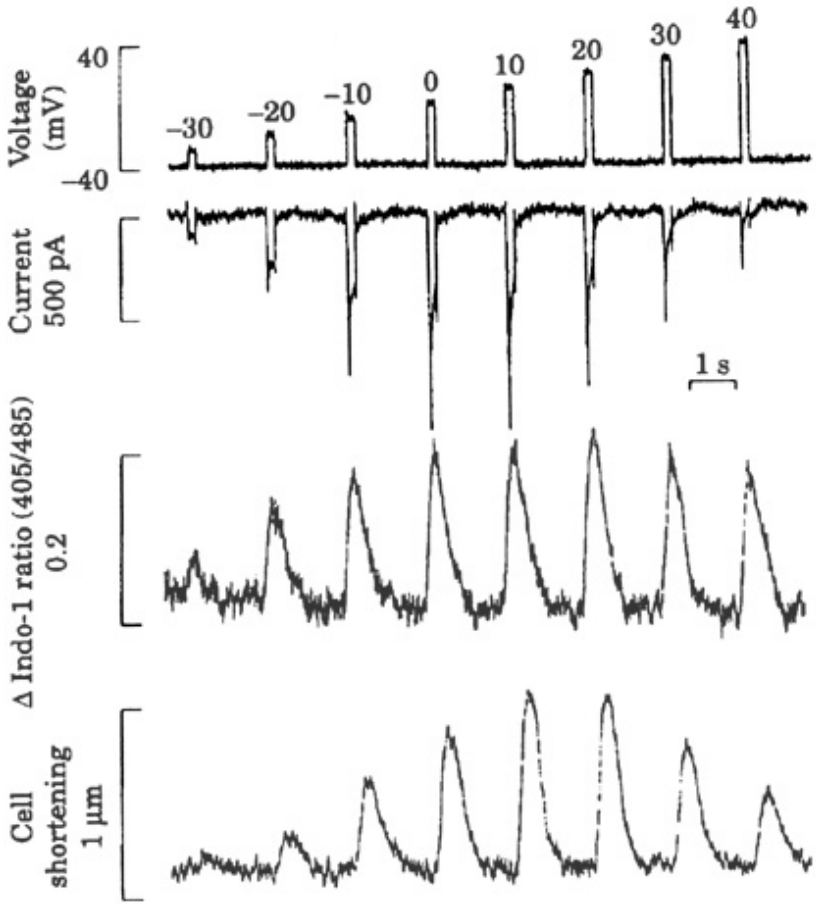


Figure 3-6: Intracellular Ca transient obtained with the bioluminescent dye Indo-1 is shown in the middle of this figure. It reflects the average instantaneous intracellular Ca ion concentration. The L-type Ca channel current modified by voltage clamping is shown in the top panel, and myocyte shortening is shown in the bottom panel. Note the voltage dependence of the Ca current and the parallel changes in both the Ca transient and shortening. (From Williams.[8] Reproduced with permission of the publisher.)

The amplification of Ca release inherent in CICR occurs because each DHP release channel induces release of Ca from more than one RyR channel (the exact number is unknown) and because of the very large Ca concentration gradient between the SR and the cytoplasm.[7,8,16,25] CICR results in an increase in the intracellular Ca concentration from a diastolic value of approximately 0.1 µ*M* to 1 to 10 µ*M* at the peak of the Ca transient. However, the actual amount of Ca released per beat constitutes only a small amount of the total stored (due to the binding proteins). The increase in intracellular Ca concentration is very transient because free Ca ions rapidly bind to the contractile proteins and are also removed from the cytoplasm by the Na-Ca exchanger and a specialized pump, the SR Ca ATPase (SERCA2).

In order for contraction to be turned off (i.e., for relaxation to occur), Ca ions bound to the contractile proteins must be returned to their storage sites in the SR, and the relatively small number that enter during the AP must be transported back to the extracellular space. As indicated earlier, the Na-Ca exchanger is

primarily responsible for extrusion of Ca out of the cytoplasm. There is also a sarcolemmal Ca pump that uses energy from ATP hydrolysis, but this does not appear to be an important means of Ca extrusion. The most important mechanism of reuptake of Ca ions by the SR is pumping by SERCA2, a SR membrane-spanning protein[7,13,27] (see Fig. 3-3). SERCA2 uses energy from ATP hydrolysis to rapidly pump the bulk of Ca ions released during CICR back into the SR. It competes with the contractile proteins and other potential uptake sites (Na-Ca exchanger, sarcolemmal ATPase, mitochondria) for Ca ions. Pump stoichiometry is two Ca ions for each ATP hydrolyzed. Functionally, Ca ions pumped back into the SR initially enter a "reuptake pool" and then move to a "release" pool.

The SERCA2 pump is partially self-regulating, since its speed increases in proportion to free Ca concentration (see below). It is also regulated by a closely associated SR protein, phospholamban (PLB), a key modulator of cardiac responses to adrenergic signaling.[28-33] PLB is a 52-amino-acid protein with a hydrophobic domain anchored in the SR membrane and a hydrophilic domain containing three phosphorylation sites. PLB inhibits SERCA2 activity, as exemplified by transgenic PLB knockout mice with increased basal cardiac contractility due to increased Ca cycling per beat but blunted adrenergic responses.[30,31] β-Adrenergic stimulation results in phosphorylation of PLB by activation of cyclic AMP-dependent protein kinase A (PKA). This reduces the inhibitory effect of PLB on SERCA2, resulting in increased Ca cycled per beat and an increased reuptake rate. These effects increase the rate and force of contraction as well as relaxation rate. (In addition to PLB phosphorylation, adrenergic stimulation of PKA also causes phosphorylation of L-type Ca channels,[8,15,34] resulting in increased transsarcolemmal Ca current and increased CICR via RyR channels.)

CONTRACTILE SYSTEM

The basic building block of the contractile system is the sarcomere[12] (Fig. 3-7), a recurring arrangement of the proteins responsible for mechanical activity. Adult myocytes are capable of increasing the numbers and changing the arrangement of sarcomeres in response to physiologic or pathologic changes in demands. An increase in sarcomeres in parallel increases force-producing capacity; an increase in series increases shortening capacity. Each sarcomere is composed of two bundles of longitudinally oriented filaments.[12] *Thick filaments*, approximately 1.6 μm long, are composed of myosin molecules in a trigonal array at the center of the sarcomere's length. Cardiac myosin is a member of a large family of myosins that function in various molecular motors. In addition to myosin, two other proteins are associated with the thick filament, titin and myosin-binding protein C. At each end of this array, a set of approximately 1-μm-long *thin filaments* composed of actin and the proteins tropomyosin (Tm) and troponin (Tn) interdigitates with the thick filaments. The other ends of the thin filaments extend to the ends of the sarcomere, where they attach to a transverse structure, the *Z-line*. The distance between sequential Z-lines is the sarcomere length. At a length of 2.2 μm (length at which maximal force is produced), the central end of each thin filament overlaps 0.7 μm of the distal ends of the thick filaments (the *overlap zone*). The 0.3-μm length of nonoverlapped thin filaments extending to the Z-line and the corresponding 0.3 μm of nonoverlapped thin filaments in the adjacent sarcomere constitute the *I-band*. The centrally positioned thick filaments constitute the *A-band*. Alternating A- and I-bands are responsible for the *striated* appearance of cardiac muscle. Thick filaments are joined at the *M-line* in the middle of the sarcomere.

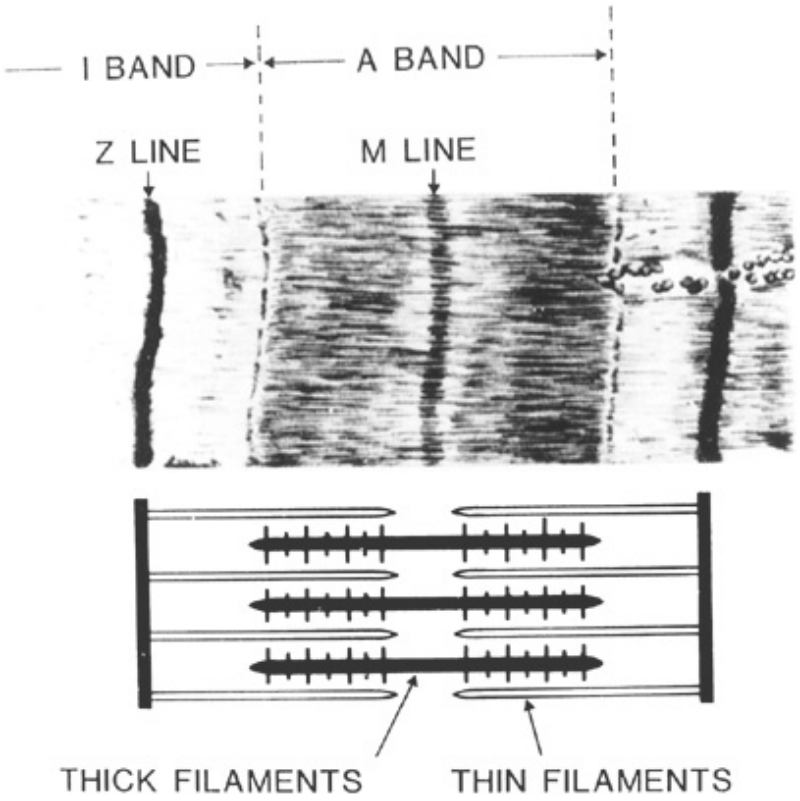


Figure 3-7: (*Top*) Electronmicrograph of sarcomere. (*Bottom*) Schematic (see text). (From Woledge et al.[58] Reproduced with permission of the publisher.)

As just indicated, a portion of each myosin molecule is oriented longitudinally to form the thick filament. In addition, a portion of the molecule protrudes from the thick filament surface and can move freely in the space between the thick and thin filaments (Fig. 3-8, Plate 28). This protruding portion includes the myosin *heavy chain* that forms the crossbridge, the molecular structure that interacts with actin and is responsible for conversion of chemical energy (high-energy phosphate bonds) to mechanical energy (force and motion).[35,36] The crossbridge head (myosin heavy chain) is a complex protein containing a domain that binds with actin and a site of ATPase activity.[37,38] Two auxiliary proteins (*light chains*) that have a role in maintaining the structural requirements for force generation (*essential light chain*) and providing fine control of force and motion (*regulatory light chain*) are adsorbed to the surface of the heavy chain. In mammalian cardiac muscle, myosin heavy chain exists primarily as two isoforms, alpha and beta.[37] The alpha isoform has higher ATPase activity and more rapid rates of crossbridge formation and velocity than beta and is dominant in adult small mammals.[38-42] The beta isoform is dominant in adult large mammals, including humans. Titin is a giant protein anchored in the Z-line on one end and closely associated with myosin on its other end.[43] A segment of titin has springlike properties and is an important determinant of the passive viscoelasticity of the myocyte[43,44] and, in turn, the ventricle. When cardiac muscle contracts below its slack, or unstressed, length, titin is compressed and recoils to its rest length.[43,44] This *restoring force* may have a role in diastolic suction (see below). Myosin-binding protein C is bound to both myosin and titin. It appears to have a role in sarcomere assembly and also may modulate myosin ATPase activity by virtue of variations in its phosphorylation.[45]

Actin monomers are arranged in a double helix to form the core of the thin filament[46-48] (Figs. 3-8, '3-9"">Plate 28, and). Tm is adsorbed longitudinally along the thin filament. Each molecule spans seven actin monomers, with a short overlap segment at the ends of adjacent Tms. Tn, composed of three subunit proteins, TnC, TnI, and TnT, is adsorbed on Tm, also in a ratio of 1 per 7 actin monomers. TnC contains a Ca-binding site, TnI variably binds to Tm and TnC (depending on activation), and TnT links Tn to Tm at the overlap zone. The combined Tm-Tn complex is responsible for the ability of Ca ions, binding to TnC, to act as a switch initiating crossbridge formation. TnI and TnT, the myosin regulatory light chain, and myosin-binding protein C all have phosphorylatable sites (mainly serines and threonines).[48,49] Phosphorylation of these contractile proteins, especially TnI and TnT, modulates the activity of myosin

ATPase, as described below.

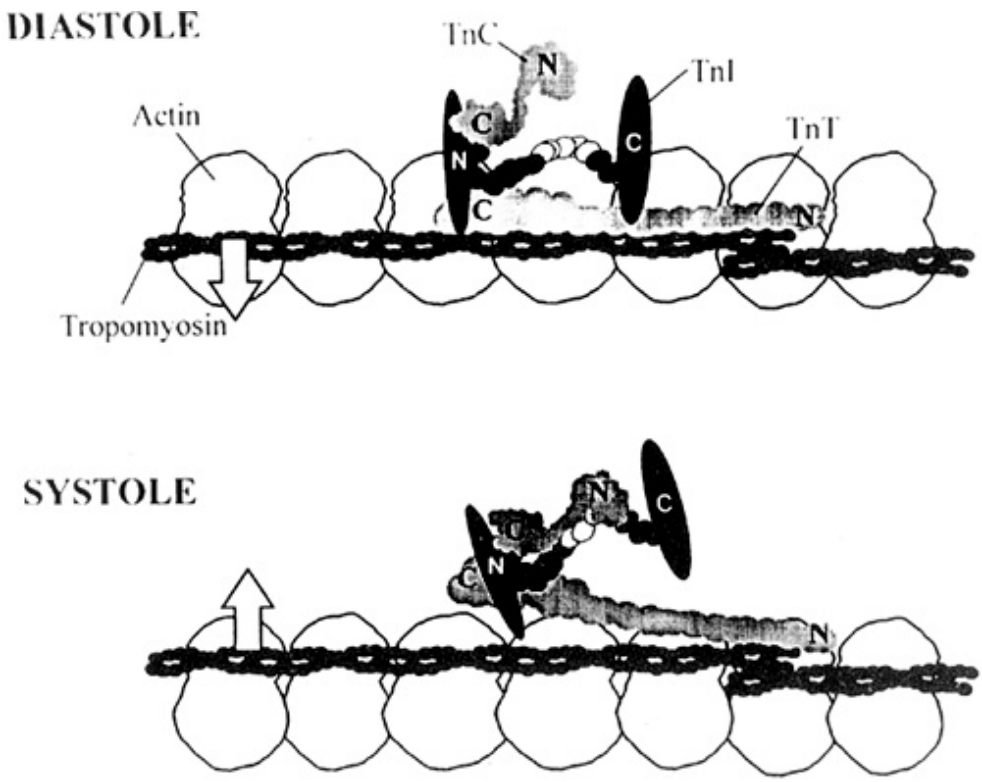


Figure 3-9: Cartoon of the thin filament with actin and regulatory proteins, Tm and Tn complex, showing conformational differences between inactive state (diastole) and activation (systole). C, COOH terminus; N, NH_2 terminus. (From Solaro and Rarick.[48] Reproduced with permission from the publisher.)

The sequence of events that ensues when the contractile system is activated by Ca ions entering the cytoplasm as a result of CICR may be summarized as follows[46-48] (see Fig. 3-9): In diastole, with low Ca concentration, Tm occupies a position on actin that inhibits interaction between actin and myosin. Strong binding between TnI and Tm appears to be responsible for maintaining this position. In the *steric blocking* model of Huxley,[50] it was hypothesized that in diastole Tm physically blocks any actin-myosin interaction; i.e., crossbridges are detached. It now appears that the situation is more complex.[48,51,52] At diastolic Ca concentrations, crossbridges exist in both a truly detached or *blocked* state and a weakly attached, non-force-producing state. Moreover, it is proposed that weakly attached crossbridges exist in two states, *closed* and *open*, depending on variations in the position of Tm on actin. With activation, Ca ions bind to TnC and cause a complex rearrangement of the Tn complex, with the most important element probably being a switch to strong binding of TnI to TnC rather than to Tm. The latter, in turn, causes a change in the position of Tm on actin that releases inhibition of actin-myosin interaction and, in addition, probably directly influences the kinetics of crossbridge formation by increasing the rate of transitions from the various non-force-producing to force-producing states.

Two other factors appear to be important in this process of *thin filament activation*. One is *nearest-neighbor interactions*[47,48] along the actin monomers, such that binding of Ca to Tn causes the process of crossbridge formation to spread down the thin filament (perhaps to as many as 12 to 14 adjacent monomers). This property appears to be related to activation-induced structural changes in TnT and Tm. The second is strong binding of actin to myosin,[48,53,54] which begins to occur once inhibition of the actin-myosin reaction is relieved. In and of itself, strong binding seems to encourage additional thin filament activation. Under most physiologic conditions, systolic Ca concentration does not achieve a level resulting in maximum force and/or shortening; i.e., the muscle is *submaximally* activated. Cardiac muscle is also highly cooperative; i.e., the relation between Ca concentration and force/shortening between diastolic and maximally activated

levels is very steep (Fig. 3-10). This property is thought to be due to both nearest-neighbor interactions and strong actin-myosin binding. Functionally, this means that contractile reserve can be recruited with modest changes in Ca concentration.

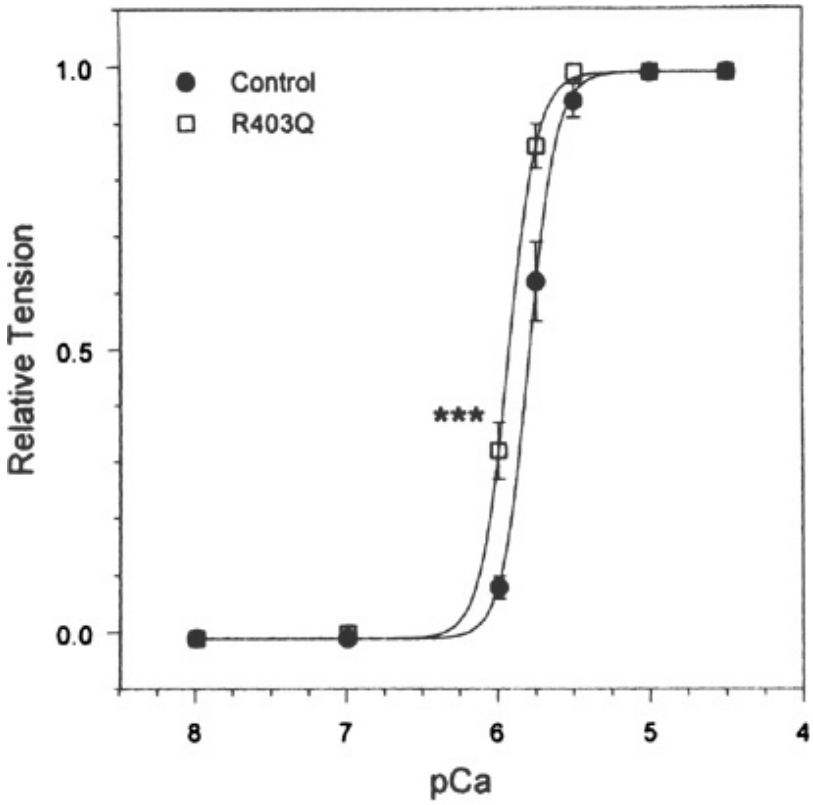


Figure 3-10: Relation between log Ca concentration (pCa) and isometric tension in detergent-treated ("skinned") strips of mouse cardiac muscle. R403Q indicates a transgenic animal with a mutation causing hypertrophic cardiomyopathy; control is wild type. Skinning results in loss of integrity of the sarcolemma and all intracellular membranes, leaving sarcomeric proteins intact. In skinned strip, the ionic milieu of the contractile proteins can be manipulated and their behavior studied in isolation from the excitation and ECC systems. Note very steep relation between isometric tension and pCa between relaxing (pCa >7) and fully activating Ca concentrations (pCa 5) in both strips. The relation is shifted to the left in R403Q mice. (From Blanchard E, Seidman C, Seidman JG, et al. Altered crossbridge kinetics in the αMHC403/+ mouse model of familial hypertrophic cardiomyopathy. *Circ Res* 1999; 84:475. Reprinted with permission of the publisher.)

Regardless of the details of thin filament activation, when Ca binds to TnC, the crossbridge cycle is switched on, and actin and myosin undergo a chemical reaction powered by ATP hydrolysis in which a series of transitions are made from detached/weakly bound states to force-producing states and back.[35,36,38,55-59] ATP hydrolysis actually occurs in conjunction with the transition from force production back to detached/weakly bound states. Energy released from hydrolysis of one high-energy phosphate bond is stored in the form of a molecular conformational change in the head of the crossbridge. While the myosin head is strongly bound to actin on the activated thin filament, conformational energy is released, causing the myosin head to rotate slightly as would the oar of a rower seated on the actin filament (Fig. 3-11). This motion generates a force propelling the thin filament along the thick filament toward the center of the sarcomere. The essential light chain appears to function as a lever arm between the thick and thin filaments. This process occurs repeatedly and randomly at millions of actin-myosin crossbridges, causing large-scale force and/or motion generation.

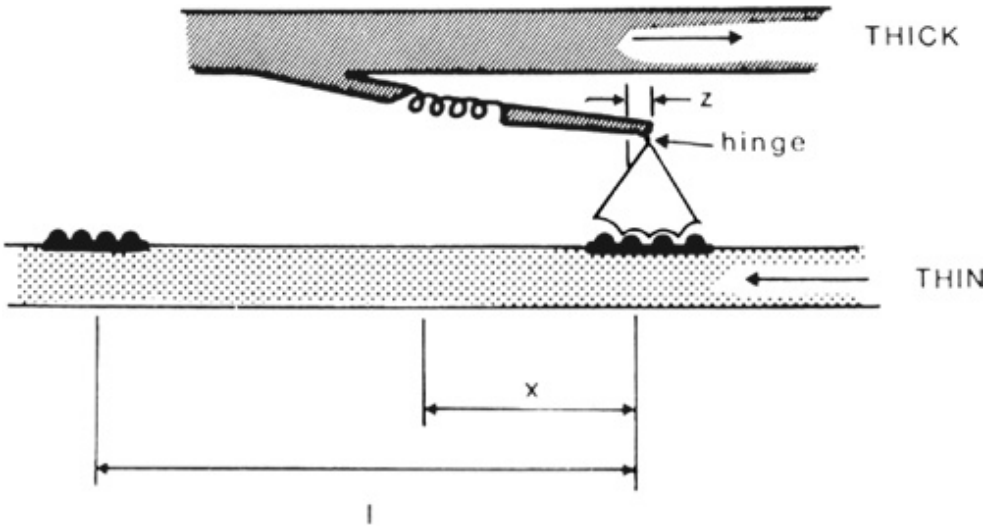


Figure 3-11: Schematic of the mechanical interaction between the myosin head (triangular structure) and actin located on the thin filament. Letter *z* denotes the distance moved by the thick filament as a result of rotation of the head region (see text). (From Woledge et al.[58] Reproduced with permission of the publisher.)

The amount of force and/or shortening that occurs as a result of crossbridge formation is related to the restraints, or *load*, placed on the muscle.[58-60] If no external restraining force is applied (i.e., *afterload* is zero), crossbridges propel the filaments at the maximum speed their chemical reactions permit, and a maximum amount of displacement and work are performed with no force generation. This is termed *unloaded shortening*. If shortening is opposed by an external load, such as during a physiologic contraction, crossbridge motion is slowed, allowing time for force to develop and more crossbridges to find binding sites on the thin filaments. At the other extreme, an *isometric* contraction in which the muscle is so restrained that there is no external shortening or work (i.e., afterload is greater than can be overcome by the ability to shorten), crossbridge energy is used almost exclusively for force development. This tradeoff between force and motion is reflected in the hyperbolic shape of the force versus velocity relation and the parabolic shape of the power or work versus load relation determined in isolated cardiac muscle (Fig. 3-12). There is also a reciprocal relation between load on the muscle and crossbridge cycling rate.[58-60] That is, the speed of the chemical reactions driving crossbridge attachment and detachment is sensitive to load and/or the resulting strains or displacements within the sarcomere. The mechanism of this relationship is uncertain, but it is a fundamental property of cardiac muscle that is required for normal function.

Another key determinant of mechanical performance of an activated sarcomere is its initial length, as reflected by the initial length of the muscle (its *preload*)[48-50,61,62] (Fig. 3-13). Force (or shortening) is maximal at an initial sarcomere length of approximately 2.2 μm and falls off very rapidly below approximately 2 μm. The ascending length-active tension/force relation is mainly caused by changes in activation of crossbridges as a function of sarcomere length.[61,62] This is most likely related to the fact that because the sarcomere maintains a constant volume, thick and thin filaments move farther apart at shorter sarcomere lengths.[63] The resulting change in geometry causes a decrease in the effective activation at any concentration of Ca; i.e., fewer crossbridges are formed. This *length-dependent activation* is the primary mechanism at the sarcomere level of the Frank-Starling law of the heart, i.e., the increase in contractile performance as ventricular preload increases. Previously it was thought that the Frank-Starling relation was best explained by changes in thick and thin filament overlap,[35,55] but the latter is probably a modest contributor at best. Although a *descending limb* of the length-tension relation is evident in isolated muscle, it does not appear to be present in the intact ventricle.

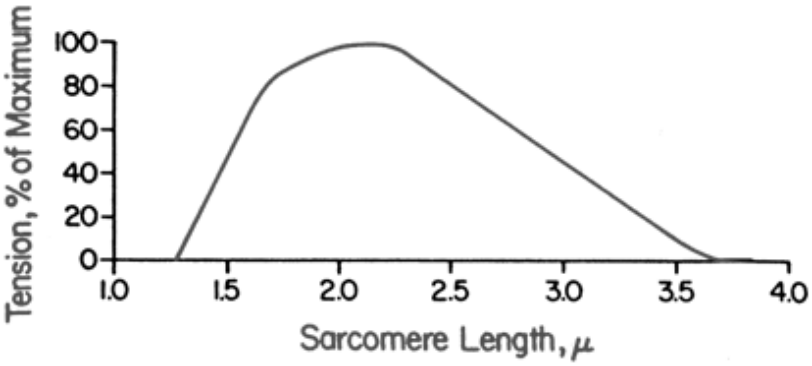


Figure 3-13: Schematic of relation between sarcomere length and developed tension (or force). Note fall in tension at lengths below approximately 2.2 μm. At very long sarcomere lengths, thick-thin filament overlap is reduced, resulting in descending limb of relation (not observed in ventricle). (Modified from Braunwald E, Ross J Jr, Sonnenblick EH, eds. *Mechanisms of Contraction of the Normal and Failing Heart*. Boston, Little, Brown, 1976:77.)

MYOCYTE RELAXATION

Myocyte relaxation is a complex process whose rate is determined by three main factors: the kinetics of crossbridge cycling (particularly the rate at which the crossbridges transition from a force-producing to a non-force-producing state), the affinity of Ca ions for TnC, and the activity and affinity of the main Ca reuptake and extrusion mechanisms.[64,65] All else being equal, slower kinetics of crossbridge cycling, increased Ca affinity for TnC, and reduced activity of SERCA2 and/or the Na-Ca exchanger slow relaxation. Relaxation is also modulated by the load on the myocyte, at least in part because of the aforementioned dependence of crossbridge cycling kinetics on load. As noted previously, relaxation also may be influenced by restoring forces generated by compression of titin.

ENERGY METABOLISM AND MECHANOENER-GETICS

Myocytes are heavily dependent on oxidative metabolism and endowed with large numbers of mitochondria. Under basal conditions, myocytes preferentially take up and oxidize fatty acids to generate ATP.[66-68] During stress, however, glucose uptake, glycogenolysis, and glycolysis become increasingly important. Certain ion pumps, e.g., SERCA2, may be especially dependent on glycolytic ATP.[69] Nitric oxide (NO) generated by vascular endothelium decreases myocardial oxygen consumption (VO_2) due to a direct effect on mitochondrial respiration, and may have a significant role in normal control of energy production and utilization.[70-72]

The processes that account for the great majority of myocardial energy consumption are crossbridge cycling (myosin ATPase), Ca reuptake by the SR (SERCA2), and basal metabolism.[59] Each crossbridge cycle consumes one high-energy phosphate bond, although at very rapid cycling rates it may be possible for one ATP to fuel more than one cycle. SERCA2 uses one high-energy phosphate bond for every two Ca ions pumped. As indicated earlier, the rate of energy consumption is heavily dependent on loading conditions and resulting work and power generation.[58,59] The thermodynamic efficiency of heart muscle, its total mechanical energy output divided by its total chemical energy input, is uncertain, in large measure because of difficulties in quantifying *total* energy output. A more conventional approach is estimation of efficiency of external work production.[58] External work efficiency is heavily dependent on loading conditions, ranging from a maximum under unloaded conditions to zero for an isometric contraction. Additional mechanoenergetic concepts are discussed below under ventricular function.

Cellular Control of Contractility

This section is divided into intrinsic and extrinsic control systems. *Intrinsic control* includes adaptive mechanisms that are components of the normal mechanical behavior of cardiac muscle. *Extrinsic control* includes both adaptive mechanisms that require the elaboration/secretion of a cardioactive substance by the myocyte or some other cell type and classic neurohumoral modulation of myocyte function.

INTRINSIC CONTROL SYSTEMS

The most obvious is the *length-dependent activation* underlying the Frank-Starling relation. This allows heart muscle to adjust its performance on a beat-to-beat basis, e.g., with respiration and changes in body position, and is discussed further under ventricular function.

Another important intrinsic control mechanism is the *force-frequency relation* (FFR)[73-75] (Fig. 3-14). At a basal rate of 60 per minute, the duration of the myocardial twitch contraction is such that relaxation would be incomplete at rates achieved during exercise and cause impaired diastolic filling. Therefore, the myocardium must have mechanisms that automatically speed contraction and relaxation at rapid rates. In conjunction with this abbreviation of contraction, the strength of contraction is markedly enhanced, allowing maintenance of SV even though less time is available for filling and emptying. The mechanism of the positive FFR involves increased and more rapid Ca cycling per beat as frequency increases.[8,59,76-79] Factors contributing to this include the direct effect of a greater number of APs per unit time, causing intracellular accumulation of Ca ions, as well as increases in SR Ca pumping. Thus Ca entry increases directly with more frequent opening of L-type Ca channels and indirectly when the Na-Ca exchanger extrudes excess Na ions arising from the increased frequency of sarcolemmal Na channel opening. Operating in isolation, these factors would risk elevation of diastolic Ca concentration. However, SR Ca pump speed increases concomitantly, increasing relaxation rate and abbreviating the contraction. In addition to PLB, SERCA2 activity is under the control of another protein, *Ca-activated calmodulin kinase*, which increases SERCA2 activity in response to increased Ca concentration and has built-in frequency sensitivity. Slight, transient increases in Ca ions, even if insufficient to directly activate the kinase, are held in binding sites long enough so that repeated increases are summated. This averaging process results in increased speed of the SERCA2 pump in response to increased average and instantaneous Ca concentration.

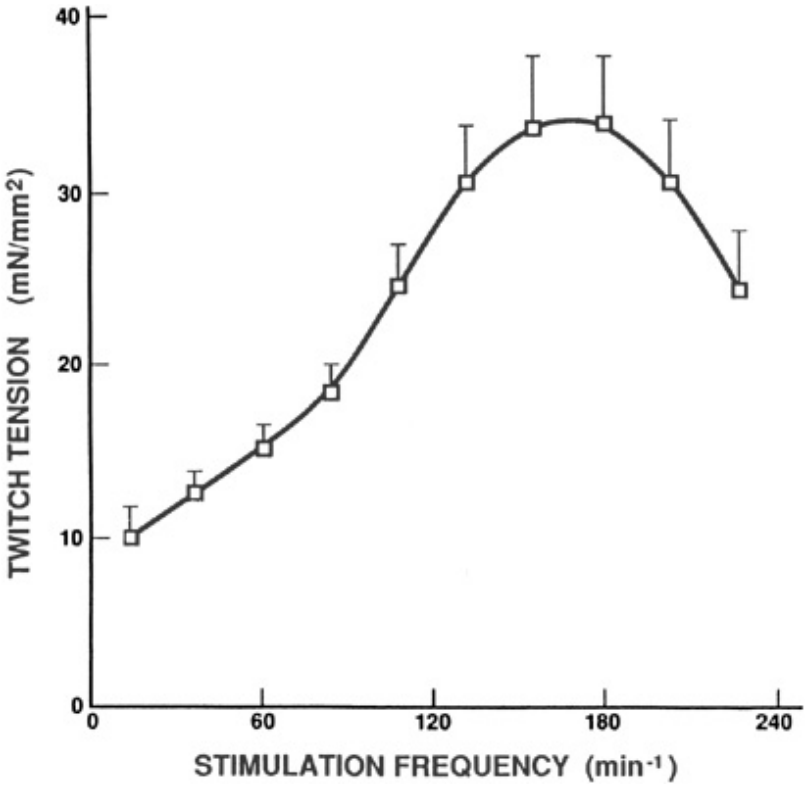


Figure 3-14: Example of average relation between developed force and stimulation frequency in strips of human myocardium obtained by epicardial biopsy from a group of patients undergoing coronary bypass surgery, all with normal LV contraction patterns. Note the marked increase in force as contraction frequency increases from typical basal level of 60 per minute to a value of 170 to 180 per minute, at which force is maximal (see text).

The FFR appears to depend on the intactness of multiple elements of Ca handling, as evidenced by the fact that it is depressed in a number of conditions in which the myocardium is diseased and/or subjected to chronic stress.[73,74,76,80] The ratio of SERCA2 pumps to PLB protein has been proposed as an important determinant of its magnitude.[77] Moreover, the FFR is markedly amplified by increased β-adrenergic stimulation.[75] Thus, during stress, increased adrenergic stimulation not only increases HR but also increases the magnitude of FFR occurring in response to the increase. This amplification appears to be related to cyclic AMP-mediated phosphorylation of PLB.[30]

EXTRINSIC CONTROL SYSTEMS

The best understood, most extensively characterized and important extrinsic control mechanism is modulation of contractility by adrenergic and cholinergic neural discharge and circulating catecholamines.[75,81-85] Increased adrenergic stimulation markedly increases contractile strength, relaxation, and HR. These effects on the myocardium may be explained as follows: Normal myocytes contain predominantly β_1 receptors, with a minority of β_2 receptors. Agonist binding to β_1- or β_2-adrenergic receptors on the surface of the cell membrane results in an interaction between membrane-associated G protein and guanosine triphosphate (GTP) in which GTP combines with active subunit G_s, which activates enzymatic conversion of ATP to cyclic AMP by *adenylate cyclase* on the cytoplasmic side of the receptor complex. Cyclic AMP in turn activates PKA, which phosphorylates both the L-type Ca channel, altering its gating to allow more Ca ion entry per AP, and PLB, which increases SERCA2 pumping. This results in more rapid removal of Ca from the contractile proteins (faster relaxation), a larger amount of Ca cycled per beat (increased activation), and potentiation of the FFR. PKA also phosphorylates TnI, resulting in decreased Ca affinity for TnC, an effect that also facilitates relaxation. Increased cholinergic stimulation decreases contractility, possibly by activation of nitric oxide synthase-3 (NOS-3) (see below). Cholinergic stimulation, though, has a much weaker influence on contractile performance than adrenergic stimulation. Cholinergic responses are important modulators of HR, however.

A number of other naturally occurring substances modulate myocyte function. These include circulating neurohormones as well as molecules produced by myocytes themselves and vascular endothelium. Alterations in these substances and their effects on myocardial function may be critically important in disease. The normal physiologic roles of these substances have been variably and in no case fully delineated, but they are almost certainly less important than the intrinsic and extrinsic control systems already discussed. Accordingly, some but not all will be discussed briefly. These substances and their complex signaling pathways are also discussed in Chaps. 5 and 6.

NO is produced in endothelial cells in proximity to cardiac myocytes and in myocytes themselves.[70-72,86,87] NOS-3 is the predominant form of nitric oxide synthase in the myocyte. NOS-3 is Ca-sensitive and is activated by levels of intracellular Ca achieved during normal beating and by muscarinic cholinergic agonists. NO produced in the myocyte or in adjacent endothelium has a negative inotropic effect, mediated via cyclic GMP.[72,86,88] The mechanism appears to involve myofilament desensitization to Ca, possibly via protein kinase G phosphorylation of TnI. NOS-3 activation also blunts catecholamine responses. Inflammatory cytokines also activate NOS-3,[88] an observation that may be important in disease. Endothelial-derived NO may have somewhat different effects than myocyte-derived NO. Thus endothelial-selective, NO-dependent vasodilators cause early and somewhat accelerated relaxation with only a modest negative inotropic effect. Although effects of NO on contractile performance have been observed in normal humans, their physiologic significance is uncertain. *Atrial natriuretic peptide* (ANP) and *brain natriuretic peptide* (BNP) produced in atria and ventricles, respectively, are naturally occurring vasodilators and diuretics. These substances appear to have effects on myocyte function similar to endothelial-derived NO. While increased secretion of these hormones has great significance in heart failure, their role in normal physiologic control of myocyte function also has not been defined.

A number of agonists, including α_1-*adrenergic agonists*,[89] *endothelin-1* (ET-1),[90-92] and *angiotensin II* (ATII),[93-95] influence myocyte function through activation of phospholipase with resulting production of inositol triphosphate (IP_3) and diacylglycerol (DAG).[96-98] (It is now well established that the heart has its

own ATII-generating system.[93-95]) IP_3 increases the release of intracellular Ca during contraction through as yet poorly understood mechanisms. DAG appears to be more importantly involved in myocyte functional responses. Its effects are mediated through activation of protein kinase C (PKC).[96-100] The effects of DAG and PKC activation have been somewhat controversial. This may be related to the fact that the effects of DAG or its analogs administered intracellularly (the normal "route") differ from those when they are administered extracellularly.[98] On balance, activation of PKC by the preceding agonists appears to result in a complex, slowly appearing, sustained positive inotropic effect. Mechanisms that may account for this effect are increased intracellular Ca due to phosporylation of L-type Ca channels and PLB. In addition, phosphorylation of the sarcolemmal Na-H exchanger may increase contractility by increasing intracellular pH. However, activation of PKC also has distinctive and contrasting effects on the contractile proteins via phosphorylation of both TnT and TnI.[47,48,101] The result is a reduction in myofibrillar ATPase activity with attendant decreases in crossbridge cycling rate, an effect that by itself would reduce measures of contractility such as rate of tension development or shortening, as well as relaxation rate. The integrated response to agents such as ET-1 is a net positive inotropic effect that may be relatively economical with respect to energy consumption because of the concomitant effects on crossbridge cycling.

Structure and Function of the Ventricles

ARCHITECTURE

The human LV is a thick-walled chamber (average approximately 1.0 cm at ED) with a truncated ellipsoid shape composed of spiraling, sheetlike layers of myocyte bundles (Fig. 3-15). The orientation of the bundles changes from subepicardium to subendocardium, progressing from relatively longitudinal (in relation to the long axis of the ellipsoid) to roughly circumferential fibers occupying about the middle two-thirds of the wall to longitudinal fibers once again in the subendocardium.[102] Regional wall thickness parallels the local radius of curvature. Near the apex, where the radius is small, thickness is relatively small. Variations in thickness may function to equalize regional wall stress.

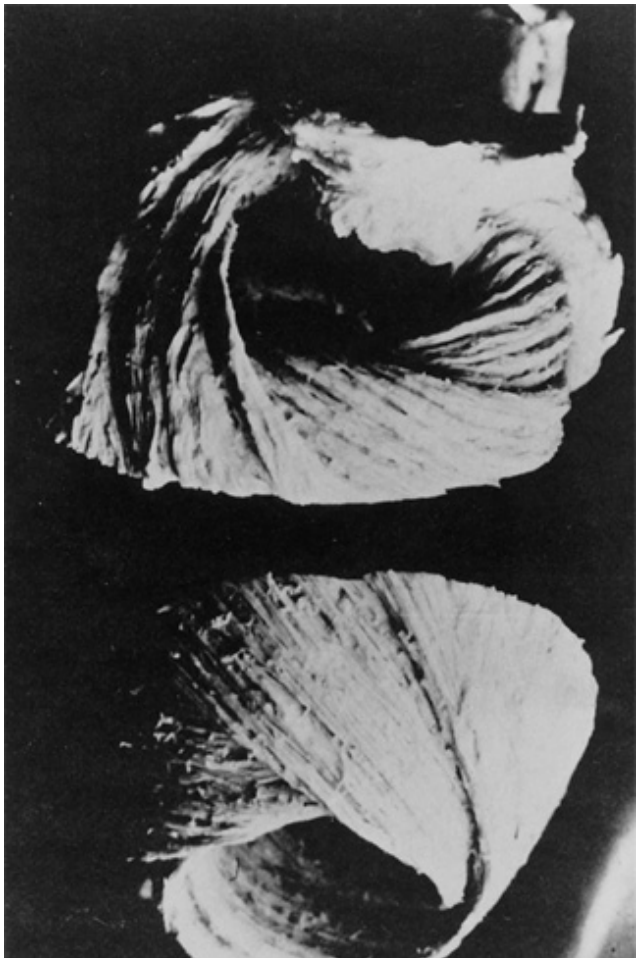


Figure 3-15: Three-dimensional architecture of LV, illustrating spiraling bundles of myofibers (see text). (From Streeter.[102] Reprinted with permission of the publisher.)

Contraction of the LV is associated with a wringing motion, or torsion, characterized by a counterclockwise rotation that progressively increases from base to apex.[103] Torsion is important for normal ejection and is an inherent feature of the normal spread of excitation and the connections between the fiber bundles.[104] It also is likely a storage mechanism for potential energy generated during systole that is converted to kinetic energy during diastole, assisting filling by suction.[105] This complex architecture results in efficient conversion of the shortening of individual myocytes and fibers to wall thickening, which is ultimately responsible for ejection of blood. Thus, even though individual fibers shorten only about 10 percent, the normal LV ejects about two-thirds of its ED volume. Interventricular septal fibers have a similar orientation and are continuous with those of the LV free wall. As a result, the septum normally functions as a part of the LV; i.e., during contraction, its endocardial surface undergoes more or less symmetric inward movement toward the center of the LV.

In line with the high-capacitance/low-resistance nature of the pulmonary vascular bed, the RV is much thinner-walled than the LV (3 to 4 mm in an adult human) and appears crescentic in cross section.[102] Its contraction has been likened to that of a bellows. The RV inflow and outflow portions are functionally distinct, with inflow contraction preceding outflow contraction.[106] A significant fraction of the mechanical output of the RV appears to be related to energy transfer from the LV through the interventricular septum (systolic ventricular interaction).[107] This is supported by the observation that destruction of much of the free wall of the RV is remarkably well tolerated.

Ventricular myocardium also has a well-developed connective tissue matrix.[108-110] Cardiac collagen is organized into a weave of fibers that forms a netlike structure around the myofibers (groups of six or more myocytes), as well as connections that link adjacent myofibers and strutlike projections connecting to adjacent blood vessels. The latter may function to help maintain vessel patency during contraction. The collagen network of the ventricles is an important determinant of their passive filling properties (see discussion below). The last major component of the ventricles is the vascular bed, described below.

THE VENTRICLE AS A PUMP

Normal pumping of the ventricles requires that they deliver appropriate amounts of blood to the tissues at acceptably low filling pressures (FPs). Thus the most physiologically relevant means of characterizing the pump is to construct a *function curve* relating FP to a measure of mechanical output (SV, minute volume, work, power). Ventricular function curves display a prominent *Frank-Starling effect*, manifest as a curvilinear relationship between FP and output (once again, there is no descending limb in the normal ventricle) (Fig. 3-16). As discussed earlier, at the myocyte level, the Frank-Starling effect is mainly caused by increased myofilament Ca sensitivity at longer sarcomere lengths. Thus a function curve relating ED *volume* (ventricular *preload*) to mechanical output is a more accurate representation of the ventricular Frank-Starling effect. However, in the clinical setting, FP (pulmonary capillary wedge or RA pressure) is usually more readily available than volume. Whether FP or volume is employed, changes in intrinsic contractile performance result in upward or downward shifts of the ventricular function curve. However, characterization of ventricular performance in terms of function curves relating FP to output is a "black box" approach; alterations in diastolic compliance (see below) produce effects that are indistinguishable from alterations in contractile performance.

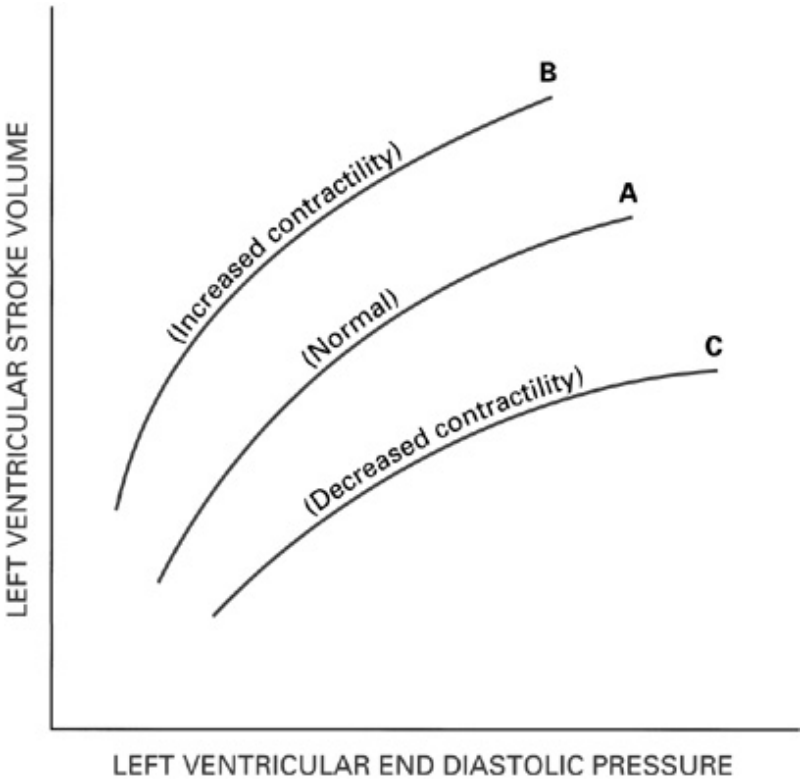


Figure 3-16: LV function curves relating SV to ED pressure (see text). *A*. Normal function. *B,C*. Augmented and depressed contractility, respectively, as occur with increases or decreases in adrenergic stimulation. Because ED pressure is plotted, identical shifts could be observed with altered diastolic compliance.

The normal heart can pump adequate amounts of blood to meet the needs of the body under the most stressful conditions. Indeed, maximal CO normally is not limited by pumping capacity but by the ability of the systemic circulation, via venoconstriction and the systemic venous system of valves and muscular pumps, to return blood to the heart.[111] Under pathologic conditions, pumping capacity may limit CO.

THE VENTRICLE AS A MUSCLE

For convenience, it is useful to consider contraction (systolic performance) as distinct from relaxation and filling (diastolic performance). This distinction is arbitrary, however. The two aspects of function overlap and interact.

Systolic Function

Systolic performance of the ventricle traditionally is characterized in terms of loading conditions (preload, afterload) and contractility.[112] Although *contractility* is a term that is employed frequently and often perfectly reasonably, it is difficult to define. We use it here as a *comparative concept* to connote differences in the intrinsic level of contractile performance either before or after some intervention *in the same heart* or *between different hearts* that cannot be accounted for by differences in loading conditions. Thus one way to define a change or difference in contractility is as a change or difference in contractile performance when loading conditions are unchanged or can be accounted for, e.g., increased shortening despite increased afterload. Unfortunately, this is often impossible in the intact heart, especially in the clinical setting. Further, any definition of contractility that attempts to neatly separate it from loading conditions inevitably encounters the fundamental problem that the two are not really separable. A good example of this problem is the Frank-Starling relation, in which *preload* influences *intrinsic* contractile performance by modulating myofilament Ca sensitivity. Similarly, afterload, by influencing shortening, determines instantaneous length and myofilament Ca sensitivity during the course of contraction. Thus, while contractility is a useful concept, the notion that it is possible to define *load-independent* contractility indices is not entirely realistic.

Loading Conditions and Contractile Performance

In classic, isolated muscle experiments,[58,60] a force in the form of a weight is applied to one end of a quiescent, quasi-linear muscle (e.g., a cardiac papillary muscle) whose other end is tethered (Fig. 3-17). This force is the *preload*, which stretches the muscle to some initial length preceding contraction. The muscle is then simulated electronically to contract and lift an additional weight, the *afterload*. Once stimulated, the muscle develops tension or force until it just meets and then slightly exceeds the opposing force of the afterload. At this point in time, the muscle can begin to lift the afterload, and shortening commences. In this system, once shortening begins, the developed force and afterload are constant (*isotonic* contraction). Force or afterload is reciprocally related to the magnitude and velocity of shortening; muscle performance is often characterized as the force-velocity or force-shortening relation (see Fig. 3-12), with upward or downward shifts reflecting changes in contractility. If both ends of the muscle are tethered, or if the afterload simply exceeds the force-generating capacity of the muscle, an *isometric* contraction ensues, in which tension is generated, but no shortening occurs. By varying the preload, the Frank-Starling effect (see Fig. 3-13) can be delineated by relating the initial length to shortening (isotonic contraction) or developed tension or force (isometric contraction).

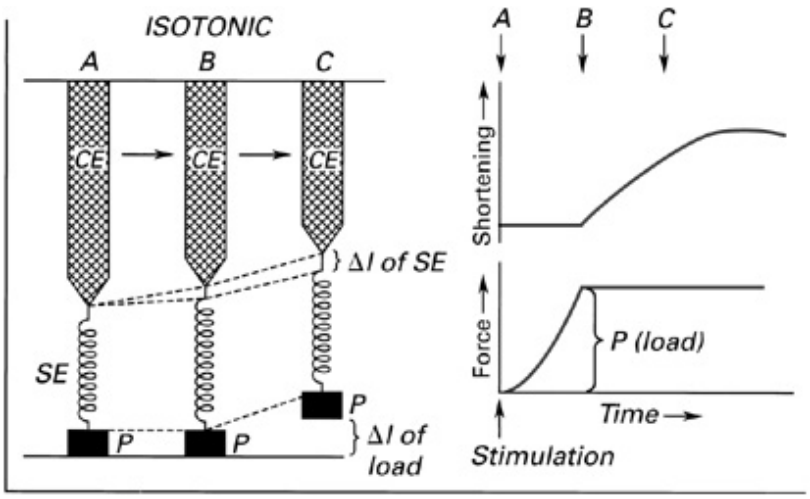


Figure 3-17: Schematic illustrating concept of preload and afterload during isotonic contraction. (*Left*) Linear muscle is depicted as consisting of contractile element (CE) (i.e., thick and thin filaments) and spring in series (SE). (*Right*) Shortening and force are depicted. *A*. Muscle is at rest, with one end tethered and the other connected to a weight (P). P is supported, however, so that muscle is only subjected to a fraction of weight (or load). This relatively small load is the preload, which stretches the muscle to the initial, resting length. *B*. Muscle begins to contract. In order to shorten, it must lift the entire weight P, which is the afterload. Initially, force increases but is insufficient to lift the weight. During this period, the CE shortens and reciprocally lengthens the SE, while total muscle length remains constant. Eventually, the developed force just exceeds the afterload, and the muscle begins to shorten (*C*). Once shortening begins, force is constant and essentially equal to the afterload. In an isometric contraction, the muscle cannot lift the load and therefore does not shorten (although the CE shortens and SE lengthens by the same amount).

In isolated muscle, load also can be expressed as *stress* (force normalized to cross-sectional area). Normalization allows comparison of muscles of different size. Normalization for stress can be transferred to the ventricle, most easily the LV because of its relatively symmetrical shape. Estimation of LV wall stress can be accomplished by using the LaPlace relation.[113] For a relatively thick-walled sphere, the LaPlace relation states that the average wall stress equals (pressure × internal radius) divided by twice the wall thickness. Variants of this equation can be employed to account for the actual shape of the LV, fiber orientation, and other geometric and structural features. Thus, for an ellipsoid, the ratio of the long to short axis (a measure of how ellipsoidal the shape is) modifies the stress; as shape changes from less to more spherical, wall stress increases.

Use of the LaPlace relation allows an estimate of the stress "seen" by the myofibers as the ventricle fills and

then contracts against its afterload. In diastole, the stress applied to the myofibers constitutes their preload and determines initial length at the beginning of the next contraction. During contraction, the stress resulting from both the preload and the afterload (or systolic load) determines the velocity and extent of ejection. Total systolic load presented to the LV by the vascular system has two components, a resistive load determined at the level of small systemic arteries and arterioles by microvascular tone and a smaller capacitive load determined by the properties of the large arteries, which absorb a certain amount of blood pumped via expansion of their walls.[114] As mentioned earlier, a component of vascular load is caused by reflection of pressure waves back to the heart from the periphery. In contrast to classic, isolated muscle experiments, during ventricular contraction, both afterload and developed wall stress vary.

Estimates of *systolic* stress using the LaPlace relation are helpful clinically in assessing and comparing contractile performance.[115] This can accomplished by relating some measure of shortening [e.g., ejection fraction (EF), defined as SV/ED volume] or shortening velocity [e.g., mean velocity of circumferential fiber shortening (V_{cf}); see discussion below] to a measure of systolic stress [e.g., peak, end-systolic (ES), or mean]. The ventricle behaves in a qualitatively similar fashion as isolated muscle; i.e., afterload (wall stress) is reciprocally related to shortening. As shown in Fig. 3-18, the stress-shortening relation can be characterized in a normal population with single data points obtained invasively or using noninvasive techniques such as echocardiography and cuff sphygmomanometry. If the value in a given patient falls above or below the normal range, this may indicate an alteration in intrinsic contractile performance.

Clinically, the most commonly employed index of ventricular contractile function is the EF (from angiography, echocardiography, or radionuclide ventriculography). Fractional shortening (minor axis diameter shortening/ED minor axis diameter) is calculated routinely from the echocardiogram and is interchangeable with EF, provided there are no regional wall motion abnormalities. Both these shortening measurements are sensitive to alterations in preload and afterload.[112] Thus normal values are indicative of normal intrinsic contractile function only if loading conditions are also normal.

Elastance Concepts in the Assessment of Ventricular Contractile Function

As an alternative to characterization of systolic function in terms of stress and shortening, Suga and Sagawa proposed an elastance approach.[116-118] This is based on the empirical observation that during systole the ventricle behaves like a spring with a time-varying elastance (or stiffness) that increases from a minimum at ED to a maximum at ES (Fig. 3-19). The elastance of a spring is the slope of the linear relation between the stress or force applied to stretch it and its length normalized to its unstressed or rest length. A "stiffer" spring requires a larger stress to extend it by a given length. By analogy, ventricular elastance is the relation between pressure and volume at any time during systole normalized to a volume at which the pressure is zero (*dead volume*, V_0 or V_d).

At any time during contraction, elastance can be estimated by varying loading conditions and generating a series of pressure-volume loops with varying ES volumes. In their original studies, Suga and Sagawa used isolated, perfused canine ventricles with controlled loading conditions and volumes.[116,117] Analysis of such a series of pressure-volume loops (see Fig. 3-19) reveals that at any time *t* during *each of the series of variably loaded contractions* (e.g., 100 ms after the start of contraction), the relation between pressure and volume is linear, and its slope reaches a maximum (maximal elastance) at ES, or t_{max}. (The volume axis intercept can be measured directly or extrapolated from the linear pressure-volume relation at any time *t*.) Elastance then decreases as the ventricle relaxes. The slope (E_{max}) of the end-systolic pressure-volume relationship (ESPVR) changes with acute positive and negative inotropic interventions. Specifically, E_{max} increases with positive inotropic interventions and decreases with negative inotropic interventions, whereas V_0 usually does not change. Based on these observations and initial studies suggesting that ED volume did not influence the ESPVR, it was thought initially that E_{max} offered the possibility of an index of contractility that was "load independent." Subsequent studies, especially those performed in the in situ heart and circulation, have modified these original conclusions.[118] Thus the ESPVR is often significantly curvilinear, especially with augmented or depressed contractility. Furthermore, as expected based on the concept of length-dependent activation, it is influenced to some extent by preload (ED volume) and also can be modified by the way in which afterload is varied (e.g., resistive versus capacitive load change).

Systolic interaction also can modify the ESPVR.[119] E_{max} must be used with caution in comparing different hearts because of difficulties in normalizing ES relationships for size and variable curvilinearity. To overcome these problems, the ESPVR has been modified by calculating ES myocardial stiffness based on wall stress estimates, and comparative analyses have been devised that take curvilinearity into account.[115,120-123] Last, the pressure-volume approach does not include rate of change of these parameters and therefore does not capture power output,[58,112] an important aspect of performance.

Despite the aforementioned cautions, the ESPVR has proven to be a useful conceptual approach to assessment of contractile function in the experimental laboratory and the clinic. Measurements have been made in hearts as small as that of the mouse,[124] whereas estimation of ES pressure and/or stress-volume relations can be obtained in patients.[115,125] Although it corresponds to only a single point on the ESPVR, the ratio of systolic arterial pressure (as a surrogate for ES pressure) to ES volume determined *noninvasively* using cuff sphygmomanometry and echocardiography also has been used as an index of ventricular function. Moreover, despite the empirical nature of the original observations, the elastance approach has been shown to be very consistent with the molecular physiology of ECC and crossbridge cycling.[126]

Two extensions of elastance theory have proven valuable in understanding ventricular function. The first is its application to ventricular *mechanoenergetics*.[127] The main determinants of VO_2 traditionally have been considered HR, afterload, and contractility (basal metabolism accounts for a significant fraction of VO_2 but is not subject to much variability). HR is obviously a critical determinant of energy consumption per unit time. However, the difficulty in even defining contractility was discussed earlier. Moreover, it is not obvious how contractility or afterload is related *quantitatively* to the two major energy-consuming processes in heart, ECC and crossbridge cycling.

As proposed by Suga,[127] use of elastance theory to quantify mechanoenergetics is based on quantification of the *total mechanical energy* of contraction. Total mechanical energy consists of two components (Fig. 3-20, top), *external work* (EW), which can be quantified as the area enclosed within the pressure-volume loop of a contraction, and *potential energy* (PE), which is dissipated as heat during relaxation and possibly also converted to kinetic energy used for filling the ventricle by suction (see below). To understand PE in this context, consider an isovolumic contraction, which can be produced experimentally. Such a contraction obviously generates mechanical energy, but none of it is EW; i.e., it is all PE. As afterload is reduced and shortening and work increase, the ratio of EW to PE increases. The novelty of elastance theory in quantifying total mechanical energy is that it provides a basis for quantifying PE. In elastance theory, the PE stored in a spring is the area under its elastance relationship between its rest length and its actual length. Correspondingly, in the ventricle, PE for any beat can be considered the area under the ESPVR between its ES point and V_0 (see Figs. 3-19 and 3-20). The sum of EW and PE is total mechanical energy and is termed *pressure-volume area* (PVA). The relation between PVA and VO_2 requires knowledge of the ESPVR and can be delineated by widely varying loading conditions while measuring LV VO_2. This is done most easily in isolated, perfused heart preparations.[123,127,128] PVA has a remarkably high linear correlation with VO_2 in several species, under a variety of loading conditions, and in both normal and abnormal hearts[123,124,127,128] (see Fig. 3-20, bottom).

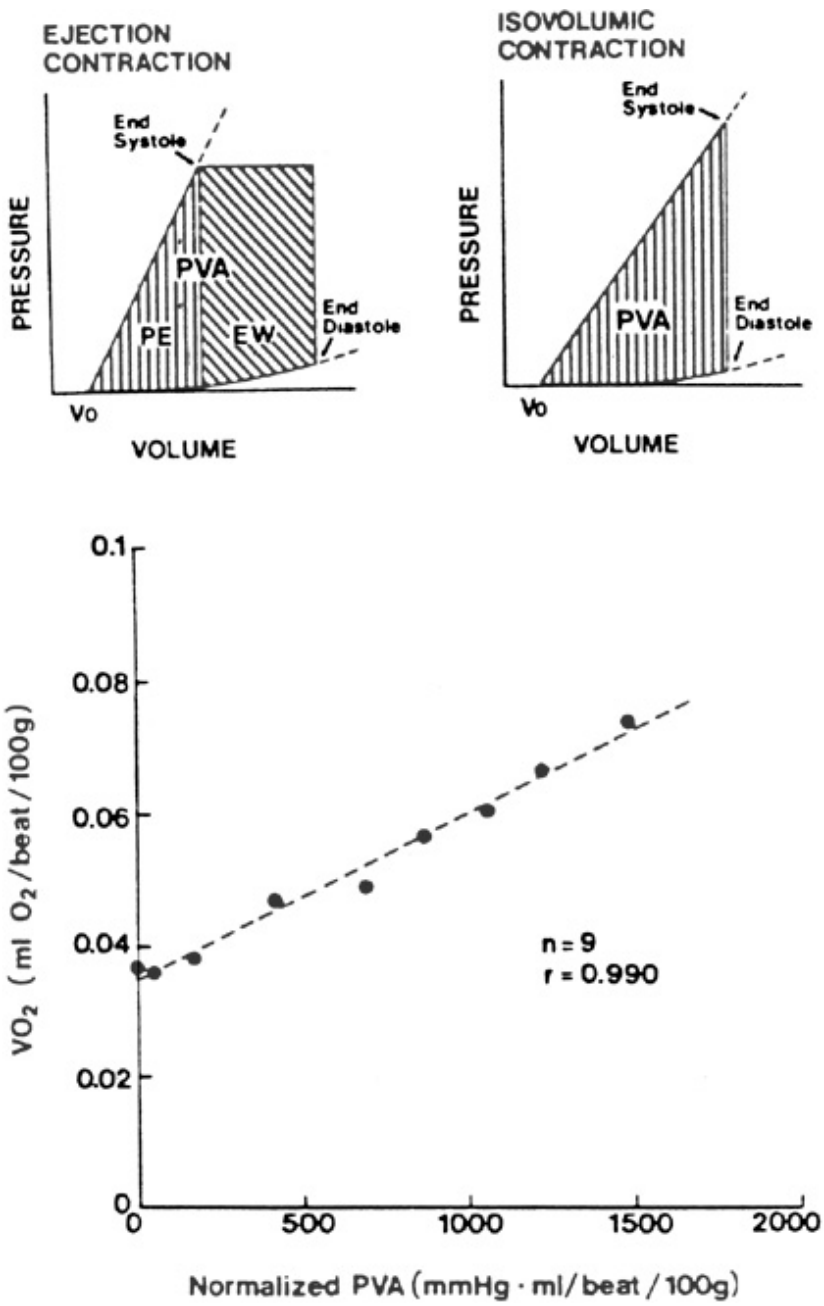


Figure 3-20: (*Top*) Schematic of VO_2-PVA concept (see text). In ejecting contraction, PVA = EW + PE; in isovolumic contraction, PVA = PE only. (*Bottom*) Correlation of PVA with VO_2. (From Goto et al.128 Reproduced with permission of publisher.)

The linear VO_2-PVA relation has a positive VO_2 axis intercept (see Fig. 3-20), unloaded VO_2, or O_2 consumption at zero PVA, when virtually no mechanical energy is produced. Unloaded VO_2 is largely accounted for by basal metabolism and Ca pumping by SERCA2, which continue under unloaded conditions. Subtraction of unloaded VO_2 from total VO_2 provides an estimate of VO_2 used by the contractile machinery, or PVA-dependent VO_2. Since VO_2 can be converted to units of energy, the ratio of PVA to PVA-dependent VO_2 (total mechanical energy output divided by total chemical energy input), or simply the inverse slope of the linear VO_2-PVA relation, is an estimate of the *efficiency* of conversion of O_2 to mechanical energy by the contractile machinery. Variations in myosin ATPase activity modulate efficiency assessed in this fashion.[124,129]

Based on the preceding analyses, it can be understood how changes in afterload and contractility as well as preload can alter myocardial energy demands and consumption (see Fig. 3-20). Assuming no change in ED volume or afterload, increased contractility increases E_{max}, resulting in a smaller ES volume and increased

EW at any preload. Even though ES volume is smaller, which in and of itself decreases PE, this is at least partially compensated by increased E_{max}, which serves to increase the area under the ESPVR. The net result is increased PVA in association with more energy used for crossbridge cycling by the contractile machinery. Most positive inotropic interventions increase the amount of Ca cycled per beat and, in turn, energy consumption by SERCA2, resulting in increased unloaded VO_2. Increased afterload increases the level of pressure at which the pressure-volume loop intersects the ESPVR, increasing PE with variable effects on EW but a net increase in PVA. In the whole LV, increases in preload have not been considered to markedly alter myocardial energy demands. Assuming constant contractility (ESPVR) and afterload, it is evident that changes in ED volume (preload) should modify EW and therefore PVA and VO_2 in direct proportion to the magnitude of the change. However, it is likely that under basal conditions the LV operates at an ED volume not too far from the point at which the diastolic pressure-volume relation becomes relatively steep. Thus there is not a great deal of room for the LV to acutely increase its preload (although its FP certainly may increase considerably). This may explain the modest effect of preload on VO_2.

A second application of elastance theory is ventricular-vascular coupling.[130,131] Just as the ventricle can be considered in terms of an elastance relationship, systemic arteries also can be characterized by an elastance relationship. Arterial elastance is largely a function of the properties of the large arteries. There exists an optimal relationship between ventricular and arterial elastance at ES such that energy transfer from the heart to the periphery is most efficient; i.e., the largest possible proportion of total mechanical VO_2 is converted to EW. In essence, this merely states that arterial loading influences the point at which the pressure-volume loop intersects the ESPVR and therefore the proportion of PVA converted to EW. The normal heart and vascular system operate at nearly optimal ventricular-vascular coupling. Vasoactive drugs can influence ventricular-vascular coupling. Moreover, in heart failure, coupling is adversely affected, resulting in less efficient transfer of energy from the heart to the vascular system.[132]

Other Approaches to Assessment of Systolic Ventricular Performance

Following is a sampling of a number of indexes that have been proposed to assess systolic function. Maximal rate of pressure rise (max *dP/dt*) is very sensitive to changes in intrinsic contractile performance but also varies somewhat with preload.[133,134] It is not markedly influenced by changes in afterload. Max *dP/dt* is especially useful in quantifying acute changes in contractility. Its use for comparisons between different patients is limited by large interindividual variations. *Mean circumferential fiber shortening* velocity (V_{cf})[135,136] is LV internal minor axis shortening ÷ (ejection time × ED minor axis dimension). It is readily calculated from echocardiograms. Although quite sensitive to changes in afterload (as is any shortening measurement), it is a useful measure of intrinsic contractile performance if afterload is normal or can be accounted for. *Maximal ventricular power index*[137] is attractive because of its physiologic importance; i.e., it takes into account both the work done by the ventricle and the time over which it is generated. This index has been normalized to minimize effects of loading and has the potential for noninvasive determination. Two empirical indexes have been devised that appear to be relatively afterload-insensitive. One of these is preload recruitable stroke work,[138] the relationship between ED volume (or strain) and stroke work. The other is the relationship between ED volume and max *dP/dt*.[139,140] Both are linear and in essence representations of the Frank-Starling relation; by incorporating ED volume, length-dependent activation is an intrinsic component of these indexes.

Diastolic Function

In addition to meeting widely varying physiologic demands for blood flow, the heart must do so at levels of FP that do not result in circulatory congestion. This requires a normal sequence of relaxation and filling. Ventricular relaxation begins at about ES (defined as the time of maximal elastance, slightly before Ao valve closure), continues through isovolumic relaxation, and does not reach completion until after AV valve opening. Before filling commences, several factors combine to determine relaxation rate, represented by isovolumic pressure decline (Fig. 3-21). After filling begins, but before relaxation is complete, other factors related to the level of ventricular volume and/or the rate of ventricular volume change also influence ventricular diastolic pressure. Once relaxation is complete, the so-called passive properties of the ventricle dominate the relation between pressure and volume as filling continues through ED.

During isovolumic relaxation, pressure falls exponentially. The rate of isovolumic pressure fall (a measure of relaxation rate) therefore has been quantified as a time constant (τ)[141,142] or simply the time to reach one-half of some starting value ($T_{1/2}$, typically measured beginning at peak negative *dP/dt*).[143] Peak negative *dP/dt*, maximal rate of pressure fall, also has been used but is less accurate. The determinants of the rate of isovolumic pressure fall are as follows:[65,141,142,144] First, as discussed earlier, myocyte relaxation rate is determined by the balance between the avidity of the contractile proteins for Ca and the rate at which SERCA2 and other uptake and extrusion mechanisms remove Ca from the contractile proteins and restore the cytoplasmic concentration to normal diastolic levels. In some pathologic conditions, e.g., certain types of ischemia, diastolic Ca may not be restored to normal.[145] Relaxation is therefore incomplete, and crossbridge cycling continues during diastole, resulting in increased diastolic tension. Isovolumic relaxation is also modulated by the load on the myocardium.[141,142,144,146150] Increased afterload through all of systole or beginning early in systole (*a contraction load*) results in delayed relaxation. Changes in load occurring late during systole (*a relaxation load*) cause opposite effects. Although changes in relaxation load may be considered to be of theoretical interest only, this may not be the case. Normal arterial waves reflected from the periphery return to the ventricle at about ES and may function to accelerate relaxation. When arteries become noncompliant, e.g., with aging, reflected waves return earlier and therefore may be converted to a contraction load, with delay of relaxation. Last, a normal temporal and spatial activation sequence results in the most rapid relaxation rate.[151]

As soon as ventricular pressure falls below atrial pressure, filling commences. As noted earlier, the magnitude and rate of ventricular filling are determined by the instantaneous AV pressure gradient (see Fig. 3-2). It is self-evident that the gradient is determined by properties of both ventricle and atrium. Immediately after AV valve opening, the rapid period of filling begins in association with a gradient of several millimeters of mercury (see Fig. 3-2). This corresponds to the E wave of mitral inflow measured with echocardiographic-Doppler techniques. During rapid filling, both ventricular and atrial pressures initially fall, but ventricular pressure falls faster than atrial pressure. Ventricular pressure soon reaches a minimum and then increases throughout the rest of diastole. The peak AV gradient occurs at or near the time of minimum ventricular pressure. (As noted earlier, it is common to observe a brief period of gradient reversal during the latter portion of rapid filling. Due to inertial effects, there is no retrograde mitral flow.) Rapid filling is succeeded by the variable slow filling phase during which the AV gradient is small to negligible. During this phase, a small, secondary increase in inflow (the L wave) is observed occasionally. The length of the slow filling phase is markedly dependent on HR, being maximal at slow rates and disappearing at rapid rates. Atrial contraction increases the AV gradient once again and injects an additional volume of blood into the ventricle.

The ventricular properties that determine pressure and the AV gradient during filling are as follows: As indicated earlier, relaxation continues past the time of AV valve opening. Therefore, the same factors (Ca reuptake, load) that modulate *isovolumic* pressure fall also influence pressure *after filling begins*. However, effects of load on relaxation rate may differ somewhat once filling begins.[144,148,150]

In addition to the ongoing process of relaxation, *restoring forces* generated during contraction also influence ventricular pressure during the early, rapid filling phase.[152,154] By a restoring force, we mean PE generated during contraction in the form of a deformation(s) of the myocyte and/or the ventricle that can be converted into kinetic energy during diastole, accelerating flow of blood from atrium to ventricle. Restoring forces are caused by functional springs whose compression during contraction is converted to elastic recoil during diastole and filling by *suction*. When present, this active, energy-requiring driving force for filling results in lowering of ventricular pressure relative to atrial pressure and a larger AV gradient. Restoring forces are probably generated by two interrelated mechanisms. One is contraction of the ventricle to an ES volume below equilibrium volume (V_{eq}), the volume at which, in the *fully relaxed* state, the pressure inside and outside the chamber is equal (transmural pressure = 0). With contraction below V_{eq}, the fully relaxed intracavitary pressure is negative with respect to the outside, and the chamber may be considered to be under compression. If allowed to fill, the PE stored in the walls results in elastic recoil and filling until V_{eq} is reached. As noted earlier, titin appears to be the site of a restoring force in the myocyte. The second mechanism involves complex, contraction-dependent three-dimensional deformations that are normally dissipated (by elastic recoil) during isovolumic relaxation and the early phase of ventricular filling. One of

these is torsional rotation. The magnitude of these deformations increases as ES volume decreases;[103-105,155] hence they parallel compressive forces related simply to contraction below V_{eq}. As a corollary, whether and how much of a restoring force is present are critically dependent on the ES volume in relation to V_{eq}. The *sine qua non* of suction is a negative transmural pressure early during diastole, but this is rarely observed because filling is occurring rapidly and is driven simultaneously by the atrial pressure. Thus the presence of suction is ordinarily obscured. However, suction appears to be important at diastolic volumes within the physiologic range and especially during the stress of exercise, when ES volume decreases.[103,104] A second myocardial property that theoretically influences ventricular pressure during rapid filling is *viscous resistance to stretch*, i.e., intrinsically greater stiffness at high lengthening rates due to elements that behave like dashpots.[156] This property does not appear to be significant under normal physiologic conditions, however.

Relaxation and the generation of restoring forces are dynamic aspects of filling whose influence varies with time. Underlying these time varying properties is the passive ventricular pressure-volume relationship, the exponential relation between pressure and volume in the fully relaxed state.[157] We will refer to this as the *end-diastolic pressure-volume relationship* (EDPVR) (Fig. 3-22). (Although usually considered only at positive transmural pressures, as discussed earlier and as shown in Fig. 3-21, the EDPVR has a negative-pressure portion. The volume at zero transmural pressure is once again V_{eq}.) Passive *chamber compliance* is the ratio of change in volume to change in pressure at any point on the EDPVR. Because the EDPVR is exponential, passive compliance is inversely related to volume. The inverse of chamber compliance is *passive chamber stiffness*. The EDPVR is determined mainly by the geometry of the ventricular chamber, especially the chamber volume to wall thickness ratio, and the intrinsic stiffness of the myocardial tissue itself. Thus, all else being equal, increases in wall thickness or myocardial stiffness increase its slope. Intrinsic stiffness is the change in stress (force normalized to cross-sectional area) occurring in association with a given change in strain (extension of the tissue above some initial length or area). Passive myocardial stiffness is largely accounted for by the properties of titin[43,44] at relatively low volumes and by connective tissue at larger volumes. Throughout all of relaxation and filling, a portion of the pressure in the ventricle is dictated by its position on its EDPVR. Early during filling, the relation between ventricular pressure and volume is determined by relaxation and elastic recoil (when present), superimposed on the EDPVR; the EDPVR alone is the prime determinant of ventricular pressure once relaxation is complete.

The EDPVR is modified by external restraints. The most important is the parietal pericardium.[158] The pericardial sac has a relatively small reserve volume; at total heart volumes in the physiologic range, the pressure in the sac is very low in relation to left-side FPs. However, with relatively modest increments in volume above the physiologic range, the *pericardial* pressure-volume relation becomes quite steep (noncompliant), and the pressure rises rapidly. This external pressure acting on the surface of the heart is transmitted to the chambers and serves to restrain further filling; i.e., it decreases chamber compliance. Even under physiologic conditions, however, pericardial pressure is significant in relation to right-side FPs, which are normally lower than left-side FPs. Thus effective pericardial pressure is normally responsible for a significant fraction of right-side FP. Restraint to filling by the pericardium becomes quite important when the heart dilates rapidly, e.g., after RV myocardial infarction. The interventricular septum constitutes about one-third of the LV wall; diastolic pressure in the RV is therefore also an external restraint to filling of the LV (and vice versa). That is, a component of LV diastolic pressure is transmitted from the RV, an effect termed *diastolic interaction*.[158] Diastolic interaction is normally modest but can become important when RV diastolic pressure is elevated, often in conjunction with augmented pericardial restraint.

An additional factor that influences the EDPVR is the volume of blood in the myocardial vascular bed, or myocardial *turgor*.[159] A significant component of pressure in the fully relaxed ventricle is accounted for by turgor. This component is almost certainly reasonably constant under normal physiologic conditions because coronary blood volume is more or less constant. The significance of turgor is evident from the substantial drop in diastolic pressure that occurs when coronary flow is terminated abruptly.[159]

Following rapid filling and the variable period of slow filling, atrial contraction injects additional blood into the ventricle (typically one-quarter to one-third of the SV). During atrial systole, ventricular pressure and

volume track the EDPVR.[157]

Atrial properties are also a key determinant of the AV gradient that drives filling.[160] During ventricular systole, the atria fill continuously. Therefore, atrial pressure at the instant of AV valve opening is determined directly by atrial compliance; the lower the compliance, the higher is the pressure and the larger is the gradient. The relationship between ventricular pressure and volume as diastolic filling proceeds is also influenced by the properties of the atrium, as well as the pulmonary veins (for the LV). This is so because the ventricle, atrium, and pulmonary veins are an open system when the mitral valve is open. The ventricles, being much stiffer, are much more important determinants of the ventricular diastolic pressure-volume relation than the atria. Last, the contractile strength of the atrium is obviously a determinant of the gradient during atrial systole.

SHORT-TERM MODULATION OF VENTRICULAR FUNCTION

Heart Rate

The ventricle has a positive FFR with an optimal frequency that parallels the myocardial FFR.[74,75] As indicated earlier, this is an important means of modulating ventricular function that is intimately connected with changes in adrenergic stimulation. Changes in contraction frequency also influence relaxation and filling. There is some shortening of relaxation in conjunction with the positive FFR even without concurrent increases in adrenergic stimulation.[73] Moreover, with increased HR, diastole is shortened much more than systole, especially the slow-filling phase.

Paracrine Modulation of Ventricular Function

This has been discussed previously in the section on cellular control of contractility. It is important to emphasize that the significance of these factors with respect to *normal* ventricular function is not established. In the ventricle, these factors tend to have more prominent effects on relaxation than on contraction.[161] NO and endothelial-dependent vasodilators cause very modest depression of systolic function and an earlier onset of ventricular relaxation. Substances whose effects are mediated by the IP_3 second-messenger system (ET-1, α-adrenergic agonists) have more or less opposite effects.

Neurohumoral Responses

The most important short-term neurohumoral modulation occurs as a result of variations in sympathetic and parasympathetic stimulation caused by both cardiac neural activity and circulating catecholamines. Stimulation of β-adrenergic receptors results in increased HR and contractility and more rapid relaxation. These effects are due to the influence of adrenergic stimulation on the sinus node and specialized conduction system and, within the myocyte, activation of adenyl cyclase with increases in cyclic AMP. Increases in HR also allow the heart to use the FFR. Adrenergic stimulation interacts with the FFR not only by increasing HR but also by increasing the gain of the relationship.[75] There are many other myocyte cell surface receptors (e.g., α-adrenergic, dopaminergic, histaminergic, angiotensin II, and endothelin receptors), but none has a clearly delineated, significant role in normal, short-term modulation of ventricular function. Vagal stimulation, of course, has profound HR slowing effects as well as modest negative effects on contractility. Correspondingly, vagal withdrawal is an integral component of HR responses during exercise and other stresses.

The heart participates in a number of reflexes that modulate HR and ventricular function in the short term.[162-165] These typically result in coordinated changes in parasympathetic and sympathetic stimulation. Thus the heart is a component of the efferent limb of arterial baro- and chemoreceptors. Acute increases in systemic arterial pressure result in slowing of HR due to increased vagal stimulation and decreased sympathetic neural stimulation with attendant effects on contractility; the reverse occurs with decreased arterial pressure. Vagal responses occur very rapidly, on a beat-to-beat basis, whereas changes in sympathetic neural stimulation take somewhat longer to take effect. Pulmonary stretch receptors are largely responsible for normal sinus arrhythmia. Atrial stretch receptors also may modulate HR via the Bainbridge

reflex, resulting in tachycardia with increased intravascular volume. Ventricular mechanoreceptors that discharge with deformation are activated when volume decreases. Discharge results in vagally mediated bradycardia and hypotension and appears to be involved in vasovagal syncope. Chemoreceptors on the ventricular epicardium also connect to vagal efferents and may discharge in response to prostaglandins secreted into the pericardial sac.

Ventricular Interaction

Diastolic ventricular interaction has been discussed previously. The ventricles also interact during systole. Left-to-right systolic interaction was mentioned earlier. There is also a modest amount of right-to-left interaction.[119] As a result, an abrupt increase in PA pressure results in a small increase in LV contractile performance. Both diastolic and systolic ventricular interaction function as internal feedback mechanisms that modulate SV on a beat-to-beat basis to ensure that left- and right-side heart outputs remain equal over time. Obviously, even tiny differences in output summated over time would have disastrous consequences.

Coronary Perfusion

Changes in coronary perfusion pressure and/or flow per se can influence ventricular function.[166,167] Increases augment systolic performance and may cause some decrease in passive compliance. Modest decreases insufficient to cause myocardial ischemia likely have opposite effects. A component of the influence of coronary perfusion on ventricular function is related to turgor. In addition to modulation of diastolic compliance, stretching of myocardial tissue due to increased turgor appears to augment the Frank-Starling effect. It is also possible that stretch-activated Ca channels[168] open as turgor increases with resulting increased activation of the myocardium. Because of *coronary autoregulation*, these effects of coronary perfusion are probably of minor importance under normal physiologic conditions.

LONG-TERM MODULATION OF VENTRICULAR FUNCTION

Chronic nonphysiologic stresses modulate ventricular function by causing pathologic hypertrophy. Chronic alterations in the demands placed on the cardiovascular system within the physiologic range can cause modest changes in cardiac mass.[169,170] However, measurable changes require very substantial changes in demand. Thus endurance athletes develop modest, physiologic hypertrophy characterized by increased ventricular chamber volume with little or no increase in wall thickness. This adaptation allows for a greater SV.

NEXT

Chapter 3: NORMAL PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

THE PERIPHERAL CIRCULATION

The essence of normal *vascular* function lies in adjusting total and regional peripheral resistance, as needed, to accommodate the metabolic demands of various organs and in ensuring adequate venous return to the heart. The goal of this section is to first provide an understanding of transcapillary exchange, the process by which tissues are nourished and normal fluid balance maintained, and to then consider the underlying physiologic mechanisms responsible for changes in regional and total peripheral resistance.

Physiology of the Peripheral Circulation

PRINCIPLES OF CAPILLARY EXCHANGE

The exchange of gases, nutrients, water, and waste material occurs at the capillary level and is governed by the interplay of two opposing but balanced forces. At the proximal end of a capillary, intravascular pressure slightly exceeds tissue pressure. The gradient in hydrostatic pressure results in hydraulic *ultrafiltration*, a process characterized by the movement of fluid through the capillary wall and into the extracellular compartment. Composed of a single layer of endothelial cells, the capillary acts as a selective filter. The degree of selectivity varies with the physical properties of the endothelium in different tissues. Passage of relatively large molecules (e.g., proteins) is largely impeded, although some leakage occurs with subsequent reabsorption into lymphatic vessels and a return to the circulation. As a result of ultrafiltration, the concentration of solute (plasma osmolarity) increases along the length of a capillary, and the associated force (termed *oncotic pressure*) acts to pull extracellular fluid back into the capillary lumen through a process of *reabsorption*. This fundamental concept was first described by Ernest Starling in 1896 and is therefore known as the *Starling hypothesis*, mathematically expressed as follows:

$$Q_f = k[(P_c + \pi_i) - (P_i + \pi_p)]$$

where Q_f is fluid movement across the capillary wall, P_c is capillary hydrostatic pressure, π_i is interstitial fluid oncotic pressure, P_i is interstitial fluid hydrostatic pressure, π_p is plasma oncotic pressure, and k is a filtration constant for capillary membrane.

A positive Q_f value indicates net filtration, whereas a negative value connotes net reabsorption. In general, if filtration exceeds reabsorption, an edematous state develops; conversely, if reabsorption exceeds filtration, plasma volume expands (primarily on the venous side), and cellular/extracellular volume decreases. It should be noted, however, that not every capillary behaves in the idealized fashion predicted by the Starling hypothesis. For example, in the renal glomerulus, hydrostatic pressures are elevated along the entire length of the capillary; hence filtration predominates. In the intestinal mucosa, the elevated oncotic forces result primarily in reabsorption, with little or no filtration.

Transcapillary exchange is modulated by a series of integrated mechanisms ranging from central neural control of CO and total peripheral resistance (the primary determinants of blood pressure) to local mechanisms within the microcirculation that modulate capillary pressure and regional blood flow. During the last decade, our appreciation of the latter has increased substantially, and it is now clear that metabolic and myogenic factors within the microcirculation play a major role in determining upstream resistance and, hence, pressure within a capillary bed.

The presence of actin and myosin in some endothelial cells, particularly those of postcapillary venules (also a site of fluid exchange), argues for the existence of a cytoskeletal mechanism for governing the geometry of interendothelial pores or clefts.[171] The state of the cytoskeleton is, in turn, regulated by physical and chemical signals that impinge on the capillary. A number of molecules, such as histamine, adenosine, and

NO, are able to alter the permeability characteristics of the endothelium and lead to rapid and significant changes in permeability. For example, *vascular endothelial growth factor* (VEGF) is a peptide that binds to receptors on the endothelium and initiates a series of intracellular signal-transduction events that result in greatly augmented permeability. Recent observations suggest that this pathway involves a receptor tyrosine kinase that is coupled to phospholipase C, an enzyme whose activation leads to the generation of second messengers that modulate both enzymatic and ionic events within the endothelial cell, including activation of protein kinase C, generation of NO, and changes in the endothelial cytoskeleton.[172] Finally, in some organs such as the brain or kidney, transcapillary exchange may be subject to modulation by pericytes, specialized cells that encircle the capillary endothelium and contribute to permeability/barrier functions by mechanisms that are as yet poorly defined. Under normal conditions, it is essential that the vascular resistance upstream of the capillary bed be regulated in such a way so as to maintain capillary pressure at levels at which normal fluid exchange may occur. The remainder of this section therefore is devoted to reviewing the principal mechanisms by which the cells of the arterial and arteriolar wall regulate arterial tone and hence vascular resistance and capillary pressure.

PERIPHERAL RESISTANCE AND ITS DETERMINANTS

Pressure, flow, and resistance are related most often through Poiseuille's equation, which was first formulated in 1842. Based on a series of careful observations of water flowing through rigid tubes, Poiseuille demonstrated that the resistance to flow R through a tube is proportional to tube length L and fluid viscosity η and inversely proportional to the tube radius to the fourth power (r^4). These variables can be related to each other in the following way:

$$R = 8\eta L/\pi r^4$$

Poiseuille's equation applies to the behavior of Newtonian fluids flowing in a nonpulsatile, nonturbulent (laminar) manner through rigid tubes. Although the vascular system satisfies none of these parameters, the equation is useful because it predicts that flow Q is proportional to r^4 (and inversely proportional to resistance: $Q \propto r^4$, or $Q \propto 1/R^4$, where r is radius and R is resistance), i.e., given the same initial pressure, doubling the inner radius of a tube will result in a sixteenfold (2^4) increase in flow. Estimates from intact vascular networks suggest that this may be an overestimation and that a third-power equation ($Q \propto r^3$) may be more accurate.[173] Nevertheless, it is clear that relatively minor changes in arterial caliber can produce large changes in resistance and flow.

The relationship between vascular resistance and blood flow may be defined by an equation that is analogous to Ohm's law for the flow of electrons, where flow = perfusion pressure/resistance. The complete formulation includes the main determinants of resistance (labeled as above in Poiseuille's equation) and is called *Poiseuille's law:*

$$Q = PP\pi r^4/8\eta L$$

where Q is flow, PP is perfusion pressure, and the determinants of resistance (inverted during the simplification of the quotient) are signified as above. Although flow resistance also can be affected by the viscosity of the blood (η) and the length of the vessel (L), as predicted by the Poiseuille formula, these parameters are normally relatively invariant within the adult cardiovascular system. For this reason, lumen diameter is the single most powerful determinant of vascular resistance (and blood flow) under physiologic conditions. Its control is the primary end point for a variety of physiologic mechanisms.

Most of the pressure drop between large conduit arteries and capillaries occurs in vessels having lumen diameters of a few hundred microns or less. For this reason, small arteries and arterioles are considered to be of primary importance in regulating and determining peripheral resistance. These muscular vessels have a high wall-thickness to lumen diameter ratio and usually contain one to three layers of circumferentially oriented vascular smooth muscle cells. They also normally possess some degree of basal tone and are capable of diameter changes that range from fully open to virtually closed. Hence their potential to affect resistance is considerable. In contrast, large conduit arteries such as the aorta only constrict by 10 to 20 percent. Unless they become diseased, they are of minor importance to peripheral resistance and blood flow control. The relationship between blood pressure, blood flow velocity, and total cross-sectional area in

various blood vessels of the systemic circulation is summarized in Fig. 3-23.

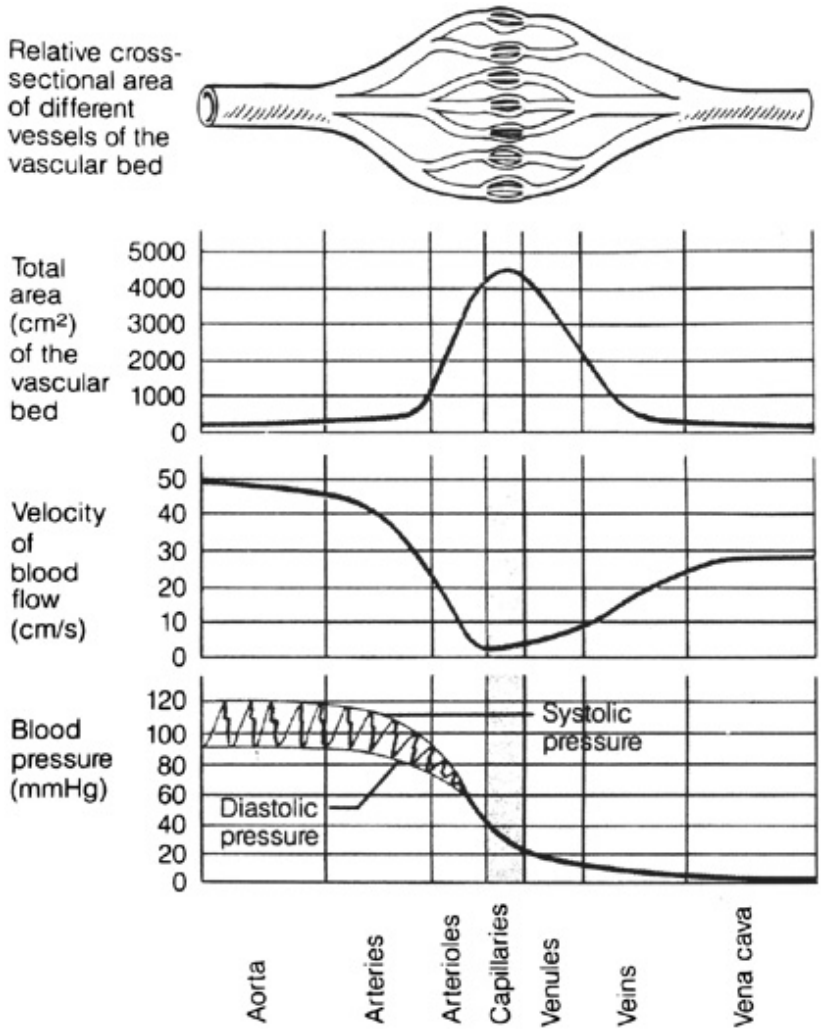


Figure 3-23: Relations between total cross-sectional area of the vascular bed (cm2), velocity of blood flow (cm/s), and blood pressure (mmHg) in various vessels in systemic circulation. (From Marieb EN. *Human Anatomy and Physiology*. Redwood City, CA: Benjamin/Cummings; 1989:629. Reproduced with permission of the publisher.)

Larger vessels do contribute significantly to resistance in some organs, such as the brain,[174] primarily due the more linear geometry of the arterial vasculature. In a *serial arrangement* of tubes, total resistance R_t is the sum of individual resistance elements ($R_t = R_1 + R_2 + R_3$, etc.). Conversely, in regional circulations in which vessels are highly and sequentially branched, resistance tends to be localized to smaller (<50 μm) arteries. This occurs because a greater number of *parallel elements* lowers the overall resistance of the array. This makes sense because, given the same driving pressure, there are more tubes to conduct flow, and in this case, total resistance is defined by a reciprocal relationship ($1/R_t = 1/R_1 + 1/R_2 + 1/R_3$, etc.). These concepts are shown in Fig. 3-24.

SYSTEMIC HEMODYNAMICS

In healthy adults, 15 percent of the blood is contained within the systemic arterial system. The remainder is distributed between capillaries (5 percent), veins (66 percent), heart (6 percent), and pulmonary circulation (8 percent). The peripheral circulation distributes CO throughout the various tissues and organs of the body. The elasticity of large conduit arteries such as the aorta serves to absorb and dampen the highly pulsatile and discontinuous flow from the heart (the Windkessel effect). As a result, the amplitude of pressure

pulsations is diminished in smaller vessels and capillaries and is virtually absent in the venous circulation. Mean pressure also decreases from a value of 90 to 95 mmHg in large arteries to about 30 mmHg in capillaries and less than 20 mmHg in veins. The peripheral circulation must adapt rapidly to changes in arterial pressure and variations in end-organ metabolic demands. Even actions we take for granted, such as getting out of bed, challenge the cardiovascular system. Thus, owing to gravitational forces, cerebral perfusion pressure and venous return are suddenly reduced, leading to transient feelings of dizziness in some individuals (orthostatic hypotension). At the same time, capillary pressures in the ankles may rise to exceed 90 or 100 mmHg. As another example, the metabolic demands of exercise require major redistribution of CO to increase perfusion of coronary, pulmonary, and skeletal muscle circulations, diminish splanchnic flow, and still maintain cerebral blood flow (Table 3-2). Regulatory mechanisms therefore must be bidirectional, i.e., allow blood flow to either increase or decrease on demand. For this to occur, the venous circulation must be able to adjust its capacitance and modulate venous return, and the arterial vasculature must operate at a point from which it can either dilate or constrict to increase or decrease flow. Because it is impossible to dilate a vessel that is already fully relaxed, some portion of the arterial circulation must operate in a state of partial constriction or tone. This theoretical supposition is supported by experimental studies in which the infusion of vasodilators into the afferent vasculature results in substantial increases in blood flow, demonstrating a dilator "reserve" (Fig. 3-25) that can only be accounted for by the presence of basal tone.

Table 3-2: Distribution of Tissue Blood Flow during Exercise

	TISSUE BLOOD FLOW (mL/min)		
Organ	Rest	Light Exercise	Strenuous Exercise
Skeletal muscle	1200	4500	12,500
Heart	250	350	750
Brain	750	750	750
Skin	500	1500	1,900
Kidney	1100	900	600
Abdominal viscera	1400	1100	600
Miscellaneous	600	400	400
TOTAL CO	5800	9500	17,500

SOURCE: Modified from Martini FH. *Fundamentals of Anatomy and Physiology*. Upper Saddle River, NJ: Prentice-Hall; 1998:735.

Integration of Circulatory Mechanisms: Blood Flow Autoregulation

Minute-to-minute control of the peripheral circulation involves a complex interplay between several physiologic mechanisms, mainly neural, myogenic, and endothelial. Metabolites released from adjacent tissues also impinge on the vascular wall (metabolic regulation). The importance of each varies with ambient conditions. Under resting conditions, skeletal muscle arteries and arterioles operate in a highly constricted state, and perfusion is relatively low. Physical activities such as running or swimming result in

manyfold increases in skeletal muscle blood flow due to a combination of increased CO and arterial dilation. The proportion of CO directed to skeletal muscles increases from 20 to more than 70 percent, and total blood flow is increased by as much as tenfold (see Table 3-2).

During exercise, dilation of skeletal muscle arteries and arterioles occurs due to metabolic factors such as adenosine and potassium and hydrogen ions that diffuse from adjacent myocytes into the vascular wall and induce hyperpolarization and relaxation of vascular smooth muscle either directly or indirectly by stimulating the release of endothelial factors such as NO and prostacyclin.[175] Increased flow itself serves as a stimulus for further vasodilation, presumably through shear stress-induced release of vasoactive substances from the endothelium.[176] The degree of local circulatory control can be quite remarkable. This is perhaps best illustrated by studies of cerebral blood flow using inhaled isotopes such as xenon in combination with scanning devices that produce a topographic map of cortical flow.[177] These studies show that when an individual begins to play the piano with his or her right hand, cerebral blood flow increases markedly, but only in the opposite hemisphere in the area of the motor cortex that controls finger and hand movements. Similarly, the act of speaking increases blood flow to the speech areas, solving mathematical equations augments flow to the frontal lobe, visual stimuli to the occipital cortex, and so on. At the same time, global cerebral flow is unaltered in the face of changing blood pressure, a phenomenon called *autoregulation*.

Autoregulation is the ability of an organ to maintain a constant blood flow despite changes in systemic arterial pressure. Although most organs can autoregulate blood flow, this phenomenon is particularly well developed in the cerebral, coronary, and renal circulations and is principally effected by adjustments in the caliber of smaller arteries and arterioles. Autoregulatory effectiveness is determined by the ability of the arteries to constrict to increased and dilate to decreased pressure so as to keep total flow relatively constant. This involves an interaction between several mechanisms, myogenic, endothelial, neural, and metabolic; others, such as tissue pressure or tubuloglomerular feedback, may occur within the cranium and kidneys, respectively.

Autoregulation occurs over a range of pressures with both upper and lower limits. If perfusion pressure falls below a certain point, tissue hypoperfusion will ensue. Transmural pressures above the upper limit of autoregulation, on the other hand, result in a "breakthrough" phenomenon in which forced dilatation of arteries occurs, leading to loss of vasomotor tone. Large increases in organ blood flow, transmission of high intravascular pressures to capillaries and veins, and vessel leakage and rupture potentially may result. Forced dilatation is thought to be important in the development of hypertensive encephalopathy, a condition characterized by increases in cerebral blood flow and extravasation of fluid and protein from the microcirculation. Experimental studies have shown that leakage occurs initially in postcapillary venules, although arteriolar damage and changes in permeability have been documented as well.[178] The ability to autoregulate flow must be reserved for some organs (e.g., brain, heart, and kidney) but not all; if increased blood pressure stimulated arterial constriction throughout the body, total peripheral resistance would increase, raising pressure further via a positive-feedback mechanism that could have dire consequences. An equally dangerous situation would occur with a fall in blood pressure and potentially lead to vascular collapse. Thus simultaneous and opposite changes in arterial and arteriolar tone and/or adjustments in venous capacitance and plasma volume (driven by nervous and endocrine systems) must occur to prevent the development of either hyper- or hypotension.

Cellular Mechanisms Involved in the Regulation of Blood Flow

VASCULAR TONE AND ITS DETERMINANTS

Vascular tone generally increases with decreasing arterial size and is greatest in the smaller arteries and arterioles that play a primary role in determining peripheral resistance and regulating regional blood flow.[179] The level of tone at any time reflects an integration of multiple excitatory and inhibitory pathways that converge on the ultimate effector, vascular smooth muscle (VSM), to "set" the level of tone. Changes in the physical forces impinging on the vascular wall (shear stress, transmural pressure), neurotransmitter release from nerves (most often located at the medial-adventitial junction), or the concentration of metabolites released from surrounding tissues all modulate the set point to either increase or decrease arterial tone, lumen diameter, and resistance. VSM itself is capable of constricting in response to pressure

or stretch. Because this occurs in isolated arterial segments that have been denuded of endothelium and in the absence of metabolic or neural factors, it appears to be a pure response of VSM to pressure or stretch and therefore is termed *myogenic tone* (see ref.[179] for review).

The endothelium, situated at the interface between blood and VSM, is also an important modulator of tone via release of a number of vasoactive factors having both inhibitory (e.g., NO, prostacyclin) and excitatory (e.g., ET-1, thromboxane) effects on VSM.[180] Moreover, in many arteries the endothelium is coupled to VSM through numerous myoendothelial junctions-areas where membranes of endothelium and VSM are in close contact.[181] The nature of the contact varies but may occur through low-resistance gap junctions that allow bidirectional transfer of information and propagation of dilatation or constriction. Spontaneous vasomotion and, in some cases, upstream ("ascending") vasodilatation have been observed in vivo in several circulatory beds and may involve cooperativity between endothelium and VSM in determining network resistance.[182]

MYOGENIC PROPERTIES OF VASCULAR SMOOTH MUSCLE

Arterial constriction to increased perfusion pressure was first described by Bayliss in 1902. Since then, myogenic responses have been documented in arteries, arterioles, and veins. The fundamental question of how a vessel is able to sense intravascular pressure and/or flow has proven difficult to answer. The identity of the myogenic sensor-the structure(s) that convert physical force into VSM contraction-has thus far eluded investigators. Some putative candidates are integrins (molecules embedded in the membrane that link the extracellular matrix with the cytoskeleton) and stretch-activated cation channels.[183] Recent studies have elucidated many of the intracellular signal-transduction pathways involved in myogenic tone. Myogenicity appears to involve a cooperativity between ionic and enzymatic mechanisms, with Ca entry and activation of the phospholipase C/protein kinase C cascade being central among them. Transmural pressure leads to depolarization of the VSM membrane and activation of L-type Ca channels that allow extracellular Ca to enter the VSM cell. Ca entry activates a variety of enzymes and promotes contraction through calmodulin-mediated myosin light chain phosphorylation that initiates actomyosin ATPase activity and crossbridge (actin and myosin) cycling. At the same time, membrane enzymes such as phospholipase C and protein kinase C become activated; many of these enzymes are Ca-dependent. Enzyme activation leads to kinase-induced phosphorylation of a number of other intracellular enzymes and ion channels (e.g., K channels) located in the membrane, as well as modulation of intracellular Ca stores through phosphoinositides such as IP_3.[179,183] Although Ca is required for constriction (inhibition of entry with channel blockers eliminates myogenic tone), enzymatic activity may "sensitize" the contractile proteins to the effects of Ca. Tone is thus controlled by a combination of mechanisms that (1) regulate VSM Ca levels (Ca entry and extrusion) and (2) modulate the effect of Ca on the contractile proteins (Ca sensitivity).

The feedback mechanisms for myogenic behavior are poorly understood but may involve Ca-induced activation of K channels whose opening facilitates K efflux and membrane hyperpolarization, opposing the depolarizing effect of transmural pressure and stabilizing membrane potential at the appropriate level.[184] An intriguing concept, first reported in cardiomyocytes,[185] invokes control of a subset of K channels that have been implicated in basal tone (KCa, or Ca-activated K channels) by highly localized intracellular "hot spots" of Ca, i.e., Ca sparks.[186] In this scenario, Ca is released from the SR in a discrete fashion that leads to localized concentrations of Ca within the cytoplasm. The proximity of the SR release site to the KCa channels, which are proteins embedded in the plasma membrane, leads to their activation. The resulting outward K current produces membrane hyperpolarization that, in turn, inhibits voltage-sensitive Ca channels, decreasing Ca entry and leading to vascular relaxation. Hence Ca sparks produce vasodilation indirectly by activating KCa channels but have little direct effect on spatially averaged intracellular Ca concentration, which regulates contraction.

ENDOTHELIAL INFLUENCES ON VASCULAR SMOOTH MUSCLE CONTRACTILITY

Although the importance of the endothelium as a nonthrombogenic surface has been known for some time, its role in modulating arterial tone was unrecognized until the early 1980s, when Furchgott and Zawadski[187] observed that this cell type was obligatory for the relaxation response to acetylcholine. Although cholinergic vasodilation in vivo had been recognized, its mechanism was difficult to study

because the event rarely could be reproduced in vitro. In their landmark paper, Furchgott and Zawadski[187] reported that endothelial denudation abolished relaxation to acetylcholine and hypothesized that cholinergic stimulation led to the release of a substance that relaxed VSM. This compound, initially called *endothelium-derived relaxing factor* (EDRF), was subsequently shown to be NO. NO is a gas produced during the conversion of the amino acid L-arginine into L-citrulline by the enzyme NO synthase.[188] In addition to its vasodilatory actions, NO is now known to be an important cytotoxic molecule used by the immune system, a neurotransmitter, a modulator of cell division,[189] and, as discussed earlier, a modulator of myocardial function and energy metabolism.

It is now clear that the endothelium performs a variety of chemo- and mechanotransduction functions and releases a host of vasoactive molecules in response to physical and chemical stimulation.[180] In addition to NO, the latter include ET-1[190] and dilator and constrictor prostaglandins (e.g., prostacyclin and thromboxane, respectively). There is also experimental evidence for a non-NO factor that hyperpolarizes VSM. This substance has been termed *endothelium-derived hyperpolarizing factor* (EDHF).[191] Endothelial secretions diffuse to adjacent VSM to activate a variety of signal-transduction mechanisms that alter intracellular concentrations of cyclic AMP (induced by prostaglandins), cyclic GMP (via NO), phospholipase C (ET-1), and membrane potential (EDHF). Release of endothelium-derived vasoactive molecules is controlled by a variety of factors, both chemical and physical. The endothelium is exposed to much higher levels of shear stress than most other tissues. Shear is thought to be an important stimulus for a number of endothelial events, including hyperpolarization (opening of K channels), Ca influx, up- and down-regulation of mRNA for many proteins (e.g., adhesion molecules, tissue plasminogen activator, heat shock proteins), induction of G proteins and a number of kinases (protein kinase C, mitogen activated protein kinase), cytoskeletal rearrangement, and release of cytokines and growth factors.[176] There is also evidence that shear stress modulates arterial growth and remodeling through an endothelium-dependent mechanism.[192] Altered small artery endothelial function (most often characterized by diminished release of vasodilator substances) has been reported in vascular diseases such as hypertension and diabetes.[193,194] In larger arteries, abnormal flow patterns (turbulence, eddy currents) associated with reduced shear stress may lead to metabolic derangements in endothelial function and accelerate the development of atherosclerotic lesions.

Autonomic Regulation of Peripheral Blood Flow

Most arteries and veins receive direct sympathetic innervation. Sympathetic tone contributes to maintenance of arterial and venous pressure under normal and stressful conditions. Sympathetic efferent activity is determined by a complex interaction of neurons in the spinal cord, medulla, pons, hypothalamus, limbic system, and portions of the forebrain and, as discussed earlier, by feedback signals arising from cardiovascular mechano- and chemoreceptors localized in discrete baroreceptor centers in the carotid sinuses, aortic arch, and the heart. The two central nervous system (CNS) areas that appear to be of principal importance in regulating sympathetic outflow are the nucleus tractus solitarius (NTS) and the rostral ventral lateral medulla (RVLM). The influence of the NTS on the RVLM is inhibitory: In animals, bilateral lesions lead to malignant hypertension. Sympathetic denervation produces widely varying effects on organ blood flow. Cerebral and coronary circulations are virtually unaffected, most likely as a result of the dominance of intrinsic autoregulatory mechanisms, whereas denervation of the skin or skeletal muscle produces substantial increases in blood flow. During intense sympathetic activation, large amounts of epinephrine (and, to a lesser extent, norepinephrine) are released from the adrenal medulla in response to activation of sympathetic preganglionic afferents. Blood pressure increases markedly, and significant redistribution of CO occurs (e.g., simultaneous increased perfusion of skeletal muscle and decreased splanchnic flow). Moreover, stimulation of the venous circulation increases venous return, thereby augmenting CO.

The efferent fibers of the cranial division of the parasympthetic system innervate the blood vessels of the head and viscera; those of the sacral division supply the vasculature of the large bowel, bladder, and genitalia. Resistance vessels are not thought to receive parasympathetic innervation, and the effect of the parasympathetic system on total resistance is minor. The parasympathetic system generally produces effects opposite those of the sympathetic division, i.e., decreased cardiac rate and output and vascular relaxation, but is thought to be of secondary importance in peripheral vascular regulation.

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Chapter 3: NORMAL PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

THE CORONARY CIRCULATION

Anatomic and Mechanical Considerations

The right and left main coronary arteries (CAs) arise at the root of the aorta and provide the blood supply to the myocardium. The right CA normally supplies the inferior surface of the LV, the RV and RA, whereas the left CA divides into circumflex and anterior descending branches that perfuse the rest of the LV and the LA. In about 10 percent of cases the left circumflex branch rather than the right CA supplies the inferior LV. Branches from the main CAs ramify and penetrate the myocardium, forming dense capillary beds. Most venous blood returns to the RA via the coronary sinus; there is also communication between the cardiac chambers and myocardium via arteriosinusoidal channels. Delivery of blood to the myocardium is complicated by compression of intramyocardial vessels during systole, which induces retrograde flow in epicardial CAs.[195-201] As a consequence, the bulk of coronary flow occurs during diastole, and the upstream perfusion pressure is the Ao *diastolic* pressure. The subendocardial layer of the myocardium is more susceptible to hypoperfusion because ventricular diastolic pressure opposes the driving pressure for flow. Moreover, compression of microvessels during systole is more prominent in the subendocardium. There has been some uncertainty about the actual driving pressure for nutrient flow, in particular whether the downstream pressure should be considered RA/coronary sinus pressure or a higher value related to tissue forces that cause collapse of the microcirculation (i.e., a critical closing pressure).

Modulation of Coronary Vasomotor Tone and Flow

The distribution of coronary vascular resistance is complex and dependent on type of vessel, region, and specific vasomotor stimuli.[198,200] Arterioles clearly comprise the main component of resistance, but small arteries and venules also contribute in a coordinated fashion to control flow to specific regions. Some vasodilators and contrictors preferentially dilate small arteries rather than arterioles. Resistance in subendocardial microvessels appears to be significantly lower than in the subepicardium. Modulation of coronary vascular resistance is exceedingly complex, and only a brief discussion will be undertaken here (see ref. 200 and Chap. 37 for additional details). As the heart varies its mechanical performance over a wide range of physiologic demands, the coronary circulation must keep pace. For example, nutritive coronary flow increases by as much as 400 percent during exercise. Since upstream Ao diastolic pressure does not change markedly during exercise (or even decreases), this requires an ability to markedly dilate coronary resistance vessels. The most potent mechanism of modulation of coronary resistance and flow is endogenous autoregulation. As discussed earlier, this is the ability of the coronary circulation to maintain flow constant over a wide range of perfusion pressures and/or alter flow in response to increased metabolic demands by changing its resistance.[198,200] Autoregulation occurs at the level of small arteries, arterioles, and venules and appears to be due to both *myogenic* and *metabolically mediated* responses.[198,200,201] As discussed earlier, a myogenic response is the ability of vessels to alter tone as a direct response to changes in pressure and/or flow. This is most prominent in arterioles and results in constriction when perfusion pressure is increased and dilatation when pressure is reduced. Although myogenic responses play a role in autoregulation, the most important factors are those related to changes in the washout of metabolites. (Of course, changes in perfusion pressure and flow themselves alter metabolite concentration.) The actual metabolites

and effector mechanisms responsible for autoregulation are incompletely defined, but the effects are most prominent in small arterioles. There is much evidence that local release of adenosine (a potent coronary dilator) under conditions of increased metabolic demand is a key mediator of autoregulation.[198,200,202,203] However, other endogenous vasoactive mechanisms also contribute. For example, local release of K and activation of ATP-sensitive K channels in small arteries and arterioles also may have a role.[204] Moreover, adenosine release itself may activate ATP-sensitive K channels. NO appears to have a significant role in autoregulation as well (see below).

Neurohumorally mediated responses also play a role in modulation of coronary vascular resistance.[198,200] Their importance under *normal physiologic conditions* is uncertain. α-Adrenergic responses are well documented in the coronary circulation. α-Adrenergic agonists constrict large epicardial and small coronary arteries/arterioles (>100 μm in diameter) and dilate smaller arterioles. At physiologic perfusion pressure, the main effect appears to be constriction of small arteries. While there is evidence of α-adrenergic activity under physiologic conditions, endogenous mechanisms mask and/or counteract this vasoconstrictive influence. Thus endothelial release of NO occurs concomitant with α-adrenergic activity. β-Adrenergic receptors are present in coronary vessels and cause dilation of large arteries and resistance vessels. However, this influence is difficult to distinguish from and likely of minor importance compared with autoregulation.

Constrictive and dilatory substances produced by the endothelium play a key role in many, if not all, of the changes in coronary tone occurring in response to a variety of physiologic stimuli, including autoregulation in general and adenosine, serotonin, acetylcholine, and adrenergic stimulation.[198,200,205,206] These endothelial-derived substances include prostaglandins, ET-1, endothelium-derived hyperpolarizing factor,[207] and NO.[198,200,204-209] At present, there is considerable information about the physiologic role of NO, but relatively little is known about the others. Although NO is a coronary vasodilator, it produces somewhat heterogeneous effects and may have quantitatively different influences on large arteries versus resistance vessels. NO appears to be the key effector of autoregulatory responses to normal physiologic stimuli, including tachycardia and vasodilation during exercise,[208-210] and is intimately connected to responses to the endothelial-derived substances mentioned earlier, as well as a variety of vasoactive drugs.

The response of the coronary circulation to changes in demand requires the coordination of the multiple modulatory mechanisms discussed earlier. The integrated response consists of heterogeneous effects that depend on the type of vessel and the region of the myocardium, which together increase nutritive flow. A scheme illustrating the complex interactions involved in the response to an increase in demand is shown in Fig. 3-26.

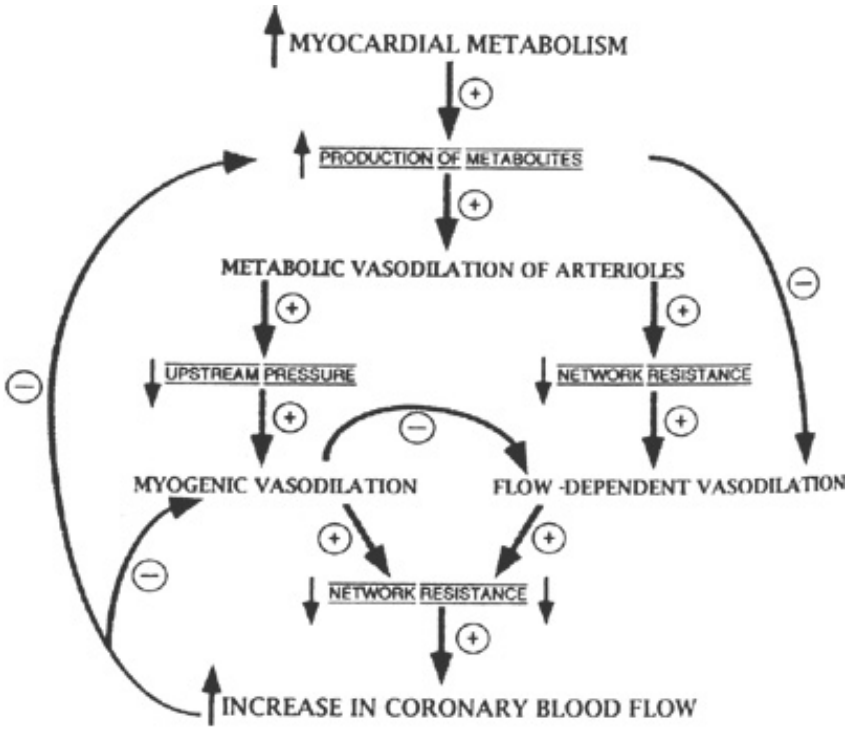

Figure 3-26: Schematic diagram of integrated response of metabolic, myogenic and flow-mediated regulation of coronary vascular resistance and flow during increase in metabolic demand. Plus sign indicates vasodilatory feed-forward steps in response to initial increase in demand. Minus sign indicates negative-feedback processes that limit vasodilation. Events marked by lines ("Production of Metabolites") occur as a reaction to metabolic or vascular changes. Bolded items are metabolic or vasoactive adjustments. (From Muller et al.[200] Reprinted with permission of the publisher.)

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Chapter 3: NORMAL PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

INTEGRATION OF THE CARDIOVASCULAR SYSTEM: THE RESPONSE TO DYNAMIC EXERCISE

Integrated functioning of the heart and peripheral and coronary circulations is exemplified by responses to dynamic exercise, especially isotonic activities such as walking, running, and swimming that entail repetitive shortening of skeletal muscle against relatively low loads. The coordinated response maximizes flow to working skeletal muscle and the heart; minimizes flow to nonworking muscle, visceral organs, and the kidneys; and ensures that flow to the brain is not compromised (see Table 3-2). In the periphery, local vasodilatory influences reduce resistance in vascular beds of working muscle. Cutaneous beds also dilate in order to facilitate heat transfer. In contrast, neurohumorally mediated responses cause vasoconstriction in nonworking skeletal muscle, abdominal viscera, and the kidneys. With isotonic exercise involving large muscle groups, there is usually a decrease in total systemic vascular resistance.

O_2 delivery to the myocardium is augmented by increased coronary flow caused by autoregulatory vasodilatation in response to increased metabolic demands. In addition to increased O_2 delivery, O_2 consumption is augmented by increased extraction, with lowering of coronary sinus O_2 saturation. Myocardial use of glycolytic metabolism increases, and NO produced in the coronary endothelium may facilitate shifts in mitochondrial respiration that tend to minimize increases in energy demands.

As noted earlier, in the normal circulation the ability to return blood to the heart is the limiting factor for increases in CO during exercise. In order to increase venous return, systemic venoconstriction decreases the volume of blood in venous reservoirs, resulting in a shift of blood volume to the arterial circulation and the heart. Working skeletal muscles in conjunction with venous valves themselves function as pumps to return blood to the heart, and increased respiratory rate causes the intrathoracic pressure to be negative a larger proportion of the time, which directly assists venous return to the right side of the heart.

In the heart itself, increased adrenergic stimulation caused by the coordinated effects of increased central nervous outflow and circulating catecholamines, along with parasympathetic withdrawal, results in increased HR (as much as three- to fivefold at maximum exercise), accelerated AV conduction, and enhanced contractility. Increased force and velocity of contraction are achieved through the effects of adrenergic stimulation (via cyclic AMP) and the FFR on Ca delivery to the myofilaments. Their effects on Ca reuptake and myofilament Ca sensitivity speed myocardial relaxation so that increased HR does not occur at the expense of incomplete relaxation. During upright exercise, ED volume remains relatively constant; during supine exercise, it increases somewhat.[211] Reflecting increased contractility, the ESPVR shifts leftward, and ES volume decreases. The combination of relatively constant or modestly increased ED volume and reduced ES volume results in a variable increase in SV and EF. With respect to augmenting CO, however, the increase in HR is considerably more important than the increase in SV.

The combination of increased HR and SV with resulting marked shortening of diastole means that ventricular filling must occur much more rapidly than under resting conditions. This is partly accomplished by the aforementioned increase in relaxation rate. However, it is likely that an increase in the generation of restoring forces due to the smaller ES volume as well as increased

deformations such as torsion result in increased suction. Thus the same mechanisms causing increased force of contraction (adrenergic stimulation, FFR) also result in more rapid diastolic filling at lower ventricular pressures.

Systolic systemic arterial pressure increases substantially during dynamic exercise as a result of increased contractility and SV, while diastolic arterial pressure decreases because systemic resistance decreases. Obviously, pulse pressure increases. Minimum ventricular diastolic pressure decreases (more rapid relaxation, increased suction) with little or no change in ED pressure. Finally, coordinated changes in arterial elastance may function to optimize ventricular-vascular coupling and efficiency of conversion of chemical energy to EW by the contractile machinery.

Predominantly isometric exercise involving relatively brief bursts of skeletal muscle shortening against a heavy load (e.g., weight lifting, handgrip) evoke different responses. This type of exercise does not require a marked and/or sustained increase in CO with selective distribution to working muscles and heart. Thus many of the complex, integrated responses present during sustained isotonic exercise are unnecessary. However, isometric exercise does elicit reflex-mediated increases in sympathetic stimulation causing increased systemic vascular resistance and arterial pressure, HR, and cardiac contractility. The increases in systolic blood pressure are comparable with those during isotonic exercise, whereas the increases in HR are much smaller in magnitude.

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Figure 3-18: Relation between EF and circumferential stress (with 95 percent confidence intervals) in human subjects with normal ventricular function (control, filled squares) and mitral regurgitation (MR, open circles) (see text). Some MR patients fall below confidence intervals. (From Starling et al.[115] Reproduced with permission of publisher.)

Figure 3-19: Schematic of elastance concept (see text). *A*. Series of variably loaded pressure-volume loops. Filled circles connected by straight lines occur at same time *t* during contraction. E_{max} is line connecting points at ES. *B*. Elastance *E(t)* increases at each time *t* during contraction until it reaches maximal value at ES. Increased contractility increases slope at any time *t*, including ES (E_{max}); vice versa for decreased contractility. *C,D*. The concept that the ventricle behaves like a spring of increasing stiffness (increased slope of elastance relations) during contraction. (From Suga H, Takaki M, Matsubara H, Goto Y. Energy costs of PVA and E_{max}: Constancy and variability. In: LeWinter MM, Suga H, Watkins MW, eds. *Cardiac Energetics: From E_{max} to Pressure-Volume Area.* Boston, Kluwer, 1996:2. Reprinted with permission of publisher.)

Figure 3-20: (*Top*) Schematic of VO_2-PVA concept (see text). In ejecting contraction, PVA = EW + PE; in isovolumic contraction, PVA = PE only. (*Bottom*) Correlation of PVA with VO_2. (From Goto et al.128 Reproduced with permission of publisher.)

Figure 3-21: Determinants of relation between LV diastolic pressure and volume during filling. Solid line, LV pressure during isovolumic relaxation, filling, and isovolumic contraction; dashed line, positive and negative portions of passive pressure-volume relation. V_{ES}, ES volume; V_0, equilibrium volume or zero pressure intercept of passive pressure-volume relation (which is not same as dead volume of ESPVR); V_{ED}, ED volume. (From Gilbert JC, Glantz SA. Determinants of LV filling and of the diastolic pressure-volume relation. *Circ Res* 1989; 64:828. Reproduced with permission of publisher.)

Figure 3-22: (*Left*) EDPVR in two ventricles with differing passive diastolic properties. Chamber stiffness is *dP/dV* at any point on the EDPVR. Chamber compliance is its inverse. Stiffer chamber (left) has steeper overall slope. (*Right*) Same data plotted as pressure versus chamber stiffness. Because of exponential nature of EDPVR, result is a straight line. Its slope (k_c) is a chamber-stiffness constant that characterizes the overall slope of the EDPVR. (From Gaasch.157 Reprinted with the permission of the publisher.)

Figure 3-23: Relations between total cross-sectional area of the vascular bed (cm2), velocity of blood flow (cm/s), and blood pressure (mmHg) in various vessels in systemic circulation. (From Marieb EN. *Human Anatomy and Physiology*. Redwood City, CA: Benjamin/Cummings; 1989:629. Reproduced with permission of the publisher.)

Figure 3-24: Illustration of principle of resistance elements arranged in series versus parallel. (*Top*) If the driving pressurer (ΔP) across each series resistance is 3 mmHg, and flow (Q) is 1 mL/min, each resistance (R) would be $\Delta P/Q$, or 3 mmHg/mL per minute, and total resistance (R_t) would be 9 mmHg/mL per minute. (*Bottom*) In parallel resistances, if driving pressure (ΔP) is 3 mmHg, and flow (Q) is 1 mL/min, total resistance is $1/R_1 + 1/R_2 + 1/R_3$, or 1 mmHg/mL per minute. When three resistances are in parallel, total resistance is only one-ninth that with resistances in series, so it would take a ΔP of only 1 mmHg to produce a 1 mL/min flow. (From Smith JJ, Kampine JP. *Circulatory Physiology: The Essentials*. Baltimore: Williams & Wilkins, 1990:20. Reprinted with permission of the publisher.)

Figure 3-25: Regional blood flow at rest (shaded areas) and at maximal dilatation (stippled areas) per organ and per 100 g tissue, illustrating the concept of arterial/arteriolar vasodilator reserve. (From Mellander S, Johansson B. Control of resistance, exchange and capacitance functions in the peripheral circulation. *Pharmacol Rev* 1968; 20:117. Reprinted with permission of the publisher.)

Figure 3-26: Schematic diagram of integrated response of metabolic, myogenic and flow-mediated regulation of coronary vascular resistance and flow during increase in metabolic demand. Plus sign indicates vasodilatory feed-forward steps in response to initial increase in demand. Minus sign indicates negative-feedback processes that limit vasodilation. Events marked by lines ("Production of Metabolites") occur as a reaction to metabolic or vascular changes. Bolded items are metabolic or vasoactive adjustments. (From Muller et al.[200] Reprinted with permission of the publisher.)

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Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 4:

PRINCIPLES OF MOLECULAR CARDIOLOGY

Author: Robert Roberts

Application of the techniques of recombinant DNA to cardiovascular disorders appears to be essential and appropriate to overcome several of the major obstacles to immediate and future progress.[1-3] The heart exhibits three characteristic adaptive responses to changes in its environment: the constitutive adaptive mechanism-namely, myofibril stretch that regulates cardiac output on a beat-to-beat basis (Starling's law)[4]; modulation of excitation contraction coupling through intramyofibril calcium leading to increased heart rate and force of contraction; and the long-term adaptation of compensatory growth (see Chap. 5). The first two adaptations were characterized extensively in the 20th century through the development, refinement, and application of hemodynamic techniques. In the 21st century, the molecular basis for the growth response will be elucidated and will include deciphering the basis for cardiac differentiation and development. This will be necessary if one desires to therapeutically modulate growth. Similarly, elimination of restenosis after angioplasty probably will require disruption of smooth muscle migration and proliferative response.[5] Unraveling the molecular basis of hereditary cardiac disorders is well underway, and with completion of the Human Genome Project within the next couple of years, this will be accelerated considerably[6,7] (see Chap. 62).

We have already entered the era of genetically engineered drugs such as recombinant tissue plasminogen activator (rt-PA),[8] which initiated a paradigmatic shift in the therapy of myocardial infarction, resulting in an acute mortality of only 6 percent.[9] The era referred to as *pharmacogenomics* is rapidly approaching, in which therapy will be individualized on the basis of a patient's genotype.[10]

HISTORICAL PERSPECTIVE OF MOLECULAR BIOLOGY

In 1953, Watson and Crick[11,12] proposed the double-helix model for DNA structure based on the results of x-ray defraction studies by Franklin and Wilkins.[13,14] The implications of DNA being a double helix, in which each strand is a mirror image of the other, were evident, namely, that one strand could serve as a template for the synthesis of a daughter strand, thus providing the means whereby genetic information could be perpetuated from parent to offspring. In 1957, Kornberg[15] described DNA polymerase, the enzyme necessary for the synthesis of DNA that was essential to recombinant DNA technology. Marmor and colleagues showed that the double helix of DNA, when subjected to high temperatures,[16,17] could be separated into its separate strands (denatured), and decreasing the temperature resulted in the reannealing, or hybridizing, of the strands, thus returning them to their previous double-stranded nature. This specific hybridization, or "base pairing" of complementary nucleotide strands, provides both the rationale and the practical basis for much of recombinant DNA technology. Crick had suggested correctly that the genetic code would be written in codons of three nucleotides for each amino acid.[12] The specific combination of three nucleotides that code for each amino acid was unraveled by Leder and Nirenberg[18] and Nishimura et al.[19] Several other necessary components were discovered subsequently, including the enzyme DNA ligase, which joins DNA fragments together.[20] All this information was known in the 1960s, as was the complete DNA code, as well as messenger RNA and the cytoplasmic

ribosomal RNA for protein synthesis, but recombinant technology was not yet born and, in fact, for the next few years did not appear promising.

Many important discoveries, including those from the 1950s, played a role in recombinant technology, but four that really brought it to fruition and made possible modern molecular biology occurred between the years of 1970 and 1977. A major obstacle to the manipulation of DNA was its large size with no means to cut it into smaller pieces of known specific size. This obstacle was overcome by the discovery of restriction endonucleases that made it possible to cut DNA into smaller pieces in a predictable fashion.[21,22] These endonucleases, more commonly referred to as *restriction enzymes*, recognize specific sequences of DNA consisting of anywhere from four to eight nucleotides and specifically cut the DNA molecules at their recognition sites, making it possible to use and manipulate DNA fragments in a variety of procedures and reactions. In 1972, the enzyme reverse transcriptase was discovered by Baltimore[23] and Temin and Mizutani[24] simultaneously, making it possible to translate messenger RNA (mRNA) into its complementary DNA (cDNA). Shortly after the first molecule was cloned,[25] recombinant DNA techniques were born, as was modern molecular biology. In 1975, Sanger and Coulson[26] and Maxim and Gilbert[27] developed techniques for the rapid sequencing of DNA. In addition to these four developments, polymerase chain reaction (PCR), a more recently developed technique to rapidly amplify small amounts of DNA or RNA several million-fold, is also having a revolutionary effect on medicine and other fields.

NEXT

Chapter 4: PRINCIPLES OF MOLECULAR CARDIOLOGY

NUCLEIC ACIDS

The Essentials of Nucleic Acids

The human genome is known to contain about three billion base pairs, which contain information that would more than fill a 500,000-page textbook. The DNA is contained in 46 chromosomes consisting of 44 autosomal and 2 sex chromosomes, but each chromosome is one continuous DNA molecule around which is wrapped several proteins. The smallest chromosome, 21, has more than 50 million base pairs, whereas chromosome 1, the largest, has over 250 million base pairs. There is enough DNA to form several hundred thousand genes; however, it is estimated that only about 67,000 genes encode for a human being. This would indicate that less than 5 percent of DNA is used to code for protein. The remainder of the DNA is used to provide spacing, structure, regulatory information, and other as yet unknown functions.

DNA consists of four building blocks referred to as *nucleotides* or merely as *bases*. A nucleotide consists of a nitrogenous base, a 5-carbon sugar (deoxyribose), and a phosphate group (Fig. 4-1). There are two purine bases (adenine and guanine) and two pyrimidine bases (cytosine and thymine) (Fig. 4-2). The triphosphate molecule is bonded to the 5′ carbon of the sugar, and the base is bonded to the 1′ carbon of the sugar. Each DNA molecule consists of millions of nucleotides joined together in a linear fashion through the phosphate group, which forms a bond with the hydroxyl group of the 3′ carbon of the next sugar. The phosphate groups form the backbone of the molecule, but because they are water-soluble, they face outward. Attached to the inner side of the sugar is the hydrophobic base, which faces inward to shield it from the aqueous environment. The molecule forms a right-sided spiral coil with a turn every 10 nucleotides (3.4 nm), referred to as a *right-sided α-helix*, and pairs with its complementary strand to form the so-called double helix (Fig. 4-3). The center of the molecule consists of the bases that face inward and are opposite to each other. This arrangement provides for the hydrogen bonding between the bases that keeps the two strands together. The hydrogen bonds are perpendicular to the helical axis. The directionality of the strands is referred to as *5′ to 3′* or *3′ to 5′*, which is based on the position of the carbons in the sugar. The end of the molecule with a phosphate or hydroxyl group on the 5′ carbon is termed the *5′ end*, whereas the end with a free terminal 3′ carbon is referred to as the *3′ end*. It is important to distinguish the two ends because the enzyme DNA polymerase always initiates replication of DNA from the 5′ end and proceeds to the 3′ end. There seems to be no constraints on which bases can be adjacent to each other; however, the hydrogen binding between the bases of the two chains is highly specific, since adenine (A) always pairs with thymine (T), and guanine (G) always pairs with cytosine (C). The sugars and the phosphate groups are always the same, whereas the sequence of the bases varies and determines the nature of the hereditary information to be passed onto the progeny. The specificity of this "base pairing" is the basis of the ability of DNA to replicate itself and pass on the genotype characteristics and also forms the basis for the specificity of essentially all the procedures used in recombinant DNA technology. During the process of DNA replication, the strands separate, and new strands form complementary to the original strands, resulting in two additional identical molecules.

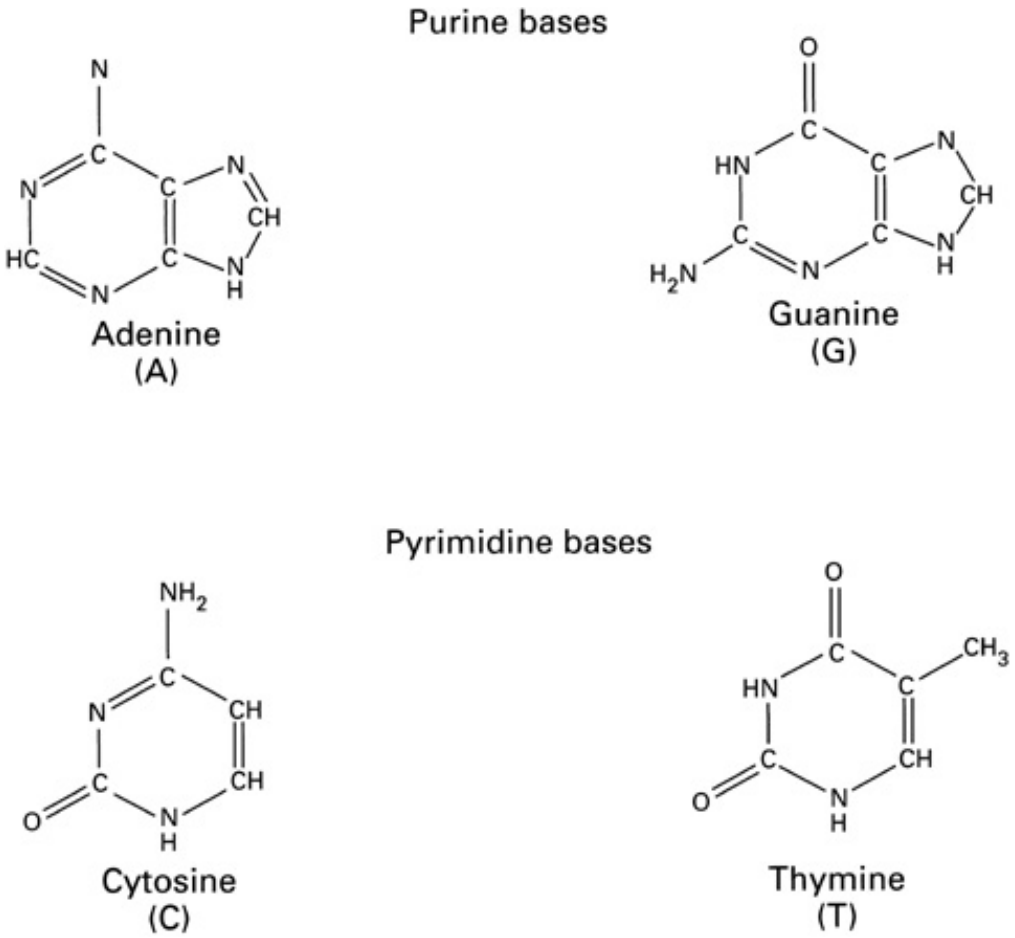

Figure 4-2: The common purine and pyrimidine bases found in DNA. Uracil is substituted for thymine in RNA. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

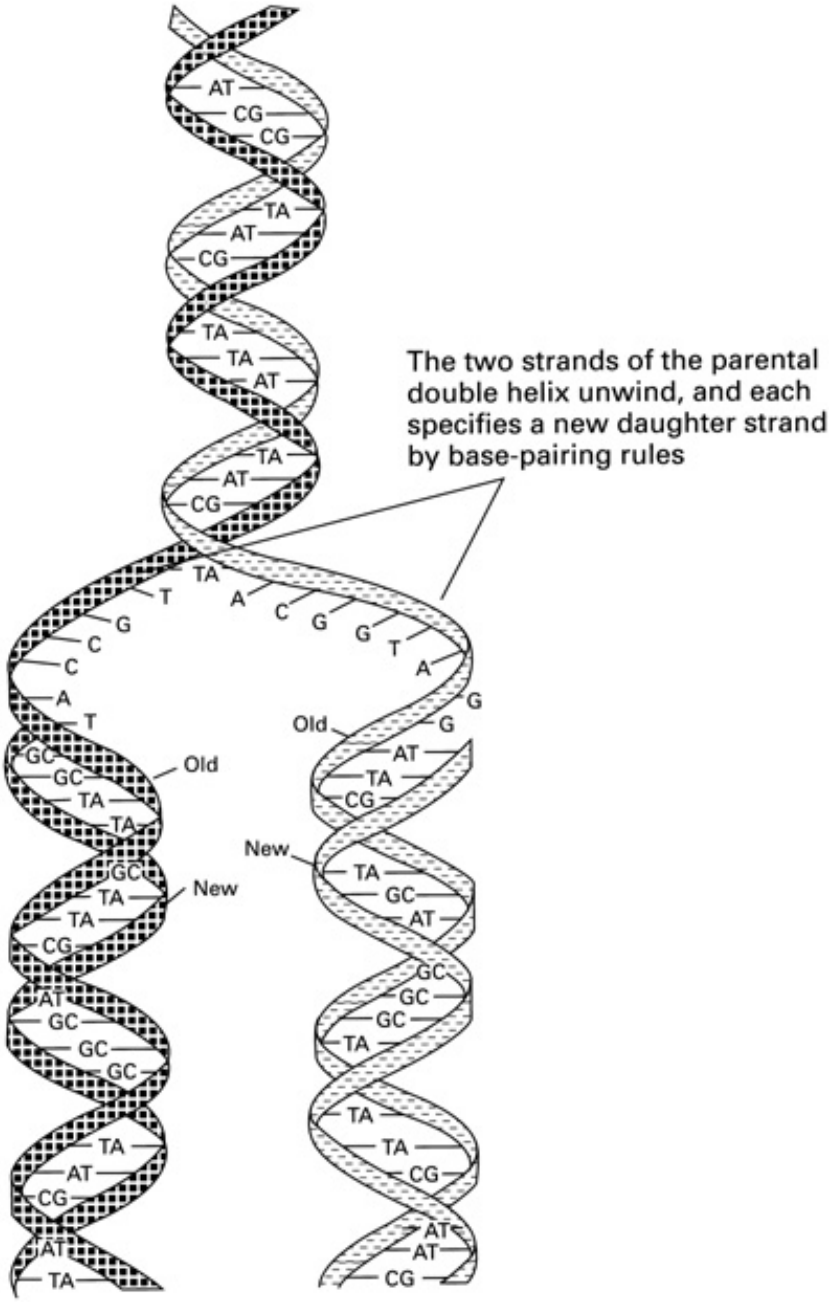

Figure 4-3: DNA replication conserves the nucleotide sequence. DNA is a double-stranded helical molecule bound together by the nucleotide bases contained on each individual strand. During cell division, two identical copies of the original parental strand are made by unwinding the DNA and then synthesis of a complementary second strand to make two identical new daughter strands.

Transcription (from DNA to RNA)

The central dogma of molecular biology is that DNA produces RNA, which in turn produces a polypeptide, the latter being the molecules that make up proteins that provide the cell structure and perform the functions of the cell (Fig. 4-4). The genetic information inherited by each individual is encoded by the sequence of the bases of the DNA (the genotype), which is translated into proteins and provides the observable characteristics of the individual (the phenotype). This overall process from DNA to protein, however, must first go through the intermediary step of RNA. The process whereby mRNA is synthesized using DNA as the template is referred to as *transcription* (Fig. 4-5). Transcription and the processing of mRNA occur in the nucleus of the cell, separated by the nuclear membrane from the cytoplasm of the cell. The process of

transcription is initiated by attachment of the enzyme RNA polymerase II to specific recognition sites where the DNA is double-stranded, but on activation by the enzyme, the strands now selectively unwind and separate (Fig. 4-6). The binding site of RNA polymerase II is always located on the 5′ end of the gene, and the enzyme remains attached to a single strand of DNA as it travels in the 3′ direction. The DNA immediately in front of it separates into two strands with just one strand of DNA (antisense) acting as a template for the synthesis of mRNA. Thus, in contrast to DNA, mRNA is a single-stranded polynucleotide. Messenger RNA also differs from DNA in that deoxyribose, the sugar found in DNA, is replaced by ribose. Moreover, uracil (U) replaces thymine (T), and like thymine, uracil pairs exclusively with adenine (A). Thus, by this mechanism, each adenine (A) of DNA pairs with uracil (U) of RNA, each cytosine (C) of DNA pairs with guanine (G) of RNA, each thymine (T) of DNA pairs with adenine (A) of RNA, and each guanine (G) of DNA pairs with cytosine (C) of RNA.

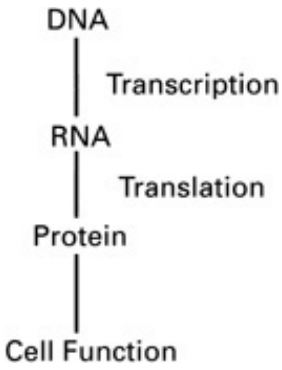

Figure 4-4: Central dogma of molecular biology.

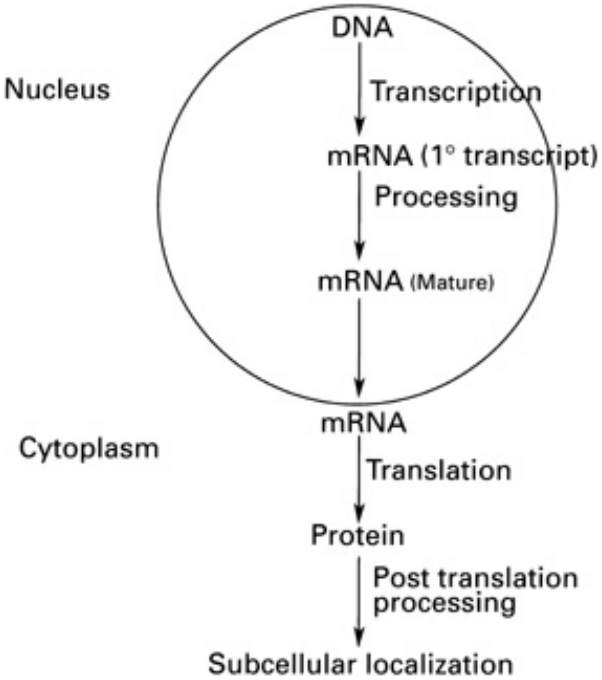

Figure 4-5: Schematic localization of the processes of transcription and translation.

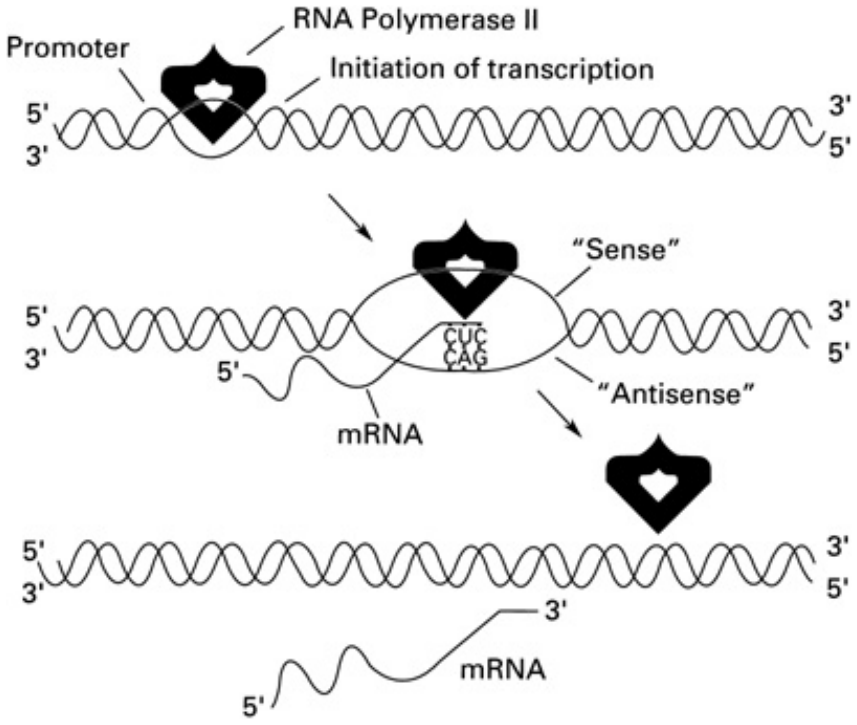

Figure 4-6: Illustration of how RNA polymerase II interacts with DNA and the promoter to generate a single-stranded mRNA. RNA polymerase II attaches to the initiation site promoted by the 5′ promoter sequence. mRNA is synthesized in the 5′ to 3′ direction from just one strand, the antisense strand. The specificity of base pairing between mRNA and the antisense strand provides for an mRNA with sequences complementary to that of the antisense strand and identical to that of the sense strand.

The mRNA, as transcribed from the DNA, is referred to as the *primary transcript*, or sometimes as *immature mRNA*, and is a complementary copy of the DNA (Fig. 4-7). Since protein synthesis occurs in the cytoplasm, the mRNA must exit the nucleus, but prior to transport, it undergoes extensive posttranscriptional processing primarily through three main events: (1) addition of a methylated guanosine (4-methylguanosine residue) to the 5′ end, referred to as a *cap*, which is important for the initiation of translation; (2) addition of a long tail of repeated adenine nucleotides, called the *poly(A) tail*, to the 3′ region of the mRNA, which is essential for stability of the message in the cytoplasm; and (3) the primary transcript, which contains introns and exons, undergoes a specific splicing process whereby the introns are removed and the exons are properly respliced together prior to exit from the nucleus as mature mRNA. The process of splicing is, in part, performed by molecules referred to as *small nuclear ribonucleoproteins* (snRNPs), which consist of RNA molecules tightly associated with a group of about 10 different proteins. Exons survive the mRNA processing and exit the nucleus (hence the name) as part of the mature mRNA. The mRNA consists of three distinct regions. The exons of the 5′ end are not translated into protein but signal the beginning of mRNA translation and contain sequences that direct the mRNA to the ribosome in the cytoplasm for protein synthesis. The exons in the second region, referred to as the *coding region*, contain the information that determines the amino acid sequence of the protein. The exons of the 3′ end do not code for protein but for signals that terminate translation and direct the addition of the poly(A) tail. Introns are portions of the gene included in the primary mRNA transcript but which are spliced out of the mature mRNA. The process of splicing out introns and rejoining exons is an important means of introducing genetic diversity, since one mRNA may provide several different mRNAs that code for different polypeptides (this will be discussed further under gene regulation). The primary transcript undergoes extensive shortening such that the mature mRNA often represents only 10 percent of the primary transcript. The mature mRNA exits the nucleus through nuclear pores, enters the cytoplasm, and attaches to a ribosome to initiate protein synthesis.

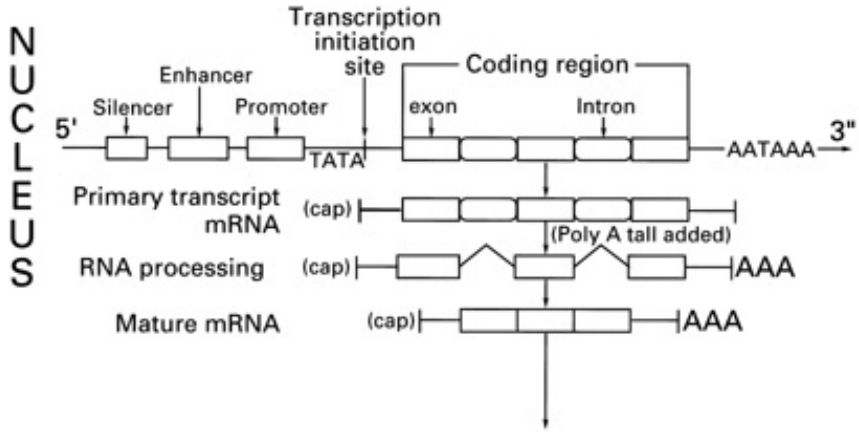

Figure 4-7: Transcription. Transcription occurs in the nucleus, producing mRNA that is processed into mature mRNA and transported to the cytoplasm. In the cytoplasm, translation occurs, with the mRNA coding for specific amino acids that are linked together to form a polypeptide and ultimately to form a mature protein. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

Translation

The final process whereby the nucleic acids of the mRNA code for a specific polypeptide is referred to as *translation*. This process is the most complex of the various processes that occur in the flow from genomic DNA (gene) to mature protein. The alphabet of the DNA or its single-stranded complementary mRNA is that of the four nucleotides (bases), whereas that of the protein is the 20 amino acids. Crick in 1961,[11] while trying to determine the code for translation from DNA to protein, showed that the genetic code was written in triplets of bases, with each amino acid being encoded by three base pairs referred to as a *codon* and specific amino acids determined by the sequence of the codon. The mRNA codons dictate which amino acids are to be selected, and the order of the codons dictates the sequence of the amino acids in the protein. Determination of the codons for each amino acid was completed in 1966. There are four different nucleotides to form the triplets; thus the number of combinations (4^3) is 64, but there are only 20 amino acids. There is considerable redundancy, referred to as *degeneracy,* and this results in most of the amino acids having more than one codon. In addition to codons for each amino acid, there is also the codon AUG, which is the start codon that initiates protein synthesis and also codes for methionine. To stop translation, there are three codons, UAA, UAG, and UGA, that signal the end of a particular polypeptide. Translation into protein requires two other RNA species, ribosomal RNA (rRNA) and transfer RNA (tRNA). The mRNA, after exiting the nucleus, recognizes the ribosome, which is the site of protein synthesis. The ribosome moves along an mRNA molecule, translating each of its codons in a 5′ to 3′ direction to assemble the polypeptide from its amino (N-terminal) to its carboxy (C-terminal) ends (Fig. 4-8).

The mRNA does not interact directly with amino acids but rather through adaptor molecules-referred to as transfer RNA (tRNA)-to which amino acids are covalently joined by a highly specific enzyme (aminoacyl tRNA synthetase) using ATP. There is at least one tRNA species corresponding to each of the 20 naturally occurring amino acids. The aminoacyl tRNA synthetase performs a special function of activating the amino acids and ensuring that each amino acid is joined to its tRNA and to no other. The structure of tRNA is now known in great detail, and its specificity is attributed to the sequence of three nucleotides complementary to the codon exposed at one end of the folded tRNA molecule, which, on the tRNA, is referred to as the *anticodon*. The

amino acid receptor site is exposed at the other end. Amino acids thus are specified at two recognition steps: one in which a specific enzyme joins the amino acid to a specific tRNA and the other in which the tRNA serving as an adaptor molecule joins the amino acid to the ribosomal-mRNA complex through a codon-anticodon specific-base-pairing interaction between the mRNA and the tRNA. Once the process of protein synthesis is initiated, the ribosome moves along the mRNA joining the amino acids via peptide bonds in the sequence specified by the mRNA to form the mature polypeptide. The process of protein synthesis from this complex of mRNA and ribosome involves over 100 enzymes. The steps involved consist of initiation, elongation, and termination of the polypeptide, with each process having its own enzymes.

The mature polypeptide consists of amino acids joined together by peptide bonds; the mature protein, however, often consists of multiple covalently bound polypeptides, and many undergo other modifications referred to as *posttranslational changes*. A more detailed analysis of protein synthesis is given in Chap. 5. Encoded in the polypeptide are other features that have been determined by the mRNA, namely, leader sequences that will direct the protein to either intracellular membranes, the plasma membrane, or organelles such as the mitochondria. There is also considerable proteolytic activity following entry of the molecule into its organelle, or membrane, as the leader sequences are removed. There are also the processes whereby disulfhydryl bonds are formed or glycosylation occurs (in the Golgi apparatus) (see Fig. 4-8). The mRNAs generally are not long-lived due to their rapid degradation by RNAses and so may last from only a few minutes to many hours. A single mRNA may code for only a few copies of the polypeptide or several thousand. The average estimate is 1400. In contrast, rRNAs and tRNAs are much less rapidly degraded and therefore have acquired the name *stable RNAs*. Their relative concentration in the cell, in large part, reflects their stability, with more than 80 percent being rRNAs, 15 percent being tRNAs, and less than 5 percent being mRNAs.

Gene Structure, Expression, and Regulation

The concept that one gene leads to one protein remains basic to the central dogma of molecular biology but does, in some cases, need to be modified slightly in view of recent observations. In the classic sense, a gene consists of a discrete unit of DNA that encodes for a specific polypeptide. Two observations must be noted: First, transcription produces two end points-ribonucleic acid (RNA) and protein. The products, or rRNA, tRNA, and small nuclear RNA (snRNA), do not get translated into protein but rather perform functions during posttranscription and translation that are pivotal to expression of the mRNA that does code for protein. The polymerases necessary for transcription of these genes are of three types, polymerase I for rRNA, polymerase II for mRNA, and polymerase III for tRNA and some other snRNAs. Second, in part because of snRNA and certain proteins, alternative splicing of the exons in the primary mRNA can lead to different mature mRNAs that each code for a slightly different polypeptide. The forms generally are isoforms of the same protein, however, such as multiple forms of tropomyosin from the same gene. The genes that do encode for proteins do so only through mRNA. The following discussion will address the regulation of those genes which encode for proteins.

The anatomy of a protein-coding gene is composed of introns and exons. The average exon is about 300 base pairs long, whereas introns are much larger and are spliced out of the mature mRNA and, thus, do not code for protein. A typical mRNA has three regions: the 5′ untranslated region that contains the cis-acting sequences that regulate translation; the central portion, referred to as the *coding region*, that codes for protein; and the 3′ untranslated end, which also has regulatory sequences and coding signals for stability of the mature mRNA. The first nucleotide to be transcribed is given the +1 number, and everything 5′ to it is referred to as *upstream* or *proximal* and is numbered with the first base pair as -1, etc. The initiation site for transcription is always upstream from the 5′ untranslated region. The 5′ regulatory untranslated region has variable sequences, but there are several consistent sequences present in the same position in most human genes. Polymerase II has no affinity for DNA and can only bind after several transcription

factors have bound. The site of transcription and its direction are determined by a TATA box, which has a consensus sequence of TATAA(T)AA(T) and is found at base pairs -25 to -30 upstream from the start site. A large complex of transcription factors (more than 25 proteins) binds to the TATA box in preparation for RNA polymerase II binding and transcription. Collectively, these transcription factors are referred to as *transcription factors for polymerase II* (TFII), with letters designating the different factors. TFIID binds first, then TFIIB, followed by RNA polymerase II, followed by several TFII factors such as E, F, G, H, and J, etc. TFIIH has kinase activity and phosphorylates RNA polymerase II, which now, independent of transcription factors, can initiate transcription. In addition, in many human genes, located at about base pair -200 upstream is the GGGCG box to which SP1 binds, and this is felt to be a regulator of housekeeping genes (Fig. 4-9).

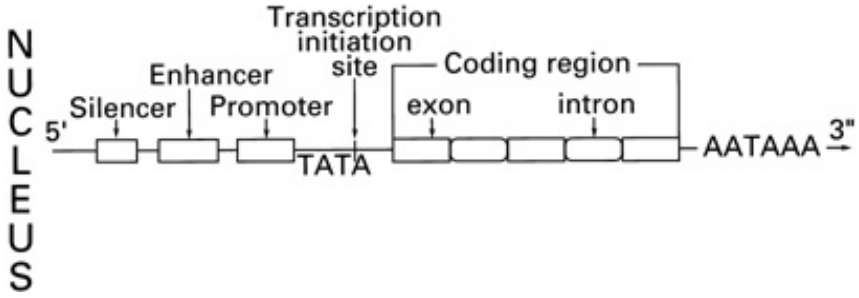

Figure 4-9: Structure of a gene. These small functional units within the nucleus contain the coding information for the synthesis of a polypeptide and on their 5′ ends have regulatory sequences that include silencers, enhancers, and promoters. The coding region consisting of exons (code for protein) as well as intervening noncoding sequences (introns) is followed by a 3′ noncoding region that is translated into the mRNA. The 3′ end appears important for exit of the mRNA from the nucleus and its stability in the cytoplasm but does not code for protein. The TATA is the initiation site for polymerase and is present in most eukaryotes at about 10 to 30 base pairs 5′ from the start codon (TAC) of the coding region. The AATAA will become the recognition site on the mRNA to which attaches an enzyme that cleaves the 3′ region and replaces the distal portion with a poly(A) tail. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

Gene expression refers to all the processes required to go from DNA to protein, from the initial unfolding of the nuclear chromatin in preparation for transcription to the mature protein emerging following completion of posttranslational changes. Regulation of this process occurs at all levels in response to signals both from within the cell and from the environment. The latter mechanism is of particular interest because it represents one of the major areas of research in molecular biology and cardiology, and it is also an area that has great potential for therapeutic intervention. The cell maintains its integrity and responds to external stimuli through signals that activate receptors (generally in the cell membrane). These in turn use signaling proteins to transfer their message to the cytoplasm or nucleus, which in some way modifies gene expression. Delineation of the receptor, the signaling proteins, and where and how gene expression is altered are of prime importance.

The most fundamental level of gene regulation involves cell differentiation (discussed later). The body contains at least 200 different types of cells that have been programmed by their genes to perform highly specialized functions. All cells have the same DNA and the same genes, but only those genes which are expressed determine the cell's phenotype. Cardiac myocytes, for example, are characterized by a set of proteins that specialize in contractile activity, whereas hepatocytes specialize in the synthesis and catabolism of proteins. Selective gene expression is the basis of cell

differentiation. Cell growth and replication occur in what is termed the *undifferentiated cell* but, through complex mechanisms, give rise to cells that cease to replicate and are programmed to take on specialized functions (cell differentiation). In the process of cell differentiation, genes-particularly those concerned with cell proliferation and undifferentiated functions-are down-regulated, whereas those genes coding for the proteins that perform the specialized functions are up-regulated. Once cells are differentiated, protein synthesis, however, remains a dynamic process to maintain cell integrity. Most of gene regulation is concerned with the maintenance of cellular integrity, and the genes responsible for this basal function are referred to as *housekeeping genes.* Housekeeping genes are constitutively regulated, as opposed to genes responsible for cell differentiation and growth, which are developmentally regulated. It is estimated that organs use about 10,000 genes (constitutive) to maintain their integrity, with one exception-the brain, which is estimated to use around 20,000 genes. Gene regulation may be classified under the following headings: pretranscription, transcription, posttranscription, translation, and posttranslation.[28]

Pretranscriptional regulation refers to the decompaction of the DNA and exposure of the region about to undergo transcription. The total DNA of a single cell would measure about 1 m in length, yet in the nucleus it is markedly compacted and is folded around specific proteins, the dominant class being histone. The coiling of the DNA appears to be in domains that can be exposed when transcription is activated. It is also at this level that methylation plays a part. Heavily methylated genes, made insensitive to digestion by the enzyme DNAse, tend not to be transcribed, whereas other areas sensitive to digestion appear to be very active in transcription. The precise mechanisms involved with chromatin conformational changes or exposure of the gene for transcription are, at present, relatively unknown. There is evidence, however, that methylation is involved in regulating cell differentiation.

The role of transcriptional control is a major rate-limiting step to gene expression. While transcription is catalyzed by the enzyme RNA polymerase II, the enzyme by itself cannot initiate transcription and acts only with the help of additional transcriptional factors. In addition to the promoter sequences previously described (TATA box and CG box), several DNA sequences in conjunction with their DNA-binding proteins act as either promoters, enhancers, or silencers of transcription and will be defined subsequently (see Fig. 4-9). The 5′ upstream region, immediately adjacent to the transcription initiation site and including the area that binds RNA polymerase II, is referred to as the *promoter region*. This region contains sequences that are specific binding sites for proteins referred to as *transacting factors,* or *transcriptional factors*. The protein-binding sites are often referred to as *cis-acting sequences* because they are on the same DNA molecule on which they act. The transcription factors (also referred to as *DNA-binding proteins*) are referred to as *transacting factors* (acting at a distance) because they are encoded by genes that may even be on another chromosome. The average promoter binding site consists of several hundred base pairs grouped into motifs of 4 to 10 base pairs.[29] It is hypothesized that all the motifs have to be bound by transcription factors of the appropriate nature and in the appropriate sequence for transcription to occur.

The promoter sequences and their corresponding DNA-binding proteins may act ubiquitously or may be tissue-specific. Promoters often increase transcription of a class of genes rather than a single gene. Another type of DNA sequence that increases transcription is referred to as an *enhancer* (see Fig. 4-9). Enhancers differ from promoter sequences in that they may be upstream or downstream from the coding region and be separated by as many as hundreds of thousand base pairs and are effective in either the 5′ to 3′ or 3′ to 5′ direction. An extreme example is the DNA sequence that enhances expression of the gene for hemoglobin, which is located more than 1 million base pairs from the transcription initiation site. These enhancers, like promoters, consist of several small motifs of 4 to 10 base pairs, and when bound by their corresponding DNA-binding proteins (transcription factors), they have a positive influence on gene transcription. Another regulatory DNA sequence that is similar to enhancers in size and location but exerts a negative influence on transcription is referred to as a *silencer* or *repressor*. It is believed that enhancer and

silencer sequences, when bound by transcription factors, communicate with promoters by DNA looping that is induced by the binding. This DNA binding that brings the enhancer, silencer, and promoter in close proximity is the mechanism responsible for the action-at-a-distance phenomenon seen in human gene regulation.

The genes that encode proteins regulating cardiac growth are many: growth factors, growth factor receptors, intracellular signaling proteins that relay growth signals from the extracellular milieu, and ultimately, transcription factors that regulate RNA polymerase and selectively induce or down-regulate gene expression.[30] Several DNA-binding proteins are recognized (transcription factors) ( Fig. 4-10), including the zinc-finger, leucine-zipper, helix-loop-helix, MADS domain, and helix-turn-helix proteins. The zinc-finger type of protein is used by developmental genes called *GATA factors* and the receptors for circulating hormones, including the glucocorticoids, progesterones, androgens, mineralocorticoids, estrogen, thyroxine, vitamin D_3, and retinoic acid. These hormones, which are lipophilic, penetrate the cell membrane and activate an intracellular receptor or nuclear receptor, which, in turn, activates gene expression through the zinc-finger transcription proteins. Many of the growth-related signaling proteins, such as c-fos, jun-B, and c-jun, dimerize through leucine-zipper proteins prior to binding to DNA. For example, c-fos dimerizes with c-jun and subsequently binds to DNA.[31] Transcription factors such as the *myo-D* family genes, which are the master genes for inducing differentiation of skeletal muscle, contain a helix-loop-helix motif. The MADS domain proteins include myocyte enhancer factor 2 (MEF2) and the serum response factor (SRF). The helix-turn-helix proteins include homeodomain-containing proteins that are important in the development of prokaryotes and eukaryotes.

Another level at which gene expression may be regulated is that of mRNA processing, whereby the introns are removed and the exons spliced together to provide the mature mRNA. In the majority of instances, each exon present in the gene is incorporated into a mature mRNA via ligation of consecutive pairs of exons and removal of all introns. This constitutive splicing process produces a single gene product from each transcriptional unit, even when the coding sequence is split into many separated exons. In other instances, however, nonconsecutive exons are joined in the processing of some gene transcripts, and this alternative pattern of primary mRNA splicing can exclude individual exons from mature mRNA in some transcripts and include them in others. The use of such differential splicing patterns creates mRNAs that generate a variety of proteins from a single gene. Differential splicing is particularly prevalent in genes of muscles and has been shown to occur in three of the eight major sarcomeric proteins studied thus far-myosin heavy chains, tropomyosin, and troponin T (skeletal and cardiac).

The 3′ non-protein-coding region of the mature mRNA contains the poly(A) tail, which is essential for message stability. It is believed that protein synthesis is, in part, regulated on the basis of alterations in message stability. The precise mechanism whereby an mRNA is induced to remain stable and encode several thousand polypeptides as opposed to being extremely unstable and encoding only a few molecules is not well understood. Nevertheless, it is likely to be an important step in regulating the response to cytoplasmic signals that require rapid synthesis of a particular polypeptide. Synthesis of a polypeptide initiated via transcription is estimated to take several minutes, whereas synthesis of a protein initiated through translation requires only seconds. Regulation of gene expression also occurs at the translational and posttranslational levels. Proteins are often translated as precursors that must undergo proteolytic cleavage. Others must undergo cleavage of leader sequences that are attached to direct them to their particular subcellular compartment. Other posttranslational modifications include protein glycosylation, the addition of polysaccharides and lipids, and the formation of disulfide bonds. Finally, polypeptides often polymerize with similar or different polypeptides to form complex tertiary structures that make up the mature proteins. The folding of polypeptides into mature proteins is guided by a group of genes that encode for so-called chaperone genes. Regulation of gene expression at the protein synthesis level is more fully discussed in Chap. 5.

Molecular Biology and the Basis for Recombinant DNA Technology

Modern molecular biology, initiated in the 1970s,[27,32] was in part due to four pivotal discoveries or inventions: restriction enzymes, reverse transcription, cloning, and DNA sequencing. Since DNA consists simply of four nucleotides joined together, it is a monotonous, repetitive molecule that, at first glance, offers no landmarks to recognize that a particular segment of DNA codes for a particular mRNA. The discovery of the restriction endonucleases provided the genetic scalpel to cut DNA into smaller pieces of predictable size that could be used in a variety of procedures. The unique feature of these enzymes is that each recognizes a specific sequence of DNA of 4 to 8 base pairs and cleaves the molecule at that particular site. Thus one knows precisely where the enzyme cuts, and using a number of different enzymes, one can identify the site and number of recognition sites for each enzyme in a fragment of DNA of interest and develop what is referred to as a *restriction map*. These enzymes also made it possible to cut DNA from different sources in a predictable manner in preparation for ligating them together into a recombinant molecule. Restriction endonucleases are obtained from bacteria, and enzymes have been purified that recognize more than 100 different cleavage sites. A restriction endonuclease is named after the bacterium from which it was isolated, taking the first letter of the genus of the bacterium, the first two letters of the species, and the first letter of the strain. An example of this would be an enzyme from *Haemophilus influenzae* referred to as *Hind-III*. The III simply refers to the third restriction endonuclease enzyme isolated from that particular species of bacteria. Thus the availability of restriction endonucleases made it possible to digest DNA into smaller molecules that could be manipulated and used in a variety of reactions and to develop a restriction map as well as develop chimeric DNA molecules, the latter being the essence of recombinant DNA technology.

The discovery that retroviruses contain an enzyme that catalyzes the formation of DNA from RNA, referred to as *reverse transcriptase,* revolutionized molecular biology. The resulting so-called complementary DNA (cDNA) (represented by the appropriate complementary bases for the mRNA, except, of course, with thymine replacing uracil) binds to the nucleotide sequences from which the particular mRNA was originally derived (Fig. 4-11). Messenger RNA, as discussed previously, codes for a specific polypeptide and is derived from a discrete, specific unit of DNA referred to as a *gene*. Reverse transcriptase reverses this process so that a cDNA is generated from an mRNA (coding part of the gene) and can be used as a gene to express the protein. The cDNA is reinserted into the genome of a vector (virus or plasmid) and subsequently replicated in an appropriate host, such as a bacterium, which made possible the first cloning of the gene. Radioactive labeling of a cDNA provides an extraordinarily powerful tool to develop known chromosomal landmarks and to isolate and identify particular genes. The labeled cDNA, referred to as a *probe,* or *indicator molecule,* is a routine, essential tool used to identify and isolate DNA or RNA fragments of interest. Development of rapid-sequencing techniques made it possible to sequence several thousand of bases per day. It is expected that a by-product of the Human Genome Project will be technology to sequence millions of bases per day.

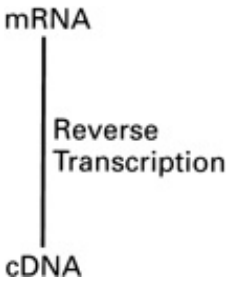

Figure 4-11: Generation of a complementary DNA (cDNA). Taking advantage of the enzyme reverse transcriptase, mRNA is converted to DNA, referred to as *complementary DNA* (cDNA). The DNA is single-stranded and complementary to the sequence of RNA, except thymine now

replaces uracil. Using DNA polymerase, one can then make the single-stranded DNA into double-stranded cDNA. The cDNA can be used as a probe to identify specific sequences or genes of the genomic DNA, or it can be inserted into vectors to be cloned or expressed in a variety of hosts.

Two features essential to all techniques of recombinant DNA technology need to be highlighted: The first is the ability of DNA to denature and anneal, or hybridize. The double-stranded DNA, held together by hydrogen bonding of the corresponding complementary bases, will, on exposure to high temperatures (95°C), separate into two strands, but under appropriate conditions (55°C), the complementary strands will again anneal precisely as originally and return to their normal double-stranded state. The process of separating into separate strands is referred to as *denaturation*, and the recombining process is known as *annealment*, or *hybridization*, with the latter term preferred if the two DNA fragments are from different sources. Second, the strands come together identically to the parent molecule because of complementary base pairing, whereby A must bind to T and C to G.

Unique Features of Recombinant DNA Technology

The techniques of recombinant DNA are unique and are not limited by some of the restrictions imposed on other scientific techniques.[3] Some of these are the abilities (1) to perform the structure-function analysis of a selected molecule or a portion thereof in the intact living cell or organism, (2) to isolate and identify genes responsible for hereditary diseases, (3) to unravel the molecular basis for the regulation of growth (including the heart), and (4) to generate large quantities of protein present only in trace amounts that otherwise would not be available, as well as the opportunity to genetically engineer proteins for maximum benefit with the least side effects. The techniques routinely used in molecular biology consist of electrophoresis, Southern and Northern blotting, DNA cloning, polymerase chain reaction (PCR), electrophoretic mobility shift assay, and the development of gene libraries. Techniques related to vessel wall biology and gene transfer are discussed in Chap. 8.

Isolation of DNA

Since the DNA of all human tissues is the same, practically any tissue can be used to obtain a DNA sample. It requires only a microgram for most procedures. In humans, lymphocytes are commonly used because they are very accessible and the DNA can be extracted easily. Lymphocytes are also used because they can be transformed by Epstein-Barr virus into an immortal cell line that can provide a continuous, renewable source of DNA. The cells can be grown in culture, frozen for years (from which samples can be obtained), thawed, and regrown, providing a renewable source of DNA for several decades. A sample of 10 to 15 mL of whole blood typically would yield about 50 to 100 μg of genomic DNA. If one's interest is restricted to the DNA sequences that are expressed, one would isolate mRNA and, using it as a template, employ reverse transcriptase to derive its cDNA. cDNA molecules represent the expressed form of a gene and thus can be used as probes to select the specific genomic DNA segments from which the mRNA was transcribed. Myocardial biopsies obtained under appropriate conditions provide adequate tissue for most DNA or RNA analyses.

Digestion and Electrophoretic Separation of DNA

One of the important physical properties of the DNA molecule is that each individual nucleotide possesses a net negative charge resulting from the phosphate group. Thus fragments of different sizes exposed to an electric field tend to migrate toward the positive electrode at differential rates depending on their size, with small fragments migrating faster than larger ones. This process of separation based on electric charge is called *electrophoresis*.[33] The DNA sample, after being digested into fragments of different size by a restriction endonuclease, is added to a gel matrix such as agarose or acrylamide. After separation by electrophoresis, the pattern of the DNA can be

visualized under an ultraviolet lamp with a fluorescent dye such as ethidium bromide (Fig. 4-12). Agarose gel electrophoresis will separate fragments from 1000 to 60,000 base pairs (60 kb) in size, and polyacrylamide gels effectively separate fragments smaller than 1000 base pairs (1 kb). The recent development of pulse-field gel electrophoresis (PFGE) made possible the separation of DNA fragments even up to 2000 kb in size. In this technique, the electric field is alternated in different directions, forcing the molecules of DNA to reorient between each pulse of electric current. Thus this technique is particularly suitable for isolating and characterizing large segments of DNA, such as to identify a known gene.

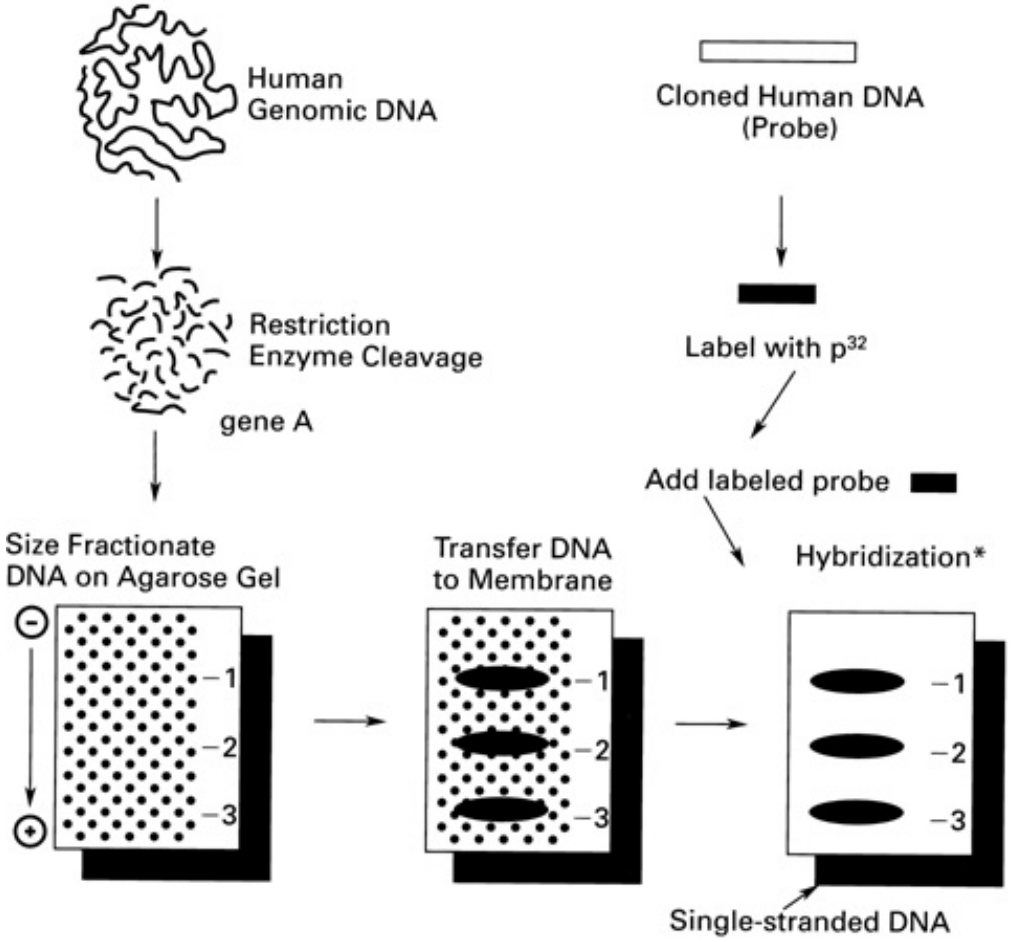

Figure 4-12: Southern blotting technique. The DNA is cleaved with an appropriately selected restriction endonuclease. The digested fragments are separated by electrophoresis on agarose gel, and the fragments of gene A are located at positions 1, 2, and 3 but cannot be seen against the background of many other randomly occurring DNA fragments. The DNA is denatured and transferred to a membrane in an identical pattern to what it was on the agarose gel. It is difficult to manipulate anything on a soft gel or to remove it. Once transferred to the membrane (filter), a solid support system, the DNA is much easier to handle. A DNA probe (cDNA) that has been labeled with 32P is hybridized to its cDNA and visualized after exposure of the nylon membrane to an autoradiograph. The transfer of the DNA from the gel to the membrane developed by Southern was a major innovation illustrated in the next figure. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

As noted previously, prior to electrophoresis, the DNA must be digested with one of the restriction endonucleases. The size of the fragments resulting from digestion will depend on the type of restriction endonuclease used, i.e., whether they recognize sequences of 4, 5, 6, or 8 base

pairs. Enzymes recognizing a 4-base-pair sequence will cut the DNA into much smaller fragments than one that recognizes an 8-base-pair sequence.

Development of a DNA Probe

A nucleic acid probe is a fragment of nucleic acid to which has been attached a label such as a radioisotope or a fluorescent compound, making it possible to easily detect and recognize the desired fragment among other native DNA molecules. The fragment labeled is usually cDNA or a synthetic oligonucleotide, although it could be RNA. It is now possible to synthesize DNA fragments of up to 30 to 40 base pairs, referred to as *oligonucleotides*, that, with an attached label, can be used as probes to identify cDNA in the human genome or mRNA. This takes advantage of the fact that at high temperatures, the double-stranded DNA probe and the native DNA will break into separate strands. On recombining at random, the labeled DNA probe can bind with either its original complementary strand or the native DNA that is complementary to the probe and thus provide a means of isolating a fragment of native genomic DNA. A probe is necessary in most recombinant DNA procedures to detect the molecule of interest following electrophoresis.

Southern, Northern, and Western Blotting

A procedure to separate and detect specific DNA fragments, referred to as *Southern blotting*, is named after E. M. Southern, who developed it in 1975.[34] Genomic DNA is isolated and digested into small fragments with restriction enzymes, and the fragments are separated by gel electrophoresis as described previously. Following separation, DNA fragments are denatured chemically into single-strand fragments. It is very difficult to handle gels and even more impractical to store them. Southern developed a technique whereby these separated single-strand fragments in the gel could be transferred by capillary action to a solid support medium (nylon or nitrocellulose membrane) and fixed permanently by heating. The pattern on the membrane reflects identically the pattern induced by electrophoresis on the gel. The process used to produce a Southern blot is illustrated schematically in Fig. 4-12. The nylon membrane and its attached single-strand DNA fragments are then incubated with a radioactively labeled complementary probe. The hybridized, radioactive double-strand product, on exposure to x-ray film (autoradiography), will exhibit the pattern of the radiolabeled DNA fragments (Fig. 4-13). In summary, the electrophoretic separation of DNA followed by its transfer to a nylon membrane for subsequent identification by radioactive hybridization is referred to as *Southern blotting*, and the autoradiogram as a *Southern blot*. The same approach to detect mRNA is referred to as *Northern blotting*. This procedure also can be used for detection of proteins, in which case it is referred to as *Western blotting* (Table 4-1). The only significant difference in detecting protein versus nucleic acid by this procedure is the probe, which is an antibody rather than an oligonucleotide, or cDNA. However, as in Southern and Northern blotting, the probe may be labeled with a radioactive isotope, a fluorescent tag, or some visual colorimetric substance.

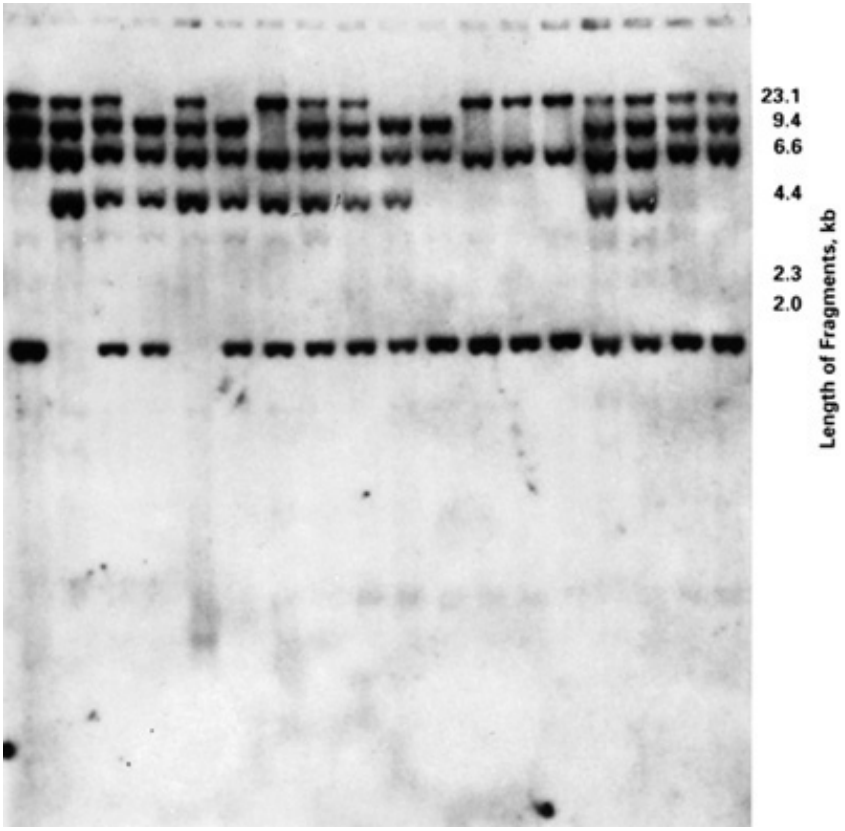

Figure 4-13: A typical Southern blot with distinct bands. Each vertical lane consists of DNA from a separate individual. All the individual DNAs were digested with the same restriction endonuclease. Following separation on electrophoresis and transfer to a nylon membrane, hybridization was performed with the selected radioactive probe, and thus only those fragments complementary to the probe are visualized. This is an analysis of a family with hypertrophic cardiomyopathy, and the different patterns reflect restriction fragment length polymorphisms (RFLPs) characteristic of the marker locus, which is linked to the disease locus. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

Table 4-1: Separation and Identification oF Molecular Species

Procedures	Molecule	Labeled Probe
Southern blotting	DNA	DNA or cDNA
Northern blotting	RNA	DNA or cDNA
Western blotting	Protein	Antibody

Cloning of a Gene

DNA cloning is a technique used to produce large quantities of a specific DNA fragment of interest.[35] It generally is quite feasible to produce a billion copies of a DNA fragment by routine bacterial cloning techniques. The DNA fragment of interest (insert) is inserted into the DNA of a vector, and the vector is amplified in an appropriate host cell. The host provides amplification of the DNA of both the vector and the foreign insert. The prerequisites for cloning are (1) isolation of the DNA fragment of interest, (2) a vector, which is often an extrachromosomal segment of DNA

with the ability to propagate independently of the host DNA, (3) a restriction endonuclease to digest both the insert and the vector so the DNA ends will be compatible for ligation (as illustrated in Fig. 4-14), (4) a DNA ligase to ligate the insert into the vector, (5) a means to introduce the vector into the host cell, and (6) a means to differentiate the host cells that have incorporated the vector from those which have not. Standard vectors used in cloning have circular DNA and fall into three classes: (1) plasmids harvested from bacterial cells (a *plasmid* is an extrachromosomal segment of DNA present in bacteria that is self-replicating and on which are located certain genes that express resistance to ampicillin or other antibiotics), (2) bacteriophages (commonly referred to merely as *phages*, they are viruses that invade and multiply in bacterial cells), and (3) an artificially developed vector (referred to as a *cosmid*). The insert and vector are enzymatically ligated together by DNA ligase into circular DNA, and the recombinant product (hence the name *recombinant*) is incorporated into a host such as a bacterium or a mammalian cell for amplification (Fig. 4-15). In order to identify whether or not the particular DNA of interest has been replicated in the host, a so-called selection gene, such as one responsible for ampicillin resistance, is incorporated into the vector. The bacteria are grown in media containing ampicillin so that only those with the resistance gene will survive. Since the resistance gene is attached to the DNA fragment of interest, it indicates that colonies (bacteria) or plaques (phage) that survive must contain the gene of interest. The size of the insert is a limitation in cloning. Plasmids can only accommodate inserts up to approximately 15,000 base pairs, phages up to 25,000 base pairs, and cosmids up to 45,000 base pairs. Recently, a new vector has been developed, namely, bacterial artificial chromosomes (BACs), that accommodates DNA fragments of up to 200,000 base pairs. The yeast artificial chromosome (YAC),[36] developed several years ago, accommodates DNA inserts of up to 2 million base pairs but is extremely difficult to work with on a routine basis; in contrast, the BACs are as convenient as plasmids or phages. This has markedly accelerated the cloning of large fragments of DNA. Cloning, as discussed, is performed to obtain multiple copies of DNA, and unless specifically designed, the DNA is neither transcribed into mRNA nor translated into protein. If one desires to express a particular DNA fragment or gene, one must then use what is referred to as an *expression vector*. It is imperative to provide a promoter element that is appropriate for the host, and the gene must contain the appropriate 5′ untranslated region for binding to the ribosome as well as the appropriate 3′ region for stability of the message. An example would be the expression of rt-PA in mammalian cells, whereby the protein is expressed and secreted to be harvested and processed commercially for use as a thrombolytic agent.

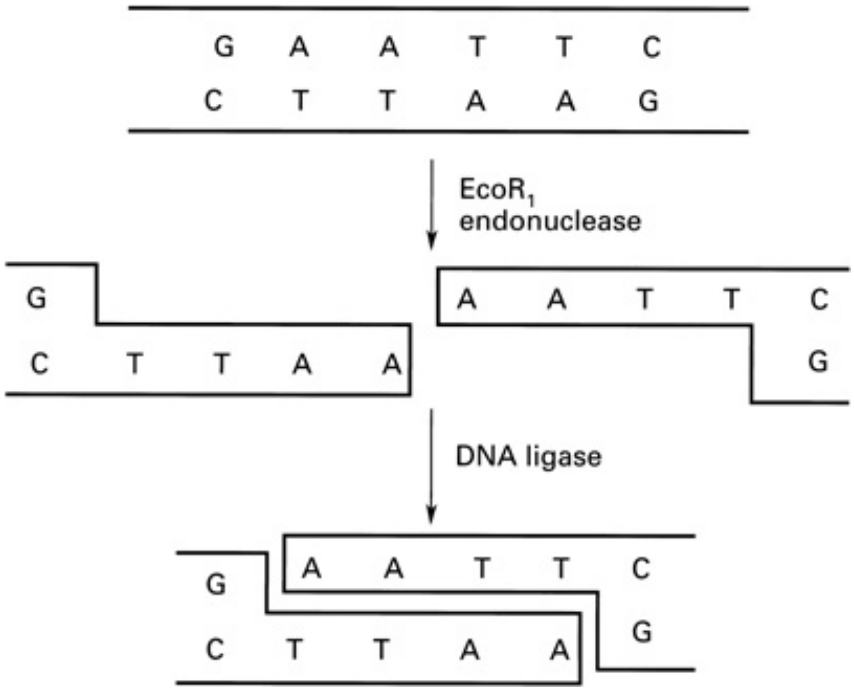

Figure 4-14: Restriction endonucleases recognize specific sequences and cut in a specific manner. The sequences recognized may be anywhere from 3 to 8 base pairs long and may cut to give a blunt end or a staggered end (EcoR1). Enzymes that provide staggered ends (cohesive or sticky ends) have unpaired bases that are easy to ligate together because they are complementary to each other, as shown in this illustration. This feature is exploited in cloning or in the formation of any recombinant DNA molecule. For cloning purposes, the fragment of DNA to be inserted is digested with the same restriction enzyme as is used to digest the DNA of the vector into which it will be inserted. Thus the sticky ends of the DNA insert and the vector will be complementary and easy to ligate together in the presence of the enzyme DNA ligase, as illustrated in Fig. 4-15.

Development of Gene Libraries

Gene libraries are usually called either genomic or cDNA libraries. A *genomic library* refers to one made from genomic DNA. A library is a collection of DNA fragments that have been cloned in an appropriate vector and grown in a particular host, usually bacteria. A major difference between a genomic and a cDNA library is that a genomic library contains DNA fragments composed of introns and exons, whereas a cDNA library is made from mRNA that represents genes expressed in a particular organ and does not have introns. The cDNA library contains genes specifically expressed in a particular tissue only. In contrast, a genomic library, whether derived from the heart or another tissue, will have the same genes. To make a human genomic library, one must first isolate the whole genome of a cell, cut it into fragments with a restriction enzyme, and insert the fragments into a vector replicated in an appropriate host, usually bacteria.[37] To increase the odds that enough fragments are cloned to represent the whole genome, certain calculations are necessary. It is assumed that the recognition site for a particular restriction enzyme occurs at random. For the restriction enzyme EcoR1, with a 6-base-pair recognition site, the average size of each fragment will be $4^6 = 4096$ base pairs. In contrast, if the recognition site involves 4 base pairs, each fragment would be $4^4 = 256$ base pairs long. If the 6-base-pair cutter were used for the human genome, the result would be the 3 billion base pairs of the human genome divided by 4096 to produce roughly 750,000 fragments requiring 750,000 colonies or clones. However, the recognition sites are not evenly or randomly distributed. Thus some fragments are larger and others are smaller, so to be certain, at least 1 million colonies would be required. Other factors also must be considered, such as the choice of vector with respect to insert size. Any part of the library that is used can be replaced by regrowing it, and thus the library is a permanent, renewable source of DNA. cDNA libraries of the whole heart and specific structures of the heart such as the Purkinje system are now available. To isolate a particular gene or fragment of DNA or cDNA from a library generally requires a radioactive cDNA probe.

Polymerase Chain Reaction

The PCR has revolutionized application of the techniques of molecular biology. This technique was not developed until 1985,[38,39] but its impact already has been felt throughout medicine and biotechnology. This procedure, conveniently and without the tedium of cloning, can provide 1 million copies of a DNA fragment in 3 to 4 h and 1 billion copies within 24 h. PCR simply and ingeniously takes advantage of the natural DNA replication process. One must know the sequence of the two ends of the DNA fragment that is to be amplified, but short sequences of 15 to 30 base pairs are adequate, and fragments in between these sequences as large as 20 kb can be amplified. The sequence is used to make two oligonucleotides, referred to as *primers*, with one for each end of the DNA fragment. The sequence of one primer is complementary to the sense direction, and the sequence of the other is made complementary to the antisense direction. The primers are used to prime the synthesis of cDNA strands and are designed such that the DNA between the primers is the fragment of interest to be amplified. If mRNA is to be amplified, it is first converted to a cDNA using the enzyme reverse transcriptase. The primers (oligonucleotides) and the necessary bases are added in excess, together with the enzyme Taq DNA polymerase (which catalyzes DNA synthesis) and a sample containing the DNA to be amplified. There are three steps to each cycle.

Initially, one must denature the DNA (separate the primers and the native DNA) into separate strands, which is done by increasing the temperature to 95°C. The temperature is then decreased to 50°C so that the primers and native DNA will reanneal to their complementary base sequences. The native DNA strands will bind not only to each other but also to the primers. The temperature is now increased to 65°C for synthesis of the new DNA fragments. Synthesis in the presence of Taq1 polymerase is initiated at the 5′ end, and further nucleotides are added in the 5′ to 3′ direction to provide the desired double-stranded DNA fragment. Taq1 DNA polymerase, isolated from *Thermus aquaticus,* is thermostable, which is of tremendous advantage in performing the PCR reaction. Since the high temperatures of up to 95°C do not destroy this polymerase, it negates the need to add DNA polymerase between each cycle. Furthermore, since Taq polymerase has an optimal activity at around 70°C, one can significantly accelerate DNA synthesis. The cycle is then repeated, and after about 30 cycles over 3 h, one should have about 1 million copies. There are many clinical applications for PCR. To make a diagnosis of viral myocarditis, for example, one can use PCR to amplify from a myocardial biopsy any specific viral RNA or DNA for which primers can be made. The sensitivity of most conventional techniques is inadequate to detect molecules unless present in 50,000 to 100,000 copies per cell. In contrast, only one copy of RNA or DNA is needed for detection by PCR, and in 3 to 4 h, up to 1 million copies can be generated, which is adequate abundance for detection by most conventional techniques. PCR offers exquisite diagnostic sensitivity and specificity for determining the etiology of cardiac disorders such as myocarditis, and in patients undergoing cardiac transplantation, it is used for detecting infection or immunologic rejection. Another application of PCR is to detect and amplify mutations associated with hereditary disorders. One also can sequence DNA directly from PCR without the need for cloning.

Electrophoretic Mobility Shift Assay (Band-Shift Assay)

This technique is used routinely to study transcriptional factors. On gel electrophoresis, DNA exhibits a certain migratory pattern owing to the large fragments moving more slowly and thus being detected as the stained bands closer to the negative electrode. If a transcription factor is bound to its DNA-binding site, migration is slowed, and the decreased mobility will be detected as a shift in the migrating band through the gel (hence the name). Using an antibody to the protein, one also can study the protein specifically. It was this technique that identified a unique family of DNA- and RNA-binding proteins that are specific for the triplet repeat CTG (or CUG) and are thought to play a role in the pathogenesis of myotonic dystrophy.[40]

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Chapter 4: PRINCIPLES OF MOLECULAR CARDIOLOGY

THE SARCOMERE AND CARDIAC CONTRACTION

Cardiac myocytes are large cells of up to 120 μm in length.[41] They are joined together in a syncytium. The sarcolemma surrounding the myocyte through the intercalated disk joins to adjacent cells and invaginates into the myofibril through the T-tubules. Cardiac muscle is composed of fibers, which in turn are composed of myofibrils. The myofibril has a periodicity imparted to it by the sarcomere, which is the working unit of contraction. The sarcomeres are joined in series with each other via the Z-lines. The sarcomere is composed of many proteins, with myosin and actin being the predominant proteins comprising the thick and thin filaments, respectively. Two regulatory proteins are attached to the actin filament-tropomyosin and the troponins C, T, and I-and two myosin light chain molecules are attached to the myosin heavy chains. The sarcomeres comprise about 50 percent of the mass of the cardiac myocyte and, depending on the state of contraction, vary from 1.6 to 2.2 μm in length, as shown in Fig. 4-16. The specific molecular functions of the proteins that comprise the sarcomere are now beingcarefully elucidated by the discovery of mutations that are responsible for inherited diseases, particularly familial hypertrophic cardiomyopathy (FHCM). It is now recognized that FHCM is essentially a disease of the sarcomere, with eight sarcomeric genes having being identified exhibiting over 100 mutations that cause hypertrophic cardiomyopathy (HCM).

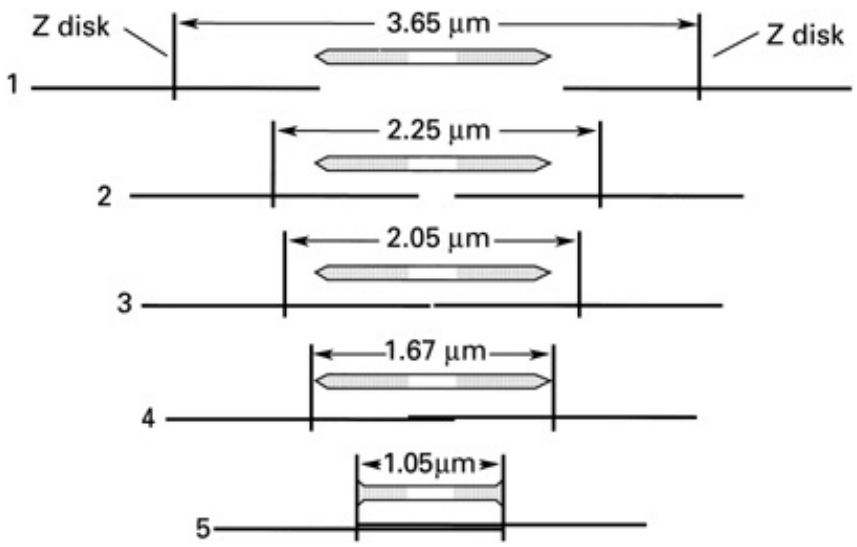

Figure 4-16: Relationship of sarcomere length and tension generated during isometric contraction of striated muscle. Maximum tension is generated at sarcomere lengths that allow maximum interaction of myosin heads and actin filaments (positions 2 and 3). If the sarcomere length is too short (positions 4 and 5), actin filaments overlap one another and prevent optimal interaction with myosin heads. (From Darnell J, Lodish H, Baltimore D, eds. *Molecular Cell Biology*. New York: Scientific American Books, W. H. Freeman; 1990. Reproduced with permission from the publisher.)

The Contractile Proteins

The proposed mechanism whereby the actin filaments slide over the myosin filaments and induce shortening or contraction is illustrated in Fig. 4-17. Cardiac contraction and relaxation are regulated in part by calcium. The sarcoplasmic reticulum (SR) induces contraction by releasing calcium and induces relaxation by sequestering it. Hydrolysis of ATP at a rate of one molecule per myosin head is required for each cycle, as the actin filament moves a distance of about 7 nm. In the relaxed state, myosin is prohibited from binding to actin by the presence of tropomyosin and troponin, which block the binding site for myosin. Myosin has minimal ATPase activity in the absence of actin; nevertheless, it does induce some hydrolysis of ATP to ADP and P_i. Systolic contraction is induced by calcium. Calcium released from the SR binds to troponin C, which induces a slight movement of tropomyosin that exposes the binding site on actin for myosin. The resulting binding of actin to myosin increases the ATPase activity of myosin by about 200-fold, which hydrolyzes the ATP to ADP. The ADP is released from the head of the myosin, which further enhances the binding of myosin to actin. The head of the myosin, which is oriented at a 90° angle to the actin, flexes to a 45° angle and in so doing moves the actin filaments closer together. Subsequently, the calcium is again sequestered by the SR, and ATP binds to the myosin head, which inhibits binding to the actin, relaxes the sarcomere, and reinitiates diastole (Fig. 4-18). Using high-intensity x-ray from a synchrotron, it has been possible to follow the changes in muscle-diffraction patterns during muscle contraction. The increase in cytosolic calcium and tropomyosin movement occur 17 ms after a muscle is stimulated. The myosin head attaches to actin after about 25 ms, and the tension is generated after about 40 ms (see also Chap. 5).

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Chapter 4: PRINCIPLES OF MOLECULAR CARDIOLOGY

CYTOSKELETAL PROTEINS

The cell *cytoskeleton* refers to the fibrous proteins that are present in the cytoplasm. The cytoskeletal fibers give the cell strength and rigidity and control movement within the cell. For example, the microtubules provide the tracks along which vesicles are transported by tubulin-binding molecules. These cytoskeletal proteins form three major classes subdivided according to size into microfilaments,[42] microtubules, and intermediate filaments.[43] The microfilaments are polymers of the protein subunit actin; the microtubules are polymers of the subunits of α- and β-tubulin, and the intermediate filaments are polymers of five different rod-shaped protein subunits. The polymerization and depolymerization of these fibers are closely regulated by the cell. Just as FHCM is essentially a sarcomeric disease, it appears that familial dilated cardiomyopathy (FDCM) is a disease of cytoskeletal proteins. Mutations in dystrophin,[44] α-dystroglycan,[44] α-sarcoglycan,[45] metavinculin,[46] actin,[47] and desmin[48] have all been shown to be associated with FDCM.

Microfilaments

In addition to the actin thin filaments of the sarcomere, which help to generate the force of contraction, actin filaments are distributed throughout the cytoplasm of essentially all cells and serve to transmit force. To serve its role as a transmitter of force, actin is linked to several other proteins. The dual function of actin is exemplified in the thin sarcomere filaments that generate force by mutations that induce FDCM,[47] whereas other mutations in the portion of the molecule that transmits force induce FHCM.[49] Titan, which binds myosin to the Z-line, is essential to the velocity and force developed by myosin-actin interaction, as is nebulin, which attaches actin to the Z-line. Dystrophin is the protein encoded by the gene responsible for Duchenne muscular dystrophy and is known to be a subsarcolemmal protein with the function of anchoring actin to the plasma membrane. Spectrin, which binds actin to the plasma membrane, has several isoforms, one of which is specific to the heart.[50]

Microtubules

Microtubules are about 24 nm in diameter, varying widely in length from a fraction of a micrometer to tens of micrometers. The microtubule wall is made up of globular subunits about 4 to 5 nm in diameter, and these subunits are arranged in 13 longitudinal rows encircling the hollow-appearing center. This basic design is present in practically all microtubules. Colchicine, which inhibits microtubule assembly, does so by binding to the tubulin. Microtubules are involved in movement and organization of cell organelles.

Intermediate Filaments

In contrast to actin and tubulin, which are widely distributed among cell types, the rather insoluble intermediate filaments are tissue- and cell-specific. Actin and tubulin are globular, and the polymers they form are rather like beads on a string. In contrast, intermediate filament subunit proteins are extended molecules that form ropelike polymers. The intermediate filament proteins include desmin, vimentin, neurofilaments, glial fibrillary acid protein, and the keratins. In cardiac myocytes, desmin filaments connect the desmosomes from one muscle cell to another and form the scaffold for both the Z-disk and the myofibrils. The desmin filament plays a role in the

transmission of the stress and strain of contractile force between cardiac myocytes. It also connects the nucleus to the plasma membrane. Recently, it was shown that a mutation in the tail region of desmin causes FDCM.[48] Mutations in the rod region induce a phenotype exhibiting skeletal and cardiac manifestations, whereas mutations in the tail region exhibit only a cardiac phenotype.[48] The restriction of the phenotype to cardiac tissue suggests a specific cardic function for the tail domain.

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Chapter 4: PRINCIPLES OF MOLECULAR CARDIOLOGY

MOLECULAR BASIS FOR CELLULAR GROWTH

Patterns of Growth (Hyperplasia, Hypertrophy, and Constitutive)

The molecular genetic basis for growth is somewhat distinct,[51,52] depending on when in the life of the organism it occurs, and may be divided into four phases: the embryonic phase of development and cellular differentiation (to be discussed later) occurring in utero, the rapidly growing phase prior to and during puberty, the normal constitutive maintenance growth throughout life, and compensatory growth in response to stimuli such as exercise or injury. Growth may be associated with an increase in the number of cells (hyperplasia) or just an increase in the size (hypertrophy) or just replacement of proteins as they are catabolized with no change in the number of cells, their size, or function (constitutive growth). During early development in the fetal and embryonic stages, practically all cells proliferate as well as increase in size and are said to be in cell cycle (Fig. 4-19). Throughout this process, certain cells drop out of cell cycle, cease proliferating, and undergo the process of differentiation. At birth or within weeks thereafter, certain cells of organs, such as the heart and brain, lose their ability to proliferate, and growth is restricted to the constitutive or hypertrophic type. Some cells undergo programmed cell death, called *apoptosis*. Many of the genes responsible for embryonic development subsequently downregulate after birth. Conversely, genes that code for proteins serving specialized functions in the differentiated cell are inhibited in the proliferating, undifferentiated cell and are only expressed on differentiation. For example, the muscle cell, on differentiation, downregulates the gene that encodes for BB creatine kinase and upregulates the gene that encodes for MM creatine kinase. Similarly, upregulation occurs for the genes that encode for myosin, actin, and other sarcomeric proteins essential to the contractile performance of the cell. It is estimated that the human body has a total of 10^{14} cells but only about 200 different types defined by their specific function. The specialized functions of a cell are determined by the repertoire of genes expressed in that particular cell.

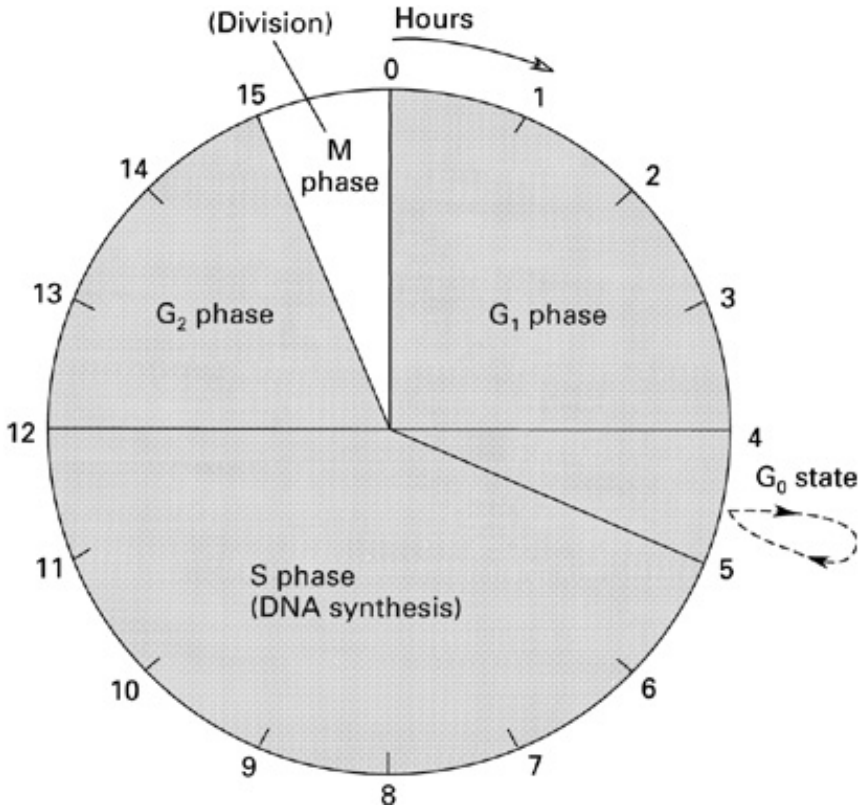

Figure 4-19: The cell cycle in a mammalian cell having a generation time of 16 h. The three phases spanning the first 15 h or so-the G1 (first gap) phase, and S (synthetic) phase, and the G2 (second gap) phase-make up the interphase, during which DNA and other cellular macromolecules are synthesized. The remaining hour is the M (mitotic) phase, during which the cell actually divides.

In the adult heart, most of normal growth is constitutive. It is estimated that most of the proteins of the heart are replaced every 5 days, except collagen, which replaces itself every 120 days; with hypertrophy, however, the half-life of collagen is only 17 days. Thus, in humans, the heart is replaced about every 3 weeks. It is estimated that all human functions are determined by about 67,000 genes, and about 10,000 genes (proteins) are required to maintain basal cellular integrity of a particular organ, except the brain, which requires about 20,000 genes. Thus, maintaining normal cellular homeostasis is a dynamic growth process. For example, in every second of a human being's life, more than a million trillion hemoglobin molecules are synthesized.

Growth Factors and Receptors Underlying the Growth Response

Normal and pathologic growth is initiated by multiple factors. Several of the circulating hormones, such as growth hormone, thyroxine, mineralocorticoids, glucocorticoids, and angiotensin II, act as growth factors. Growth factors such as transforming growth factor beta (TGFβ) and the fibroblastic growth factors (FGFs) are produced locally, released into the immediate environment, and mediate their effect on growth through what is termed *paracrine* or *autocrine mechanisms. Paracrine* refers to a growth factor that is secreted and affects the growth of adjacent cells. *Autocrine* refers to a growth factor that binds to the receptors of the same cell from which it was produced and secreted. *Intracrine* refers to a growth factor that induces growth in the same cell from which it was produced without being secreted. An external stimulus that influences growth is detected by a receptor that usually sits on the cell's surface as an intramembrane receptor and is relayed through several signaling or transducing proteins to the nucleus of the cell, where the ultimate effector molecule is a transcription factor (Table 4-2). The effector molecule also may affect growth through regulation of translation. The latter, however, is usually more transient, whereas a sustained change in growth almost always is mediated through

transcription. The signaling proteins usually involve kinases and phosphatases, which through phosphorylation transfer ATP to amplify the signal and by dephosphorylation decrease it or in some way alter it (Fig. 4-20). Regulation of protein synthesis also may result from altered stability of mRNA. The growth response to circulating hormones or locally produced growth factors occurs several hours after the initial stimulation and is more likely to occur if two or more growth factors have been activated (see Chap. 5). In the case of the heart, a common signal is increased intraventricular pressure, which results in compensatory hypertrophy (see Chap. 5).

Table 4-2: Cascade for Relaying Growth Signals

Receptor
↓
Coupling protein
↓
Signaling molecule
↓
Effector protein (transcription factor)

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Chapter 4: PRINCIPLES OF MOLECULAR CARDIOLOGY

THE CARDIAC GROWTH RESPONSE

The growth response of the myocardium to injury, whether it be myocardial infarction, hypertension, or valvular disease, is a major determinant of morbidity and mortality. Growth is the major long-term adaptive mechanism of the heart (see Chap. 5). In hypertrophy, the sarcomeres are added in parallel, which gives rise to thickened walls of the cardiac chambers.[53] In contrast, in cardiac dilatation, the growth is achieved by adding sarcomeres in sequence.[54] It remains to be determined whether dilated cardiomyopathy occurring as a pathologic entity is a normal compensatory response or represents abnormal growth or an inadequate growth response.

Developmental growth in utero or during prepuberty and puberty is associated with orchestrated stimuli from a variety of hormones such as growth hormone. This is in sharp contrast to the restricted cardiac growth observed in the adult in response to injury. For example, in aortic constriction, the left ventricle responds with increased mass, while the right ventricle is not affected. Hammond et al.[55] in 1979 demonstrated that the growth stimulus was indeed localized to the affected organ. Left ventricular hypertrophy was induced by aortic coarctation in the dog. Supernatants of the homogenized, hypertrophied left ventricle from dogs with aortic coarctation and normal dogs were used to perfuse a normal canine heart. Messenger RNA of the perfused heart was increased by extracts from the hypertrophied left ventricle but not from the normal myocardium, indicating the presence of a growth factor in the hypertrophied ventricle. This established the presence of a localized cellular stimulus acting through autocrine, paracrine, or intracrine mechanisms to induce cardiac hypertrophy. This was confirmed by Imamura et al.[56] in 1990; they showed that hypertrophy occurs in the left ventricle in response to aortic coarctation without growth in other chambers of the heart, while banding the pulmonary artery induced hypertrophy of the right ventricle without involvement of the left ventricle. Similarly, hypertrophy induced by volume overload, myocardial infarction,[57] or other forms of injury is restricted to the cardiac chamber involved. Despite the myocyte not increasing in number in the adult heart during hypertrophy, certain other features are interesting and unique. Cardiac myocytes, during their normal growth response, exhibit DNA synthesis (multiple nuclei)[58] and the reexpression of several fetal proteins otherwise expressed only in embryonic cells.[59] The rational basis for the reexpression of fetal protein is not obvious. The response has been referred to as *adaptive*, *maladaptive*, or part of a *triggered program response*.[28] The atrial natriuretic factor gene is expressed in the atria and ventricles in the embryonic state but not in the normal adult ventricle. It is reexpressed in the ventricle during hypertrophy.[60] Calcium ATPase, an enzyme essential to cardiac contractility, is decreased in the hypertrophied human ventricle.[61] It is well documented in the developing mammalian heart in utero that the initial actin gene expressed is that of smooth muscle type, followed by that of skeletal muscle and finally cardiac muscle.[62] The functional significance, if any, of the reexpression of fetal genes when the cardiac growth program is turned on in the adult heart is unknown. It is possible that the growth response can only be activated through expression of a family of genes. The master gene controlling expression of such a family could be triggered by a growth factor stimulated by pressure overload; this could result in a cascade of genes expressed, most of which are incidental rather than adaptive or maladaptive. For example, in skeletal muscle there is a master gene, *myo-D*,[63] that triggers the differentiation of skeletal muscle. When this occurs, a cascade of genes is downregulated, and another cascade of genes is upregulated. *Myo-D* is not expressed in cardiac muscle, and no such triggering factor has been found for cardiac myocyte differentiation (see Chap. 9).

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Figure 4-9: Structure of a gene. These small functional units within the nucleus contain the coding information for the synthesis of a polypeptide and on their 5′ ends have regulatory sequences that include silencers, enhancers, and promoters. The coding region consisting of exons (code for protein) as well as intervening noncoding sequences (introns) is followed by a 3′ noncoding region that is translated into the mRNA. The 3′ end appears important for exit of the mRNA from the nucleus and its stability in the cytoplasm but does not code for protein. The TATA is the initiation site for polymerase and is present in most eukaryotes at about 10 to 30 base pairs 5′ from the start codon (TAC) of the coding region. The AATAA will become the recognition site on the mRNA to which attaches an enzyme that cleaves the 3′ region and replaces the distal portion with a poly(A) tail. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

Figure 4-10: Types of transcription factors that affect gene activation. Schematic representation of the shapes of four types of protein transcription factors that bond to DNA and influence gene activation. Helix-turn-helix is a protein with two α-helices separated by a β-turn. Leucine zippers are protein dimers with entering leucine amino acids. Zinc fingers have a peptide loop connected at the base by a zinc ion tetrahedran between cysteine and/or histidine in amino acids. The helix-loop-helix consists of α-helix but uses leucine zippers and has a loop between the α-helices. The darkened areas are believed to be the regions of the protein that interact with the DNA to modulate transcription.

Figure 4-11: Generation of a complementary DNA (cDNA). Taking advantage of the enzyme reverse transcriptase, mRNA is converted to DNA, referred to as *complementary DNA* (cDNA). The DNA is single-stranded and complementary to the sequence of RNA, except thymine now replaces uracil. Using DNA polymerase, one can then make the single-stranded DNA into double-stranded cDNA. The cDNA can be used as a probe to identify specific sequences or genes of the genomic DNA, or it can be inserted into vectors to be cloned or expressed in a variety of hosts.

Figure 4-12: Southern blotting technique. The DNA is cleaved with an appropriately selected restriction endonuclease. The digested fragments are separated by electrophoresis on agarose gel, and the fragments of gene A are located at positions 1, 2, and 3 but cannot be seen against the background of many other randomly occurring DNA fragments. The DNA is denatured and transferred to a membrane in an identical pattern to what it was on the agarose gel. It is difficult to manipulate anything on a soft gel or to remove it. Once transferred to the membrane (filter), a solid support system, the DNA is much easier to handle. A DNA probe (cDNA) that has been labeled with 32P is hybridized to its cDNA and visualized after exposure of the nylon membrane to an autoradiograph. The transfer of the DNA from the gel to the membrane developed by Southern was a major innovation illustrated in the next figure. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

Figure 4-13: A typical Southern blot with distinct bands. Each vertical lane consists of DNA from a separate individual. All the individual DNAs were digested with the same restriction endonuclease. Following separation on electrophoresis and transfer to a nylon membrane, hybridization was performed with the selected radioactive probe, and thus only those fragments complementary to the probe are visualized. This is an analysis of a family with hypertrophic cardiomyopathy, and the different patterns reflect restriction fragment length polymorphisms (RFLPs) characteristic of the marker locus, which is linked to the disease locus. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

Figure 4-14: Restriction endonucleases recognize specific sequences and cut in a specific manner. The sequences recognized may be anywhere from 3 to 8 base pairs long and may cut to give a blunt end or a staggered end (EcoR1). Enzymes that provide staggered ends (cohesive or sticky ends) have unpaired bases that are easy to ligate together because they are complementary to each other, as shown in this illustration. This feature is exploited in cloning or in the formation of any recombinant DNA molecule. For cloning purposes, the fragment of DNA to be inserted is digested with the same restriction enzyme as is used to digest the DNA of the vector into which it will be inserted. Thus the sticky ends of the DNA insert and the vector will be complementary and easy to ligate together in the presence of the enzyme DNA ligase, as illustrated in Fig. 4-15.

Figure 4-15: DNA cloning. The basic objective of cloning is to provide multiple copies of a DNA fragment of interest. The fundamental principles for in vitro cloning of specific DNA fragments are as follows: (1) The human genome DNA of interest is isolated after digested by a restriction endonuclease, which is often referred to as the *DNA insert*. (2) A DNA vector is selected (shown on the right); the vector is a plasmid that has circular DNA and contains the necessary replication site and the reporter gene (drug resistance gene) to subsequently recognize which host has the insert. The vector and the DNA fragment to be inserted are digested with the same restriction endonuclease so that the ends are complementary for ligation. (3) DNA ligase ligates compatible insert and vector ends together. (4) Finally, host cells are transformed by incorporating vectors containing insert fragments and are identified by characteristics encoded by resident genes on the vector. Some of the clones will be viable and others not. (From Mares A Jr, Towbin J, Bies RG, Roberts R. Molecular biology for the cardiologist. *Curr Probl Cardiol* 1992; 17:9-72. Reproduced with permission from the publisher and authors.)

Figure 4-16: Relationship of sarcomere length and tension generated during isometric contraction of striated muscle. Maximum tension is generated at sarcomere lengths that allow maximum interaction of myosin heads and actin filaments (positions 2 and 3). If the sarcomere length is too short (positions 4 and 5), actin filaments overlap one another and prevent optimal interaction with myosin heads. (From Darnell J, Lodish H, Baltimore D, eds. *Molecular Cell Biology*. New York: Scientific American Books, W. H. Freeman; 1990. Reproduced with permission from the publisher.)

Figure 4-17: Sarcomere ultrastructure.

Figure 4-18: Molecular basis of myocardial contraction. (Adapted with permission from Alberts B, Bray A, Lewis J, et al, eds. *Molecular Biology of the Cell*, 2d ed. New York: Garland; 1991:621.)

Figure 4-19: The cell cycle in a mammalian cell having a generation time of 16 h. The three phases spanning the first 15 h or so-the G1 (first gap) phase, and S (synthetic) phase, and the G2 (second gap) phase-make up the interphase, during which DNA and other cellular macromolecules are synthesized. The remaining hour is the M (mitotic) phase, during which the cell actually divides.

Figure 4-20: Illustration of many proteins with varied functions for which oncogenes are known to encode. It is clear from this diagram that oncogenes encode proteins that function as growth factors, receptors, coupling proteins, signaling proteins, and transcription factors.

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Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 5:

MOLECULAR AND CELLULAR BIOLOGY OF THE NORMAL, HYPERTROPHIED, AND FAILING HEART

Author: Richard A. Walsh

INTRODUCTION

Growth of the heart is a dynamic process that occurs during embryogenesis, postnatal development, maturity, and senescence and in response to changing environmental and pathologic conditions. Cardiac growth occurs at the cellular level as a consequence of the interplay between *hyperplasia* (increase in cell number) and *hypertrophy* (increase in cell size) or a combination of both processes. The relative importance of each of these two mechanisms depends upon the cell type, developmental stage, and the nature of the growth stimulus. These two forms of cell growth are variably modulated by *apoptosis*, or programmed cell death.[1,2] This phenomenon is of importance in the determination of heart shape and chamber formation during cardiogenesis and may contribute to altered cardiac chamber geometry in response to pathologic stimuli. Physiologic and pathologic cardiovascular growth are generally mediated by developmental programs, mechanical deformation, and injury in various combinations. These processes stimulate a repertoire of biochemical signals that alter the cardiovascular phenotype. The application of molecular and cell biological approaches to this problem is rapidly defining the precise factors responsible for normal and pathologic growth of the heart and the mechanisms responsible for altered cardiac function.

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Chapter 5: MOLECULAR AND CELLULAR BIOLOGY OF THE NORMAL, HYPERTROPHIED, AND FAILING HEART

CARDIAC GROWTH AND HYPERTROPHY

Cardiac hypertrophy is a process wherein there is an increase in chamber mass produced largely by an increase in the size of terminally differentiated cardiomyocytes. Although cardiomyocytes make up only one-third of the total cell number, they are responsible in aggregate for over 70 percent of cardiac volume. Cardiac hypertrophy may be reasonably categorized as either physiologic or pathologic (Fig. 5-1).

Physiologic Hypertrophy

Physiologic hypertrophy includes cardiogenesis during embryonic development, postnatal cardiac growth, a modest additional increase in heart size that evolves during senescence, and the increase in heart size that occurs in response to athletic conditioning. The earliest stage of cardiac growth in utero depends on a genetically determined developmental program, since it can occur in the absence of contractile activity. Subsequently, mechanical forces become increasingly important in the development of the normal cardiac phenotype. Throughout the embryonic period and for a few weeks after birth, cardiac growth occurs as a consequence of hyperplasia and hypertrophy of myocytes (see Chap. 9). Classically, adult myocytes have been described as terminally differentiated-that is, incapable of reentering the cell cycle. This issue is currently undergoing reexamination. It is critical to make a distinction between DNA synthesis and cell division. In the adult cardiomyocyte, DNA synthesis may clearly result in either multinucleation or polyploidy (an increase in the DNA content of a single nucleus). By contrast, there is little evidence that cardiomyocytes are capable of division under normal conditions after the early postnatal period.[3,4] The capacity to reactivate hyperplasia in the terminally differentiated cardiomyocyte is an area of intense research interest, with potentially important therapeutic implications in the hypertrophied and failing heart.[5]

From birth to maturation, the mammalian heart undergoes a sixfold increase in mass. The normal heart/body weight ratio is species-specific. The largest hearts relative to body size occur in animals with survival requirements that depend on sustained exercise rather than on burst activity.[6] In humans, intense, prolonged exercise training can produce an increase in cardiac mass. Isotonic exercise, such as running, produces *eccentric hypertrophy*, characterized by a normal ratio of wall thickness to dimension, whereas isometric exercise, such as weight lifting, stimulated *concentric hypertrophy*, associated with an increased ratio of wall thickness to dimension.[7] Senescent animals and humans free of organic heart disease develop mild concentric left ventricular hypertrophy as a consequence of age-related decreases in the distensibility of the peripheral vasculature.[8] The molecular, biochemical, and physiologic changes associated with physiologic hypertrophy differ both qualitatively and quantitatively from those that occur during pathologic hypertrophy. Physiologic studies in animal models and humans have demonstrated no substantial alterations in isolated muscle or intact heart function. There is also little evidence of alterations in the molecular determinants of excitation-contraction coupling. Most importantly, epidemiologic data fail to demonstrate adverse risk associated with the modest hypertrophy that occurs as a consequence of athletic conditioning. It is, therefore, important clinically to distinguish physiologic hypertrophy from hypertrophic cardiomyopathy in athletes (see Chap. 67).

Pathologic Hypertrophy

Pathologic hypertrophy is an important adaptive response to abnormal global or regional increase in cardiac work. Initially, the increase in cardiac mass serves to normalize wall stress and permit normal cardiovascular function at rest and during exercise in *compensated hypertrophy*. If the stimulus for pathologic hypertrophy is sufficiently intense or prolonged, *decompensated hypertrophy* and heart failure ensue. Pathologic hypertrophy may be caused by pressure overloading, as in systemic or pulmonary arterial hypertension, left ventricular outflow obstruction, or aortic coarctation. Pressure overloading produces an increase in systolic wall stress and results in concentric ventricular hypertrophy. Volume overloading, as occurs in mitral or aortic regurgitation or as a result of arteriovenous fistulas, also produces pathologic hypertrophy. These latter conditions induce an increase in either diastolic wall stress (mitral regurgitation) or both systolic and diastolic wall stress (aortic regurgitation and arteriovenous fistulas) and result in eccentric left ventricular hypertrophy. Regional hypertrophy that occurs in viable myocardium adjacent to and remote from an area of infarction has the characteristics of eccentric hypertrophy.

There are exceptions to the principle that pathologic hypertrophy occurs as a result of excessive increases in external work. For example, hypertrophic cardiomyopathy is produced by point mutations of the sarcomeric proteins, in particular the β-myosin heavy chain. These mutations result in massive asymmetric or concentric hypertrophy in the absence of augmented peripheral hemodynamic requirements (see Chap. 62). It is possible that the massive myofibrillar disarray that characterizes this genetic form of hypertrophy increases internal cardiac work, which, in turn, increased cardiac mass.[9,10] Genetically engineered mice with cardiac-specific postnatal overexpression of the β_2 adrenergic receptor[11] or targeted ablation of the phospholamban gene[12] have enhanced cardiac function throughout life but no significant increase in cardiac mass. By contrast, similar cardiac overexpression of the sarcoplasmic reticulum-binding protein calsequestrin in mice results in hypofunction of the heart, with decreased external work and substantial cardiac hypertrophy.[13] Finally, tachycardia-induced heart failure in animal models and humans is associated with increased external cardiac work, decreased cardiac function, and no alteration in cardiac mass. These recent observations suggest a critical reexamination of the primary role of mechanotransduction in the etiology of pathologic hypertrophy.

Mechanisms for the Development of Cardiac Hypertrophy

STIMULI AND SIGNAL TRANSDUCTION PATHWAYS

Stretch-Induced Growth Factors

Dynamic or static stretch of neonatal or adult cardiomyocytes, papillary muscle, isolated heart, or intact heart produces increased cardiac protein synthesis and resultant cellular hypertrophy.[14] The process by which stimuli in the physical domain activate intracellular growth-signaling pathways is known as *mechanotransduction*.[15] There is evidence that this process may be accomplished in the cardiomyocyte by stretch-activated sarcolemmal ion channels, G protein-coupled receptors, NA^+/H^+ antiporters, tyrosine kinase-containing receptors, and/or an extracellular matrix-integrin linked pathway. These cell-surface mechanotransducers then activate cytosolic signal transduction pathways that initiate gene transcription and translation of increased quantities of protein (Fig. 5-2). Important signal transduction pathways that are clearly activated by mechanical deformation include protein kinase C (PKC), mitogen activated protein (MAP) kinases, stress-activated protein kinase, and possibly cyclic adenosine monophosphate (cAMP)-dependent protein kinase.[16] In particular, stretch of neonatal cultured cardiomyocytes produces G protein-mediated activation of membrane-bound phospholipase C, which, in turn, hydrolyzes phosphatidylinositol bisphosphate (PIP_2) to inositol trisphosphate (IP_3) and diacylglycerol (DAG). Diacylglycerol then activates PKC.[17,18] Phosphorylation of downstream cytosolic and nuclear proteins and transcription factors by PKC is known to be of critical importance for growth in a

number of cell types, while inositol triphosphate is an important modulator of cytosolic calcium homeostasis by the interaction with its receptor on the sarcoplasmic reticulum. Angiotensin II receptor coupling appears to play a critical role in the activation of phospholipase C;[19,20] however, α_1-adrenergic and endothelin receptor stimulation can also activate this pathway, with resultant hypertrophy in the neonatal cardiomyocytes and in transgenic mice.[21-23]

Current information suggests that mechanotransduction and a number of interrelated autocrine, paracrine, and endocrine effects of hormones and growth factors mediate cardiac hypertrophy[24] (Fig. 5-2). The resultant activation of multiple signal transduction pathways, which have demonstrable cross talk and considerable redundancy, provides a powerful mechanism by which the heart can respond to changing chronic hemodynamic requirements. A point of downstream convergence of multiple signal transduction pathways in the heart and noncardiac systems appears to be the phosphorylation of mitogen-activated protein kinase [MAPK, also known as extracellular signal regulated kinase (ERK)].[25] Mammalian MAPKs are serine-threonine protein kinases that are activated by signal transduction pathways coupled to both phosphatidylinositol hydrolysis/PKC activation and receptor protein tyrosine kinases (Fig. 5-2). Of particular importance to cardiac hypertrophy is the observation that important transcription factors (c-*jun*, c-*myc*, $p62^{TCF}$) are known substrates of MAPK phosphorylation. Recently, transfection of an antisense nucleotide to MAPK was shown to prevent hypertrophy in cardiomyocytes. Information from noncardiomyocyte cell systems, neonatal and adult myocytes, and genetically engineered mice has demonstrated considerable complexity, redundancy, and cross talk among these and other intracellular signaling pathways in the development of the cardiac hypertrophy phenotype in response to stretch and other stimuli.[26] In particular, ischemia, hypoxia, oxidative stress, neurohormones, and cytokines can activate downstream signaling and resultant nuclear transcriptional events, including cardiomyocyte hypertrophy and fibroblast hyperplasia.

Non-Stretch-Induced Growth Factors

Gαq-coupled receptors-which include angiotensin II, phenylephrine, endothelin, prostaglandin F2α, and thrombin-can induce hypertrophy of neonatal cardiomyocytes in culture in the absence of altered mechanical forces and in vivo in genetically engineered mice when the receptor is overexpressed.[27]

Cytokines

Cytokines were initially characterized by their pleiotropic effects upon the cellular components of the immune system. They have recently been implicated in normal and pathologic cardiac growth by a variety of in vitro and in vivo animal studies and by clinical investigation. Cytokines of the interleukin-6 and cardiotrophin family activate the gp130 cardiomyocyte transmembrane receptor and rapidly stimulate cytoplasmic Janus kinases (JAK); these, in turn phosphorylate other cytoplasmic proteins called signal transducers and activators of transcription (STAT). Various components of gp130 and JAK-STAT pathways have induced hypertrophy in vitro and in vivo when overexpressed in transgenic mice.[28] By contrast interleukin-1 and tumor necrosis factor alpha (TNF-α) use a distinct pathway that involves activation of a phosphatidylcholine-specific phospholipase C with generation of diacylglycerol.[29] These cytokines are elevated in the plasma of patients with congestive heart failure, and inhibition of their effects is a current therapeutic target for clinical heart failure. There is increasing evidence that stimulation of cell-surface tyrosine-kinase receptors can elicit a hyperplastic or hypertrophic response in neonatal cardiomyocytes. Both acidic and basic fibroblast growth factors (FGFs), which act as ligands for tyrosine-kinase receptors, can induce myocyte growth.[30] Acidic FGF produces a hyperplastic response, whereas basic FGF stimulates an increase in protein synthesis with resultant hypertrophy.[31] In contrast to its role in vascular smooth muscle growth, transforming growth factor beta (TGF-β) does not induce a growth response under these conditions.[32]

In addition to FGF and TGF-β, insulin-like growth factor 1 (IGF-1) is expressed in the myocardium in response to pressure overload hypertrophy.[33] These and other peptide growth factors [neural growth factor (NGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and insulin] bind to receptor tyrosine kinases (RTK). These receptors undergo ligand-mediated homodimerization with resultant autophosphorylation of tyrosine residues on the cytoplasmic domain. These tyrosine complexes recruit signaling molecules such as the monomeric GTP-binding protein P21 ras to the membrane, where transient complexes stimulate downstream signaling to the nucleus. Increasing evidence using loss of function and gain of function in in vitro studies of neonatal myocytes implicates this signaling molecule and its downstream effector raf-1 as potential mediators of cardiac growth.[34]

Hormones

Thyroid hormone is generally considered the classic hormonal mediator of cardiac hypertrophy. Administration of excess thyroid hormone to experimental animals produces increased heart weight that is associated with transcriptionally mediated alterations in the myosin heavy chains (MHCs), calcium-cycling proteins, and other functional constituents of the cardiomyocyte in small animals and primates.[35] Thyroid hormone-induced hypertrophy appears to be an indirect effect of the T_3-mediated increased oxygen consumption and resultant augmentation of cardiac work. For example, heterotopic transplantation of a nonworking rat heart into the abdominal aorta of the hyperthyroid animal is unassociated with hypertrophy, despite the presence of the transcriptionally mediated effects of the hormone in the transplanted organ and hypertrophy and typical transcriptional events in the native working heart.[36,37]

In addition to the indirect effects of thyroid hormone on cardiac growth, other endocrine mediators of hypertrophy have been examined. Growth hormone, which mediates its effects in large part though IGF-1, may be a mediator of physiologic hypertrophy. By contrast, there is preliminary evidence that retinoic acid and vitamin D may inhibit cardiac growth.[38,39]

Calcium Signaling

Increases in intracellular calcium have been associated with hypertrophic cardiomyocyte growth in vitro (see Figs. 5-2 and 5-3).[40,41] For example, use of the calcium ionophore BAYK8644 enhances while application of a membrane-permeable calcium chelator inhibits the cellular hypertrophic response by affecting calcium-calmodulin-dependent protein kinase. In addition, calcineurin, a phosphatase activated by intracellular calcium, dephosphorylates nuclear factor for activation of transcription (NFAT), which translocates to the nucleus, where it activates numerous transcription factors such as GATA-4. In vitro and in vivo studies using genetically engineered mice have demonstrated that augmented levels of activity of calcineurin, NFAT, or both can initiate a hypertrophic response. However, the relative role of this pathway in normal and pathologic growth of the heart is unclear at this time.[42,43]

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PROTEIN CONTENT AND ISOFORM DIVERSITY

The hallmark of cardiac hypertrophy is a net increase in protein synthesis above protein degradation. Under normal circumstances, these two processes are matched and result in nitrogen balance. Since the average half-life of cardiac proteins is 5 days, the composition of the adult heart is regenerated approximately every 3 weeks. The more rapid rate of cardiac growth in response to increased hemodynamic load could result from an augmentation in either the efficiency or the capacity of protein synthesis or a combination of the two.[44,45] Efficiency of protein synthesis is usually measured as moles of amino acid incorporated per milligram of cellular RNA per hour; capacity is assessed by determining the number of milligrams of RNA per gram of tissue. Experiments in a variety of systems indicate that the critical determinant for cardiac hypertrophy is an increased capacity for protein synthesis, which is mediated by augmented ribosomal content. Protein degradation appears to be modestly increased in cardiac hypertrophy and may play a critical role in the distinctive geometry of the ventricles in response to pressure or volume overloading, regression of hypertrophy, and cardiac atrophy.[46,47] The mechanisms for protein degradation in the heart involve the activation of both lysosomal and cytosolic proteases. Posttranslational processes are increasingly being recognized as important factors in the production of the cardiac phenotype in cardiac hypertrophy and failure.[35,48]

In addition to increased total protein content, cardiac hypertrophy is characterized by alterations in the relative abundance and isoform composition of the cardiomyocyte contractile, regulatory, and calcium-cycling proteins and other subcellular constituents. These processes provide an additional degree of plasticity for the heart to adapt to changing functional requirements. It is clear that there is considerable species specificity in the capacity for isoform switching. In small mammals with rapid heart rates, such as mice and rats, imposition of a pressure overload produces a transcriptionally mediated shift from the α- to the β-MHC and from cardiac to skeletal α-actin.[49-51] α-Myosin has a three- to sevenfold greater ATPase activity than β-myosin. The greater abundance of β-MHC in response to pressure overload in small animals increases the efficiency of force development by producing the same absolute muscle tension at a slower rate.[52] Despite identical cardiac muscle mechanics in response to hypertrophy, large animals with slower heart rates, including humans, possess β-MHC almost exclusively throughout embryogenesis and postnatal development.[53] It is possible that, in higher mammalian species, altered myosin ATPase in response to pressure-overload hypertrophy may be mediated in part by a posttranslationally produced low-molecular-weight variant of the β-MHC or isoform shifts in other myofibrillar proteins. For example, cardiac isoforms exist for essential and regulatory light chains, troponin (I, C, and T), tropomyosin, and the sarcolemmal Na^+, K^+-ATPase. Isoform switching of each of the components of the cardiomyocyte has been reported in hypertrophy and failure, but the functional significance of this has been unclear. The ability to ablate or overexpress these isoforms in genetically engineered mice will more clearly elucidate their role in the normal and hypertrophied heart.

Extracellular Matrix and the Cytoskeleton

Although cardiomyocytes make up the bulk of cardiac mass by volume, they are tethered in an extensive extracellular network of collagen and other structural proteins, including fibronectins and proteoglycans. The extracellular and intracellular myofibrillar scaffolding is a critical

determinant of cardiac shape during normal and pathologic cardiac growth.[54-56] Collagen is synthesized principally by fibroblasts but also by vascular smooth muscle cells in response to a variety of pathologic stimuli, including increased oxidative and mechanical stress, ischemia, and inflammation. Most of the molecules and signal transduction pathways operant in cardiomyocyte growth play a role in hyperplasia of fibroblasts and in the elaboration of collagen. The resultant fibrosis produces altered myocardial stiffness and arrhythmogenesis in ischemic heart disease, cardiac hypertrophy, and congestive heart failure. Collagen synthesis is continuously and variably offset by extracellular matrix resorption mediated by matrix metalloproteinases (MMPs). The activity of these enzymes is increased in dilated cardiomyopathy. Conversely, the activity of a class of enzymes known as tissue inhibitors of matrix metalloproteinases (TIMPs) is reduced in this setting. The resultant excessive collagenolyses may induce myofibrillar slippage and contribute to the dilated thin-walled chamber geometry that characterizes acute and chronic heart failure. This process has been termed *chamber remodeling* by clinicians.[57]

Cardiomyocytes are tethered to the extracellular matrix by membrane-spanning proteins called *integrins.* The extracellular portion of these molecules binds to fibronectins in the extracellular matrix while the cytoplasmic domain is associated with a nonreceptor tyrosine kinase called focal adhesion kinase (FAK).[58] Downstream targets for FAK phosphorylation are the SRC kinases src and fyn. This pathway is differentially activated by mechanical stretch ischemia and oxidative stress in the myocardium and provides an additional mechanism for altered growth during pathologic conditions.[59] Perimyocyte extracellular proteins such as dystrophin and dystrophin-related proteins contribute to normal cardiogenesis; when altered in abundance, they can produce a cardiomyopathy in Duchenne's muscular dystrophy and some familial cardiomyopathies, respectively (see Chap. 62).

The cardiomyocyte cytoskeleton is the intracellular scaffolding that provides a framework for the orderly arrangement of sarcomeres in striated cardiac and skeletal muscle. Titin-the third most abundant protein in the heart-desmin, and vinculin have differing intracellular spatial distributions that contribute to resting tension of cardiac muscle. The amount and polymerization status of the proteins that make up the microtubular network of the cardiomyocyte cytoplasm (tubulin and β actin) are important determinants of the viscous properties of heart muscle and contribute to altered cardiac function in pathologic states.[60,61]

Cardiac hypertrophy and failure are associated with changes in the relative abundance of the various intra- and extracellular structural proteins. All forms of cardiac hypertrophy are associated with increased collagen deposition in the extracellular matrix, which contributes to the observed alterations in passive chamber and muscle properties. Pressure overload (but not volume overload) hypertrophy has been associated with changes in the levels of the cytoskeletal proteins titin, desmin, and tubulin. Depolymerization of tubulin with colchicine reversed abnormalities in cardiac function in feline right ventricular hypertrophy but not in guinea pig left ventricular hypertrophy.[60,61]

Excitation-Contraction Coupling and Calcium Homeostasis (see Fig. 5-3)

Cardiomyocyte membrane depolarization is initiated by the intracellular movement of sodium through its ion channel, while repolarization is achieved by the extracellular movement of potassium via a family of sarcolemal K^+ channels. Membrane depolarization enhances the transmembrane conductance of calcium through a dihydropyridine-sensitive *l*-channel. The resultant increase in cytosolic calcium concentration permits binding of this cation to the ryanodine receptor on the surface of the sarcoplasmic reticulum. This process results in release of calcium from sarcoplasmic reticulum stores and further elevation of cytosolic calcium concentrations. The resultant hundredfold elevation of calcium permits binding to the myofilament regulatory protein troponin C. Calcium binding to troponin C promotes a steric movement of troponin I away from the actin binding site on the myosin molecule. This permits

actin-myosin cross-bridge formation and resultant tension development. The activity of troponin I can be modulated via phosphorylation by protein kinase A and C, while the affinity of troponin C for calcium is altered by intracellular pH. These processes may result in substantial alteration of myofilament calcium. Energy for cross-bridge cycling is produced by hydrolysis of ATP via myosin ATPase. Calcium is released from troponin C and resequestered into the sarcoplasmic reticulum by a specific SR-ATPase. The activity of this enzyme is inhibited by the phosphoprotein phospholamban. Phosphorylation of phospholamban by cAMP (PKA)-dependent protein kinases, protein kinase C, or calcium-calmodulin-dependent protein kinase results in disinhibition and resultant enhancement of calcium uptake in the SR. Steady-state sarcoplasmic reticulum calcium content is determined by the abundance of the anionic storage proteins calsequestrin and calreticulum. Reequilibration of cytosolic sodium and potassium levels produced by the depolarization and repolarization cycle is facilitated by the activity of the sarcolemmal Na^+,K^+-ATPase. Extrusion of transarcolemmal mediated calcium influx is mediated by the coordinated interplay between the membrane situated Na^+-H^+ and Na^+-Ca^{2+} exchangers. Isolated changes in the stoichiometry between the sarcoplasmic reticulum ATPase and its inhibitor, phospholamban, have been demonstrated to have functional significance in genetically engineered mice. Targeted ablation of phospholamban enhanced cardiac inotropic and lusitropic function, whereas cardiac-specific overexpression produced the opposite result.[62,63]

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CARDIAC FUNCTION OF THE HYPERTROPHIED HEART

The phenotypic consequences of the increased cardiac mass and altered protein abundance and composition of the hypertrophied heart are considerable and depend upon the model utilized; the animal species; and the nature, intensity, and duration of the hypertrophic stimulus. Taken together, available clinical and animal studies suggest that functional alterations evolve along a continuum from normal chamber and myocyte function to abnormal chamber and normal myocyte function to abnormalities of both chamber and myocyte function (Fig. 5-1).

Electrical Properties

The most typical electrical abnormality of the hypertrophied heart is prolongation of the duration of the action potential.[64] Recent studies using the single-cell voltage-clamp technique have begun to elucidate the ionic mechanisms responsible for this phenomenon. In mild hypertrophy, increases in calcium and calcium-activated currents (including the NA^{+}/Ca^{2+} exchanger) appear to be important. In severe hypertrophy, prolongation of the action potential is also determined importantly by a reduction in the potassium currents Ik*l* and Ito. The relations between these changes in membrane current properties of hypertrophied hearts and altered mechanical behavior at the myocyte and whole-heart level are not clearly understood at present. Hypertrophied myocardium is more likely than normal tissue to precipitate arrhythmias. The mechanisms for arrhythmogenesis are multifactorial and are operant at the tissue and cardiomyocyte levels. Increased dispersion of refractoriness and slowed conduction results from myocyte loss and fibrosis. Prolongation of the duration of the action potential increases the likelihood of early afterdepolarizations, which may result in triggered arrhythmias. Reduced coronary artery flow reserve and accelerated atherosclerosis of epicardial coronary vessels predispose toward ischemia-induced arrhythmias.[65] In concert, these mechanisms contribute to the finding of cardiac hypertrophy as the most powerful predictor of cardiovascular mortality in the Framingham Study (see Chap. 1).

The application of molecular biological and molecular genetic approaches is providing increasing insight into the cellular mechanisms of arrhythmogenesis. Normal cardiomyocyte excitation and arrhythmogenesis involve voltage-dependent ion channels, mechanosensitive channels, sarcolemmal electrogenic transporters, and gap junctions. The latter are two channels or connexins that enable ion current flow between and among cardiomyocytes. Connexons are composed of a class of molecules called *connexins*. Isoform diversity of the connexins are determinants of ion conductance and sensitivity.[66,67] The genes for each of the cardiomyocyte ion channels, transporters, and connexins have been cloned. Structure-function relations are being defined in vitro using site-directed mutagenesis and in vivo using loss of function or gain of function mutations in genetically engineered mice. In parallel, the abundance and/or function of the molecular determinants of excitability and arrhythmogenesis are beginning to be elucidated in animal models and human cardiovascular disease (see Chap. 23).

Genetic linkage analysis of familial arrhythmias and resultant identification of culprit gene defects of cardiomyocyte ion channels or channel modulators has provided complementary insight into the cellular mechanisms of arrhythmogenesis. The long-QT syndrome is now known to result from mutations in genes responsible for various outwardly rectifying potassium channels and the

cardiomyocyte sodium channel.[68-70] Analyses of other inherited arrhythmias are under way.

Mechanical Properties

Mechanical function of the hypertrophied heart has been studied at the isolated myocyte, muscle, and chamber levels and in the intact circulation.[71-73] The results of these studies have revealed variable alterations in the rate and extent of contraction and relaxation, in the amount of force development, and in resting muscle and chamber properties. In the intact circulation, altered systolic and diastolic function is a composite result of subcellular changes in the myocyte, changes in the extracellular matrix, altered chamber geometry and mass, altered ventricular-vascular coupling, and the modulatory effects of neural and hormonal influences.

The earliest changes in mechanical performance observed in isometrically contracting papillary muscles extracted from hypertrophied hearts consist of a prolongation of time to peak tension and relaxation, despite normal peak twitch tension normalized for cross-sectional area of the muscle.[74] Afterloaded isotonically shortening papillary muscle preparations from hypertrophied hearts of a variety of animal species typically reveal a decrease in the force-velocity relationship and a depression of V_{max} (the extrapolated maximal unloaded shortening velocity).[75] V_{max} has been directly related to the calcium-activated myosin ATPase activity. Both myosin and myofibrillar ATPase activity are typically depressed in hypertrophied myocardium. In small rodents, this is due to the transcriptionally mediated switch from α- to β-MHC. In higher mammals including humans, the decreased myosin ATPase activity of the hypertrophied heart may be due to alterations in the troponin isoform composition[76] or the posttranslational generation of a lower molecular variant of the β-MHC.[48]

The dissociation between depressed rate-dependent indices of contraction and relaxation and normal maximal force development and extent of shortening in early cardiac hypertrophy has also been demonstrated in isolated cardiomyocytes and in the intact circulation of the nonhuman primate.[71,73] *These results suggest the rate of cross-bridge cycling is reduced but that the effective number of active cross bridges per unit of myocardium is preserved in compensated cardiac hypertrophy.* In decompensated hypertrophy, reduced absolute levels of force development and diminished contractility ultimately ensue.

In addition to alteration in excitation-contraction coupling and relaxation, the increased cardiac mass and changes in geometry significantly affect passive muscle and chamber properties of the hypertrophied heart. Concentric hypertrophy is characterized by an increased resting muscle and chamber stiffness, which results in an increase in pulmonary venous pressure for any given left ventricular volume. The resultant pulmonary congestion at rest or with exercise is an important determinant of symptoms in patients with hypertensive left ventricular hypertrophy or hypertrophic cardiomyopathy and normal or elevated ejection fraction. Pure volume overload hypertrophy, as occurs with mitral regurgitation, is typically associated with no change or a decrease in passive muscle or chamber stiffness. As a result, patients with chronic volume overload may remain asymptomatic for long periods despite appreciable increase in regurgitant fraction (see also Chaps. 56 and 57).

Coronary Circulation

Clinicians have long recognized that myocardial blood flow may be abnormal in the hypertrophied heart, since such patients may have exertional angina, resting or exercise-induced electrocardiographic or perfusion abnormalities, or pathologic evidence of subendocardial fibrosis, despite the presence of angiographically normal epicardial coronary arteries.

Morphologic studies of hypertrophied hearts from experimental animals and patients with

pressure-overload hypertrophy demonstrate that the ratio of capillaries to myocytes remains unchanged.[77] Since myocyte cross-sectional area is increased, there is a resultant increase in nutrient diffusion distance in the hypertrophied heart. This anatomic change results in a reduced vasodilatory reserve in response to various stimuli in experimental and clinical studies.[78] Myocardial blood flow and oxygen consumption per unit of myocardium are normal in compensated pressure overload-left ventricular hypertrophy, where wall stress has been normalized by an increase in wall thickness. The impairment in vasodilatory reserve produces evidence of ischemia during increased myocardial oxygen demand. In right ventricular pressure-overload hypertrophy, differences in perfusion between the ventricles result in increased right ventricular blood flow per unit of myocardial mass at rest and no increase in minimum coronary resistance of hypertrophied right ventricular myocardium.[79]

Few data are available regarding changes in the coronary circulation in experimental or clinical volume-overload hypertrophy. Most studies have reported normal resting flow values per unit of myocardial mass. In contrast to pressure overload, volume-overload hypertrophy has been associated with normal or mildly increased minimum coronary resistance and normal or mildly decreased coronary reserve.[80] The coronary circulatory abnormalities associated with cardiac hypertrophy appear to be reversible with removal of the hypertrophic stimulus and resultant decreased chamber mass.[81]

Important recent studies have begun to elucidate the molecular and cellular mechanisms responsible for reversible functional consequences of ischemia and ischemia reperfusion. The syndrome of *myocardial stunning,* which refers to the variable period of regional or global myocardial hypofunction consequent to ischemia and reperfusion, is believed to involve two mechanisms. Either hydroxy-free radical generation, calcium overload, or both may be involved.[82] Downstream effects of these two pathologic processes include activation of protein kinase C, tyrosine kinases, and stress-activated kinases. In addition, proteolytic degradation of troponin I has been observed and is associated with uncoupling of excitation from contraction due to reduced myofilament calcium sensitivity. Transgenic overexpression either of a PKC isoform or the proteolytic degradation product of troponin I in mice produces both myocardial dysfunction and reduced myofilament calcium sensitivity responsiveness.[83]

Brief repetitive periods of ischemia and reperfusion also produce a powerful cardioprotective effect against myocardial necrosis. This process, called *ischemic preconditioning,* is also associated with activation of similar signal transduction pathways. The precise mechanism(s) for reduced myocyte cell death from necrosis, apoptosis, or both are presently unclear. *Hibernation* or myocardial hypofunction associated with reduced steady-state coronary blood flow may, in fact, result from repetitive periods of stunning.

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MECHANISMS FOR THE TRANSITION FROM COMPENSATED HYPERTROPHY TO HEART FAILURE

In contrast to hypertrophied skeletal muscle, chronically increased work eventually results in depressed contractility and relaxation of the hypertrophied heart. Compensated hypertrophy, which is characterized by abnormal chamber function but preserved muscle and myocyte function, evolves into a decompensated phase characterized by abnormal chamber, muscle, and myocyte function (Fig. 5-1). Attempts to elucidate the underlying mechanisms for this transition have involved multidisciplinary studies of clinical end-stage heart failure, longitudinal studies in experimental animals, and characterization of cardiovascular function in genetically engineered mice, where attempts are made to mimic human disease (Fig. 5-4).[84]

Current information suggests that decompensated hypertrophy may result from a number of mechanisms that are both intrinsic and extrinsic to the cardiomyocyte. These include necrosis; apoptosis;[85,86] altered growth secondary to altered signal transduction pathways; alterations in cardiomyocyte contractile, regulatory, calcium-cycling, and structural proteins; alterations in the extracellular matrix, and remodeling (Fig. 5-4). Because of the complex combinatorial alterations that occur in human heart failure and conventional animal models of hypertrophy, studies in genetically engineered mice in which a protein of interest is either overexpressed or ablated using homologous recombination hold particular promise in determining the relative importance of various candidate genes. For example, mice bearing the mutation in the β-MHC that occurs in familial cardiomyopathy have many features of the human disease.[87] Overexpression of the α subunit of the G protein that couples to the β-adrenergic receptor has produced dilated fibrotic hearts with altered cardiovascular function.[88] Overexpression or ablation of genes involved in cardiomyocyte calcium-cycling proteins has been associated with altered heart function and abnormal calcium kinetics. It is of interest that, with few exceptions,[89] the resultant cardiac phenotype has failed to reproduce completely human decompensated hypertrophy and failure. This observation further supports the multifactorial nature of the condition and the importance of genetic background on the phenotype observed after loss-of-function or gain-of-function genetic engineering.

A common prominent feature of many experimental and clinical studies of decompensated hypertrophy and failure is a derangement of cardiomyocyte calcium homeostasis (Fig. 5-3). Studies of human cardiomyocytes extracted from the hearts of patients with end-stage heart failure have revealed elevated diastolic calcium levels with either no change or a reduction in the amplitude of the calcium transient.[90-93] Longitudinal studies of hypertrophy in experimental animals have revealed depression of steady-state mRNA levels[94] and sarcoplasmic reticulum ATPase and phospholamban proteins in decompensated, but not compensated, pressure-overload hypertrophy.[72] These changes were associated with distinctive contractile depression of isovolumically contracting heart function, increases in the EC_{50}, and decreases in the V_{max} for sarcoplasmic reticular membrane uptake of calcium. Transgenic overexpression of the sarcoplasmic reticulum ATPase inhibitor phospholamban depressed cardiomyocyte function and calcium kinetics, whereas targeted ablation of the phosphoprotein produced the opposite result. Whether altered levels of the calcium-cycling proteins occur by transcriptional, translational, or posttranslational levels is currently unknown. In addition to altered levels of the various calcium-cycling proteins in hypertrophy and heart failure, there is evidence that abnormal spatial

organization of the *l*-channel and SR may be contributory. Specifically, increased distance between the *l*-channel and the ryanodine receptor may contribute to abnormal calcium cycling.[95]

In addition to altered calcium homeostasis, there is increasing evidence that abnormal signal transduction plays a critical role in the development of cardiac hypertrophy and failure. In vitro studies with neonatal myocytes have demonstrated that phenylephrine, endothelin, and angiotensin II cause cardiomyocyte hypertrophy. These vasoactive peptides have cognate receptors that signal via the α subunit of the Gq protein (see Fig. 5-2). Cardiac-specific overexpression of Gαq produced cardiac hypertrophy, apoptosis, and contractile depression in transgenic mice.[96,97] By contrast, overexpression of a protein inhibitor of Gαq in a similar manner prevented cardiac hypertrophy due to pressure overload.[98] Transgenic overexpression of receptors that couple through Gαq, such as α_1 and angiotensin II, produces a similar phenotype: cardiac-specific postnatal overexpression of the calcium-sensitive PKC isoform B produced cardiac hypertrophy and failure. Pretreatment of mice overexpressing PKC B with a highly specific inhibitor prevented or reversed this hypertrophy-heart failure phenotype.[99] Part of the contractile depression observed with excess PKC B activity was due to phosphorylation of troponin I and resultant reduced myofilament calcium sensitivity.[100] Augmented PKC activity and elevated levels of the calcium-sensitive PKC α and β isoforms, but not Gαq, were found in human end-stage cardiomyopathic heart failure.[101,102] It is also known that PKC may be stimulated by pathophysiologic levels of stretch[103] and ischemia-reperfusion and directly by oxidative stress.[33] Taken together, these lines of evidence suggest that *PKC mediated signal transduction plays a critical role in the development of cardiac hypertrophy and failure.*[104]

A variety of studies with end-stage human cardiomyopathic heart tissue, conventional animal models, and genetically engineered mice suggest that apoptosis may contribute to the heart failure phenotype.[105] The key issue that remains unclear is the quantitative importance of the phenomenon. This problem is further complicated by the fact that a number of signaling molecules (e.g., Gαq and TNF-α) produce both hypertrophy and apoptosis. By contrast, gp130 heterodimerizes with LIF (leukemia inhibitory factor) receptor to permit binding of the interleukin-6 family of cytokines, such as cardiotrophin 1. Receptor binding stimulates the hypertrophic response while inhibiting apoptosis. Elimination of the gp130 by loss of function mutations of the gene results in mice that have structurally normal hearts. However, when a pressure overload is imposed, a rapidly progressive dilated cardiomyopathy ensues, which is associated with massive apoptosis.[106] The application of molecular genetic and biological approaches to elucidate mechanisms responsible for myocardial hypertrophy, cardiac failure, arrhythmogenesis, and ischemic dysfunction will permit improved diagnostic and therapeutic approaches to congenital and acquired heart diseases.[107]

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calcium channel, leading to increased calcium entry, by phosphorylating phospholamban and resultant enhanced SR ATPase activity, and by phosphorylating regulatory proteins of the myofilament leading to decreased calcium sensitivity. The net enhancement of intracellular calcium concentration is restored by the coordinated activity of the Na+-H+ and Na+-Ca2+ exchangers (Ex).

Figure 5-4: Schematic diagram of the mechanisms responsible for the development of the anatomic and functional cardiac phenotypes in physiologic and pathologic hypertrophy. Abnormalities at one or multiple levels in this putative closed-loop system may be responsible for the transition between compensated and decompensated hypertrophy.

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Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 6:

MOLECULAR AND CELLULAR BIOLOGY OF BLOOD VESSELS

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It has become apparent that a diverse number of pathologic processes all contribute to common vascular diseases such as atherosclerosis and hypertension. During the past several years, these pathologic events have been defined with increasing clarity at a cellular and molecular level, and strategies are emerging to treat these primary processes rather than simply treating the secondary manifestations of vascular disease. Because of this, understanding normal function of vascular cells and how these are altered by various vascular insults has become essential for both basic investigators and clinicians caring for patients with peripheral vascular disease, coronary artery disease, and hypertension. This chapter is designed to introduce important concepts in vascular biology and to emphasize how fundamental aspects of vascular control are altered by common disease conditions.

STRUCTURE OF THE VESSEL WALL

Arteries consist of three layers: the innermost intima, the media, and the outermost adventitia. The intima is comprised of a single layer of endothelial cells embedded in an extracellular matrix. The internal elastic lamina separates the intima from the media. The media consists of smooth muscle cells, elastic laminae, bundles of collagen fibers, and elastic fibrils, all embedded in an extracellular matrix. The adventitia is the most variable layer, containing dense fibroelastic tissue, nutrient vessels, and nerves.

The actual composition of each of these layers varies with the type of blood vessel. Large, conduit arteries are typically referred to as *elastic arteries*, because of their high ratio of elastic laminae to smooth muscle cells. Muscular arteries are generally smaller and have a prevalence of smooth muscle cells, whereas arterioles consist of only one to two layers of smooth muscle cells. Capillaries are the smallest vessels, made up of a single layer of endothelial cells that are occasionally apposed to pericytes-smooth muscle-like cells that serve a contractile and synergistic nutritive function. The venous system has a similar architecture to that of the arterial system, the main difference being the orientation and mass of the smooth muscle cells within the wall.

Physiologically, the two best understood cell types in the vascular system are the endothelial and vascular smooth muscle cells (VSMCs). The endothelial cell is generally oriented with the direction of blood flow parallel to the main axis of the vessel. Endothelial cells are held together by junctional complexes that regulate permeability and control cell-to-cell communication. The smooth muscle cell is a spindle-shaped cell whose orientation varies with the type of artery, but is generally helical in large, elastic arteries and concentric in muscular arteries. Vascular smooth muscle cells contain three types of filaments: thick (myosin), thin (actin), and intermediate. The proteins that form these filaments undergo phosphorylation upon exposure to certain vasoactive agonists, thus altering their orientation and interactions and supporting force development (see below). In normal arteries, the smooth muscle cells are primarily in the aforementioned *contractile* phenotype. In contrast, in response to vascular insults such as hyperlipidemia or angioplasty, smooth muscle cells lose their contractile phenotype and acquire a so-called *synthetic* phenotype. This is characterized by a loss of contractile proteins, a rounded shape, and a dramatic change in biochemical properties. This change in phenotype and function is thought to be

important in the genesis of the myointimal cell that populates the atherosclerotic subintimal space.

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Chapter 6: MOLECULAR AND CELLULAR BIOLOGY OF BLOOD VESSELS

PHYSIOLOGY OF THE ENDOTHELIAL CELL

Normal endothelial cell function is crucial to homeostasis in the vascular system. During the past decade, it has become apparent that diseases such as atherosclerosis are ultimately manifestations of endothelial dysfunction. The endothelium has three major functions: (1) it is a metabolically active secretory tissue; (2) it serves as an anticoagulant, antithrombotic surface; and (3) it provides a barrier to the indiscriminant passage of blood constituents into the arterial wall. The implications of these physiologic properties for vascular biology will be considered separately.

Endothelial Cell Metabolism and Secretion of Vasoactive Factors

As discussed in more detail below, endothelial cells secrete vasoactive substances that play a major role in the control of vascular tone. These molecules include vasodilators such as prostacyclin, endothelial-derived relaxing factor (EDRF), and endothelial-derived hyperpolarizing factor (EDHF).[1-3] In addition, the endothelium produces vasoconstrictor substances, including endothelin[4] and vasoconstrictor prostanoids.[5]

Endothelial cells also manufacture and secrete substances such as factor VIII antigen, von Willebrand's factor, tissue factor, thrombomodulin, and tissue plasminogen activator, which are all involved in coagulation/fibrinolytic pathways. Structural components of the extracellular matrix synthesized by these cells include collagen, elastin, glycosaminoglycans, and fibronectin.[6,7] The composition of the extracellular matrix is dynamically modulated by matrix metalloproteinases, enzymes that degrade matrix protein and participate in its remodeling. These enzymes are secreted by both endothelial and smooth muscle cells.[8,9] In addition, endothelial cells synthesize and secrete heparans and growth factors that regulate smooth muscle cell proliferation.[10-13] Finally, endothelial cells are able to clear and metabolically alter bloodborne and locally produced substances, including plasma lipids and lipoproteins,[14] adenine nucleotides and nucleosides,[15] serotonin, catecholamines, bradykinin, and angiotensin I.[16]

Endothelial cells are involved in the metabolism of plasma lipids in several ways. Lipoprotein lipase, an enzyme that hydrolyzes triglycerides into constituent fatty acids, is bound to the endothelial cell surface by heparan sulfates.[17] The interaction of this enzyme with chylomicrons or very low density lipoprotein (VLDL) particles results in the release of free fatty acids, which can then cross the subendothelial space to the underlying smooth muscle or inflammatory cells in atherosclerosis. In addition, endothelial cells possess receptors for low-density lipoprotein (LDL),[18] which regulate the transport and modification of LDL. Normally, LDL receptors are downregulated because receptor processing is inhibited in the nonproliferating monolayer.[18] There are, however, two other pathways for uptake of LDL. First, LDL can be transported across the endothelium by an unknown, active, receptor-independent mechanism.[19] Second, modified, or oxidized LDL can be taken up by "scavenger" LDL receptors,[20] the expression of which is unaffected by the growth state of the endothelial cells. These cells also have the capacity to modify LDL,[21] thus enhancing its uptake and ultimately leading to an increase in cholesterol esters in the vessel wall and, importantly, facilitating LDL uptake by inflammatory cells in disease.

The Endothelial Cell and Thrombosis

Quiescent endothelial cells normally present an antithrombotic surface that resists platelet adhesion and does not activate coagulation. (For a more detailed discussion of thrombosis, see Chap. 44.) The continuity of the endothelium is essential to this function, and nonthrombogenicity has been attributed in part to the negative charge on the surface of these cells.[22] Endothelial cells are, however, capable of synthesizing and secreting prothrombotic factors, especially when stimulated with cytokines or other inflammatory agents. The endothelium thus represents a functional antithrombotic-thrombolytic/thrombotic balance. Potent anticoagulants elaborated by the endothelium include prostacyclin, which inhibits platelet aggregation,[23] heparin-like molecules,[24] and thrombomodulin, which activates protein C.[25] In addition, antithrombin III binds to the surface-bound heparin-like molecules and serves as a clearance (via internalization) molecule for thrombin, as well as a thrombin inhibitor.[26] These cells also produce tissue plasminogen activator (tPA) and plasminogen activator inhibitor I (PAI-I), and can bind plasminogen on their surface via fibronectin and thrombospondin.[27] The relative amounts of tPA and PAI-I can be upregulated or downregulated, respectively, by thrombin, angiotensin II, and other vasoactive substances to control clot lysis.[28]

As alluded to earlier, the endothelium, under conditions of injury or inflammation, may become prothrombotic (Fig. 6-1). On stimulation with inflammatory cytokines, endothelial cells increase the surface expression of tissue factor[29] and leukocyte adhesion molecules,[30] and decrease the expression of thrombomodulin.[29] Thrombin itself stimulates further production of von Willebrand's factor,[31] which, along with thrombospondin and fibronectin, participates in the thrombotic response. Furthermore, endothelial cells can bind factor IX,[32] which, when tissue factor is expressed, can be activated by tissue factor VIIa complex, leading to activation of factor X in the presence of factor VIII. Activated factor X (Xa) can then promote assembly of the prothrombinase complex. Thus, under inflammatory conditions, endothelial cells can amplify the prothrombotic response. Not all of the factors controlling the expression of pro- and antithrombotic/fibrinolytic molecules are known, but it is clear that the endothelium functions as a major regulator of hemostasis.

Barrier Function and Endothelial Cell Permeability

There are three ways that the endothelium regulates influx of macromolecules into the arterial wall: intercellular tight junctions, vesicles and/or transendothelial channels, and the lipid phase of the endothelial membrane. These pathways enable the intact endothelium to serve as a barrier, preventing or impeding highly mitogenic, thrombotic, or vasoactive substances from coming into direct contact with the underlying vascular smooth muscle. Each route has both active and passive components, and the extent to which they are utilized depends to a certain degree on the location of the endothelial cells. Thus, capillaries and postcapillary venules respond to vasoactive agents, some of which (histamine, prostaglandins) are secreted by the endothelial cell itself, with increased flux through tight junctions.[33] The tight junctions found in arteries tend to be more occlusive, but may also be influenced by hypertension[34] and various agonists. Vesicular transport is mainly utilized by the cell to transfer water-soluble macromolecules from the luminal surface to the abluminal surface, but the permanence of such structures and whether they form transendothelial channels is a matter of debate. It has recently been shown that caveolae, vesicles containing the structural protein caveolin that are pinched off from the plasma membrane, are involved in transendothelial transport of macromolecules. Multiple such vesicles may link together to form functional pores from the luminal to abluminal surface.[35,36] Lipid-phase transport has been proposed as a mechanism whereby lipid-soluble molecules (e.g., free fatty acids) could be transferred to the abluminal surface of the endothelial cell.[37] These molecules could enter the outer leaflet of the membrane from the circulation and diffuse along the lipid bilayer to be released or bind to extracellular matrix components in the subintimal area.

Another major mechanism modulating endothelial barrier formation occurs via contraction of these cells in a fashion analogous to smooth muscle contraction. This occurs in response to a variety of agonists, including thrombin, histamine, and ionomycin, and results in cell shape change that opens gap junctions between cells. It is likely that this contractile response is a major mechanism for edema formation in response to histamine and bradykinin and is also involved in solute transport. This phenomenon is mediated by a series of intracellular signaling events, including activation of protein kinase C, myosin light chain phosphorylation, activation of tyrosine kinases, and stimulation of the small G-protein Rho.[38-40]

Thus, the endothelium has both passive and active roles in the control of vascular permeability by acting as a physical permeability barrier and by modulating the expression of cell surface and secreted agonists and molecules that are capable of altering permeability.

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Chapter 6: MOLECULAR AND CELLULAR BIOLOGY OF BLOOD VESSELS

PHYSIOLOGY OF THE VASCULAR SMOOTH MUSCLE CELL

The smooth muscle cell normally responds to hormonal stimulation with contraction or relaxation. In certain disease states, however, growth and/or hypertrophy and migration to the intima are the predominant responses. Some of the biochemical signals generated by these vasoactive agonists are similar for both types of responses, with the final physiologic response dictated by the phenotype and environment of the cell, and the exact biochemical pathways activated. Thus, in normal arteries, growth factors can act as vasoconstrictors[41] while, in modulated smooth muscle cells, vasoconstrictors can stimulate hypertrophy or hyperplasia.[42]

Second Messengers Traditionally Associatedwith Contraction

Some of the earliest signals generated within the cell following stimulation with calcium-mobilizing vasoactive agonists involve hydrolysis of a specific class of membrane lipids: the phosphoinositides.[43] There are three major inositol phospholipids in the plasma membrane that serve as substrates for a class of enzymes called phospholipase Cs. Phospholipase C cleaves phospholipids to liberate the water-soluble head group and the lipophilic molecule, diacylglycerol (Fig. 6-2). The water-soluble head group that is most important for signal generation is inositol trisphosphate (IP_3), which has been shown to release Ca^{2+} from intracellular stores.[44] Ca^{2+}, in turn, activates a cascade of enzymes leading to contraction or growth (see below). Diacylglycerol is a potent activator of protein kinase C, a Ca^{2+}- and phospholipid-dependent enzyme that phosphorylates numerous cellular proteins.[45] Diacylglycerol can be further metabolized to phosphatidic acid or to glycerol, fatty acids, and, ultimately, eicosanoids and leukotrienes that may themselves modulate tone. Additionally vasoconstrictor agents cause a sustained intracellular alkalinization[46] and an influx of extracellular Ca^{2+},[47] both of which serve to sustain and enhance vasoconstriction.

Contraction Cascade

Contractions induced by various vasoactive hormones differ not only in magnitude and time course, but also differ between vessels. In general, there is an initial, rapid component of force generation and a more sustained phase of contraction. Some agonists, such as angiotensin II, induce only a transient constriction of many vessels, whereas others, including norepinephrine and vasopressin, nearly always cause a sustained contraction. The initial phase of force development has been shown to depend on the formation of actin-myosin cross-bridges, but the mechanisms underlying the sustained phase of contraction are less clear.

A sliding-filament mechanism similar to that found in skeletal muscle is thought to regulate phasic contraction of smooth muscle. Force generation is accomplished by attachment of the myosin heads (or cross-bridges) to actin filaments. This attachment catalyzes ATP hydrolysis to generate tension and occurs in a cyclic manner for the duration of the stimulus. Smooth muscle has a relatively greater content of actin and a lower content of myosin than does skeletal muscle and, in contrast to skeletal muscle, the major site of calcium regulation of smooth muscle actomyosin is on the myosin molecule. Smooth muscle myosin consists of two large subunits, each with a molecular weight of 200 kDa, and two small subunits of 20 and 16 to 17 kDa, known as the *myosin light chains*. Force generation in smooth muscle is regulated by the phosphorylation/dephosphorylation of the 20-kDa protein (Fig. 6-3). Once phosphorylation

occurs, actin-activated Mg^{2+}ATPase activity is stimulated, resulting in cross-bridge cycling. Myosin light chain phosphorylation is mediated by an enzyme known as myosin light chain kinase (MLCK). This protein associates with calmodulin, a calcium-binding protein required for activation of numerous cytoplasmic enzymes. Thus, when Ca^{2+} increases within the cell in response to hormonal stimulation, it binds to calmodulin, which, in turn, associates with MLCK, converting it from an inactive to an active form. MLCK then phosphorylates the myosin light chain, enabling actin activation of the Mg^{2+}-ATPase ultimately resulting in cross-bridge formation. When the intracellular Ca^{2+} concentration drops below about 100 nM, Ca^{2+} dissociates from calmodulin, calmodulin detaches from MLCK, and MLCK becomes inactive. Myosin light chain phosphatase activity then predominates, myosin is dephosphorylated, and cross-bridge cycling ceases. During sustained contraction, however, the intracellular Ca^{2+} concentration is low, and energy consumption is reduced, suggesting the development of a latch-bridge, or of a low cycling state.[48] Alternatively, the sensitivity of the contractile apparatus to Ca^{2+} may be increased, a response posited to be regulated by protein kinase C.[49]

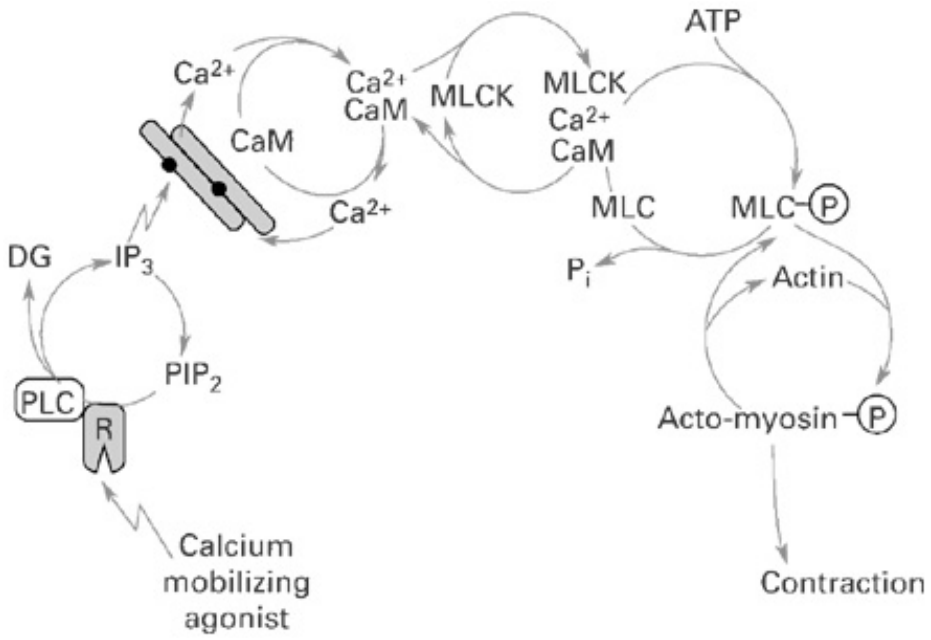

Figure 6-3: Contraction cascade. Activation of smooth muscle by a vasoconstrictor hormone leads to a cascade of biochemical signals, ultimately resulting in phosphorylation of actomyosin, cross-bridge formation, and force generation. The release of Ca2+ from intracellular stores is one of the major initiating events, since Ca2+ combines with calmodulin to activate myosin light chain kinase. This enzyme phosphorylates the myosin light chain, which is then able to interact with actin. ABBREVIATIONS: R = receptor; PLC = phospholipase C; DG = diacylglycerol; PIP_2 = phosphatidylinositol 4,5-bisphosphate; IP_3 = inositol trisphosphate; CaM = calmodulin; MLCK = myosin light chain kinase; MLC = myosin light chain; P = phosphate. (Courtesy of Bernard Lassègue, Ph.D.)

Biochemical Signals Traditionally Associatedwith Proliferation

Classic growth factors, such as platelet-derived growth factor (PDGF), activate many of the same signaling pathways as do vasoconstrictors: phosphoinositide hydrolysis, Ca^{2+} mobilization and influx, Na^+/H^+ exchange and intracellular alkalinization. Receptors for these growth factors are intrinsic tyrosine kinases, leading to the tyrosine phosphorylation of numerous proteins that are essential for growth. The importance of tyrosine phosphorylation in mediating the growth

response is shown by the observation that mutant PDGF receptors, which lack the normal, intrinsic tyrosine kinase domain, are incapable of mediating proliferation in response to PDGF.[50] In addition, tyrosine kinase inhibitors have been shown to inhibit growth.[51] There is also increasing evidence that tyrosine phosphatases can counteract the mitogenic effects of growth factors by inhibiting tyrosine phosphorylation of specific substrates.[52]

A complex of substrates becomes associated with activated growth factor receptors and subsequently activates multiple signaling cascades leading to the final cellular response.[53] Some proteins, such as phospholipase C-γ, the tyrosine kinase c-Src, and phosphatidylinositol-3-kinase, bind directly to receptor tyrosine kinases, whereas others, including the tyrosine kinase Pyk-2 and the cytoskeletal protein paxillin, associate with the receptor via linker proteins such as Grb and Shc. Upon addition of growth factors, the receptors dimerize and auto-tyrosine phosphorylate, and each of the aforementioned proteins is phosphorylated on tyrosine, presumably leading, either directly or indirectly via association with the activated receptor, to their activation. In addition, Shc and Grb2 link these receptors to Ras, a ubiquitous GTPase that initiates a kinase cascade that includes mitogen-activated protein kinase (MAP kinase) and ultimately leads to growth. Recent evidence suggests that many of these proteins are also activated by seven-transmembrane-spanning G-protein-coupled receptors,[54] an observation that may partially explain the growth-promoting properties of some vasoconstrictor hormones.

An additional pathway that is activated under some conditions by growth factors and vasoactive agonists is phospholipase D-mediated hydrolysis of plasma membrane phosphatidylcholine.[55] In this reaction, phosphatidic acid and choline are released. This pathway is receiving increasing attention because phosphatidic acid may have a role in mediating the growth response[56] and because phospholipase D activation seems to be required for the proliferative response.[57]

Growth

Vascular smooth muscle cell growth occurs via two processes: hypertrophy and hyperplasia. In general, hypertrophy occurs in response to long-term stimulation with vasoconstrictor-type agents, whereas hyperplasia occurs in response to the classic growth factors. Hypertrophy is characterized by an increase in smooth muscle cell mass due to increased protein synthesis and has been shown to occur in response to angiotensin II[58] and thrombin[59] and in large vessels during hypertension. Hyperplasia is characterized by cell replication and is stimulated by growth factors such as PDGF and fibroblast growth factor (FGF)[60-62] following vascular injury. The biochemical processes leading to hypertrophy and hyperplasia are currently under investigation. It is clear that the aforementioned tyrosine kinase pathways are important in both types of growth.[53,54] In addition, generation of reactive oxygen species, including superoxide and hydrogen peroxide, serves to transduce the growth signal by activating specific proteins such as p38 mitogen-activated protein kinase and Akt/protein kinase B.[63,64]

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Chapter 6: MOLECULAR AND CELLULAR BIOLOGY OF BLOOD VESSELS

THE EXTRACELLULAR MATRIX

The extracellular matrix is a major component of the vessel wall. It is the medium through which nutrients are transported, a repository for products secreted by the cells of the vascular wall, the site of accumulation of cell debris, and a substrate for migration and proliferation of endothelial cells, monocytes, and vascular smooth muscle cells. The matrix consists of several proteins that have distinct functions in maintaining the integrity of the wall (Table 6-1).

Table 6-1: Components of the Extracellular Matrix

Matrix Component	Function
Proteoglycans	Resistance to deformation
	Arterial permeability, filtration, ion exchange
	Transport and deposition of plasma elements
	Regulation of cellular metabolism
Collagens (types I and III)	Mechanical strength
Collagens (types IV, V, and VI)	Attachment of vascular cells to the matrix
	Components of the basal lamina
	Linking collagens to noncollagenous structures
Elastin	Regulation of vascular elasticity
Fibronectin	Cell-cell adhesion
	Cell-substrate adhesion
	Cell motility
	Specific binding of collagen, heparin
Laminin	Attachment of endothelial cells to type IV collagen

Extracellular matrix degradation and reformation is an extremely important biological process with profound clinical implications. It is impossible for vascular cells to hypertrophy, proliferate, or migrate without an initial degradation of the matrix. One of the earliest events in angiogenesis is the degradation of the extracellular matrix to enable tube (capillary) formation. Vascular cells, including endothelial cells, VSMCs, resident macrophages and fibroblasts, may secrete matrix metalloproteinases (MMPs), enzymes that selectively digest the individual components of the matrix. In addition, these cells elaborate tissue inhibitors of metalloproteinases (TIMPs).[8]

MMPs belong to three main groups: the type IV collagenases (also called gelatinases), the stromelysins, and interstitial collagenase. The characteristics of these proteins are described in Table 6-2. MMPs are produced as inactive zymogens that can be activated by plasmin.[9] The activity of MMPs is also regulated by cytokines at transcriptional and posttranslational levels, as well as by the relative levels of TIMPs. MMP-

2 is usually found complexed with its specific inhibitor, TIMP-2.

Table 6-2: Matrix Metalloproteinases and Inhibitors

Class	Nomenclature	Molecular Weight[a]	Vascular Cell Type	Expression
Interstitial collagenase	MMP-1	~45	VSMC, EC, microvascular EC	Inducible by PDGF, PMA, IL-1, VEGF
Type IV collagenase	MMP-9, gelatinase B, type V gelatinase	92	VSMC, EC	Inducible by IL-1α, PMA; inhibited by retinoic acid
	MMP-2, gelatinase A, type IV gelatinase	72	VSMC, wounded EC, microvascular EC	Constitutive, ↑ by TNF-α, IL-1α (VSMC); ud by retinoic acid (EC)
Stromelysin	MMP-3	50	VSMC, EC, microvascular EC	Inducible by IL-1 (VSMC); TNF-α, PMA (EC)
TIMP-1	Inhibits MMPs	30	VSMC, EC, microvascular EC	Constitutive
TIMP-2	Inhibits MMP-2	~20	VSMC, EC, microvascular EC	Constitutive, ↑ by retinoic acid (EC)

[a]The molecular weight of MMP-1 and MMP-3 depends on the species.
ABBREVIATIONS: EC = endothelial cell; IL = interleukin; MMP = matrix metalloproteinase; PDGF = platelet-derived growth factor; PMA = phorbol 12,13-myrisate acetate; TIMP = tissue inhibitor of metalloproteinase; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor; VSMC = vascular smooth muscle cell.

In venous or microvascular endothelial cells, MMP-1 (interstitial collagenase), MMP-2 (72-kDa gelatinase), and TIMPs-1 and 2 are constitutively expressed. Although MMP-3 is only weakly expressed, it can be induced synergistically by incubation of the cells with the cytokine tumor necrosis factor α (TNF-α) and phorbol ester tumor promoters.[8] This treatment also induces MMP-9 expression. Since MMP-2 and TIMP-2 are unaffected by TNF-α, cytokine activation of endothelial cells can change the complement of metalloproteinases produced. In VSMCs, MMP-2 is constitutively expressed, whereas MMP-1, MMP-9 (92-kDa gelatinase), and MMP-3 (stromelysin) are induced by cytokines such as interleukin 1 and TNF-α.[9] Cytokines can also activate MMP-2 zymogen.[65] Thus, cytokine stimulation increases the range of active metalloproteinases secreted by smooth muscle cells to encompass proteases capable of degrading all the major matrix components. In contrast, although TIMP-1 and TIMP-2 are constitutively expressed by vascular smooth muscle, their expression is unaffected by cytokines.[9] The net effect of cytokines on the vascular wall may be to tip the balance between the production of MMPs and TIMPs in favor of extracellular matrix degradation and remodeling.

Of particular importance, several reactive oxygen species have been shown to stimulate both activation and expression of MMPs, in particular MMP-9.[66,67] This is likely to be very important in diseases like atherosclerosis and hypertension, where vascular oxidant stress is increased. Activated macrophages accumulate at shoulder regions of the atherosclerotic plaque and secrete both MMPs and reactive oxygen species,[66,68] contributing to plaque rupture in this region.

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Chapter 6: MOLECULAR AND CELLULAR BIOLOGY OF BLOOD VESSELS

ENDOTHELIAL CELL-VASCULAR SMOOTH MUSCLE INTERACTIONS

Endothelial Control of Vascular Tone

The endothelium serves a dual function in the control of vascular tone (Fig. 6-4). It secretes relaxing factors such as nitric oxide and adenosine, and constricting factors such as the endothelins. Vessel tone thus depends on the balance between these factors, as well as on the ability of the smooth muscle cell to respond to them. The most important regulatory molecules are discussed separately.

ENDOTHELIUM-DERIVED RELAXING FACTOR/NITRIC OXIDE

An EDRF was first described by Furchgott and Zawadzki,[2] who observed that aortic rings dilated in response to acetylcholine only when the rings maintained an intact endothelium. The predominant form of EDRF, derived from L-arginine by the action of the enzyme nitric oxide synthase (NOS), is nitric oxide (NO), or a closely related nitroso compound.[62]

Many factors have been shown to regulate the release of EDRF/NO[69] by increasing intracellular Ca^{2+}. These include hormones such as acetylcholine, norepinephrine, bradykinin, thrombin, ATP, and vasopressin; the platelet-derived factors, serotonin and histamine; fatty acids; ionophores; and physical forces. NO easily crosses the smooth muscle cell membrane and binds to the heme moiety of the soluble guanylate cyclase, thereby enhancing the formation of cyclic GMP. Cyclic GMP, in turn, reduces intracellular Ca^{2+} concentrations leading todephosphorylation of the myosin light chain and relaxation.[70] It should be noted that the drug nitroglycerin exerts its vasodilator effects by being converted to NO, thus substituting for a natural product. Deficiency in release of active NO is an important contributing factor leading to vasospasm.

NO is produced by the action of the enzyme NOS, which oxidizes the guanidino nitrogens of L-arginine to form citrulline and NO. This enzyme has been cloned from brain (nNOS, for neuronal NOS, type I),[71] macrophages (iNOS, for inducible NOS, type II),[72] and endothelial cells (eNOS, for endothelial NOS, type III).[73] The three isoforms of NOS share important consensus sequences for NADPH, flavin adenine dinucleotide, and flavin mononucleotide cofactor-binding sites, as well as a Ca^{2+}-calmodulin-binding site. During the past several years, a great deal has been learned about how these enzymes function.[74] All NO synthases function as homodimers, and each subunit consists of a carboxy-terminal reductase domain and an amino-terminal oxygenase domain, connected by a calmodulin-binding region. The NADPH- and flavin-binding sites reside in the reductase domain, where electrons derived from NADPH are stored by the flavins. For both the neuronal and endothelial isoforms of the enzymes, increases in intracellular calcium lead to calmodulin binding to the calmodulin-binding site, which in turn enables electrons to flow from the reductase domain to the amino-terminal oxygenase domain. This region contains binding sites for heme, tetrahydrobiopterin, and L-arginine. Electrons transferred from the reductase domain are initially bound by the ferrous iron in the prosthetic heme group. The precise role of tetrahydrobiopterin remains unknown, although it appears critical in allowing electrons to be transferred from the heme to the guanidino nitrogens of L-arginine, resulting in the formation of NO. Interestingly, when tetrahydrobiopterin or L-arginine is absent, the electron flows to molecular oxygen, resulting in the formation of the superoxide anion.[75] This phenomenon has been termed *uncoupling* of NOS, and there are substantial data that this may occur in a variety of disease states, perhaps because of oxidation of tetrahydrobiopterin.

Although increases in intracellular calcium clearly activate eNOS via stimulation of calmodulin, there are additional ways that the enzyme is activated that seem independent of calmodulin or calcium. For example, shear stress acutely stimulates the release of NO from the endothelium, and this depends only on calcium

during the first few seconds of the response.[76] The continued activation of eNOS in response to several minutes or hours of shear seems independent of calcium and calmodulin. Phosphorylation of eNOS is almost certainly important in this calcium-independent stimulation.[77] Recently, specific sites of the enzyme have been identified that are phosphorylated in response to shear.[78] Phosphorylation by the kinase Akt leads to a calcium-independent activity of the enzyme.[79] Other phosphorylation sites have also been implicated.

Although expression of the endothelial enzyme (eNOS) was originally thought to be constitutive, it is now clear that its expression is highly regulated. Increases in shear stress rather markedly enhance expression of eNOS.[80] Likewise, low shear is associated with a decrease in eNOS expression. Exercise training dramatically increases eNOS expression in endothelial cells, likely because of the increased shear stress caused by the high cardiac output that accompanies sustained exercise.[81] In contrast, inflammatory cytokines such as TNF-α decrease eNOS expression.[73] This is caused by destabilization of eNOS mRNA, rather than by decreasing the rate of eNOS transcription.[82] Several other conditions and stimuli seem to alter eNOS expression by changing the half-life of mRNA. These include exposure to oxidized LDL,[83] hypoxia,[84] and changes in endothelial cell growth state.[85] The mechanisms underlying regulation of eNOS mRNA stability are incompletely understood, but are the focus of intense investigation.

ENDOTHELIUM-DERIVED HYPERPOLARIZING FACTOR

Shortly after the identification of the EDRF, it was suspected that the endothelium could release more than one relaxing factor, depending on the vessel size, the stimulus, and the species studied. Initial studies showed that some vasodilators produce hyperpolarization of the vascular smooth muscle membrane in an endothelium-dependent manner. It is now clear that this is due to the release of a hyperpolarizing factor from the endothelium that is almost certainly different than NO.[86] Its production is stimulated by many of the same stimuli that evoke the release of NO and depends on intracellular calcium. Although there is some debate regarding the nature of this factor, increasing evidence suggests that it is a cytochrome P450 metabolite of arachidonic acid and perhaps other fatty acids.[87] This epoxide, when released from the endothelium, opens calcium-activated potassium channels in the adjacent vascular smooth muscle, resulting in vasodilation.[88] It has also been shown that these epoxides have important anti-inflammatory effects.[89]

PROSTACYCLIN

Prostacyclin, or prostaglandin I_2 (PGI_2), which is a prostanoid derived from the action of cyclooxygenase on arachidonic acid, is released by the endothelium and relaxes vascular smooth muscle by increasing its intracellular content of cyclic AMP.[90] Prostacyclin is also platelet suppressant and antithrombotic, and reduces the release of growth factors from endothelial cells and macrophages.[23] Among the agonists that stimulate prostacyclin synthesis are bradykinin (one of the most potent), substance P, platelet-derived growth factor and epidermal growth factor, and adenine nucleotides,[23] whereas aspirin has been shown to inhibit it transiently. Therapeutically, the debate about the appropriate dose of aspirin in ischemic coronary syndromes revolves around finding a dose that will inhibit platelet function without inhibiting endothelial PGI_2 synthesis.

ADENOSINE AND RELATED COMPOUNDS

Both adenine nucleosides (adenosine) and nucleotides (ADP and ATP) are released by the endothelium in response to such stimuli as thrombin[91] and flow.[92] Adenine nucleosides bind to P1 purinergic receptors that activate cyclic AMP leading to relaxation, whereas adenine nucleotides stimulate P2 receptors that are coupled to phosphoinositide hydrolysis. Stimulation of P2 receptors in endothelial cells results in an increase in intracellular Ca^{2+} and release of EDRF/prostacyclin,[93] whereas P2 receptors on vascular smooth muscle mediate contraction.[94] Thus, depending on the relative amounts of adenosine, ATP, and ADP in the vessel wall, and the presence of a functional endothelium, these compounds can have a net dilatory or constrictor effect on vascular smooth muscle. Additionally, the endothelium possesses an extracellular ectonucleotidase enzymatic system that mediates the conversion of ATP or ADP to adenosine, thereby regulating the local levels of these compounds.[15] These systems are important in determining the vascular response to ADP released from platelets at the site of thrombus formation.

ENDOTHELIN

The endothelins are a family of closely related peptides made and secreted by endothelial cells in some, but not all, vascular beds. There are three endothelins (ET-1, 2, and 3), all of which are 18 amino acid peptides. Endothelins are initially synthesized as preproendothelin, which undergoes preprocessing to big-endothelin. Big-endothelin is released and is converted to active endothelin by the endothelin-converting enzyme. The vascular effects of endothelin are mediated by endothelin receptors, of which three subtypes have been identified (ET-A, B, and C). The receptors have differing specificity for the individual endothelin peptides and activate somewhat different signaling pathways. In the vessel, the ET-A receptor is predominantly found on vascular smooth muscle, whereas the ET-B receptor resides on endothelial cells. Activation of the former stimulates potent vasoconstriction, whereas activation of the latter stimulates release of NO and thus favors vasodilation.[95]

The slow, intense, and sustained contraction caused by ET-1 appears to be the result of activation of the phosphoinositide/protein kinase C signaling pathway, as well as of opening voltage-dependent L-type calcium channels.[96] Importantly, even low, subthreshhold concentrations of ET-1 enhance vasoconstriction to a variety of other vasoconstrictor agents, including serotonin, angiotensin II, and α-adrenergic agonists, seemingly via activation of protein kinase C. This has been suggested to contribute to the *rebound phenomenon* that occurs after nitroglycerin has been administered for several days and suddenly discontinued.[97]

ET-1 is also a potent growth factor for smooth muscle,[98] is a chemoattractant for monocytes,[99] and plays a role in nitroglycerin tolerance.[97] Importantly, angiotensin II has been shown to stimulate the production of ET-1 by VSMCs in culture[100] and, in vivo, some of the hypertensive effect of angiotensin II is mediated by endothelin.[101]

ANGIOTENSIN-CONVERTING ENZYME

Endothelial cells synthesize and express on their surface angiotensin-converting enzyme (ACE),[102] the protein that converts angiotensin I to the potent vasoconstrictor angiotensin II and degrades and inactivates bradykinin. Of note, vascular cells contain almost all components of the renin/angiotensin system, and thus local production of angiotensin II can contribute importantly to vascular function. This local production of angiotensin II can explain why ACE inhibitors and angiotensin receptor antagonists are often effective even when the circulating levels of renin or angiotensin II are not elevated.

Endothelial Control of Vascular Growth

As with vascular tone, the endothelium also exerts a dual effect on vascular growth (Fig. 6-5). Both growth-promoting and growth-inhibitory factors are made and secreted by endothelial cells, making them pivotal in the control of smooth muscle responsiveness. Endothelial cells are involved in two types of vascular growth: angiogenesis and abnormal growth of smooth muscle during disease.

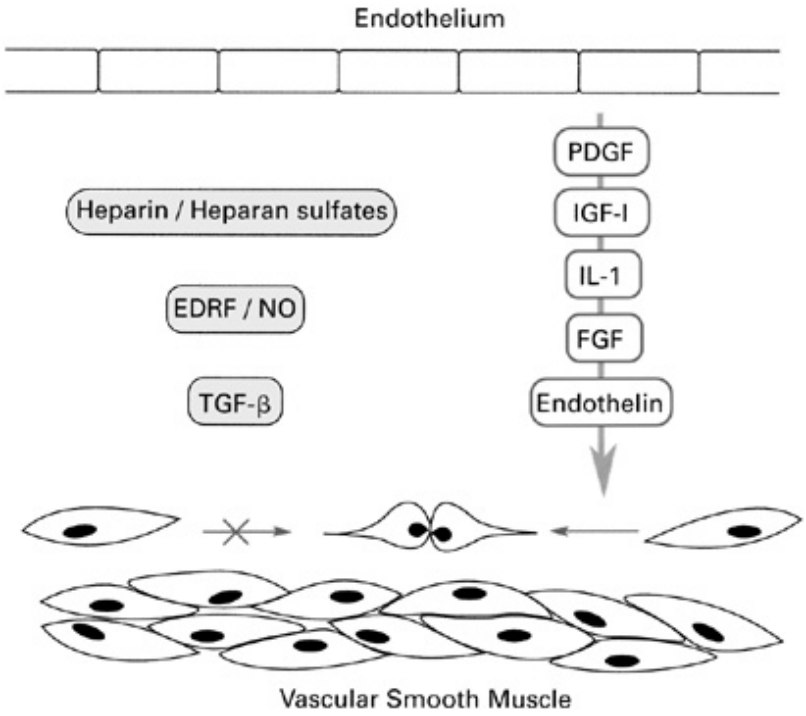

Figure 6-5: Endothelial control of vascular growth. As with vasoactive substances, endothelial cells make and secrete both growth-promoting (*white boxes*) and growth-inhibitory (*colored boxes*) compounds. Under normal conditions, the net effect of the endothelium is growth inhibitory. ABBREVIATIONS: EDRF = endothelial-derived relaxing factor; NO = nitric oxide; TGF-β = transforming growth factor-β; PDGF = platelet-derived growth factor; IGF-I = insulin-like growth factor-I; IL-1 = interleukin-1; FGF = fibroblast growth factor. (Courtesy of Bernard Lassègue, Ph.D.)

ANGIOGENESIS

Angiogenesis in vivo occurs during normal wound healing and during the vascularization of solid tumors. It is a complex process involving degradation of the basement membrane, the migration and proliferation of endothelial cells, and tube formation. Several factors have been shown to stimulate angiogenesis, including FGF, vascular endothelial growth factor (VEGF), transforming growth factor α (TGF-α), angiogenin, transforming growth factor-β (TGF-β), TNF-α,[103] and insulin-like growth factor 1 (IGF-1).[104] Their properties are summarized in Table 6-3. Some of these factors stimulate angiogenesis by inducing endothelial cell migration and proliferation (FGF and VEGF); others appear to do so by stimulating endothelial cell differentiation (TGF-β and TNF-α) or by activating a secondary cell type to produce angiogenic factors (angiogenin, TGF-β, and TNF-α). Angiogenesis may be negatively regulated by both naturally occurring and synthetic compounds. It can be inhibited by the combination of heparin and cortisone,[105] thrombospondin, platelet factor IV, and γ-interferon. Many of these agents bind to heparin, suggesting that they exert their growth-inhibitory effects by blocking the action of heparin-binding growth factors, such as FGF. It is likely that the control of angiogenesis rests on the maintenance of a balance between the stimulatory and inhibitory factors, the regulation of which is not yet fully understood.

Table 6-3: Angiogenic Stimulators and Inhibitors

	Angiogenesis	Origin	Release	Endothelial Cell Proliferation	Endothelial Cell Chemotaxis	Tubule Formation
FGF	+	Endothelial cells	Cell lysis	+ +	+ (EC)	+
VEGF	+	Endothelial cells	Secreted	+ +	+	+
TGF-α	+	Transformed fibroblasts, macrophages (adenocarcinoma cells)	Secreted	+ +		
Angiogenin	+	Lymphocytes, liver	Secreted	0	-	
TGF-β	+	Endothelial cells	Secreted	-	-(EC)+ (Monocytes)	+
TNF-α	+	Activated macrophages, tumor cells	Secreted	-	+	+
Angiostatic steroids	-	Synthetic	-	-		
Thrombospondin	-	Platelets	Secreted	-		
Platelet factor IV	-	Platelets	Secreted	-		
?-Interferon	-	Activated T cells, macrophages	Secreted	-		

ABBREVIATIONS: EC = endothelial cell; FGF = fibroblast growth factor; TGF = Transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

ENDOTHELIAL-DERIVED INHIBITORS OF SMOOTH MUSCLE CELL GROWTH

Normally, smooth muscle cells are relatively refractory to growth stimuli and are maintained in a quiescent, differentiated state. It has been proposed, based on at least two lines of evidence, that the endothelium is important in maintaining this smooth muscle phenotype. First, removal of the endothelium experimentally allows initiation of the mitogenic response and, second, regrowth of normal endothelium inhibits further proliferation.[106] One mechanism by which such a tonic inhibitory influence on smooth muscle cell growth could be effected is the secretion by endothelial cells of specific inhibitors of cell proliferation. Alternatively, the endothelium could be an effective barrier limiting access of bloodborne growth factors to vascular smooth muscle. Attention so far has focused on heparin and other glycosaminoglycans (including heparan sulfate) as possible candidates for endothelial-derived growth-inhibitory factors. Heparin inhibits VSMC mitogenesis and migration in vivo and in vitro, and reduces neointimal proliferation if administered during the first 3 days after vascular injury.[107] However, the inhibition is not complete, and it seems likely

that other endothelial cell factors may be involved. Another possibility is NO, which is usually associated with vascular relaxation. NO is released tonically from the endothelium of large arteries, which have a relatively minor role in the control of vascular tone, suggesting that it may have an additional function in these vessels. Studies on cultured VSMC have shown that pharmacologic agents such as sodium nitroprusside and 8-bromo-cyclic GMP, which mimic the effect of NO on vascular smooth muscle G kinase, can inhibit mitogenesis.[108] This raises the possibility that NO may have an important role in maintaining the normal artery in a state refractory to mitogens. It is of interest that the myointimal proliferation in response to balloon injury can be inhibited by overexpression of NO synthase using gene transfer techniques.[109,110] Finally, endothelial cells have been shown to make and secrete TGF-β,[12] which is subsequently activated by smooth muscle cells. This growth factor inhibits smooth muscle growth directly[111] and alters PDGF secretion,[112] as well as extracellular matrix composition. The extracellular matrix may itself have a very important influence on smooth muscle proliferation.

The response of VSMCs to growth factors depends on the balance of the hormonal and environmental influences to which the cells are subjected. For example, intact arteries are relatively unresponsive to FGF, only showing a proliferative response when the endothelium has been damaged or removed.[61] This raises the possibility that the cellular mechanism of action of factors secreted by the endothelial cells is to induce a protein or factor in smooth muscle cells that makes them refractory to mitogenic stimulation. One candidate for such a protein is a tyrosine phosphatase. As already noted, most growth factors activate a cascade of tyrosine kinases as an initial step in the mitogenic stimulus. The level of tyrosine in cellular proteins is also controlled by tyrosine phosphatases, enzymes that remove phosphates from tyrosine residues. Thus, in cells with very active tyrosine phosphatases, tyrosine kinases may be unable to induce a sustained phosphorylation of proteins on tyrosine, theoretically inhibiting the growth response. Evidence for such a mechanism of growth control is only now becoming available, with the discovery that somatostatins act as growth inhibitors in neoplastic cells through activation of a tyrosine phosphatase.[52] Angiopeptin, a somatostatin analog, has been shown to inhibit neointimal proliferation after balloon injury,[113] suggesting that activators of tyrosine phosphatases may be important in growth control in the vasculature. These observations raise the possibility that one of the mechanisms by which endothelial cells help to maintain smooth muscle quiescence is by the induction of tyrosine phosphatase activity in the smooth muscle cells.

ENDOTHELIAL-DERIVED STIMULATORS OF SMOOTH MUSCLE CELL GROWTH

Endothelial cells have the capacity to secrete several factors that are thought to be involved in the abnormal smooth muscle cell growth seen during atherogenesis and hypertension. As noted previously, the most well studied of these factors is PDGF, so named because it was originally isolated from platelets. PDGF is a dimer, composed of two distinct peptide chains (designated A and B chains), and can be produced as an AB heterodimer or as an AA or BB homodimer. Endothelial cells contain the mRNA for both peptides,[112] although the precise form in which PDGF is secreted is unclear. Release of PDGF from the endothelium is regulated by second messengers such as cAMP and activators of protein kinase C; other growth factors including TGF-β, FGF, and TNF; circulating factors; and locally produced factors such as thrombin.[112] A second growth factor made and secreted by endothelial cells is IGF-1,[13] which is a progression factor that facilitates movement of cells through the cell cycle but, by itself, is not a particularly strong mitogen. In vitro, it enhances the mitogenic effect of PDGF on smooth muscle.[114] IGF-1 production by endothelium has been shown to be regulated by PDGF and has been shown to be a major player in vascular hypertrophy and hyperplasia.[115]

Other factors made by the endothelium that are able to alter smooth muscle proliferation include interleukin 1 (IL-1), FGF, and endothelin. IL-1 is an inflammatory cytokine that has numerous vascular effects in addition to mitogenesis, including the stimulation of procoagulant activity,[116] induction of leukocyte adhesiveness (see below), and inhibition of contraction.[117] IL-1 regulates its own expression,[118] and, in addition, its production is regulated by TNF-α,[103] lipopolysaccharide, and γ-interferon.[118] As already noted, basic FGF has been detected in endothelial cells[17] and acts as a potent smooth muscle mitogen, particularly after denuding injury.[61] FGF does not contain the signal peptide that usually provides a mechanism for transporting proteins out of cells and thus may not be secreted by endothelial cells. It is, however, present

and stored in the subendothelial matrix and may be released on cell lysis or death.[119] FGF released from VSMCs may be particularly important in the growth response induced by injury to the arterial wall after balloon angioplasty. FGF bound to the matrix can be released by heparin and proteinases,[120] suggesting that the matrix may serve as a store for rapidly mobilizing this growth factor. Finally, the vasoconstrictor endothelin has also been shown under certain circumstances to act as a smooth muscle mitogen,[121] possibly by increasing PDGF-A chain secretion in the smooth muscle cells themselves.

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ENDOTHELIAL CELL-LEUKOCYTE INTERACTIONS

Endothelial cells participate actively in the development of inflammatory reactions. They are central to the recruitment of leukocytes to sites of inflammation by secreting chemotactic molecules and expressing adhesion molecules that interact with surface proteins on leukocytes.

Inflammatory cytokines increase synthesis of vasodilators by the endothelium, which causes increased blood flow to the injured area. Histamine, which is released at the site of vascular inflammation, also contracts endothelial cells in certain areas, thus increasing permeability.[122] Cytokines stimulate endothelial secretion of leukocyte chemoattractant proteins (interleukin 8) and monocyte chemotactic protein 1 (MCP-1), and expression of adhesion molecules such as intercellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2), endothelial leukocyte adhesion molecule 1 (E-selectin), vascular cell adhesion molecule 1 (VCAM-1), and GMP-140, which are important regulators of leukocyte accumulation on the vascular surface.[123] E-selectin and GMP-140 bind resting, but not activated, neutrophils; VCAM-1 binds to the VLA-4 antigen on monocytes and T lymphocytes; and ICAM-1 and 2 bind to the LFA-1 integrin receptor on B lymphocytes.[123] The expression of these molecules appears to be differentially regulated by cytokines, thrombin, and histamine,[123] so that their surface expression determines the type of leukocytes attached to the endothelial monolayer. It has been suggested that the sequential accumulation of different leukocyte classes at sites of inflammation can be explained by the differential induction of these endothelial cell adhesion molecules.[124] Leukocyte adhesion molecules and chemoattractant proteins are also likely to be important in atherogenesis (see below).

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ENDOTHELIAL RESPONSES TO HEMODYNAMIC INFLUENCES

In addition to being influenced by the interaction of circulating blood cells, VSMCs, and matrix, the endothelium responds to the physical forces of pressure, stretch, and shear stress imposed by the hemodynamics of the circulation. Flow-mediated, endothelium-dependent vasodilation has been described in many vascular beds,[125] and shear stress has been proposed to play a role in controlling endothelial cell proliferation.[126] Elevated pressure, stretch of the vessel wall, and shear stress have all been shown independently to affect endothelial cell morphology and/or function. Pressure alone appears to have a role in the generalized hypertrophy of the vessel wall that occurs during hypertension. Studies in cultured cells have shown that stretching endothelial cells leads to changes in cell shape, intracellular signal generation with an increase in calcium concentration, and proliferation.[126] Shear stress has numerous effects on endothelial cells. Initially, it was found that exposure of endothelial cell monolayers to elevated shear stresses in vitro caused them to align in the direction of flow. This reorientation was accompanied by changes in the cytoskeleton of the cells, including reorganization and alignment of the actin filaments and microtubules (Fig. 6-6). Similar mechanisms presumably also account for the orientation of endothelial cells parallel to the longitudinal axis in areas of laminar flow in the arterial system. The function of endothelial cells is also altered by shear stress: a K^+ current is activated; secretion of vasoactive and growth factors, including NO, endothelin, prostacyclin, and basic FGF (bFGF) is increased; tissue factor expression is increased; uptake of LDL is elevated; and tPA secretion is increased.[126]

The importance of these observations lies in the variation in hemodynamic forces throughout the circulation. High pressure, such as that which occurs in hypertension, causes changes in the morphology and function of the vessel wall.[127] In addition, the areas of the vasculature exposed to low shear stress (branch points and curvatures) exhibit a predilection to the formation of atherosclerotic lesions.[128] It is thus clear that the hemodynamic environment of the endothelium and underlying smooth muscle is a potentially powerful regulator of vascular function.

The mechanism(s) by which the endothelial cell can sense and transduce mechanical signals has not been defined definitively. Possibilities include signaling through focal adhesion complexes, a surface mechanoreceptor, a flow-sensitive ion channel, changes in cytoskeletal stress due to deformation, and flow-dependent gradients of bioactive substances along the surface of the cell. Recent data have implicated heterotrimeric G-protein activation.[129] Furthermore, caveolae, which are budding, membrane vesicular structures as described previously, are rich in signaling molecules such as G proteins and may be involved in signal generation in response to shear stress.[130]

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ENDOTHELIAL DYSFUNCTION AND VASCULAR SMOOTH MUSCLE ABNORMALITIES

In general, the normal endothelium is in an inhibitory mode-inhibiting contraction, thrombosis, white cell adhesion, and vascular smooth muscle growth (Figs. 6-4 and 6-5). *Endothelial dysfunction* is one of the important concepts that has developed in vascular biology over the last decade. Implicit in the term is the recognition that the fundamental or normal functions of the endothelium are not fixed, but are mutable. Thus, the endothelium in a given area may lose its vasodilator predominance, become prothrombotic or less thrombolytic, begin to support leukocyte adherence (which may be a normal response in the inflammatory process), or stimulate rather than inhibit smooth muscle migration and proliferation. *It is likely that endothelial dysfunction accounts ultimately for a large portion of cardiovascular diseases*.

Oxidative Stress and Vascular Disease

In the past several years, it has become clear that vascular cells, including endothelial, vascular smooth muscle, and adventitial cells, can produce reactive oxygen species (ROS). These include superoxide anion, hydrogen peroxide, NO, and peroxynitrite. In numerous pathophysiologic conditions, the production of ROS in the vascular wall is increased, resulting in a situation commonly referred to as *oxidant or oxidative stress*. Several enzyme systems have been implicated in production of ROS.

Recent studies suggest that an NADH/NADPH-driven oxidase is a major source of ROS in endothelial and vascular smooth muscle cells. This oxidase is a multisubunit enzyme that has only partial similarity to the neutrophil respiratory burst oxidase. For example, in VSMCs, the subunit p22phox has been shown to be critical for its function, whereas the gp91phox subunit appears to be absent.[131] In endothelial cells, the existence of all of the neutrophil subunits has been demonstrated, although it is not clear that they function together to produce ROS as they do in the neutrophil.[132] The adventitia also contains fibroblasts and macrophages that express multiple oxidase subunits.[133] Importantly, the NADH/NADPH vascular oxidase is activated by several pathophysiologic stimuli, including angiotensin II, mechanical stretch, cytokines, and thrombin.[134-137]

A second source of ROS is eNOS. As discussed previously, in the absence of tetrahydrobiopterin or L-arginine, this enzyme becomes "uncoupled" so that it produces hydrogen peroxide and superoxide, rather than NO.[75,138] Importantly, this uncoupling process seems to occur in several common disease states, including hypercholesterolemia,[139] hypertension,[140] and diabetes, although the mechanisms responsible for this process are poorly understood.

An important source of radicals in the vasculature is the lipoxygenases and in particular 12,15-lipoxygenase. These do not form superoxide, but react directly with unsaturated fatty acids (e.g., linoleic or arachidonic acid) to form a lipid radical ($L_{\bullet}$), which in turn can react with molecular oxygen to produce alkoxy radicals ($LO_{\bullet}$) and lipid peroxy radicals ($LOO_{\bullet}$). These lipid radicals are biologically very active and can stimulate gene expression, consume NO, oxidize NADH, and serve as a source of other radicals.[141]

Other sources of ROS in vascular cells are xanthine oxidase, cytochrome P450, cyclooxygenase, and mitochondrial electron transport.[141] There is now substantial interest in the role of these various sources of ROS and how they contribute to vascular oxidant stress.

In the next several paragraphs, we consider how endothelial dysfunction and vascular smooth muscle abnormalities contribute to several vascular diseases. A recurring theme in these conditions is that ROS play a central role. For example, superoxide rapidly reacts with NO, forming the strong oxidant peroxynitrite. The latter can oxidize lipids, damage lipid membranes, deplete cellular thiols, and alter function of several enzymes.[142] This inactivation of NO alters vasomotion and can predispose one to or even cause hypertension.[143] A substantial component of VSMC hypertrophy caused by angiotensin II is mediated by hydrogen peroxide.[144] ROS also contribute to vascular inflammation by stimulating expression of adhesion molecules in endothelial cells.[145] These issues discussed in the context of several vascular diseases.

Atherosclerosis

Atherosclerosis is the prototypical disease characterized by endothelial dysfunction, which may explain many of its cardinal features. Thus, mononuclear and lymphocytic infiltration, hypercontractility, LDL modification, smooth muscle cell growth, and intimal migration are likely related to abnormalities of the endothelium induced by hyperlipidemia, hypertension, smoking, and unknown hereditary factors. The pathogenesis of atherosclerosis viewed as a disease of endothelial dysfunction is depicted in Fig. 6-7. (For a more detailed discussion, see Chap. 41.)

Clinically, endothelial dysfunction in atherosclerosis has primarily been defined by impairment of endothelial-dependent relaxation.[146] This defect, which likely accounts for the vasospastic tendency of diseased arteries, appears to be attributable to defective generation or delivery of active EDRF/NO.[147] Coronary endothelial-dependent vasodilator function is impaired in patients with risk factors such as hypercholesterolemia, prior to angiographically demonstrable coronary disease.[148] As previously discussed, increased inactivation of NO by the superoxide anion is likely one cause of this abnormality.[147,149] Other causes may include "uncoupling" of the eNOS enzyme, altered calcium signaling of eNOS, and diminished expression of the eNOS enzyme, which clearly occurs late in the atherosclerotic process.[150] Of note, LDL and cytokines have been shown to downregulate eNOS by destabilizing the eNOS mRNA. This is prevented by HMG-CoA reductase inhibitors even without lowering of cholesterol. New evidence suggests that this process involves the lipid modification of the small GTPase Rho by the attachment of a geranylgeranyl and lipid moiety, which facilitates its localization to the cell membrane, suggesting a new target for the HMG-CoA reductase inhibitors.[151]

A second manifestation of a dysfunctional endothelium that is apparent very early after initiation of cholesterol feeding in animals is the recruitment of monocytes and macrophages into the vessel wall.[152] This recruitment is likely the result of induction of VCAM-1 expression,[153] as well as secretion of MCP-1.[154] The molecular linkage between hyperlipidemia and MCP-1/adhesion molecule expression is unknown, but may reflect in part the oxidative stress imposed by this change in milieu. Inflammatory cytokines are also important mediators of adhesion molecule expression,[155] and their production by the endothelium and inflammatory cells in the vessel wall may also contribute to adhesion molecule expression in both the early and the late stages of the disease.

The intimal proliferation observed in atherosclerotic lesion formation results from migration and hyperplasia of VSMCs[156] and accumulation of extracellular matrix.[157] Proliferation has been attributed to growth factors such as PDGF, FGF, and IGF-1. Since these growth factors can be

produced by the endothelium in vitro, it is very likely that the dysfunctional endothelium in atherosclerosis also produces growth factors while shifting from a growth-inhibitory to a growth-promoting mode. Furthermore, there is evidence that products of oxidative metabolism may also release growth factors and activate matrix metalloproteinases,[67] thus contributing to intimal lesion formation on multiple levels.

The recent advances in our understanding of vessel wall biology provide insight into the biological mechanisms responsible for the pathogenesis of atherosclerosis. A unifying concept of the disease has arisen that revolves around endothelial dysfunction mediated by changes in oxidative metabolism. Oxidative stress and oxidatively modified LDL thus assume central roles in atherogenesis (Fig. 6-7). As discussed previously, a major source of lipid oxidation is lipoxygenase. Recently, the 12,15-lipoxygenase gene has been deleted in mice. When these animals were crossed with apolipoprotein E-deficient mice (which spontaneously develop atherosclerosis), atherosclerotic lesion development was strikingly reduced.[158] These data indicate that 12- and 15-lipoxygenases are almost certainly involved in the atherosclerotic process. The role of oxidized LDL is discussed more completely in Chap. 35, and the relationship of the cell biology of atherosclerosis to coronary ischemic syndrome is discussed in Chap. 41.

Hypertension

Hypertension is characterized by dysfunction of both endothelium and vascular smooth muscle. In chronic hypertension, endothelium-dependent relaxations are impaired in both conduit and resistance arteries.[159-162] Relaxations to some platelet factors are also altered, but have been found to be augmented or diminished, depending on the hypertensive model studied.[163] Furthermore, the endothelium-dependent constrictor activity is increased in some models of hypertension.[163] These alterations in endothelial function would tend to increase the tone of hypertensive vessels. The mechanism responsible for this effect is not entirely clear. Data from experimental animals make it seem likely that the alterations in endothelium-dependent responses in hypertension result from a combination of altered endothelial and VSMC function.

Hypertension is also characterized by an increase in vessel wall mass. In the aortas of spontaneously hypertensive and Goldblatt hypertensive rats, this increase can be attributed to an increase in the size of the existing smooth muscle cells.[164,165] Hypertrophy is accompanied by an increase in ploidy; that is, an increased DNA content per cell.[164,165] In contrast, resistance vessels from these same animals appear to increase their mass by hyperplasia of the smooth muscle cells.[166] The stimuli responsible for these changes in the hypertensive vascular wall are unknown. Vascular remodeling appears to have two stages: (1) an initial, reversible intense vasoconstriction mediated by neural or endogenous signals, followed by (2) a remodeling of the vessel wall characterized by increased smooth muscle mass and narrowing of the vessel lumen. There is some evidence that this response is dependent on the presence of the endothelium.[127]

Vasospasm

When the endothelium becomes dysfunctional as in atherosclerosis, the underlying smooth muscle cells often become hyperreactive to certain vasoconstrictor stimuli, including serotonin and ergonovine.[167] Coronary spasm leading to myocardial infarction is one of the most clinically relevant problems arising from this phenomenon. Proposed mechanisms underlying this vasoconstrictor abnormality that can result in total occlusion include supersensitivity of the smooth muscle cells to constrictor stimuli and loss of endothelial-dependent relaxing mechanisms. The increased tendency toward thrombus formation in dysfunctional endothelium, due to a loss of the normal anticoagulant properties, also promotes the release of thrombus-related factors (serotonin, thromboxane A_2, ADP, thrombin, and PDGF) in the vicinity of the smooth muscle cells, which can promote vasoconstriction.[168]

Restenosis

Restenosis is the development of a neointima that occurs following angioplasty, often leading to reocclusion of the initial lesion. The response of the arterial wall to the injury induced by angioplasty (removal of the endothelium and stretching of the vessel wall) involves several distinct events (Fig. 6-7). Removal of the endothelium not only alters the paracrine hormonal environment in which VSMCs exist, but it also exposes a thrombogenic surface to which platelets and other circulating factors can adhere, resulting in the formation of a thrombus. In addition, injury to the underlying smooth muscle may release factors such as FGF, which have mitogenic effects on the remaining smooth muscle cells. Finally, infiltration and subsequent activation of macrophages into the denuded vessel wall bring an additional set of hormonal influences to bear on the vascular smooth muscle. The pathophysiologic consequences of these complex events include migration and proliferation of smooth muscle cells into the intimal area, resulting in the formation of a neointima over a period of weeks to months.

Balloon injury has been extensively studied in several animal models, including pigs, rabbits, rats, and baboons. In the rat carotid artery, the events following injury can be divided into three stages: initial (injury to 48 h), migratory (3 to 7 days), and proliferative (7 days to 3 to 4 weeks). During the initial response to injury, growth-related genes in the smooth muscle cells are induced, including c-fos, PDGF-A, PDGF-β receptor,[169] and MCP-1.[170] It also appears that deep injury to smooth muscle cells results in an outpouring of FGF, a potent smooth muscle mitogen.[119] This initial response does not appear to depend on platelet factors, but does appear to be directly related to the removal of the endothelium.[106] During the migratory phase, a large increase of thymidine incorporation in the vessel wall occurs, accompanied by further increases in the mRNA encoding IGF-I[171] and the PDGF-β receptor.[169] This phase of the response can be modulated by platelet factors and inhibited by the endothelium.[106] Finally, the proliferative phase is characterized by marked intimal thickening, with a decreased percentage of thymidine-labeled cells. Some of the increased area is due to deposition of extracellular matrix, and the majority of the proliferative activity occurs at the luminal surface of the vessel. This proliferative phase seems ultimately to be inhibited by regrowth of normal-functioning endothelium.

Thus, during the process of restenosis after angioplasty, both the loss of endothelium and the transformation of smooth muscle cells appear to contribute to neointimal formation. At least two lines of evidence implicate the endothelium as having a crucial role in the response of the vessel wall to injury. First, removal of the endothelium allows initiation of the mitogenic response and, second, regrowth of normal endothelium inhibits further proliferation. Furthermore, gentle denudation with a nylon loop, accompanied by rapid regeneration of endothelium, results in significantly less neointimal proliferation.[172] In addition, proliferating smooth muscle cells have characteristics distinct from the differentiated smooth muscle cells in the medial layer. Their cytoskeleton is similar to that found in cultured cells. It seems likely, therefore, that two of the most important causes of restenosis are the loss of endothelium-derived growth-inhibitory factors and the transformation of smooth muscle cells into a phenotype able to respond to platelet- and endothelial-derived factors with proliferation.

ROS are not only thought to be centrally involved in the pathogenesis of atherosclerosis, but very likely are major mediators of the proliferative, hypertrophic, and fibrotic responses that frequently occur in arteries after percutaneous transluminal coronary angioplasty (PTCA) resulting in renarrowing or restenosis of the lumen (see Chap. 45). Migration and growth of VSMCs into the intima contribute significantly to restenosis, and intracellular signaling pathways mediating growth, hypertrophy, and migration are stimulated by ROS.[173,174] As discussed previously, both proinflammatory pathways and matrix metalloproteinases, which facilitate vascular remodeling, involve redox-sensitive controlling mechanisms. The apparent broad role for oxidative signaling mechanisms in the vascular wall led to testing of the concept that antioxidants might inhibit

restenosis. The production of superoxide is increased in vessels following balloon injury and, in the porcine model of restenosis, vitamins E and C have been shown to reduce neointimal development.[175,176] Further, several clinical studies have shown that the potent antioxidant probucol reduces late lumen loss after balloon angioplasty.[177-179] Larger clinical trials are under way to test the hypothesis that antioxidants are effective in inhibiting the vascular remodeling processes leading to post-PTCA restenosis.

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FUTURE DIRECTIONS

Defining the molecular and cellular basis for dysfunction of the arterial wall in vascular diseases provides information critical to developing clinical strategies for patient management, as well as new therapeutic targets. It is now clear that both endothelial function and smooth muscle function are compromised by a variety of risk factors for vascular disease, due in part to oxidative stress. Further research is required to determine at a more basic level the molecular events that link these risk factors to these diseases. In the near future, the human genome will be fully sequenced, and via the use of bioinformatics, it will be possible to identify genetic profiles that predispose people to the development of vascular pathologies. Clinical trials in the future will be targeted to these populations in new and powerful ways, and basic research will address the roles of these newly identified genes in vascular physiology and pathophysiology.

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Figure 6-4: Endothelial control of vascular tone. Endothelial cells synthesize and secrete both vasodilator substances (NO, EDHF, and PGI_2) and vasoconstrictor compounds (Ang II and ET-1). Secretion of these factors occurs in response to receptor stimulation and hemodynamic forces such as shear stress. Vessel tone depends on the balance between these factors, as well as on the ability of the smooth muscle cells to respond to them. ABBREVIATIONS: $NO\cdot$ = nitric oxide; NOS = nitric oxide synthase; EDHF = endothelial-derived hyperpolarizing factor; PGI_2 = prostaglandin I_2; ACE = angiotensin-converting enzyme; Ang = angiotensin; ET-1 = endothelin-1; cGMP = cyclic guanosine monophosphate; cAMP = cyclic adenosine monophosphate; 5-HT-5-hydroxytryptamine.

Figure 6-5: Endothelial control of vascular growth. As with vasoactive substances, endothelial cells make and secrete both growth-promoting (*white boxes*) and growth-inhibitory (*colored boxes*) compounds. Under normal conditions, the net effect of the endothelium is growth inhibitory. ABBREVIATIONS: EDRF = endothelial-derived relaxing factor; NO = nitric oxide; TGF-β = transforming growth factor-β; PDGF = platelet-derived growth factor; IGF-I = insulin-like growth factor-I; IL-1 = interleukin-1; FGF = fibroblast growth factor. (Courtesy of Bernard Lassègue, Ph.D.)

Figure 6-6: Effect of shear stress on endothelial cells. In bovine aortic endothelial cells grown in static conditions, F-actin filaments assume a random orientation as visualized by rhodamine-labeled phalloidin staining (*left*). Upon exposure to shear stress (30 dynes/cm2, 24 h), these filaments align (*right*). Bars = 100 μm. (Courtesy of Lula Hilenski, Ph.D.)

Figure 6-7: Theoretical initiating events in vascular lesion formation. *Non-denuding injury:* Low-density lipoprotein (LDL) enters the subendothelial space where it is converted to oxidized LDL (ox-LDL), which induces monocyte chemoattraction and endothelial dysfunction. Dysfunctional endothelial cells (ECs) express cell adhesion molecules (ICAM, ELAM, and VCAM), leading to increased monocyte adhesion and movement into the vessel wall. Monocytes in the vessel wall differentiate into macrophages, take up lipids, and remain locally as foam cells, subsequently evolving into fatty streaks. The foam cells in the fatty streak and the overlying endothelium express monocyte chemotactic protein 1 (MCP-1), resulting in further enhanced monocyte chemoattraction and adhesion. Dysfunctional ECs may synthesize less nitric oxide synthase (NOS) or superoxide dismutase (SOD, an enzyme that metabolizes oxygen radicals that have been shown to inactivate NO). This decreases endothelial-derived relaxing factor (EDRF) release/activity. The loss of EDRF together with the direct effects of ox-LDL, or growth factors secreted by the foam cells or endothelium, act on the quiescent contractile smooth muscle cells in the vessel wall, giving rise to the proliferative phenotype, with division and migration into the intima. *Denuding injury:* Loss of endothelium leads to platelet deposition, tissue factor-mediated activation of extrinsic coagulation to generate thrombin, cleavage of fibrinogen to fibrin, and the formation of thrombus. Thrombin gives rise to endothelial expression of adhesion molecules and consequent monocyte attachment, together with secretion of platelet granular constituents. Monocytes enter the thrombus and differentiate into phagocytic macrophages expressing tissue factor and MCP-1. This leads to further monocyte chemoattraction into the vessel wall. Smooth muscle cell proliferation is produced by (1) thrombin generation at the site of denuding injury, (2) platelet-derived growth factor (PDGF) or other growth factors released from platelets in the thrombus, (3) factors secreted by the macrophages ingesting the thrombus, and (4) the loss of EDRF activity caused by endothelial dysfunction. *Proliferative response:* Modulated smooth muscle cells (SMCs) proliferate and synthesize factors that promote plaque development. SMCs synthesize (1) PDGF and other growth factors that cause self-perpetuating autocrine or paracrine stimulation of SMC proliferation, (2) tissue factor (TF) and plasminogen activator inhibitor 1 (PAI-1) that act locally to produce thrombin or inhibit fibrinolysis of the fibrin network used to facilitate cell migration, and (3) MCP-1, which increases monocyte chemoattraction into the lesion, thereby leading to lesion development. (We thank Drs. Laurence Harker, Josiah Wilcox, and Bernard Lassègue for their creative and intellectual development of this figure.)

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Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 7:

UNRAVELING THE HUMAN GENOME AND ITS FUTURE IMPLICATIONS FOR CARDIOLOGY

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THE HUMAN GENOME

The term *genome* refers to all of the DNA, including the genes, responsible for an organism. The term *proteome* refers to all of the proteins responsible for an organism. The genes exert all of their influence through the proteins they produce. In general, the dogma is still true that each gene produces a unique protein, although it is preferable to refer to the end product as a polypeptide, since some proteins are made of two or more polypeptides and occasionally certain genes, through alternative splicing, may produce more than one polypeptide. The human genome is contained in 23 pairs of chromosomes. Twenty-two of these pairs are homologous chromosomes (one from the father and one from the mother), referred to as autosomes, and the remaining pair contain the sex chromosomes, which in the male consists of an X and a Y chromosome and in the female of two X chromosomes. Only a small portion of the X and Y chromosomes are homologous which is referred to as the pseudoautosomal region. Each pair of autosomal homologous chromosomes carries the same set of genes, with one inherited from each parent. Despite their homology and potentially identical function, some of the genes have a slightly different DNA sequence from that of the corresponding gene on their homologous partner, which may slightly or markedly alter their function. For example, the gene encoding for angiotensin-converting enzyme (ACE) has three forms (alleles): D, DI, and II. Thus, the chromosome from the mother may have the D form and the homologous chromosome from the father the I form; nevertheless, both genes encode for ACE and convert angiotensinogen to angiotensin II. However, there is increased plasma enzyme activity associated with the D form, leading to an exaggeration of ACE function. Studies suggest that individuals who are homozygous for the DD gene are predisposed to develop cardiac hypertrophy.[1,2] These minor differences give rise to individual's genetic distinguishing features and in some instances predispose to the disease.

It is estimated that the difference in the DNA sequence among all humans is about 0.1 percent, which means that 99.9 percent of the DNA sequence is identical. However, there is a difference in over 3 million bases of the DNA sequence. Each chromosome is a long molecule made of DNA. DNA is made up of only four bases: **adenine (A), guanine (G), cytosine (C), and thymidine (T). If one visualizes a chromosome, it consists of repetitions of these four bases and is extremely monotonous. Nevertheless, the sequence of these four bases determines all of one's inherited characteristics. The average length of a chromosome is about 135,000,000 base pairs. The longest chromosome, chromosome 1, has over 250,000,000 base pairs. The smallest, chromosome 21, has only 50,000,000 base pairs. The 23 chromosomes together contain a total of 3 billion base pairs (Table 7-1). Genes themselves are discrete units with a start and stop point and vary in size from 10,000 to 2,000,000 base pairs. The estimated average is about 20,000 base pairs. Despite the fact that the whole of the human genome has 3 billion base pairs, it is estimated that only about 3 percent is used to make genes.[3] Genes themselves do not participate in specific functions, but function through an intermediary, their single-stranded templates, referred to as messenger RNA (mRNA). The mRNA leaves the nucleus and goes to the ribosome in the cytoplasm, where it provides the template for protein synthesis. It is estimated there are between 50,000 and 100,000 genes.[3]

Table 7-1: The Human Genome

Base pairs	3 billion
Genes estimated	50,000-100,000
Percent of DNA contained in genes	<3%

The intervening DNA sequences between the genes that do not exit the nucleus are referred to as introns, and the DNA sequences transcribed into mRNA that exits the nucleus to form the template for protein synthesis are referred to as exons. The function of the introns is largely unknown. A small proportion of the introns has the important regulatory function of determining when and how often the gene make, mRNA. Another function of the introns is, presumably, maintaining the structure and integrity of the DNA molecule. On a simple mathematical basis, the introns also offer some protection of the genes from mutations. The natural mutation rate is 1 every 200,000 years per gene. The mutation rate is higher in the introns, but, since the intron is not expressed in the protein, they are benign and nondisease producing. The DNA used to make genes consists of just one copy of each gene per chromosome. However, the introns not infrequently have many repeating units of the same sequence throughout the genome. The most frequent example of this is the ALU repeats, which consists of a 300-base pair repeat with over 500,000 copies scattered throughout the human genome. The role of these repeat sequences is also not known, but they may play a role as replication or initiation sites for duplication of DNA. While foreign DNA is usually destroyed, some, such as the genomes of retroviruses, does get incorporated into the human genome. It is estimated that 35 percent of the human genome is composed of DNA from evolutionary relics of mobile DNA elements transposed into the human genome with no known function.[4] Mutations that induce single-gene diseases inherited as Mendelian disorders occur at a frequency of less than 1 percent. In contrast, mutations that induce more subtle changes (genes that predispose to polygenic diseases; e.g., DD versus II) or none at all may be located in exons or introns and occur more frequently, in the range of 10 to 20 percent. One form of these polymorphisms, single-nucleotide polymorphisms,[5,6] which occur every 1000 base pairs, is discussed subsequently as the most promising marker for identifying genes responsible for polygenic diseases.

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THE HUMAN GENOME PROJECT

The Human Genome Project is the first large international effort in the history of biological research.[7] The overall objective of the Human Genome Project was to determine the sequence of the bases throughout each chromosome of the human genome, which is a total of 3 billion bases. The Human Genome Project was initiated on October 1, 1990, to be completed in the year 2005.[8] The National Institutes of Health and the Department of Energy in the United States are expected to produce 60 to 70 percent of the sequences, with the remainder from the Sanger Institute, at Cambridge, England, and other international partners.[7] However, with improvements in technology and increasing demands, the timetable has been accelerated. Initially, the Human Genome Project announced that it would have all of the genes sequenced by the year 2003, and most recently it was announced that a rough draft of 90 percent of the human sequences will be available by the spring of 2000.[7] At least two commercial enterprises involved in sequencing human genes have claimed they will have all of the human genes sequenced by the year 2001.[9] Regardless of the precise timetable and whether every gene is to be identified as indicated, it is now evident there will be an avalanche of genes available to the cardiologist within the next 2 to 3 years. At the end of 1999, only one-third of the human genome was sequenced, and there were less than 1000 human genes available in GenBank. There will be at least 20,000 to 30,000 genes, if not more, available within the first couple of years of the new millenium. It is part of the policy of the Human Genome Project that all of these genes will be available to the public. As it is sequenced, each gene is entered into a publicly accessible database and available at no cost. In the United States, GenBank (accessible at http://www.ncbi.nlm.nih.gov) run by the National Center for Biotechnology Information, serves as the public repository of sequence information. The results of the efforts of the publicly funded Human Genome Project consist not only of DNA sequences of the various genes but also of the intervening sequences. In addition, each sequence is anchored to one of the known genetic markers, integrating the physical and genetic maps. The first chromosome to be sequenced was chromosome 22, which was announced in November 1999. Investigators from Great Britain, the United States, and Japan teamed up to sequence 32,000,000 bases. While there remain some gaps, there is general agreement that essentially all of the genes of chromosome 22, together with most of the intervening sequences, have been sequenced.[10]

Charles Delisi, of the Department of Energy, in commenting on the initiation of the Human Genome Project, stated that the goal was to decipher the blueprint for the development of a single fertilized egg into a complex organism of more than 10^{13} cells. The blueprint is written in a coded message given by the sequence of nucleotide bases-the As, Cs, Gs, and Ts-that are strung along the DNA molecules in the human genome. The goal was to sequence from one end to the other and then to try to decipher all of the instructions included in this massive coding sequence. In 1990, the best of the laboratories were probably sequencing only a few hundred bases per day; at that rate, it would have required centuries to complete the human genome. However, technological improvements have enabled some laboratories engaged in the Human Genome Project to sequence more than 1 million bases per day. While the overall objective was to sequence the human genome, other goals completed along the way markedly accelerated the efforts of all investigators involved in biological or medical research. The first goal was to develop a genetic map. This meant developing markers along each chromosome that would be readily identifiable and highly informative signposts for the identification of nearby genes. This goal has now been achieved. Investigators in France and the United States published 6000 markers spaced less than 1 million

base pairs apart throughout the entire human genome.[11] Thus, a complete set of genetic markers is now available for each chromosome. This provided the necessary tool for widespread application of genetic linkage analysis, a technique that has led to the mapping of numerous genes responsible for disease of the cardiovascular system (Chap. 62) and other organs.

The next goal was to develop a genomic physical map. This map would involve sequence tagged sites (STSs) throughout the genome that has been completed.[12] Over 50,000 STSs were given their approximate chromosomal location which made it possible to relate them to the location of a locus genetically linked to a disease of interest.[13] The next goal was to develop a physical map of that part of the DNA that is expressed as genes. These markers are referred to as expressed sequence tags (ESTs) and contain short sequences of 200 to 300 base pairs. These sequences are unique and believed to represent a specific gene. If, indeed, each one of these ESTs represents a gene, we are at present in the position of having available 60,000 genes to be identified.[14] One may wonder how it is possible to obtain such ESTs and be certain that they represent only sequences that are expressed in genes. As indicated previously, all genes are first synthesized as single-stranded mRNA that leaves the nucleus to travel to the ribosome in the cytoplasm, where it serves as a template for its unique protein product. Thus, if one extracted all of the RNA in the cell, it would include all of the mRNAs and, thus, at that moment in time, all of the genes expressed in that cell. This is, in fact, the approach for obtaining ESTs: mRNA is isolated from cells of all organs in the body, and collectively they represent all of the body's expressed genes. The mRNA is then converted to complementary deoxyribonucleic acid (cDNA) with the enzyme reverse transcriptase, and sequences from these cDNAs are amplified by polymerase chain reaction. From these amplified sequences, unique sequences are selected and entered into GenBank as ESTs. These ESTs are cloned in vehicles such as bacteria and, thus, provide a library of human ESTs. Many of these ESTs are now being mapped to their chromosomal location to be used as markers to find genes responsible for disease. The ultimate aim is to have an EST every 100,000 base pairs evenly distributed throughout the 23 chromosomes. The development of the genetic map and that of the physical map, which followed, were great contributions that have tremendously accelerated the efforts of all investigators throughout the world in identifying genes responsible for disease.

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FUNCTIONAL GENOMICS (PROTEOMICS)

One of the great accomplishments-and perhaps the greatest of the twenty-first century or even the new millenium-will be the identification of all the genes responsible for humankind. This development is often compared to another great landmark in physics, namely, the identification of the table of physical elements. This analogy emphasizes a very important point for the future. The table of physical elements (periodic table) provided the physicists with the tools to determine the composition of the earth, to understand many natural phenomena, and also to create artificial constructs, many that were essential to modern civilization and others that were destructive, such as the atomic bomb. Identification of the genes will be to the biologist or physician what discovering the physical elements was to the physicist. Leroy Hood refers to the human genetic map as the "periodic table of life." The identification of all human genes provides the tools for the first step: determining gene function and how to manipulate genes to benefit humankind. Determining the function of known and unknown genes was addressed at a recent workshop in Cold Spring Harbor, New York.[15] At present, we know of only about 2000 proteins. Thus, we do not know the protein composition of most genes and so would not be expected to know their function. It was estimated that determining the function of 100,000 genes by conventional techniques-namely, eliminating the gene from the mouse by homologous recombination or overexpressing the gene (transgenic mouse)-would take a century. The theme of Human Genome Project II will undoubtedly be determining functions of the proteins, and the project has been referred to by several names emphasizing function, such as The Proteome, Gene Health and Disease, or Functional Genome II. It is imperative that the efforts to determine the functions of human genes receive a boost from improved technology and increased awareness. New approaches are already emerging from the Human Genome Project to address this issue.

In parallel with the progress for sequencing the human genome has been the success of efforts to sequence simpler genomes of single-cell organisms. The first organism for which the genome was sequenced and the genes identified was *Haemophilus influenzae,* in 1995, consisting of 1.4 million base pairs and 1740 genes. Within 3 years of this initial effort, the genomes of over 40 single-cell organisms were completely sequenced and all of the genes identified. Several notable organisms were sequenced: *Saccharomyces cerevisiae,*[16] which is the cause of vaginitis, and spirochete *Treponema pallidum,*[17] which causes syphilis. These organisms, many of which are bacterial, offer the potential for the diagnosis and treatment of human infectious diseases, whether they affect the heart or other organs. Identification of the genes responsible for these various organisms has ushered in a new era for antibiotics based on a variety of molecular mechanisms made possible through the identification of genes and the various pathways they regulate. A significant step forward in our understanding of the function of human genes came with the sequencing of the genome responsible for *Caenorhabditis elegans* (*C. elegans*).[18] This was the first multicellular organism for which the genome and all of its genes have been sequenced. *C. elegans,* although a tiny worm that is not visible to the naked eye, has 959 cells, all of which have been identified and characterized. Its genome consists of over 97,000,000 base pairs, with a total of over 19,000 genes. This represents one-fifth of the number of genes present in the human genome. The more important features are, however, that 36 percent of the genes in *C. elegans* are virtually identical to human genes, with many others having homologous consensus. The *C. elegans* is a transparent worm, and, thus, it is possible under the microscope to observe development from a single cell to a multicellular organism and now to do so with the armamentarium of knowing all the genes. Thus, it should be possible, by determining the function of many genes in *C. elegans* homologous

to human genes, to learn of their approximate function in humans. Several other multicellular organisms are being sequenced, including the fruit fly (*Drosophila*)[19] and the mouse, which will provide an immense opportunity for determining the function of human genes with similar functions.[20] This will considerably accelerate our efforts to determine the function of human genes and how to utilize them to diagnose, prevent, and cure disease.

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COMPUTERIZED GENE BANK NETWORKS AND BIOINFORMATICS

It became evident to investigators and physicians involved with genetics that the amount of information to be derived from unraveling the genome would be exhaustive. It was thus necessary to develop a computerized network of gene databases in which information would be rapidly entered worldwide and available worldwide at no cost. GenBank, a computerized network of gene banks, was established in the United States, Britain, and Japan, and all investigators have agreed to input their data daily. This database resource has been invaluable to medical scientists throughout the world. Information on DNA and genes from all species is entered into this network and cataloged for readily accessible use. Over 2 billion DNA bases have been collected from over 39,000 species, and that number is rapidly expanding on a daily basis. There are over 500,000 queries per day for information from GenBank alone. The information in GenBank provides available access to all investigators identifying genes.

The storage of gene sequences is likely to directly contribute to the determination of gene function. The functions of certain genes are often first determined in simple organisms, such as single-cell bacteria or viruses. It is also well recognized that certain genes, because of their function, have been conserved through evolution. Thus, when a DNA sequence is identified in the human genome with consensus sequence to one of the genes of known function in simpler organisms, one immediately has an important clue to the function of that sequence in humans. Such comparative genomic techniques are expected to significantly accelerate our search for the function of genes. A DNA sequence from the human genome with unknown function can be entered into a gene bank network such as GenBank (http://www.ncbi.nlm.nih.gov) and a consensus sequence sought. It is possible with GenBank to travel back in time over 1 billion years to very simple organisms of which much more is known of the function of their genes. Although the human genome may contain 100,000 genes, it is highly likely that many of these genes can be grouped into families that have a common function, such as the genes that encode for kinases. These proteins all have a common function: the transfer of high-energy phosphate from one compound to another. Therefore, genes encoding for kinases will share this common functional motif. This common motif can be used to group unknown genes that have the motif in their sequences to encode for kinases. It is estimated there are over 3000 genes encoding for various kinases. Thus, in addition to computerized comparative genomics, another function of bioinformatics is to cluster based on common functional motifs. Another emerging contribution from bioinformatics is the grouping of genes that have in common a functioning pathway, whether it be that of metabolism or message signaling. Several such signaling pathways have been identified, including the map kinases, the inositol phosphatases, and the tyrosine kinases. It is expected that several metabolic pathways, such as glycolysis, the Kreb's cycle, the hexosmonophosphate shuttle, and others, will have a common group of genes. The cascade of signaling proteins responsible for growth and development of the heart is likely to be very similar across the invertebrate, vertebrate, and mammalian cardiac genetic systems. It is of note that all mammals have a similarly sized genome of 3 billion bases with an estimated 100,000 genes. Similarly, the network of molecules that process the electrical activity to decipher and analyze messages in the brain is likely to have common genetic pathways. It is anticipated that information on human disease-causing genes available from GenBank will be transmitted to nursing stations and made available to all personnel, including physicians, nurses, genetic counselors, and others. Determining the function of genes through such bioinformatics techniques as comparative genomics and gene clustering is likely to contribute greatly to our understanding of the role of

genes in human physiology and disease.

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THE DNA CHIP TECHNOLOGY

A major obstacle in applying the progress made in molecular genetics to the practice of medicine is inability to detect mutations rapidly and accurately. At the turn of the millenium, there were already 1000 genes in GenBank known to cause disease, with over 25,000 mutations. To perform genetic screening for known mutations and determine individuals at risk for disease is still a formidable task at an unacceptable cost. The various techniques for detecting mutations are time consuming, expensive, and, ideally, require confirmation by DNA sequencing. Technologies to perform these tasks on a daily basis with results available within a reasonable time from hours to days are essential. Several technologies are evolving, the most promising being the DNA microarray chip.[21] Several thousand genes are attached to glass or plastic, and each base is color coded to detect mismatches in hybridization (mismatch mutations; Fig. 7-1). This technique has the potential for robust high-throughput detection of thousands of mutations within hours. Other techniques include high-pressure liquid chromotography and mass spectrometry, both of which also have the potential for high-throughput analysis. Genetic testing of individuals, for example, with familial hypertrophic cardiomyopathy (FHCM) or arrhythmogenic right ventricular dysphasia could prevent the death of thousands of individuals each year in competitive sports. Another use of the DNA chip technology is in the field of pharmacogenomics, or genoptying to individualize therapy. This technique could also provide screening for multiple genes that are up- or down-regulated during the response of a particular organ to various physiologic or pathologic stimuli.

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RESTORATIVE BIOLOGY

It is highly likely that, within the first decade of the new millenium, significant progress will be made in our ability to generate organs. While the average human has over 200 trillion cells, it is estimated there are only about 206 distinct cells as defined by a unique function. These cells are derived from stem cells that are pluripotent, which means that with appropriate stimulation they can develop into any kind of cell. There are two types of stem cells: embryonic and adult.[22,23] Embryonic stem cells have not yet specialized into any type of cell and are obtained from two sources: (1) fetal tissues from miscarriages or abortions, and (2) in vitro embryos discarded by fertility clinics that cannot be implanted. Adult stem cells are committed to develop into a specific cell but have some limited capacity to be directed to develop into some other cell. At present, investigators have been relatively unsuccessful in obtaining stem cells from most organs in adults. Stem cells in limited numbers have been obtained from bone marrow, liver, and skeletal muscle. These stem cells, exposed to the appropriate cardiac growth factor, would be expected to develop into cardiac myocytes.[24] There are already considerable preliminary data to show that fibroblasts can be transformed into skeletal muscle.[25,26] The key gene that commits a cell to become a skeletal muscle cell has been identified, namely, MyoD. Transfection with MyoD has been shown to induce the phenotype of skeletal muscle in fibroblasts and several other cells.[26] Myocardial infarction may be thought of as a myocyte deficiency disease in which a part of the myocardium is replaced by fibrous scar tissue. Myoblast, an adult skeletal muscle stem cell, has been transplanted with some success into the heart of a rat that had undergone a previous myocardial infarction.[27] Bone marrow stem cells are being used with some degree of success in regenerating bone marrow in the treatment of leukemias. The National Institutes of Health has already developed goals to begin the pursuit of research to repair or regenerate human organs (http://www.bioethics.gov). Extensive research will be required to understand the molecular factors necessary to convert stems cells into a pretargeted, specific cell. Nevertheless, this research has great potential for diseases such as myocardial infarction.

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A NEW ERA FOR UNRAVELING POLYGENIC DISORDERS

The extraordinary similarities in the height, weight, body habitus, and facial features of identical twins underscore the extremely limited variation in physical features of individuals who share complete genetic identity. The wide variation that is seen in these features among unrelated individuals in the general population strongly implies that much of this variation is attributable to variation in DNA sequence. Therefore, it comes as no surprise that this same principle applies to variation in disease susceptibility and that virtually all human diseases have an inherited component. In some cases, referred to as Mendelian diseases, mutation in a single gene is sufficient to produce disease in a high proportion of individuals inheriting that mutation. For other diseases, the inherited contribution is more subtle, requiring inheritance of variants in a number of genes, with disease development also being influenced by environmental factors. In this setting, inheritance of a particular genetic variant may be neither necessary nor sufficient for disease development. These genetically complex diseases thus have multifactorial determination.

With the development of complete genetic maps of the human genome, a new approach to identifying genes contributing to Mendelian diseases, called positional cloning, became available.[28] Positional cloning proceeds in several stages: (1) the collection of families' segregating traits of interest; (2) determination of the chromosomal location of disease genes by comparing the inheritance of chromosome segments to the inheritance of disease in families; (3) refinement of the interval containing the disease gene and identification of genes in the disease interval; and (4) screening genes in the interval for mutations that alter the structure or expression of the encoded protein. In the Mendelian paradigm, independent mutations that alter the encoded protein and segregate specifically with the disease in families constitute proof that the disease gene has been identified. This approach has to date resulted in identification of nearly 1000 human disease genes, of which over 100 are associated with cardiac diseases, and almost all have been identified within the last decade. While these Mendelian disorders are typically uncommon or rare, they have in many cases provided fundamental new insight into disease biology that has proved relevant to more common forms of disease.

Nonetheless, the truly common diseases of mankind, such as coronary artery disease, stroke, diabetes, and hypertension, are believed to be generally multifactorial in nature. For these diseases, the positional cloning paradigm that has been so successful for Mendelian diseases may have limited power, since, even within single families, affected individuals may have different combinations of inherited and acquired risk factors; moreover, the number of factors and the magnitude of the impact of any single risk locus is unknown. These barriers to identifying the genes underlying common diseases are formidable. Evidence that these diseases have an inherited component come from a variety of studies, including studies of twins, demonstrating that monozygotic twins, who share 100 percent of their genes, are more concordant in disease status than are dizygotic twins, who share only 50 percent of their genes, and studies of familial aggregation, showing that diseases recur within families more often than expected from their prevalence in the general population. A relatively simple means of assessing recurrence risk in families is determination of the so-called ō sib, defined as the risk of disease recurrence in a sibling of a patient with the disease divided by the prevalence in the general population.[29] A ō sib of 1.0 would indicate no familial contribution to disease risk, while a ō sib of 10 would indicate that all familial factors together increase the risk of disease tenfold. It is important to note that, while these approaches can provide strong evidence for the impact of inheritance on disease risk,

none indicates how many genes underlie the inherited disease risk, their mode of transmission, or the magnitude of the effect imparted by any single locus. For example, the same tenfold familial increase in disease risk could be determined by the effects of two genes, each imparting fivefold increased risk, or, alternatively, 50 genes, each imparting 1.2-fold increased risk. The best study design for identifying underlying disease genes is considerably confounded by this imprecise knowledge.

There are a number of potential approaches to unraveling the inherited contribution to these complex disorders. One is to simplify the analysis by identifying sub- or intermediate phenotypes in which the genetic contribution is more homogeneous or contributes to a larger fraction of disease risk. For example, the considerable etiologic heterogeneity of coronary artery disease can be reduced by focusing on cases sharing diabetes, hypertension, or hypercholesterolemia as contributing factors. Similarly, further refinement of these subgroups might define physiologic subsets with more homogeneous genetic contribution, potentially defining Mendelian subsets to which the power of Mendelian genetics can be applied.[30]

Despite this potential, few useful intermediate phenotypes have been defined for common diseases, often requiring investigation of non-Mendelian traits. In this setting, linkage approaches like those used for Mendelian diseases might be successful if any single locus imparts a relatively large effect on disease risk, and collecting large extended kindreds may be worthwhile. In the absence of evidence of a substantial Mendelian component, a modification of the linkage approach analyzing large numbers of sibling or relative pairs concordant or discordant for disease has potential advantages. In this approach, one scans the genome for chromosome segments that are shared among phenotypically concordant siblings more often than expected by chance. This approach has the advantage that can detect linkage despite complications in which a disease locus does not contribute to disease in every affected individual and not all individuals inheriting a disease allele develop disease. Nonetheless, success with this approach requires that individual risk loci impart relatively large effects on disease risk.[31]

Another approach that will become increasingly used for complex trait analysis is identification of risk alleles by study of patients and control subjects. As indicated above, there are estimated to be approximately 3 million common single nucleotide polymorphisms (SNPs) in the human genome (Table 7-2). A fraction of them will ultimately prove to underlie multifactorial traits by altering the expression or function of the gene in which they reside. The ability to identify and genotype these SNPs motivates their use for genetic studies. It is anticipated that the vast majority of common SNPs in human populations will be identified in the next 5 years and that many of the alleles contributing to common diseases will be found among them. If one tested a SNP whose variation contributes to, for example, coronary artery disease, comparison of SNPs allele frequencies in patients with the disease and in a matched cohort of control subjects free of disease would demonstrate a significantly different distribution of allele frequencies. This approach has substantially higher power than does linkage to detect variants with small effects on disease risk.[31] This case-control approach is associated with a number of important caveats, however. First, patients and control subjects must be well matched for genetic background. If they are not, many SNPs will show a false-positive association with disease. This is a current and serious problem with case-control studies. Unless disease associations are highly reproducible using the same SNP alleles and the same clinical phenotype, their significance should be regarded with caution. One means of eliminating this vexing problem is to collect the parents of affected individuals to permit use of transmission disequilibrium.[32] If a SNP allele contributes to disease risk, it ought to be transmitted from a heterozygous parent to an affected offspring more often than the expected Mendelian proportion of 0.5. This test thus eliminates the problem of poorly matched cases and control subjects and holds considerable promise for the investigation of complex genetic traits. Proof that a disease-associated SNP is itself a functional variant contributing to disease may be problematic, since some of these SNPs may well be common alleles in the population. Proof can be pursued by clinical studies of the physiology of individuals with and without the disease allele,

biochemical studies of the wild-type and variant gene and gene product in vitro, and construction and investigation of animal models based on the variant gene.

Table 7-2: Single Nucleotide Polymorphisms

SNPs per human genome	3 million
SNPs per 1000 base pairs	1
SNPs in typical human genome involving amino acid substitutions	24,000-40,000

A second caveat regarding this SNP approach is that at present we have a limited number of SNPs for examination and also a limited capacity for SNP genotyping. As a result, we cannot readily perform comprehensive genome-wide searches for disease variants with this approach, instead being limited to investigation of candidate genes. While this approach may prove successful, we are currently largely limited to implicating genes in pathways we can already associate with disease. There are two approaches to extending this case-control approach to a genome-wide analysis. One is to investigate populations that have been established from a small number of founders in relatively recent times. In such cases, one expects relatively long ancestral chromosome segments to be preserved in the present-day population such that genetic markers at considerable distance from one another remain in *linkage disequilibrium*. Thus, one may be able to screen for the chromosome location of disease susceptibility loci using a relatively modest number of SNPs distributed across the genome; proceeding from initial map location would be analogous to the positional cloning paradigm for Mendelian traits. Alternatively, with identification of complete SNP maps of the human genome, we will have many or all of the common SNPs in hand; one can contemplate performing extremely high-density SNP genotyping in outbred populations to identify disease susceptibility alleles. In order to retain analytic power, this approach may require performance of 10^9 to 10^{10} genotypes; such a study is clearly beyond the capacity of present implemented technology but is not inconceivable in the future.[31]

Ultimately, one can envision that alleles that contribute to susceptibility to common disease will be identified. These findings will have important consequences for clinical medicine. First, these findings will permit identification of individuals with specific inherited disease susceptibility before disease has become manifest, affording new opportunity for targeted lifestyle or pharmacologic intervention in individual patients. Second, identification of these susceptibility alleles will define the physiologic pathways that contribute to disease, providing "validated targets" whose altered activity can be predicted with high likelihood to alter disease development; these will highlight opportunities for development of new therapies. Third, we currently treat multifactorial diseases as though they are of homogeneous causation, with largely empiric therapies. The ability to identify specific risk alleles in individual patients may afford the opportunity to tailor treatment in individual patients to the specific inherited abnormalities underlying their disease susceptibility.

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BIOETHICAL IMPLICATIONS AND GENETIC COUNSELING

Molecular genetics will soon be part of routine clinical practice. While most genetic screening currently performed for cardiovascular disease is done as part of a research protocol, many diseases, such as the familiar cardiomyopathies or those associated with the long Q-T syndrome, will soon enter the realm of routine genetic screening and diagnosis. It is estimated that less than 5 to 10 percent of cardiologists have any understanding of genetic testing and that even fewer are capable of interpreting the results of genetic testing. It is well recognized that there are too few genetic counselors and medical geneticists to meet present demands, let alone the demands within a few years, following the exposition of the human genome.[33] It was realized from the very beginning of the Human Genome Project that, in parallel with the scientific effort, there had to be a formal initiative to plan for the ethical, legal, and societal implications (ELSI) of this new paradigm. The National Institutes of Health have allocated 5 percent of the budget of the Human Genome Project for ELSI and the U.S. Department of Energy has allocated 3 percent of the HGP budget. A detailed review of the Human Genome Project and the ELSI have been prepared by the U.S. Department of Energy and the Human Genome Project and made available on the internet (http://www.ornl.gov/hgmis/tko/index.html).

The working group for ELSI developed an agenda with the following main goals: (1) stimulate research on issues through grant making; (2) refine the research agenda through workshops, commissioned papers, and invited lectures; (3) solicit public input; (4) provide massive education through multiple media, including the internet; and (5) encourage international collaboration. A major objective would be to develop policies regarding professional, institutional, governmental, and societal levels to ensure that genetic information would be used to maximize benefit to individuals and society. Three issues were identified as particularly important: privacy of genetic information, safety and efficacy of new testing options, and fairness in the use of genetic information.

The Hereditary Susceptibility Working Group of the National Action Plan on Breast Cancer (NAPBC), coordinated by the Public Health Service Office on Women's Health, recently joined with the National Institutes of Health/Department of Energy ELSI group to address the issue of genetic information in the workplace. The working group recommendations are as follows:

1. Employment organizations should be prohibited from using genetic information to affect the hiring of an individual or to affect the terms, conditions, privileges, benefits, or termination of employment unless the employment organization can prove that this information is job related and consistent with business necessity.
2. Employment organizations should be prohibited from using genetic information or requiring collection or disclosure of genetic information prior to a conditional offer of employment, and, under all other circumstances, employment organizations should be prohibited from requesting or requiring collection or disclosure of genetic information unless the employment organization can prove that this information is job related and consistent with business necessity, or otherwise mandated by law. Written and informed consent should be required for each request, collection, or disclosure.
3. Employment organizations should be restricted from access to genetic information contained in medical records released by individuals as a condition of employment, in

claims filed for reimbursement of health care costs, and other sources.

4. Employment organizations should be prohibited from releasing genetic information without prior written authorization of the individual. Written authorization should be required for each disclosure and include to whom the disclosure will be made.
5. Violators of these provisions should be subject to strong enforcement mechanisms, including a private right of action.
6. The task force recommends genetic testing be made available to individuals in the context of clinical investigation and research; however, the information obtained must remain available only to the patient, physician, and investigator. Information must not be made available to any other party or individual.

In regard to genetic diagnosis and screening, there is as yet no consensus on who should undergo genetic testing, how to protect the privacy of the results, or how this information should be applied in the routine practice of medicine. Most genetic testing in cardiology at present is performed as part of research and as such is regulated by Recombinant Regulatory Committee (RRC) and the local institutional review board. In a recent Bethesda, Maryland, conference of the American College of Cardiology on Bioethics and Molecular Genetics,[33] there was a consensus that certain rules must be followed in the routine use of genetic testing: (1) informed written consent must be obtained prior to obtaining the sample; (2) every effort should be made to provide the necessary education in terms understandable to the concerned individual, and (3) genetic testing must not be performed unless accompanied with counseling. The Bethesda conference offered the following guidelines, recognizing that they will continue to evolve and are as yet not definitive:[34]

1. The use of genetic testing and diagnosis as a research tool should continue along the guidelines outlined for research.
2. Genetic testing (usually prenatal) for devastating fetal disease or early-onset disease, such as Down's syndrome, is performed routinely and should be continued. It has been shown that, if the results are positive, whether the parents seek an abortion or not, the information provided is considered beneficial.
3. Use of genetic testing in someone with a phenotype to confirm or exclude a genetic cause should be permitted. An example would be FHCM with concomitant hypertension.
4. In families with a known history of a familial disease, genetic testing when sought by a family member should be performed. Testing of other members of the family should be performed only at their request.
5. Testing at birth or during childhood for asymptomatic disorders that develop later in life remains investigational until more data are available.

It has been customary not to perform genetic screening in high school students unless there is an immediate medical benefit. However, recent studies[35] from Montreal and Hong Kong show that genetic screening during high schoool has successfully decreased the incidence of Tay-Sachs disease and β-thalassemia. A major issue associated with the cardiovascular disorder FHCM, the most common cause of sudden death in the young, particularly in the athlete, is whether athletes at the high school and college level with a family history or suspected HCM phenotype should be screened prior to participating in competitive sports.[36]

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A NEW PARADIGM FOR MEDICINE

The genetic revolution that has already begun will usher in the beginning of a new paradigm in the diagnosis and treatment of cardiac disorders. Physicians traditionally have been taught to diagnose and treat disease. Cardiology in the past 50 years has advanced more than perhaps in the previous 2000 years.[37] Nevertheless, despite our ability to diagnose, we seldom know the precise molecular defect or pathogenesis of a particular phenotype. In the near future, a single blood sample will make available to the physician 100,000 etiologies with their multiple mutations. This represents a new era in which specific etiologies will be looking for their respective diseases. This will further challenge the physician to attempt to associate genes with physiological functions and mutations with disease. The physician will be well positioned to advance functional genomics through translational research at the bedside. In fact, until recently, physicians who saw individuals without complaints were often questioned as to the appropriateness of their practice. We are now entering an era of prevention, and thousands of genetic risk factors will soon be available on which to base comprehensive and effective preventive therapies. In the near future, physicians will yearn to assess individuals early in life in the hope of aborting major disease, such as atherosclerosis, hypertension, cancer, and osteoporosis. This, too, will represent a new paradigm for all physicians. It will stimulate changes in health care delivery as well as means to finance such programs. The developent of an electronic medical record will be essential, and protection of the individual's rights and privacy will be paramount.[34]

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Figure 7-1: Illustrated here is the means of detecting genes or their mutations. Oligonucleotides are single short strands of DNA of about 15 to 30 bases artificial synthesized to have the sequence of the desired gene. These oligonucleotides are bound to glass with each of the four bases labeled with a distinct fluorescent color. The DNA extracted from the patient's white blood cells is denatured into separate strands and brought in contact with the artificial oligonucleotides DNA. If the sequence in the patients DNA is complementary to the oligonucleotide, hybridization will occur and the laser beam will detect the appropriate colors. If there is a mutation present, there will be a mismatch and a different color will be exhibited by the laser indicating where the mutation is.

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Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 8:

CARDIOVASCULAR TISSUE MODIFICATION BY GENETIC APPROACHES

Authors: Elizabeth G. Nabel, Victor J. Dzau

The field of cardiovascular gene therapy had its origins in the mid-1980s as a result of rapid advances in the molecular genetics of the cardiovascular system. The cloning of genes important for the development and function of the cardiovascular system increased our understanding of the normal biology and pathology of cardiac diseases. In turn, this genetic information provided new opportunities for novel therapeutics using gene-transfer approaches.

Somatic gene transfer is the introduction of recombinant genetic material (DNA or RNA) into host cells such that gene expression within the host cell is altered to achieve a therapeutic effect. The genetic material includes eukaryotic genes (often with transcriptional regulatory elements) and RNA that encodes intracellular or secreted gene products. *Vectors* are used commonly to introduce the genetic material into cells (Table 8-1). These vectors include replication-incompetent viruses and biochemical substances. The genetic material can be delivered directly into vascular or myocardial cells in vivo, referred to as *direct gene transfer*, or into tissues, such as a venous bypass graft ex vivo that in turn is returned to the host. This latter approach is termed *indirect gene transfer*. Local delivery catheters are required for the introduction of vectors and cells (Fig. 8-1).

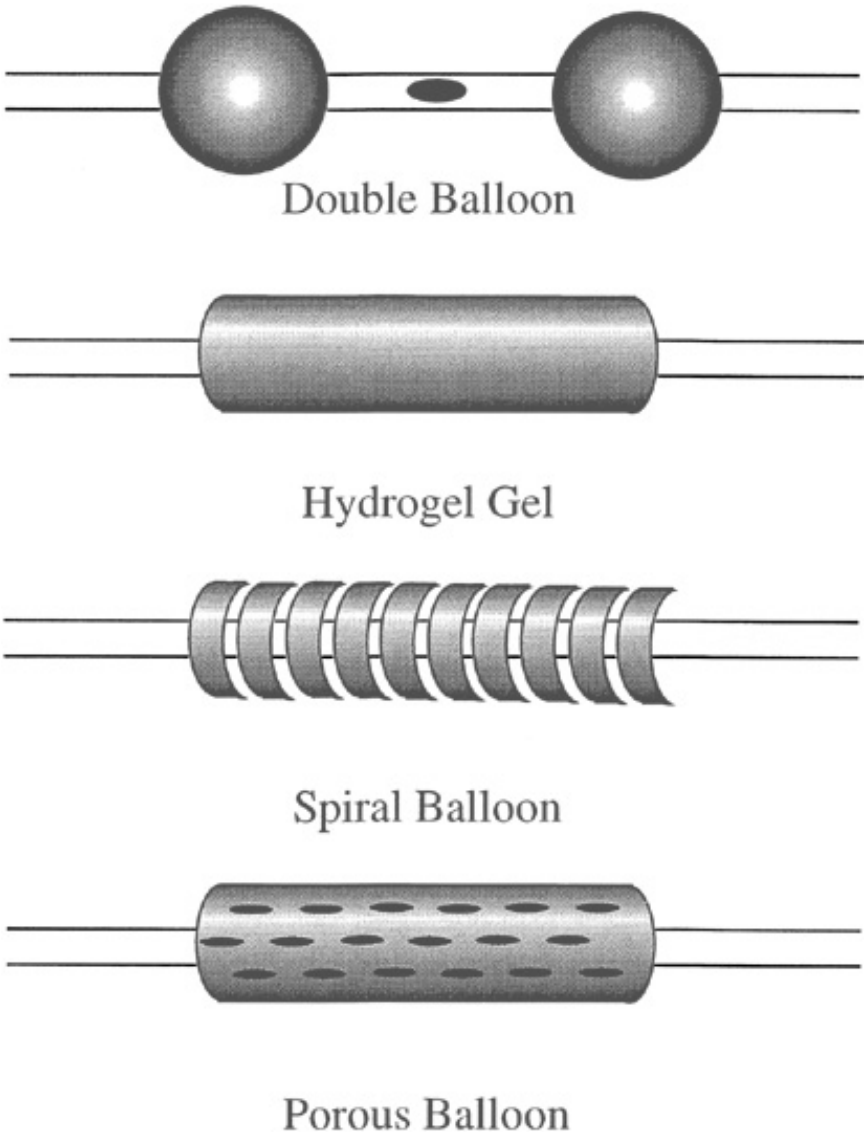

Figure 8-1: Catheters for cardiovascular gene therapy. (From Nabel,[95] with permission.)

Table 8-1: Gene Transfer Vectors

Viral vectors	Nonviral vectors
Retrovirus	Cationic liposomes
Adenovirus	Fusigenic liposomes
Adeno-associated virus	DNA plasmid vectors

This chapter reviews our current understanding of genetic therapies, including stem cell biology, for cardiovascular diseases. This discussion will examine vector systems for delivering genes, disease targets and preclinical animal models, recent results of clinical trials, and new, emerging opportunities for cell transplantation with pluripotent stem cells.

VECTORS FOR GENE TRANSFER

Viral Vectors

RETROVIRAL VECTORS

Retroviruses were the first viruses adapted for use as vectors owing to the simplicity of their genomes and their capacity to stably integrate their genome into the host chromosome. A retroviral vector is constructed in several steps.[1,2] First, the structural genes required for viral replication are deleted to render the vector nonreplicating. After insertion of the exogenous gene of interest into the viral backbone, the recombinant retrovirus contains the exogenous gene, regulatory sequences, and packaging signals but lacks the actual structural genes required to produce a complete virion. It requires a helper cell to produce infectious viral particles. Nabel et al. demonstrated the feasibility of transfecting blood vessels with foreign DNA in vivo by transfecting pig iliofemoral arteries with a recombinant amphotropic retroviral vector containing a β-galactosidase gene.[3,4] Several cell types in the vessel wall were transduced, including endothelial and vascular smooth muscle cells. Using a β-galactosidase retroviral vector to modify endothelial cells, Wilson et al.[5] demonstrated β-galactosidase expression up to 5 weeks after transfection in prosthetic vascular grafts seeded with the genetically transformed cells. Retroviral vectors have not been effective vectors for cardiovascular applications because they require actively dividing cells for integration and expression of the viral genome. Since most myocardial and vascular cells are not dividing, transfection efficiency with retroviral vectors in these cells has been low.

ADENOVIRAL VECTORS

Adenoviral vectors are widely used for cardiovascular gene transfer because adenoviruses infect nondividing cells and do not integrate into the host genome. Adenoviruses are double-stranded linear DNA viruses that in their wild type cause a self-limited respiratory tract infection in humans.[6] The wild-type adenovirus genome is a 36-kDa DNA molecule that is divided into 100 map units. The majority of adenoviral vectors are derived from adenovirus serotypes 2 and 5. These vectors are constructed by deletion of the E1 region (map units 1-9) of the genome that normally encodes E1A and E1B motifs that are required for the expression of late viral genes and for the induction of the lytic phase of the virus. Without the E1 region, the virus cannot replicate. This region is replaced with the transgene of interest, up to 7.5 kb in size. Because the E1 deletion renders them replication-incompetent, adenoviral vectors are propagated in a helper cell line that expresses E1 protein in transfection. These vectors can be produced in high titers for in vivo delivery.[7] Adenoviral vectors enter mammalian cells by receptor-mediated endocytosis and α2β3 integrins.[8] Aortic smooth muscle cells[9] and cardiac myocytes[10] were transfected successfully using replication-defective adenovirus carrying the β-galactosidase or chloramphenicol acetyltransferase reporter gene, respectively. In vivo transfection by adenoviral vectors was demonstrated in vascular tissue by direct infusion into vessels,[9,11,12] in myocardial tissue by direct injection into the myocardium,[10,13] and in the circulation after adenoviral infection of skeletal muscle.[14] Limitations of the first-generation adenoviral vectors include transient gene expression and host inflammatory and immune responses against the transgene[15] and viral antigens.[16,17] These limitations are being overcome by the development of "gutted" adenoviral vectors.[18] These vectors retain viral coat proteins for receptor attachment and internalization but lack other viral proteins that are immunogenic.

ADENO-ASSOCIATED VIRAL VECTORS

Adeno-associated virus (AAV) is a defective human parvovirus that is not able to replicate unless a helper virus, such as adenovirus, is also present.[19] There are several features that make AAV an attractive vector. The virus can be prepared at high titer, is not pathogenic in humans, and infects a broad range of cell lines.[20] Wild-type AAV integrates in a site-specific manner in a 7-kb region of human chromosomes.[20,21] The AAV genome is a single-stranded, linear, 5-kb DNA molecule.

The genome is flanked by two 145-bp inverted terminal repeats (ITRs) that contain the sequences required for packing, integration, and DNA replication. The coding region contains two open reading frames (ORFs). Either of these ORFs can be replaced with the transgene and regulatory elements to construct an AAV vector. The ORF can only accept a transgene of 4 to 5 kb, thus limiting the size of the transgene insert. Propagation of AAV vectors requires AAV Rep and Cap proteins and five adenoviral proteins: E1A, E1B, E2A, E4, and VA. These are complex packaging requirements, and thus it has been difficult to construct a packaging cell line. Instead, AAV vectors are propagated by cotransfection of the AAV vector with a plasmid wild-type or mutant helper adenovirus. AAV vectors have been used very successfully when injected into skeletal muscle to produce proteins secreted into the circulation, such as factor IX for hemophilia B.[22] Cardiovascular applications include cardiac myocytes, where Svensson et al. have demonstrated stable expression.[23] Whether AAV vectors can be adapted to efficiently transduce vascular endothelial cells and smooth muscle cells is not known.

Nonviral Vectors

CATIONIC LIPOSOMES

The encapsulation of DNA in artificial lipid membranes (i.e., liposomes) can facilitate its uptake and cellular transport. Cationic liposomes have been used for cellular delivery of DNA[24] and antisense oligonucleotides.[25] The activity of cationic liposomes is postulated to be mediated by (1) spontaneous capture of the negatively charged polynucleotides with cationic lipids by a condensation reaction, (2) increased cellular uptake due to interaction of positively charged complexes with negatively charged biologic membranes, and (3) membrane fusion (or transient membrane destabilization) with the plasmalemma or the endosome to achieve delivery into the cytoplasm while avoiding degradation in the lysosomal compartment. Recent data indicate that movement of DNA from the cytoplasm to the nucleus and successful dissociation of DNA from the lipid complex appear to be important variables for lipid-mediated gene transfer.[26] Expression of recombinant genes after cationic lipid-mediated gene transfer has been demonstrated in vivo in several animal models.[27-29] Gene expression after liposome-mediated arterial gene transfer may be augmented in the presence of ongoing proliferation (e.g., intimal proliferation after balloon injury).[30]

FUSIGENIC LIPOSOMES

This method uses a combination of fusigenic proteins of the Sendai virus (hemagglutinating virus of Japan) and neutral liposomes. Hemagglutinating virus of Japan (HVJ) is an RNA virus that belongs to the paramyxovirus family, which has HN and F glycoproteins on its envelope. HN binds with glycol-type sialic acid and degrades the receptor by its own neuraminidase activity. F glycoprotein is cleaved to generate a hydrophobic fusion peptide by proteases, and the activated F protein can interact directly with the cellular lipid bilayer and induces fusion. A nuclear protein, namely, high-mobility group 1 (HMG-1), that binds DNA enhances the integration of transfected DNA into the nucleus.[31] HVJ liposomes consist of neutral liposomes complexed with ultraviolet (UV) light-inactivated HVJ virus. It is postulated that after fusion of the liposome complex with the cell membrane, the DNA is released directly into the cytosol without undergoing endocytosis, thereby reducing lysosomal destruction of the DNA construct and facilitating the nuclear uptake.[32] HVJ liposome methods have been employed successfully for gene transfer in vivo to liver,[31] kidney,[33] and vasculature.[34,35]

PLASMID DNA

Direct injection of plasmid DNA in cardiac or skeletal muscle results in stable transfection of a

small percentage of cells.[36] Following direct injection to the heart muscle, expression of a reporter gene was demonstrated for up to 4 weeks.[37] Expression of injected genes can be targeted to specific cell types in vivo (e.g., cardiac muscle cells) and can be modulated by the hormonal status of the animal.[38]

SYNTHETIC OLIGONUCLEOTIDES

Antisense oligonucleotides (ASOs) are short, 10- to 30-bp, chemically synthesized DNA molecules that are designed to be complementary to the coding sequence of a target RNA. ASOs can be introduced into cells simply by diffusion or complexed with liposomes, such as HVJ.[32] Inside the cell, ASOs form double-stranded complexes with their complementary RNA and decrease translation of RNA. Mechanisms of antisense inhibition include interference with ribosome binding and processing of mRNA, interference with mRNA conformation or mRNA splicing, and RNase-H activation of mRNA digestion.[39,40]

ASOs are attractive agents for in vivo gene therapy. They can be chemically synthesized in large quantities, and they do not require a viral component for in vivo delivery. However, there are several limitations to their use in vivo. ASOs have a short half-life in vivo due to nuclease degradation. Chemical modifications, such as substitution of sulfur for one of the nonbridging oxygens of a phosphate group (phosphorothiorates), renders ASOs more stable to degradation in serum.[41] Several nonspecific effects of ASOs have been noted that account in part for their biologic effect.[39,42] ASOs can have nonspecific cytotoxic effects due to binding to intracellular and cell surface proteins. Some ASOs affect the expression of multiple genes in addition to the gene of interest. This effect is sequence-specific and cannot be controlled for by scrambled oligonucleotides. ASOs containing C_pG dinucleotides have been shown to have nonantigen activation of the humoral immune system.[43] Despite these relative limitations, ASOs are well suited to the treatment of diseases where transient reductions in gene expression are required. ASOs theoretically can be used to specifically reduce the expression of one or more genes. The uptake of ASOs can be enhanced by complexing the oligonucleotide with cationic liposomes[25] or HVJ liposomes.[34,35]

Synthetic double-stranded oligonucleotides containing binding sites for transcription factors serve as "decoys" to block the binding of nuclear factors to promoter regions of targeted genes, resulting in the inhibition of gene transactivation.[41,44] Morishita et al.[45] have shown that a single administration of an E2F decoy (containing the E2F cis element) that binds the transcription factor E2F inhibits smooth muscle cell hyperplasia in a rat carotid balloon injury model[45] (Fig. 8-2). The binding of E2F prevents it from transactivating the gene expression of cell cycle regulatory proteins such as PCNA, c-myc, and cdk2, thereby inhibiting vascular smooth muscle cell proliferation and subsequent neointimal formation in vivo.

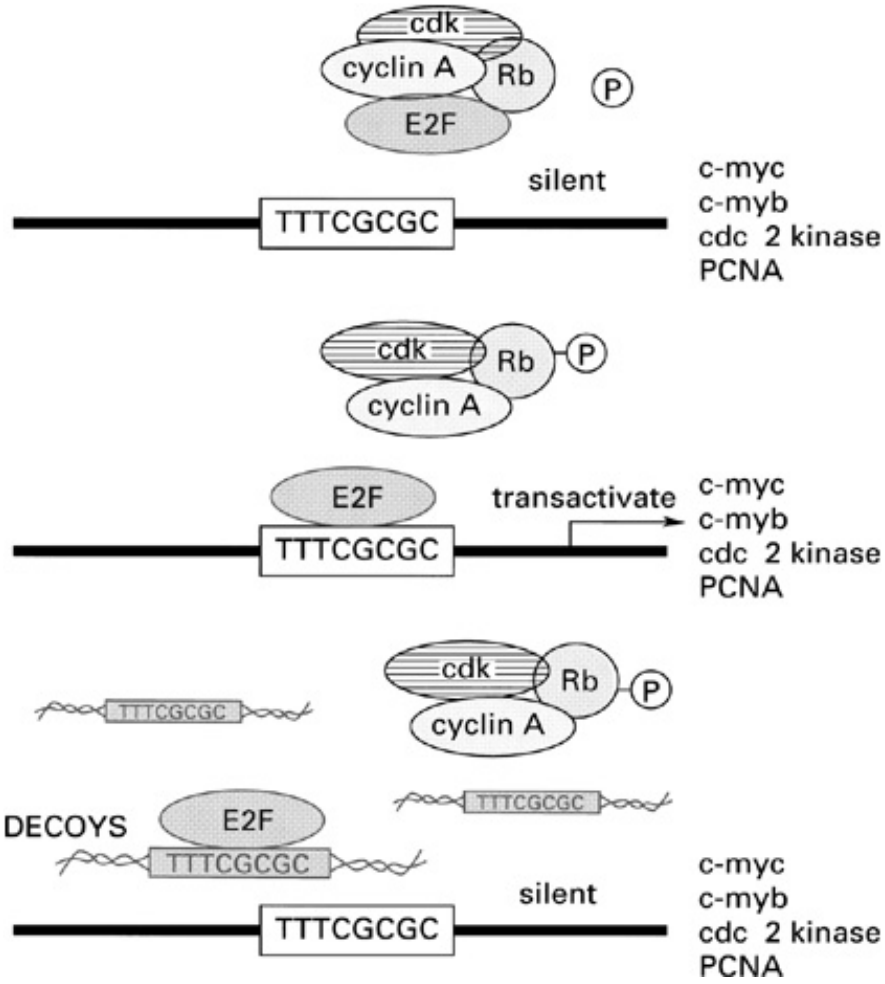

Figure 8-2: Principal of E2F "decoy" strategy. TTTCGCGC is the consensus sequence for the E2F binding site. In the quiescent cell state, the transcription factor E2F is complexed with Rb (retinoblastoma gene product), cyclin A, and the cyclin-dependent kinase cdk2 (*top*). Phosphorylation of Rb releases free E2F, which binds to cis elements of the cell cycle regulatory genes, resulting in the transactivation of these genes (*middle*). The E2F decoy cis-element double-stranded oligonucleotide binds to free E2F, preventing E2F-mediated transactivation of cell cycle regulatory genes (*bottom*). (From Morishita et al.,[45] with permission.)

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CELLULAR TRANSPLANTATION

The implantation of cells expressing recombinant genes into the heart or vasculature is termed *ex vivo gene transfer*. Nabel et al.[3] demonstrated a cell-based vascular gene-transfer technique. By reimplanting endothelial cells transfected ex vivo with a retroviral β-galactosidase vector on the surface of balloon-injured porcine iliofemoral arteries, genetically modified cells could be detected up to 2 to 4 weeks following reimplantation. Wilson et al.[5] demonstrated expression of a reporter gene from endothelial cells implanted on a Dacron graft and placed in the carotid arteries of dogs. In addition to endothelial cells, ex vivo-transfected smooth muscle cells have been introduced in the vasculature.[46] Lynch et al.[47] reported the seeding of smooth muscle cells transfected with the adenosine deaminase gene into endothelium-denuded blood vessels. Another application of ex vivo gene transfer is the engineering of vascular grafts seeded with endothelial cells previously transfected in a culture dish.[48] Seeding of vascular grafts with soluble vascular cell adhesion molecules (sVCAMs) (see Chap. 5) using adenoviral ex vivo gene transfer was reported by Chen et al.[49]

Implantation of genetically modified myoblasts or fibroblasts into skeletal muscle is an attractive gene-transfer method because the gene product can be delivered systemically. Indeed, several investigators have reported successful gene delivery using these approaches.[50-52] In a mouse model, myoblasts were transplanted and supported sustained delivery of functionally active erythropoietin to correct anemia associated with renal failure.[53] The myoblast method potentially could provide an approach for the delivery of insulin (diabetes), atrial natriuretic peptide (hypertension or heart failure), or apolipoprotein AI (atherosclerosis).

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GENE TRANSFER AND VASCULAR DISEASE

Gene transfer into the vasculature has been used to investigate the pathophysiology of vascular diseases and to develop novel therapies for these diseases. This field has expanded rapidly in the past decade. A number of models in the mouse, rat, rabbit, dog, and pig have been created to dissect vascular pathophysiology in peripheral, coronary, renal, pulmonary, and cerebral blood vessels. A full discussion of these animal models is beyond the scope of this chapter, and the reader is guided to pertinent reviews.[54-58]

Experimental Applications of ASOs

INTIMAL HYPERPLASIA

Simons et al.[59] reported that the administration of ASOs against c-myb applied by pluronic gel to the adventitial layer of rat carotid arteries inhibited neointimal hyperplasia in response to balloon injury. Data from Morishita et al.[34] demonstrated that a single HVJ liposome-mediated administration of ASOs against proliferating cell nuclear antigen (PCNA) and cdc2 kinase inhibited neointimal lesion formation after balloon injury for at least 8 weeks after transfection. The combination of antisense cdc2 kinase and cdk2 kinase oligonucleotides also resulted in almost complete inhibition of neointima formation.[35] Bennett et al.[60] showed an inhibition of vascular smooth muscle cell proliferation by administration of c-myc ASOs to the adventitial surface of injured carotid arteries in a pluronic gel solution. Two other studies reported inhibition of neointima formation after application of ASOs. Delivery of antisense PCNA oligonucleotides by pluronic gel (in a rat carotid model) and of antisense c-myc oligonucleotides by direct application through a porous balloon (in a porcine coronary artery model) resulted in significant inhibition of neointimal hyperplasia.[61,62]

VEIN GRAFT DISEASE

Autologous vein grafts remain the most commonly used conduits for surgical revascularization of the heart and lower extremities. Given the failure of traditional therapies at improving long-term vein graft function, gene therapy offers a new opportunity for reducing the morbidity and increased costs associated with the current limitations on functional graft survival. The vein graft offers an unusual opportunity for combining intact tissue in vivo gene-transfer techniques with the increased safety of an ex vivo application of the transfection medium. Manipulation of transfection conditions, including increased exposure time and controlling components of the transfection medium, also can be more easily achieved. Some researchers have begun to explore the possibility of ex vivo virus-mediated gene transfer in autologous vein grafts. Chen et al.[49] demonstrated the expression of the marker gene β-galactosidase along the luminal surface and in the adventitia of porcine vein grafts infected with a replication-deficient adenoviral vector at the time of surgery. In this same study, short-term expression of soluble VCAM-1 was documented after transfection of vein grafts.

The Dzau laboratory hypothesized that genetic engineering could alter the ability of the grafts to mount a hyperplastic response to acute injury while leaving intact their ability to respond to chronic hemodynamic stress via a hypertrophic response, such as that seen in arteries exposed to

hypertension. This group used HVJ liposomes to deliver a combination of ASOs to cdc2/PCNA to rabbit veins at the time of grafting into the carotid artery and observed a greater than 90 percent inhibition of smooth muscle cell (SMC) proliferation during the first postoperative week[63] (Fig. 8-3). This blockade of cell cycle progression resulted in a near-complete inhibition of neointimal hyperplasia. Instead, the vein graft wall was shifted to an adaptive process of medial hypertrophy. Having redirected the genetically engineered grafts away from neointimal hyperplasia and toward medial hypertrophy as an adaptation to the arterial environment, the susceptibility of these ASO-treated grafts to accelerated atherogenesis was tested. Control ASO-treated and untreated grafts placed in cholesterol-fed rabbits developed significant foam cell lesions and plaque within 6 weeks after surgery. ASO-treated grafts that had remained free of neointima formation, however, resisted macrophage invasion and the development of macroscopic plaque. This inhibition of cell cycle progression is likely to have effects on the phenotypes of the vascular cells undergoing remodeling after vein grafting, and these changes are likely to affect the proatherogenic environment of the normal graft wall. For example, the endothelium of ASO-treated grafts retained more of its capacity to produce nitric oxide and resist monocyte adhesion in comparison with untreated or control ASO-treated grafts.[64]

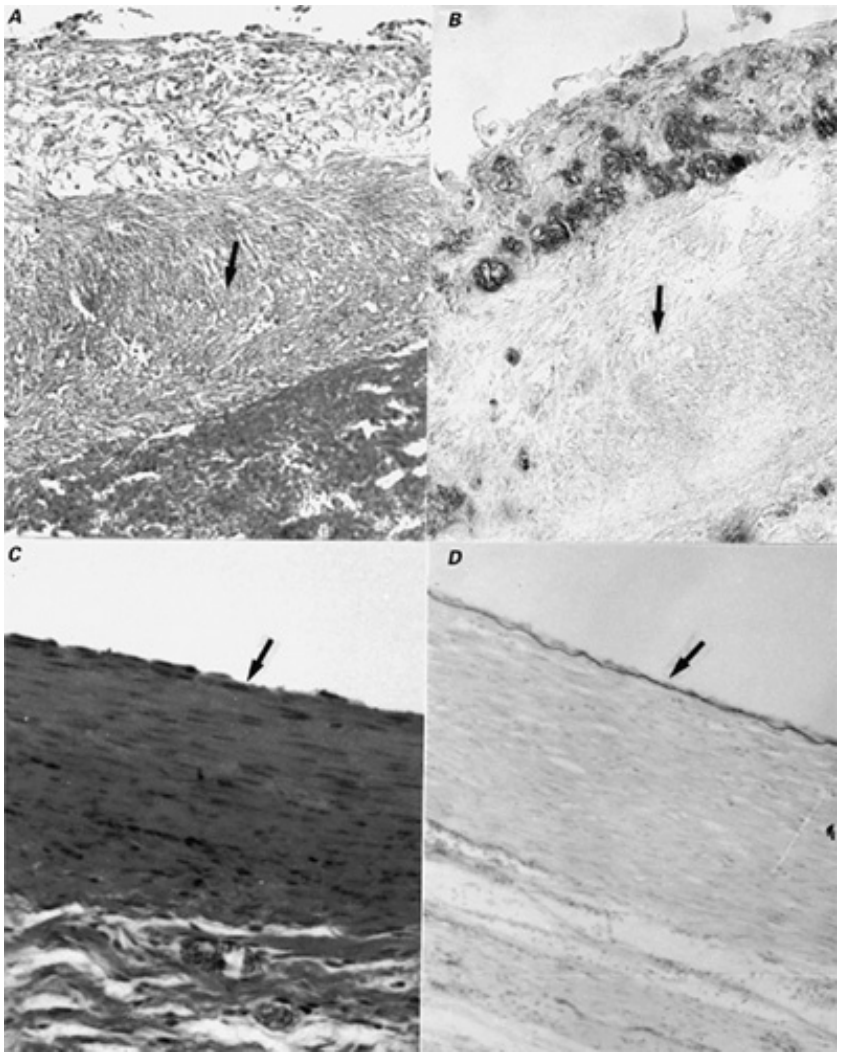

Figure 8-3: Control oligonucleotide-treated (*A* and *B*) and ASO (against cdc2 kinase/PCNA)-treated vein grafts (*C* and *D*) in hypercholesterolemic rabbits 6 weeks after surgery (×70). Sections of 5 mm were stained with hematoxylin/van Gieson (*A* and *C*) and a monoclonal antibody against rabbit macrophages (*B* and *D*). Arrows indicate the location of the internal elastic

lamina. (From Mann et al.,[63] with permission.)

Gene Transfer and Vascular Remodeling

Molecular cardiovascular research has resulted in significant gains in the knowledge of disease processes at cellular and molecular levels and has led to the characterization of expressed genes in diseased blood vessels. These gene products play autocrine and/or paracrine roles in vascular pathophysiology.

Nabel et al.[65] overexpressed an expression vector encoding a secreted form of fibroblast growth factor 1 (FGF-1) in porcine arteries. FGF-1 expression was associated with intimal thickening of the transfected vessels together with neocapillary formation in the expanded intima. These findings suggest that FGF-1 induces intimal hyperplasia in the arterial wall in vivo, and through its ability to stimulate angiogenesis in the neointima, FGF-1 could stimulate neovascularization of atherosclerotic plaques. In the same porcine model, the overexpression of transforming growth factor β1 (TGF-β1) in normal arteries resulted in substantial production of extracellular matrix accompanied by intimal and medial hyperplasia.[65] These findings demonstrated that TGF-β1 differentially modulates extracellular matrix production and cellular proliferation in the arterial wall and plays a reparative role in response to arterial injury. The increased production of extracellular matrix that accompanied the intimal and medial hyperplasia was not observed following expression of other growth factor genes in the vessel wall, including genes for platelet-derived growth factor (PDGF-BB)[27,66] or the secreted form of FGF-1.[62] Porcine arteries transfected with human PDGF-BB demonstrated intimal hyperplasia with increased numbers of intimal smooth muscle cells. An increased deposition of procollagen, however, as seen in TGF-β1-transfected vessels, was not observed. By stimulating the formation of extracellular matrix, it is possible that TGF-β1 could promote healing following vascular injury, limiting the extensive cellular intimal hyperplasia observed with PDGF-BB.[66]

The pathogenesis of vascular diseases such as hypertension involves a process of vascular remodeling associated with increased vascular hypertrophy and activation of the local angiotensin system. Angiotensin II has been shown to stimulate the growth and proliferation of vascular smooth muscle as well as collagen biosynthesis in vitro. Its in vivo role has been inferred from experiments using angiotensin converting enzyme (ACE) inhibitors. Since these drugs produce hemodynamic effects, a direct role of local angiotensin in vascular remodeling was not clear. To study the local effects of angiotensin, Morishita et al.[67] overexpressed ACE within the vascular wall. Immunoreactive ACE activity was noted in medial vascular smooth muscle cells as well as in intimal endothelial cells. Vascular ACE activity was associated with increased DNA synthesis and vascular protein content via the local production and action of vascular angiotensin II without changes in systemic blood pressure. Parallel to these biochemical changes, medial thickening of ACE-transfected vessel segments was noted, without changes in luminal diameters, implying medial wall hypertrophy by local production of angiotensin II. In a subsequent study, Nakajima et al.[68] demonstrated that overexpression of the type 2 angiotensin II (AT2) receptor in balloon-injured rat carotid arteries exerts an antiproliferative effect, counteracting the growth action of AT1 receptors.

One approach to the treatment of vascular diseases that are characterized by excessive cell proliferation is to overexpress a gene that inhibits cellular proliferation. It is important that expression of the gene proceed during the time period when intimal cells undergo proliferation following vascular injury. This may vary between animal models, and it is likely that in humans, cell proliferation following angioplasty, stent placement, or bypass graft surgery may proceed over a longer period of time than in animal models. Nonetheless, several gene products have proven efficacious in appropriate animal models of vascular injury. Most of these approaches are

based on arresting vascular cells in G1 or S phase of the cell cycle (Fig. 8-4). One approach is to express the herpes simplex virus thymidine kinase gene (*HSVtk*). *HSVtk* encodes for the enzyme thymidine kinase that phosphorylates the nucleoside analog ganciclovir or acyclovir into a metabolite that disrupts replication of DNA during S phase of the cell cycle. A by-product of this biochemical reaction is diffusible to adjacent cells, where it is incorporated in replicating cells, leading to inhibition of cell replication. This property is termed a *bystander effect* and allows for inhibition of replication in a greater number of cells than transfected. This model was established initially in a pig peripheral artery model of vascular injury, where intimal hyperplasia was decreased by 50 percent.[69] Subsequent investigations in the rat, rabbit, and a transplant model also demonstrated reductions in cell proliferation and lesion formation by about 50 percent.[70-73] This approach is currently being investigated in a model of in-stent restenosis. Chang et al.[74] demonstrated that localized arterial infection with a replication-defective adenovirus encoding a nonphosphorylatable, constitutively active form of the retinoblastoma gene product at the time of angioplasty significantly reduced SMC proliferation and neointima formation in both the rat carotid and porcine femoral artery models of restenosis. The cyclin-dependent kinase inhibitors p21 and p27 that arrest smooth muscle cells in G1 phase of the cell cycle are also potent negative regulators of lesion formation after vascular injury.[75-78] Ras proteins are key transducers of mitogenic signals from the cell membrane to the nucleus. The local delivery of vectors expressing *ras* transdominant negative mutants, which interfere with ras function, reduced neointimal lesion formation in a rat carotid artery balloon-injury model.[79]

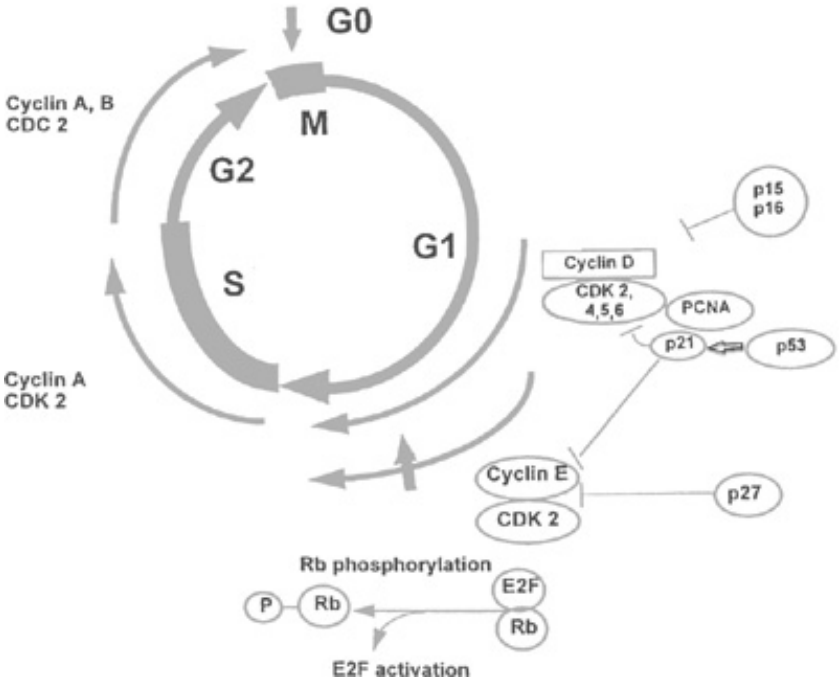

Figure 8-4: Regulation of the cell cycle. Progression through the G1 phase of the cell cycle is regulated by the assembly and phosphorylation of cyclins and cyclin-dependent kinases (CDKs). The cyclin-CDK complexes are inhibited by cyclin-dependent kinase inhibitors (CKIs), of which p21 and p27 are examples. These CKIs lead to G1 arrest. Inhibition of Rb phosphorylation, inactiviation of E2F, or inhibition of cyclin A and B also lead to disruption of DNA synthesis and inhibition of cell proliferation. (From Tanner et al.,[96] with permission.)

To assess the effect of endothelial cell nitric oxide synthase (ecNOS) on vessel lesion formation, a DNA vector encoding ecNOS was expressed in a rat model of arterial injury[80] (Fig. 8-5). Four methods were used to verify ecNOS expression: transgene protein expression by Western blot, localization of enzyme expression by in situ histochemical staining, enzymatic activity of the

transgene product, and vascular reactivity in response to the transgene. Overexpression of ecNOS led to vasorelaxation and 70 percent inhibition of neointima formation after balloon injury. This same approach has been investigated in a pig coronary model.[81] The loss of ecNOS may play a fundamental role in the pathogenesis of vascular diseases, including atherosclerosis. The overexpression of ecNOS may be useful for gene therapy of neointimal hyperplasia and associated local vasospasm after vascular injury.

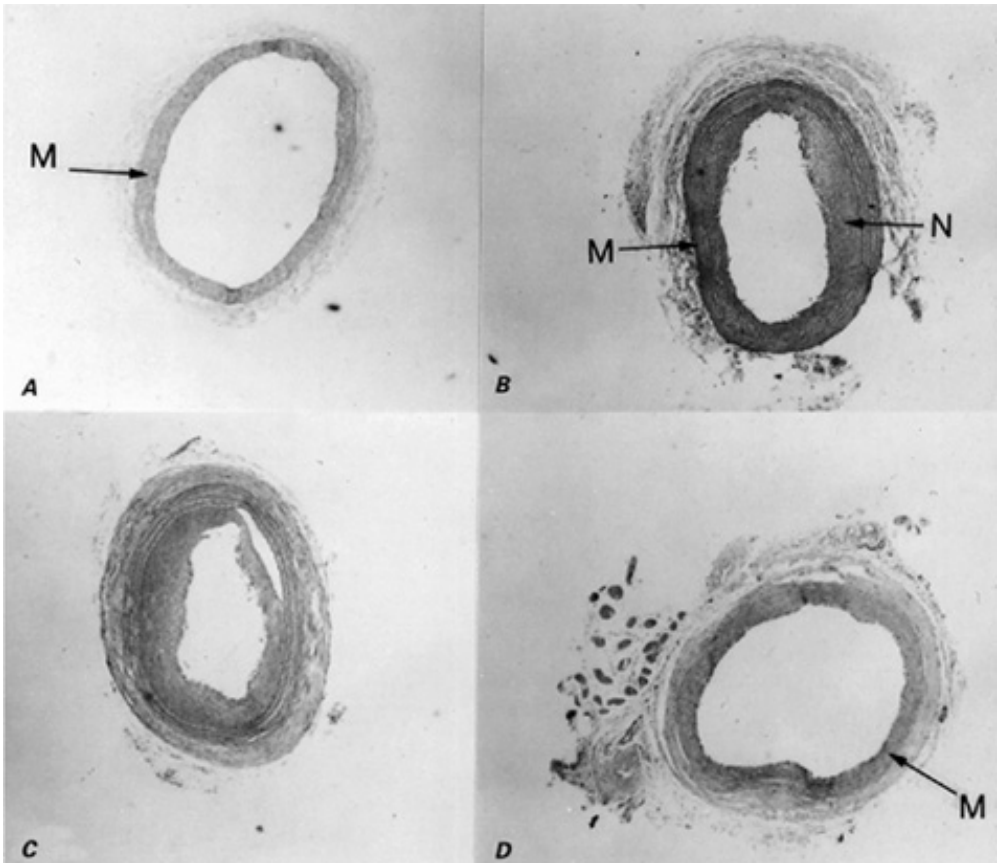

Figure 8-5: Inhibition of neointimal hyperplasia by in vivo gene transfer of endothelial cell nitric oxide synthase (ecNOS) in balloon-injured rat carotid arteries. *A*. Normal artery. *B*. Injured, untransfected artery. *C*. Injured, control vector-transfected artery. *D*. Injured, ecNOS-transfected artery. M, media; N, neointima. (From von der Leyen et al.,[80] with permission.)

Angiogenesis

Angiogenic growth factors may be useful to augment collateral artery development in animal models of myocardial and hind limb ischemia. Initial studies using intramuscular injections of angiogenic proteins, including basic fibroblast growth factor (bFGF) and acidic fibroblast growth factor (aFGF) into the hind limbs of rabbits with surgically induced ischemia lead to increased capillary densities and augmented blood flow.[82,83] These findings have been extended to gene-transfer approaches using vascular endothelial growth factor (VEGF). Following gene transfer of VEGF via a hydrogel balloon, increased numbers of capillary vessels also were observed in a rabbit model of hind limb ischemia, and improvement of resting and maximum flow was achieved that was comparable with that of a single administration of VEGF protein.[84] Intracoronary delivery of a recombinant adenovirus that encodes FGF-5 has been shown to induce collateral blood flow and restore myocardial function in a pig model of myocardial ischemia.[85] While the studies are encouraging, our understanding of the process by which VEGF, angiopoietin, and

other angiogenic proteins lead to blood vessel formation and maturation is still incomplete.

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MYOCARDIAL GENE TRANSFER

Direct injection of DNA into myocardial tissue has been shown to be effective in local delivery of a transgene to the heart. Lin et al.[37] reported in vivo expression of β-galactosidase in cardiac myocytes for at least 4 weeks after direct injection into the left ventricle. Direct injections of a major histocompatibility complex (*MHC*) gene and the reporter gene *luciferase* under the control of an MHC promoter also resulted in the regulated expression of these genes.[38] Subsequent studies also showed increased gene expression after myocardial injection of adenoviral vectors.[10,13]

Healing and remodeling of the ventricle after myocardial infarction remain as important clinical problems. Some candidate genes (e.g., those for TGF-β1 and myogenin) may enhance the healing and recovery of myocytes after injury associated with infarction. The induction of neovascularization or angiogenesis in ischemic myocardium after coronary artery occlusion using gene transfer may salvage myocardium at risk by enhancing blood supply to the ischemic areas. Indeed, intracardiac myoblast grafts stably transfected with an inducible TGF-β1 construct were associated with increased DNA synthesis in vascular endothelial cells, consistent with a sustained angiogenic response.[86] The success of intracardiac grafting with genetically modified cardiomyocytes depends on the ability of grafts to couple with host myocytes. Soonpaa et al.[87] demonstrated that fetal cardiomyocytes isolated from transgenic mice carrying a fusion protein of the cardiac α-MHC promoter with a β-galactosidase reporter gene were connected to the host myocardium by nascent intercalated disks formed after grafting. Chronic heart failure is accompanied by a reduction in the number of myocardial β-adrenergic receptors and inotropic responsiveness. Cardiac-specific overexpression of a β_2-adrenergic receptor in a transgenic animal model with subsequent increased myocardial function suggests a potential gene-therapy approach to heart failure.[88]

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CLINICAL TRIALS

Clinical trials in cardiovascular gene therapy have gone forward in two areas: vascular proliferative diseases and angiogenesis. The results of a Phase I/II randomized study of a cell cycle inhibitor have been reported recently.[89] In this study, cell cycle blockade by ex vivo gene therapy of experimental vein grafts was accomplished with a dominant negative transcription decoy, E2F, that leads to G1 arrest and inhibition of cell proliferation. The investigators hypothesized that this transcription decoy would inhibit the neointimal hyperplasia and subsequent accelerated atherosclerosis that lead to human bypass graft failure. This hypothesis was tested in a prospective, randomized, controlled trial to investigate the safety and biologic efficacy of intraoperative gene therapy in patients receiving bypass vein grafts. Patients undergoing infrainguinal bypass grafting were randomized to decoy oligodeoxynucleotide (which binds and inactivates E2F), scrambled oligodeoxynucleotides, or no treatment. Oligonucleotide was delivered to grafts intraoperatively by ex vivo pressure-mediated transfection. Since this was a Phase I/II study, the primary end points were safety and inhibition of target cell cycle regulatory genes and of DNA synthesis in the grafts. The investigators found that the E2F decoy treatment reduced proliferating-cell nuclear antigen and c-myc mRNA concentrations as well as cell proliferation indices. Twelve months later, there were fewer clinical complications in the E2F treatment group, defined as fewer graft occlusions, revisions, or severe lesions. The investigators concluded that the intraoperative transfection of human bypass vein grafts with E2F decoy oligodeoxynucleotide was not only safe and feasible but also achieved inhibition of cell cycle genes and cell replication.[89]

Several protocols have now been initiated to promote angiogenesis for myocardial and peripheral ischemia. These studies have administered recombinant protein, plasmid DNA, or adenoviral vectors encoding bFGF, VEGF, aFGF, or FGF-4 by direct injection into the heart or limb muscle or by direct intracoronary infusion. Thus different genes, vectors, routes of delivery, and tissues are being examined. These studies to date have been Phase I (i.e., safety and toxicity) studies in which clinical efficacy is not an end point due to the small number of patients. Some of these Phase I protocols have been completed and reported. In a study to treat myocardial ischemia, recombinant aFGF was injected directly into the anatomosis site of the left internal mammary artery (LIMA) and into the left anterior descending artery (LAD) of patients undergoing coronary bypass surgery.[90] Patients with peripheral ischemia have been treated with direct injections of plasmid DNA encoding VEGF.[91] These Phase I studies are promising. The treatments to date have been safe, with no substantial toxicities. Progression to Phase II/III studies in which dose escalation, double-blind randomization, and measurements of clinical efficacy are performed is warranted.

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STEM CELL BIOLOGY

Recently, pluripotent human stem cells have been discovered or derived from human embryos.[92] These stem cells have the potential to differentiate into any kind of cell and thus may be used to treat or cure many diseases, including heart disease, diabetes, Parkinson's disease, Alzheimer's disease, and others.[93] There are two types of stem cells: embryonic and adult stem cells. Embryonic stem (ES) cells have not become differentiated and hence are pluripotent. Adult stem cells have undergone differentiation, and their potential to regenerate damaged tissue is limited. There is controversy surrounding stem cell research with regard to funding for the derivation of human embryonic stem cells and for research on ES cells once derived.

The following scenario could be envisioned. ES cells are derived by culturing a several-day-old human embryo or blastocyst. The trophoblast will form the placenta, while the inner cell mass will form the embryo. The inner cell mass is isolated. This tissue contains ES cells that have the potential to differentiate into any kind of tissue. The ES cells are cultured in media to grow colonies of cells. Special factors can be applied to encourage differentiation. Subpopulations of cells can be separated, i.e., bone marrow cells, cardiac myocytes, neurons, etc. The differentiated cells are then engineered to be an immunologic match with the patient and then can be administered. For example, ES cells that have differentiated into cardiac myocytes can be injected into a patient having sustained a myocardial infarction or heart failure.

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SUMMARY AND FUTURE DIRECTIONS

Since the 1980s, there has been remarkable progress in the design of vectors, the enhancement of gene expression by optimizing regulatory units, the development of animal models, and the translation of basic science studies into clinical applications. Despite this progress, there are significant hurdles and challenges that must be met if the promise of gene therapy is to be fulfilled. There is a persistent need for improved vectors that increase transgene expression and program expression specifically to cardiovascular tissues. Cell-specific promoters are being studied. Improved catheters are needed to deliver vectors and transgenes to vascular and myocardial tissues.[94] A better understanding of the pathways leading to cardiovascular diseases will permit more careful delineation of candidate target genes. There is no doubt, however, that enthusiasm and optimism remain high that this technology can lead to successful cardiovascular therapies.

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PREVIOUS

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Part 1: BASIC FOUNDATIONS OF CARDIOLOGY
Chapter 9:

MOLECULAR DEVELOPMENT OF THE HEART

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The wide spectrum of congential cardiovascular anomalies that present from the prenatal period into adulthood has challenged clinicians and scientists for centuries.[1,2] Equally daunting historically have been the complex and varied descriptions of cardiac embryology and the pathogenesis of congenital cardiovascular malformations.[3-6] Fortunately, scientific advances, including the availability of cell-specific immunohistochemistry, rapid advances in molecular biological techniques, expansion of investigations into integrated embryonic cardiovascular physiology, and dramatic improvements in the three-dimensional imaging of the embryonic cardiovascular anatomy, make the specific determination of pathogenesis for most cardiovascular anomalies a realistic goal in the next decade (Fig. 9-1).[7-11]

This chapter will discuss current ideas about normal development of the heart and vasculature and illustrate how this knowledge can help one understand the pathogenesis of congenital cardiovascular malformations. As with all complex developmental events, cardiovascular morphogenesis must be defined in a stepwise fashion, and this chapter details some of these pivotal developmental events. Although many of the mechanisms that lead to the development of the fully septated, four-chambered vertebrate heart are interdependent (e.g., the formation of the muscular ventricular septum and the membranous portion of the atrioventricular septum), many of these events are discussed in separate sections for clarity. It needs to be emphasized, however, that none of these remodeling events are isolated processes (e.g., formation of the outflow tract and closure of the interventricular foramen). The information presented in this chapter focuses on human development. However, a rapidly growing number of animal models generated by using sophisticated molecular biological techniques are becoming available and will accelerate the investigation of a wide variety of aspects related to normal and aberrant cardiovascular morphogenesis.

MOLECULAR DEVELOPMENT OF THE HEART TUBE

Embryo Patterning

Morphogenesis of the heart begins with the initial patterning of the embryo that determines the three axes of the embryo: anterior-posterior, dorsal-ventral, and left-right. These axes are imprinted onto the cellular program as cell populations expand to form the embryo and extraembryonic tissues. Specific genes have been identified that alter axis determination in a range of species, including the mouse.[12,13] After determination of the embryo axes, subpopulations of cells are programmed in a segmental body plan. Much of the current understanding of the body plan comes from developmental studies of *Drosophila*, an insect with a head, thorax, and abdomen.[14] In mammals, maternal gene products control the cell through the first two cell cycles and then control switches to the embryonic genome. These patterning (homeobox) genes are arranged along the anterior-posterior axis of the embryo.[15] Structural asymmetry is apparent at the blastodisc stage, when the primitive streak defines the anterior-posterior axis and the dorsal-ventral axis is defined by the position of the yolk sac. Myocyte commitment in the chick embryo

occurs in the early blastula stage, followed by clonal expansion in the bilateral heart-forming regions located in the lateral splanchnic folds after gastrulation. Molecular studies also have confirmed the segmental patterning of the cardiac tube, linking gene products with morphologic boundaries between segments that eventually integrate to form the future atria, ventricles, and outflow tract in chick, mouse, and human hearts.[16]

The process of mesoderm formation is integral to the organization of the primary axis of the embryo and the differentiation of the right and left sides. At the blastodisc stage of development, there are two primitive germ layers-endoderm and ectoderm-and then the endoderm layer splits into splanchnic and visceral layers with interposed mesodermal cells (Fig. 9-2). Mesoderm is formed as ectodermal cells migrate through the primitive streak coursing adjacent to Hensen's node (organizer). Hensen's node contains retinoic acid and serves as an embryonic organizer that may confer positional information on the mesodermal cells.[17] At this critical phase in cell determination, exogenous retinoic acid is extremely teratogenic. Interestingly, retinoic acid has a gradient-like effect on the determination of the heart tube, with the greatest effect at the arterial pole and the smallest effect at the venous pole.[18] After migration, this crescent of mesodermal cells forms the precardiac region from which the heart and the precursor cells of the great vessels originate.

Molecular Factors Involved in Cardiogenesis

Defining the molecular basis that underlies the establishment and maintenance of cardiac muscle differentiation has presented a fundamental challenge in developmental biology and molecular genetics. Despite the shared expression of numerous contractile protein genes by both cardiac and skeletal striated muscles, the molecular mechanisms for cell determination, differentiation, and tissue patterning are quite distinct. The following section presents some of the current, relevant information on molecular cardiogenesis, as defects in these molecular mechanisms have been shown to be associated with structural and/or functional heart diseases in children and adults (Fig. 9-3).

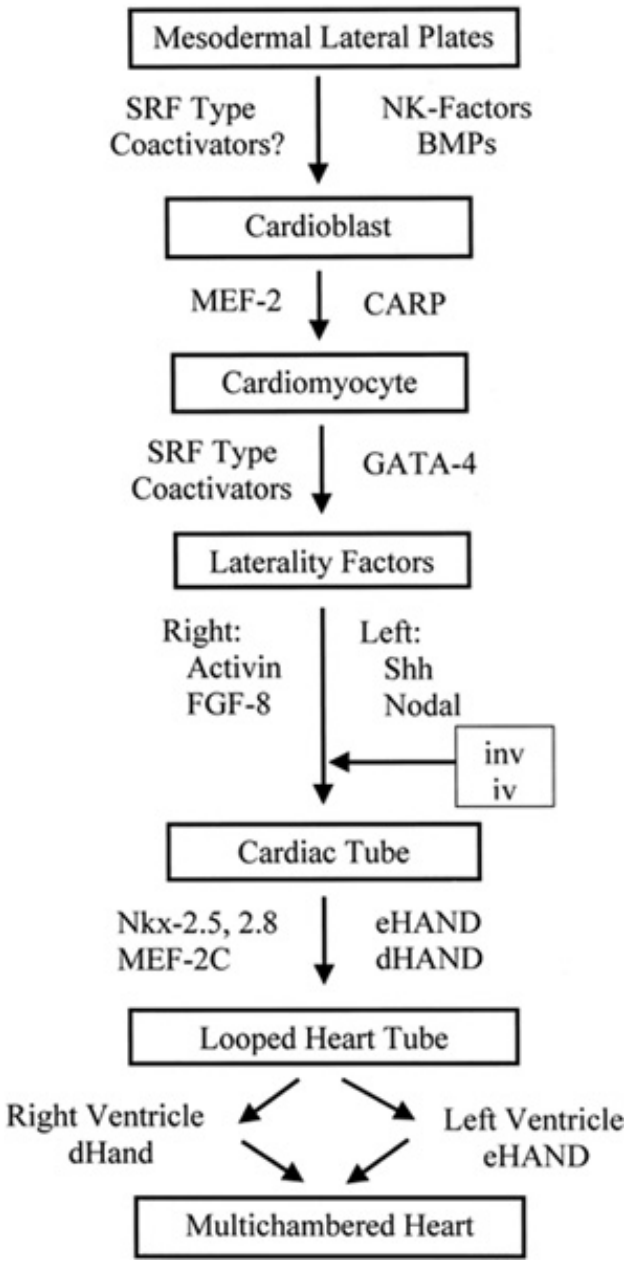

Figure 9-3: A lateral plate of mesoderm on each side of the midline forms the progenitor for the development of the heart and portions of the great vessels. The NK-Factor homeobox genes, such as *Nkx2.5*, in combination with multiple other genes, such as the serum response factor (SRF), are responsible for activating commitment of these undifferentiated cells to cardioblasts. Myocyte enhancer factor (MEF) has a binding site in practically all muscle genes and is essential to the development of cardiac myocytes. The CARP gene is downstream of *Nkx2.5* in the cardiac lineage. The genes responsible for the fusion of the two lateral mesodermal plates into a single tube are unknown, but experiments show that GATA-4 is necessary, along with SRF and many other genes yet to be identified. Genes involved in laterality include *Activin*, *FGF-9*, *Shh*, and *nodal*. The cardiac tube that forms a loop to the right requires *Nkx* genes and the *eHAND* and *dHAND* as well as *inv* (inversion of embryonic turning) and *iv* genes. The *dHAND* gene is responsible for the formation of the right ventricle, and the *eHAND* for that of the left ventricle.

Basic Helix-Loop-Helix Factors and Muscle Development

One of the initial, critical discoveries related to muscle development was the observation that a specific transcription factor, Myo-D, expressed in myoblasts[19] is sufficient to convert a variety of mesodermal and nonmesodermal cell types to stable myoblasts with active muscle-specific gene

expression. Using Myo-D as a probe, several additional regulatory factors that specify skeletal muscle cell lineage in fibroblasts have been identified: myogenin,[20,21] Myf5,[22] MRF4-herculin, and Myf6.[23-25] These factors share extensive homology within a basic region and an HLH motif that mediate DNA binding and dimerization, respectively.[26] HLH proteins share the ability to recognize the DNA consensus sequence CANNTG, known as an *E-box*, which first was identified with the immunoglobulin enhancer[26] and subsequently was found in regulatory regions of most muscle-specific genes. Thus, the regulatory paradigm for skeletal muscle differentiation is centered on the bHLH myogenic regulatory factors, but Myo-D, myogenin, Myf5, MRF-4, and Myf6 are not expressed in the heart.[27]

In the heart, there are other basic HLH factors. dHAND and eHAND are two bHLH transcription factors that share high homology in their bHLH regions and show segment-specific expression patterns.[28] In the mouse, HAND expression coincides with that of other cardiac transcription factors. dHAND expressed in the endocardium is maintained throughout the straight heart tube but is restricted to the conotruncus and the future right ventricle as the heart tube forms a loop. eHAND expressed in the myocardium rapidly becomes restricted to the conotruncus and the left ventricle.[29] Expression of dHAND and eHAND precedes separation of the two ventricles, representing early chamber specification. In addition to cardiac expression, dHAND (HAND1) is expressed in early trophoblast tissue and is required for the nutritional support of the developing mouse embryo.[30] It is of interest that *Nkx-2.8* has an expression pattern that overlaps eHAND, being restricted to the rostral and caudal regions of the heart tube after looping and being expressed in the endoderm of the pharyngeal arches. The deletion of dHAND by gene targeting showed that dHAND expression is necessary for the formation of the right ventricle.[29,31] Thus, it appears that dHAND may specify the right ventricle, and eHAND the left ventricle. In addition, dHAND and eHAND specify right ventricle (RV) and left ventricle (LV) specific morphology independent of situs.[32] Expression of cardiac-specified genes *αMHC, MLC2A, MLC2V, ANF,* and *Nkx-2.5* was not affected by elimination of the dHAND gene. GATA-4 in the myocardium was downregulated by dHAND-deficient hearts and appears to be a downstream target of dHAND.

Drosophila tinman Is Required for Insect Heart Development

The identification of molecular mechanisms involved specifically in heart development has depended on the investigation of simpler biological models, including the fly *Drosophila*. Homeotic genes are genes that determine a change in structure and have in common a domain that codes for 60 amino acids. Genes with this sequence, referred to as homeobox (*Hox*) genes, generally are upregulated during early differentiation and appear in a time-dependent sequence. Homeobox genes have been studied extensively in *Drosophila,* where they are involved in the commitment of cells to specific developmental pathways and play an important role in pattern formation.[33]

Recently, the NK homeobox family of genes (*NK-1/S59*, *NK-2/vnd, NK-3/bagpipe*, and *NK-4/msh-2/tinman* and *H6*) was identified in the mouse.[34] Nkx-2 factors are DNA-binding proteins (transcriptional factors) that are capable of activating transcription; their 60-amino-acid homeodomain includes three helices, in which helix II and helix III form a helix-turn-helix motif.[35] Helix III fits across the AT-rich major groove of the DNA binding site. *Nkx-2.5* has been shown to bind to novel NKE sites,[36] certain serum response elements of the cardiac alpha-actin promoter,[37] and the NKE sites in the cardiac atrial natriuretic factor promoter.[38] Gajewski and associates[39] showed that two NKE promoter sites direct *Drosophila* MEF2(dMEF2) expression in response to *tinman*. Mutations in the *tinman* gene result in loss of heart formation in the *Drosophila* embryo.[40] In addition, *tinman* is known to regulate NK-3/bagpipe expression in the visceral mesoderm[41] and the expression of dMEF2.[39] These observations suggest that *tinman* may be involved in cardiac mesoderm patterning and make it a likely marker for cardiac mesoderm induction.

Tinman and Other Related NK-2 Genes Are Required for Vertebrate Heart Morphogenesis

Homeobox genes of the NK class also may function in early cardiac development in vertebrates. The murine NK-2 homeobox gene *Nkx-2.5/Csx* is expressed in early cardiac progenitor cells before cardiogenic differentiation and continues through adulthood.[42,43] Superimposed on the appearance of *Nkx-2.5* in cardiac progenitor cells is the sequential expression of the cell type-restricted cardiac alpha-actin and MHC genes.[42] The *Nkx-2.5* factors identified in other vertebrates, such as zebrafish,[44] *Xenopus*,[45] and chickens,[46] were highly related in sequence and expression pattern to the mouse gene and to cardiac development.

The similarity in expression patterns between *Nkx-2.5*, *XNkx-2.5*, *ceh-22*, *tinman*, and *bagpipe* suggested that the function of these genes might be conserved. Another member of the Nkx-2 family, *Nkx-2.8*, which was recently isolated from avian species, is closely related to *Xenopus*, chicken, and zebrafish *Nkx-2.5* homeoboxes and is expressed in the developing embryo in the lateral plate mesoderm and underlying pharyngeal endoderm.[47] An attractive hypothesis is that these homeodomain factors function in phylogenetically conserved myogenic pathways occurring in muscle types that do not utilize the Myo-D family. Whether the vertebrate *Nkx-2.5* or other Nkx-2-related genes expressed in the early heart play a role in heart specification or whether they are downstream regulators of cardiac gene expression remains to be determined. In this respect, it is interesting to note that although it does not inhibit formation of the cardiac tube, homologous recombination knockouts of the endogenous murine *Nkx-2.5* gene do result in cardiac dysmorphogenesis at the looping stages of development and embryonic lethality.[48]

The partially overlapping expression pattern of *Hox* genes in embryos has led to the concept of a "*Hox* code."[49] The term *Hox code* means that a particular combination of *Hox* genes is functionally active in a region and thus specifies the developmental fate of this region. The existence of eight Nkx-2 family members, their overlapping DNA-binding specificities, and, most important, their partially overlapping patterns of expression raise the possibility of an "Nkx code."[47] Overexpression of *Nkx-2.5* in a zebrafish embryo results in an enlarged heart.[44] Thus, inactivation of the Nkx genes by homologous recombination and their overexpression as transgenes offer promise in addressing the functional significance of the expression domains and thus also of the Nkx code. As is mentioned below, patients with secundum atrial septal defect have been identified to have specific mutations in the human homolog to the *Nkx2.5* gene.[49]

Cardiac-Restricted Ankyrin Repeat Protein Gene

The cardiac-restricted ankyrin repeat protein (*CARP*) gene encodes a nuclear coregulator for cardiac gene expression which lies downstream of the cardiac homeobox gene *Nkx 2.5* and is an early marker of the cardiac muscle cell lineage.[50] The expression of the *CARP* gene is developmentally downregulated and dramatically induced as part of the embryonic gene program during cardiac hypertrophy. A distinct 5′ cis regulatory element directs heart segment-specific expression, such as atrial versus ventricular and left versus right. In addition, a 213-base-pair sequence element of the gene confers conotruncal segment-specific expression.[50] In addition, an essential GATA-4-binding site is present in the proximal upstream regulatory region of the gene and cooperative transcriptional regulation is mediated by *Nkx2.5* and GATA-4. This cooperative regulation is dependent on the binding of GATA-4 to its cognate DNA sequence in the promoter, which suggests that *Nkx2.5* controls CARP expression, at least in part, through GATA-4.[50]

SRF and MEF2, MADS Box Factors Involved with Cardiogenesis

Serum response factor generally was presumed to be a ubiquitous and constitutive trophic factor[51] but was later shown to be highly expressed in the embryonic heart.[52] Serum response factor (SRF) represents an ancient DNA-binding protein whose relatives shared a highly conserved DNA-

binding/dimerization domain of 90 amino acids, termed the *MADS box*. SRF-related proteins that are capable of binding to sites found in the regulatory regions of both nonmuscle- and muscle-specific genes also belong to the MADS box family of trophic factors.[53] SRF-related proteins are capable of binding MEF2 sites, CTA(A/T)4TAG, which can be found in the regulatory regions of both nonmuscle- and muscle-specific genes.[54,55] Like SRF, MEF2 factors contain a MADS box and an adjacent MEF2 box. Expression and mutagenesis studies in *Drosophila* have shown that MEF2 proteins are necessary for myogenic differentiation during development[56,57] and are activated by *tinman*.[39]

In the mouse embryo, MEF2 genes are highly expressed in the early heart and skeletal muscle progenitor cells before the induction of cardiac and skeletal muscle structural genes, implicating MEF2 as key regulator of cardiac and skeletal muscle differentiation programs.[58-60] Four MEF2 genes have been isolated in vertebrate species and are referred to as MEF2A-MEF2D.[60,61] The four MEF2 gene products are highly homologous in the MADS box domain but are divergent in the carboxy termini, arising from alternative splicing mechanisms. MEF2C shows a tissue-restricted expression pattern, being expressed exclusively in skeletal muscle, brain, and spleen, and is induced by myogenin in fibroblasts during myogenic differentiation in tissue cultures.[62]

Transactivation of the Cardiac Alpha-Actin Gene by Nkx-2.5 and SRF

Gilman and coworkers[63,64] showed that human SRF interacts with a novel human homeodomain protein, Phox, which shows similarity to the homeodomains of two murine Pax genes. The highest similarity is to a partial murine cDNA termed S8[65] and to MHox, a novel homeodomain protein expressed in mesoderm.[66] Phox interacts with SRF to enhance the exchange of SRF with its binding site in the *c-fos* gene. It has been shown that *Nkx-2.5* transactivates the cardiac alpha-actin gene by binding to SRF, but only after SRF has bound to DNA.[67]

The Role of the GATA Family in Cardiogenesis

The GATA family of proteins has been subdivided, with GATA-1/2/3 being linked to hematopoiesis and GATA-4/5/6 thought to be involved with cardiac, gut, and blood vessel formation. Each of the six GATA proteins contains a highly specific DNA-binding domain consisting of two C4 zinc fingers that bind to the DNA sequence element (A/T)GATA(A/G) and that may be able to interchange with each other. GATA-4 and 6 have been found to be expressed in a developmentally and lineage-specific pattern within cardiac mesoderm and gut epithelium.[68-70] GATA-5 expression is restricted to the endocardium. Experiments have shown that GATA-4 regulates the expression of cardiac-specific genes such as cardiac troponin C[71] and alpha-MHC.[72] Mice without the GATA-4 gene display a severe defect in the formation of the cardiac tube. Several studies have demonstrated that the GATA-4 transcription factor plays an important role in regulating cardiac-specified genes and appears to be downstream to the *Nkx-2.5* gene.

Cardiogenesis, an Nkx-2-Dependent Paradigm

An attractive hypothesis from the analysis of these NK-2 homologues is that these homeodomain factors function in phylogenetically conserved pathways in muscle cell types that do not utilize the Myo-D family. Expression of *Nkx-2.5* in fibroblasts demonstrated that downstream targets such as the cardiac alpha-actin gene are not directly activated by *Nkx-2.5* alone but require the collaboration of additional factors, such as SRF.[37,67] Whether the vertebrate *Nkx-2.5* or other Nkx-2-related genes with SRF are sufficient to play the primary role in heart specification and serve as regulators of other downstream cardiac genes remains to be determined. It is reasonable to postulate that the vertebrate MEF2C genes and the GATA-4 factor are high in the hierarchical order of regulatory factors that, in combination with *Nkx-2.5* and SRF, specify the cardiac cell

lineage.

Role for Bone Morphogenic Proteins in Initiating Early Myocardial Cell Differentiation

One type of signaling molecule responsible for cardiogenic commitment was identified to be composed of the bone morphogenic proteins (BMPs), which are members of the transforming growth factor-beta family of signaling molecules. BMP-2 and -4 appear to be capable of inducing the cardiac regulatory factors *Nkx-2.5* and GATA-4 when ectopically applied to regions of chick embryos that usually are not specified to become heart tissue.[46] In mice with the BMP-4 gene eliminated (knockout mice), there was little or no mesoderm differentiation. Some of the mice deficient for BMP-2 gene that lacked *Nkx-2.5* expression also failed to develop beyond the early stages of looping.[73] Thus, BMPs appear to have an early influence on cardiogenesis and *Nkx-2.5* expression.

Laterality of the Cardiac Tube

Correct laterality is fundamental to the developing embryo, and situs solitus has the lowest risk of congenital cardiovascular malformations.[74] The first grossly asymmetric feature to develop is the heart tube, which forms from the fusion of cardiac primordia at the midline (see Fig. 9-2). Subsequently, the initially symmetric heart acquires a dextral loop. The tubular heart initiates rhythmic contractions at about day 23 in humans and then undergoes rightward looping. This pattern of left-right asymmetry occurs in all vertebrate internal organs as a result of a signaling cascade present before gastrulation. On the right side of Hensen's node, the secreted morphogen activin represses Sonic hedgehog (Shh) expression and induces expression of the genes for the activin receptor and fibroblast growth factor 8. On the left side, Shh induces Nodal expression in lateral plate mesoderm and subsequent left-sided expression of the bicoid-like homeobox gene *Pitx2*. The homeobox gene *Nkx3.2* is asymmetrically expressed in the anterior left lateral plate mesoderm (LPM) and head mesoderm in the chick embryo.[75] Misexpression of the normally left-sided signals Nodal, Lefty2, and Shh on the right side or ectopic application of retinoic acid results in upregulation of *Nkx3.2* contralateral to its normal expression on the left. FGF8 is an important negative determinant of asymmetric *Nkx3.2*, and ectopic application of FGF8 on the left side blocks *Nkx3.2* expression, whereas an FGF receptor-1 antagonist implanted on the right side results in bilateral *Nkx3.2* expression in the LPM.[75]

There is a genetic basis for left-right asymmetry, as several types of unlinked mutations affecting left-right laterality exist in mice and humans. For example, in the offspring of *iv* mice (lacking the *iv* gene), 50 percent have situs inversus.[76] The *iv* gene has been mapped to mouse chromosome 12 and has been identified to code for the structural protein dynein. The *inv* (inversion of embryonic turning) gene mapped to chromosome 4 causes complete reversal of left-right symmetry and cardiac looping.[77,78] *Nkx3.2* expression also was found to be asymmetric in the mouse LPM, but unlike in the chick, it was expressed in the right LPM. In the inversion of embryonic turning (inv) mouse mutant, which has aberrant left-right (L-R) development, *Nkx3.2* was expressed predominantly on the left side. Thus, *Nkx3.2* transcripts accumulate on opposite sides of mouse and chick embryos, although in both the mouse and the chick, *Nkx3.2* expression is controlled by the L-R signaling pathways.

Myocardial Expansion and Differentiation

Retrovirus labeling studies have demonstrated that the ventricular myocardium expands by a process of clonal expansion of the epitheliod myocytes of the cardiac tube (see Figure 9-7).[79,80] The regulation of myocyte specification and differentiation is complex and probably involves cell adhesion molecules, including N-cadherin, extracellular proteases, and morphogenetic signals from the transforming growth factor-beta (TGF-beta) and FGF families of growth and

differentiation factors.[80-84]

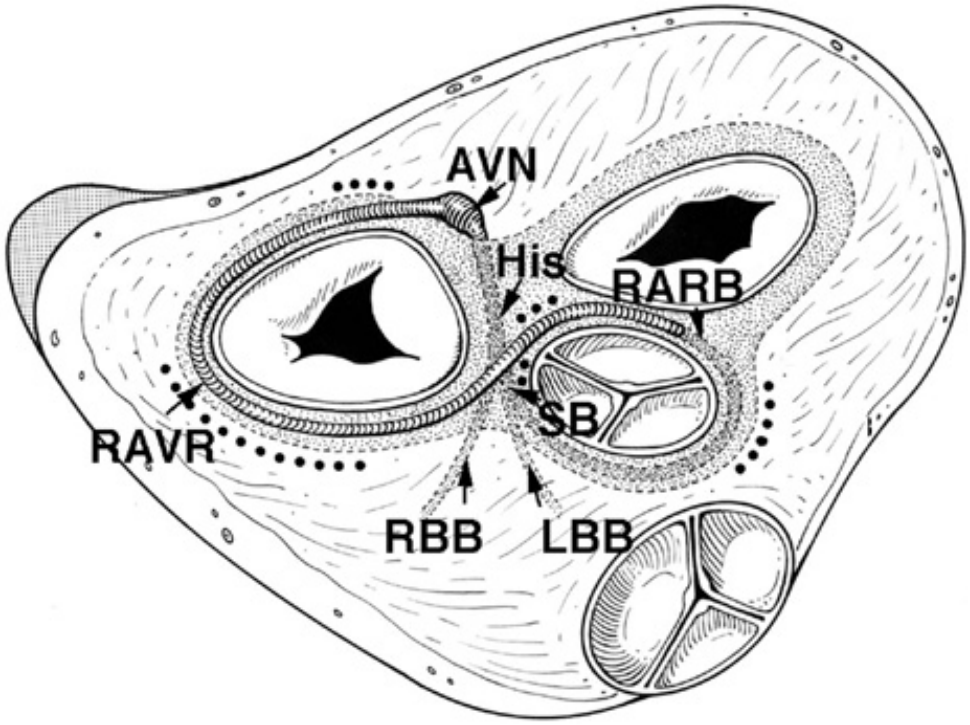

Figure 9-7: Schematic representation of the localization of remnants of the primary ring in the neonatal human heart. The ring is projected on a superior view of the aortic mitral fibrous unit of the adult heart. The black dots indicate the areas in which remnants of the ring are detected in a series of neonatal hearts. 1 = anterolateral part of the right atrioventricular ring; 2 = posteromedial part of the right atrioventricular ring; 3 = "dead-end" tract of the conduction axis; 4 = lateral part of the retroaortic rootbranch; 5 = posterior part of the retroaortic rootbranch. AVN = atrioventricular node; AoV = semilunar valve of the aorta; LBB = left bundle branch; mi = mitral valve; PuV = semilunar valve of the pulmonary trunk; Rbb = right bundle branch; SB = septal branch; tri = tricuspid valve. (Adapted from Wessels et al.[126])

The Neural Crest and Cardiac Development

The cardiac neural crest is an important migratory cell population that contributes to cardiovascular morphogenesis. The cardiac neural crest arises from the dorsal margin of the neural tube before fusion and migrates ventrally to form the autonomic ganglia, melanocytes, and Schwann cells. The crest cells move in waves through the branchial arches during the first 4 weeks of human development. The eventual fate of the neural crest cells likely is determined long before the initial phenotypic expression of a heart tube by activation of the cellular gradients of *Hox* genes and other morphoregulating factors.[85,86] The cranial neural crest region defines a developmental field that includes the heart, hindbrain, face, and branchial arch derivatives.

Experimental disruption of cranial neural crest produces a spectrum of abnormalities. In a series of elegant ablation and chick quail chimera studies, Kirby and Waldo defined the range of cardiac neural crest that is integral to the septation of the conotruncal region of the heart and branchial arch derivatives, including facial abnormalities, thymus, parathyroid, and autonomic derivatives.[85] These neural crest cells are site-specific and carry information for the formation of structures appropriate to their origin rather than being defined at the destination of migration.

Several genes have been identified as important in the proper migration and differentiation of the

cardiac neural crest. The Splotch mutant mouse is characterized by a mutation in the *Pax-3* gene.[87] Homozygote Splotch mutants have a complete neural crest ablation phenotype, including persistent truncus arteriosus and aortic arch anomalies,[88] similar to the CV phenotype of neural crest ablation in the chick embryo.[86,89] *Hox* gene abnormalities also are associated with defects in the derivatives of cranial neural crest. A transgenic murine model of *Hox* 1.1 overexpression has neural crest ectomesenchymal tissue abnormalities, including cleft palate, nonfused pinnae, and open eyes. *Hox* 1.5-deficient mice have features of DiGeorge's syndrome.[86] In humans, DiGeorge's syndrome, velo-cardio-facial syndrome, and conotruncal anomaly face syndrome are associated with chromosomal deletions in the 22q11 region on the long arm of chromosome 22.[90-93] Recent studies have indicated a number of candidate factors in the pathogenesis of these syndromes (referred to as catch22 syndrome). In addition, retinoic acid is a potent teratogen in humans and produces a syndrome involving all the derivatives of the cranial neural crest.[94]

Myocyte Differentiation

In the human embryo, the heart begins to contract at day 17 as the machinery of contraction and relaxation becomes functional. These functional units include the sarcomere, composed of the contractile elements; the mitochondria, containing the enzymes for energy production and modulation; and the sarcolemma, the cell envelope with specialized components of the t tubular system linked to the sarcoplasmic reticulum. In the mature myocardium, sarcomeres are organized parallel to the lines of peak systolic stress. In the embryonic myocyte, myofibrils initially appear disarrayed and become aligned as development proceeds.[95] Despite this disordered appearance, the contraction pattern of the early embryonic heart is isotropic.[96]

The temporal and spatial expression of contractile proteins in the developing heart is under intense investigation. At the precardiac tube stage, smooth muscle alpha-actin is the only isoform present. With formation of the cardiac tube, there is progressive expression of the cardiac form of sarcomeric actin with the onset of cardiac pumping. The alpha smooth muscle actin may act as a scaffolding during assembly of the sarcomere.[97,98]

Mitochondria multiply concurrently with the myofibrils in the differentiating myocyte. In the mature heart, mitochondrial enzymes are the major source of high-energy phosphate necessary for contraction and probably begin this function during embryonic development. In the chick, the mitochondria account for about 10 percent of myocyte volume.[95] In the rat embryo, total volume increases from 22 to 34 percent between days 6 and 10, and the mitochondria also change morphologically with development, becoming larger with more cristae and a denser matrix.[99] The myocyte mitochondrial volume fraction correlates directly with heart rate and oxygen consumption among animals.[100]

Maturation of the sarcoplasmic reticulum and the apparatus for excitation-contraction coupling occurs coincident with the structural morphogenesis of the embryonic heart. The sarcolemma contains ion pumps, channels, and exchangers that maintain chemical and charge differences between extracellular and intracellular spaces.[101] During maturation of the heart, the resting potential increases (becomes more negative) in both birds and mammals [102,103] Ca^{2+} influx through Ca^{2+} channels may play a relatively important role in transsarcolemmal Ca^{2+} influx in the immature heart. However, peak Ca^{2+} current density is actually decreased compared with that measured in mature cells.[104,105] Although Ca^{2+} influx by way of the Na^{+}-Ca^{2+} exchanger is less important for excitation-contraction coupling in mature myocardium, Na^{+}-Ca^{2+} exchange may play an important role in myocytes from relatively immature rabbit hearts.

Relaxation, an active process by which the myocardium returns to steady state after contraction, depends on rapid removal of Ca^{2+} from troponin C. This is mediated primarily by active transport of Ca^{2+} back into the sarcoplasmic reticulum (SR). The SR Ca^{2+} pump ATPase (SERCA2a)

usually couples hydrolysis of adenosine triphosphate (ATP) to active Ca^{2+} transport. The rate of SR Ca^{2+} uptake correlates well with the observed rate of myocardial relaxation. Regulation of SR Ca^{2+} pump activity is mediated by the intrinsic SR protein phospholamban. Ca^{2+} also is removed from the myofilaments by extrusion across the cell membrane. In the steady state, the amount of Ca^{2+} removed from the myocyte equals the amount entering through the Ca^{2+} channels.[106]

Segmental Basis of Heart Tube Formation

Formation of the cardiac tube is a complex morphogenetic event. The primitive, bilateral heart tubes each contain an inner layer of endocardium, a middle layer of cardiac jelly, and an outer layer of myocardium. At the cephalic end of the embryo (on each side of the midsagittal plane), myocytes within a section of each heart tube acquire contractile elements, and the position of the heart tubes shifts first to be parallel and close to each other within the cephalic part of the developing body cavity (intraembryonic coelom), ventral to the foregut, followed by fusion of the heart tubes in the ventral midline to form the linear or straight heart tube.[4,5107-109]

It is important to note that the primitive linear heart tube does not contain all the segments present in the mature heart. During morphogenesis, the proximal portion of the aortic sac is incorporated into the outflow tract of the right ventricle (along with migrating neural crest cells) and the sinus venosus is incorporated into developing atria. Thus, each "segment" of the mature heart arises at a unique time during embryogenesis.[110] One critical aspect of this segmental assembly and maturation of the heart is that there likely are both temporal and spatial "windows" that are developmentally regulated, and this may explain why similar morphogens such as retinoic acid produce a wide spectrum of teratogenic effects depending on the time in gestation of exposure. Another aspect of this segmental paradigm is the concept that cardiac morphogenesis depends on molecular and cellular as well as mechanical interactions between the respective segments in the developing heart.[110]

Cardiac Jelly

Prior to looping, the acellular space between the myocardium and the endocardium in the heart is filled with a deformable extracellular matrix. This "cardiac jelly" forms before cardiac tube fusion and is closely associated with the primordial myocytes.[111] At the pretubular heart stages, the extracellular matrix contains collagen types I and IV, fibronectin, and laminin. The primordial endothelial cells destined to form the endocardium interact and migrate through this matrix during the establishment of the primitive, bilateral heart tubes. Radioactive labeling has demonstrated that proteins produced in the myocardium flow toward the endocardium and are incorporated into the basal lamina.[112] The cardiac jelly has a variety of functions related to hemodynamic performance, cardiac looping and cell migration in cardiac septation, and the formation of the endocardial cushion valves at the atrioventricular (AV) junction and outflow tract of the heart.

The protein composition of the cardiac jelly modulates differentiation of the endothelium. Recent information explains the role of genes from the TGF-beta family of peptide growth factors as regulators of morphogenesis.[113] TGF-beta2 proteins are in the extracellular matrix and are an integral component of the morphogenetic changes at the AV cushion level, acting through second messengers such as protein kinase C.[114] In addition, fibronectin probably serves to set up migratory pathways in the cardiac jelly. These protein strands are arranged radially in the cushion, presumably along the lines of stress. The fibronectin strands also may serve as a template for the fibrous skeleton of the AV valve leaflets.[115-117] The extracellular matrix proteins stimulate transdifferentiation of the endocardium in these regions, prompting endothelial cells to transform to mesenchymal cells which migrate into the cushion matrix. Laminin and type IV collagen are stabilizing signals or markers, since these compounds are absent in the cushion regions but are present adjacent to the endocardial cells that maintain a typical epithelial integrity.

Endocardial Maturation

The endothelial cells that make up the lining of the embryonic heart initially are arranged as a single sheet. This squamous-like sheet has the morphologic features of an active tissue, including microvilli, ruffles, and intercellular openings.[118] The endocardium participates in the formation of endocardial cushions at the AV junction and in the outflow tract.[119] Transdifferentiation of the endocardium occurs in the endocardial cushions, where cells round up, produce pseudopodia, and migrate into the cardiac jelly.[120] These cells eventually make up a portion of the fibrous skeleton of the cardiac valves. Inductive chemical signals from the myocardium contribute to the endocardial transdifferentiation and regulate the migration of the mesenchymal cells.[120] In addition, hemodynamic alterations can influence the orientation of endocardial cells on the endocardial cushions[121] and the loci of dead and dying cells in the chick embryo heart.[122] This interaction likely is similar to the relation between the endothelium and smooth muscle of the mature vascular bed.[123] Finally, expansion of the endocardium is critical to the process of ventricular trabeculation, as is discussed below.

Looping

Following the formation of the straight heart tube, the human embryo is about 2 mm long and 23 days old. At the cephalic (or cranial) end of the myocardial heart tube, the nonmyocardial aortic sac can be recognized. The aortic sac is connected to the first pair of aortic arches and later also to the second, third, fourth, and sixth arches (the fifth pair of aortic arches does not normally develop in mammals or is very rudimentary). The extreme caudal part of the myocardial tube receives the paired confluence of veins that lie extrapericardially and are embedded in mesenchyme. In the early tubular stage, the heart hangs suspended from the ventral foregut by the so-called dorsal mesocardium. This structure disintegrates in the midportion of the tube, leaving the heart connected at the anterior pole at the level of the aortic sac and at the posteriorly located venous pole (atria and sinus venosus). At least three different biomechanical mechanisms may act in combination to generate the characteristic bend to the right of the cardiac tube: locally constrained growth, active cell deformation, and prestressed dorsal mesocardium.[124]

As the tubular heart continues to grow, it bends to the right and anteriorly (Fig. 9-4). This results in a compound sigmoid structure with a so-called d-loop (rightward) configuration. At this stage, it is easy to distinguish the sinus venosus, the common atrium, the atrioventricular canal, the future left and right ventricles, and the outflow segment. Internally, the developing muscular interventricular septum is recognizable, its crest characteristically expressing the molecular marker GLN2/HNK-1.[125,126] It is important to note that at this stage, all the future segments of the heart are still basically connected in series and that the common atrium connects, via the atrioventricular canal, completely to the left ventricle [i.e., double-inlet left ventricle (DILV)], while the outflow tract is connected exclusively to the right ventricle [i.e., double-outlet right ventricle (DORV)]. This is schematically depicted in Fig. 9-5.

The transition from a tubular heart in which the future segments are arranged in series (atrium to LV to RV to outflow tract) into a four-chambered heart in which the definitive chambers are arranged in parallel, separated by septa and valves, raises two important questions. The first is how the right atrium becomes connected to the right ventricle, and the second is how the left ventricle gains access to the aortic portion of the outflow tract. The remodeling of the so-called inner curvature of the looping heart tube plays an important role in this process and involves a rightward expansion of the AV canal and a concomitant leftward shift of the aorta. Immunohistochemical studies have demonstrated that this remodeling is intimately related to the development of the so-called primary ring (Fig. 9-6).[125,126] In the postnatal human heart, derivatives of the primary ring are found in the AV conduction system, in the right AV junction

(the right AV ring), and behind the aorta (the retroaortic root branch) (Fig. 9-7).[126]

ANOMALIES

Ventricular Inversion with Transposition of the Great Arteries

If the cardiac tube loops to the left and anterior (L-loop) rather than to the right and anterior, most of the structures adjacent to and including ventricular segments of the heart tube (the AV valves, the ventricles, and the arterial roots) will develop in an inverted position. Subsequently, the right atrium is connected via a morphologic mitral valve to a morphologic left ventricle and the left atrium is connected via a morphologic tricuspid valve to a morphologic right ventricle. Within the aortic sac, the aorticopulmonary septum develops in a normal fashion. However, as partitioning of the inverted conotruncus (outflow track) takes place in mirror image, the end result is L-transposition of the great arteries, with the aorta arising anteriorly from a left-sided, morphologically right (systemic) ventricle and the pulmonary trunk arising posteriorly from a right-sided, morphologically left (venous) ventricle. Because systemic and pulmonary venous return are still routed to the pulmonary and systemic arterial circulations, respectively, this anomaly commonly is referred to as "corrected" transposition.

Double-Outlet Right Ventricle

DORV is due to a failure in the leftward repositioning of the aortic portion of the outflow tract, resulting in the persistence of the more "primitive" embryonic morphology in which the entire outflow tract originates from the right ventricle. One morphologic hallmark of the failure of completion of the leftward shift of the aorta is the presence of myocardial tissue between the left AV valve and the aorta (mitral-aortic separation). This anomaly is found after a wide range of hemodynamic, metabolic, and genetic insults to the embryo, suggesting that the phenotype of the DORV may be a final common expression of a range of primary abnormalities that result in the persistence of the embryonic configuration.[127]

Myocardial Trabeculation

The processes of primary myocardial trabeculation, expansion of secondary and tertiary myocardial trabeculae, and myocardial compaction are critical to the structural maturation of the ventricular chambers. This process results in the transformation of the smooth-walled endocardial lining into complex three-dimensional structure of the right and left ventricular myocardium. Rapid cell division and interposition of endothelial cells along the right and left ventrolateral borders of the endocardial tube is associated with a rapid resorption of cardiac jelly, resulting in myocardial ridges and trabeculae lined with single layers of endocardial cells.[128] The initial number and orientation of the myocardial ridges differ between species.[129] In general, myocardial trabeculation begins at the ventricular outer curvature (future apex) and then extends proximally and distally. The intersection between the outer, compact myocardium and the base of the trabeculae probably is a site of peak wall stress, and myocyte division is most active at this site.[130,131] Retroviral marker studies also have shown that ventricular myocardial growth is associated with a transmural distribution of clonally related myocardial cells extending from the epi- to the endocardium.[79,80] Of note, these cells reside in muscle bundles that are oriented at an angle to the longitudinal axis of the heart, consistent with the adult myocardial architecture that results in efficient twist and contraction.[79,80] However, the mechanisms that regulate clonal myocardial expansion and compaction have not been defined.

With the onset of myocardial trabeculation, diverticula first appear as two sharply defined areas along the right and left ventrolateral borders of the endocardial tube (Fig. 9-8).[132] These diverticula develop initially at the expense of the cardiac jelly and later penetrate the myocardium

as it increases in thickness, producing a spongy mass of trabeculae.[128] The filling capacity of the heart is increased by the added intertrabecular spaces. The trabeculating embryonic heart now can be divided into primitive right and left ventricles as there are distinct morphologic differences between the trabecular architectures of the developing ventricular chambers. The developing LV is trabeculated along the majority of its greater curvature, while the developing RV has a significant portion of the greater curvature that is smooth-walled.[133] At this stage of development, the embryo is approximately 3 mm long and has an ovulation age of about 25 days.[107] The common outflow tract of the developing heart can be classified as having a proximal (conus) segment and a distal (truncus) segment. The conus eventually septates into the outflow portions of each ventricle with the incorporation of migrating neural crest cells, while the truncus contributes to the formation of the semilunar valves and the development of the aortic and pulmonary roots.

ANOMALIES

Noncompaction of the Ventricular Myocardium

Noncompaction of the ventricular myocardium is a rare, familial congenital cardiomyopathy that results from incomplete compaction of the trabecular embryonic myocardium.[134,135] The characteristic echocardiographic findings consist of multiple, prominent myocardial trabeculations and deep intertrabecular recesses communicating with the left ventricular cavity. The disease uniformly affects the left ventricle with or without concomitant RV involvement and results in systolic and diastolic ventricular dysfunction and clinical heart failure. Recent studies have characterized this disease in both children and adults. A higher incidence of Wolff-Parkinson-White syndrome was found in children, whereas left bundle branch block was more rare than reported in adults. Familial recurrence is high.[136] Recently, a case of ventricular noncompaction was identified in a patient who also had a haplotype deletion on the long arm of chromosome 5.[137] The affected region included the locus for the cardiac-specific homeobox gene *Nkx2.5*, suggesting an association between ventricular myocardial noncompaction and haploinsufficiency of *Nkx2.5*.

NEXT

Chapter 9: MOLECULAR DEVELOPMENT OF THE HEART

MECHANISMS OF CARDIAC SEPTATION

Cardiac and Extracardiac Orientation

Because of rapid growth and the progressive curvature of the longitudinal axis of the embryo during organogenesis, it is critical to define cardiac morphogenesis, including septation, with reference to extracardiac morphologic landmarks that relate to the longitudinal axis of the embryo.[138] In the following discussion of cardiac septation, therefore, the diaphragm (septum transversum) is assumed to maintain an approximately horizontal position, as it does in the mature heart. The terms *anterior*, *posterior*, *superior*, and *inferior* are employed accordingly. Although the formation of the various cardiac septa occurs almost simultaneously, for clarity it is necessary to consider their development separately.

Cardiac Septation

Cardiac septation involves the formation of several septal (myocardial and mesenchymal/fibrous) and valvar structures. All the original tissues of the tubular heart (myocardium, endocardium, endocardial cushion tissues) as well as the so-called extracardiac cell populations, which arrive in the heart at relatively late stages of development (neural crest, epicardium, ventral neural tube cells), appear to play a role during valvuloseptal morphogenesis.

The Sinus Venosus

In the 3-mm human embryo, the sinus venosus consists of a central, transverse portion of the sinus venosus and the right and left sinus horns (Fig. 9-9). The sinus venosus receives three pairs of veins: the omphalomesenteric (vitelline) veins, the umbilical (allantoic) veins, and the common cardinal veins. The proximal portions of the umbilical veins soon disappear. As a result of the increased blood flow associated with the right and left systemic veins, the right sinus horn and the proximal cardinal and vitelline veins attain a vertical position, increase in size, and form the smooth-walled, intercaval part of the atrium. The transverse portion and the proximal left sinus horn become the coronary sinus. Infolding of the sinoatrial junctional tissue at the right border of the sinoatrial foramen results in the formation of the right venous valve.[139,140] The left valve develops as a result of active growth, similar to that of the primary atrial septum (i.e., the left valve does not develop as a fold) (Fig. 9-10). Thus, the vertical sinoatrial orifice is flanked on each side by a valvelike structure in the 4- to 6-mm human embryo. Superiorly, the venous valves join to form the septum spurium. The venous valves, particularly the right venous valve, are relatively large in the 16-mm embryo. The superior aspect of the right venous valve eventually develops into the crista terminalis, or terminal crest. The left sinus valve fuses partly with the atrial septum. Inferiorly, the left venous valve intersects with the inferior part of the right venous valve. As a result, the right venous valve becomes divided into the relatively large inferior vena caval (or eustachian) valve and a smaller coronary sinus (or thebesian) valve.

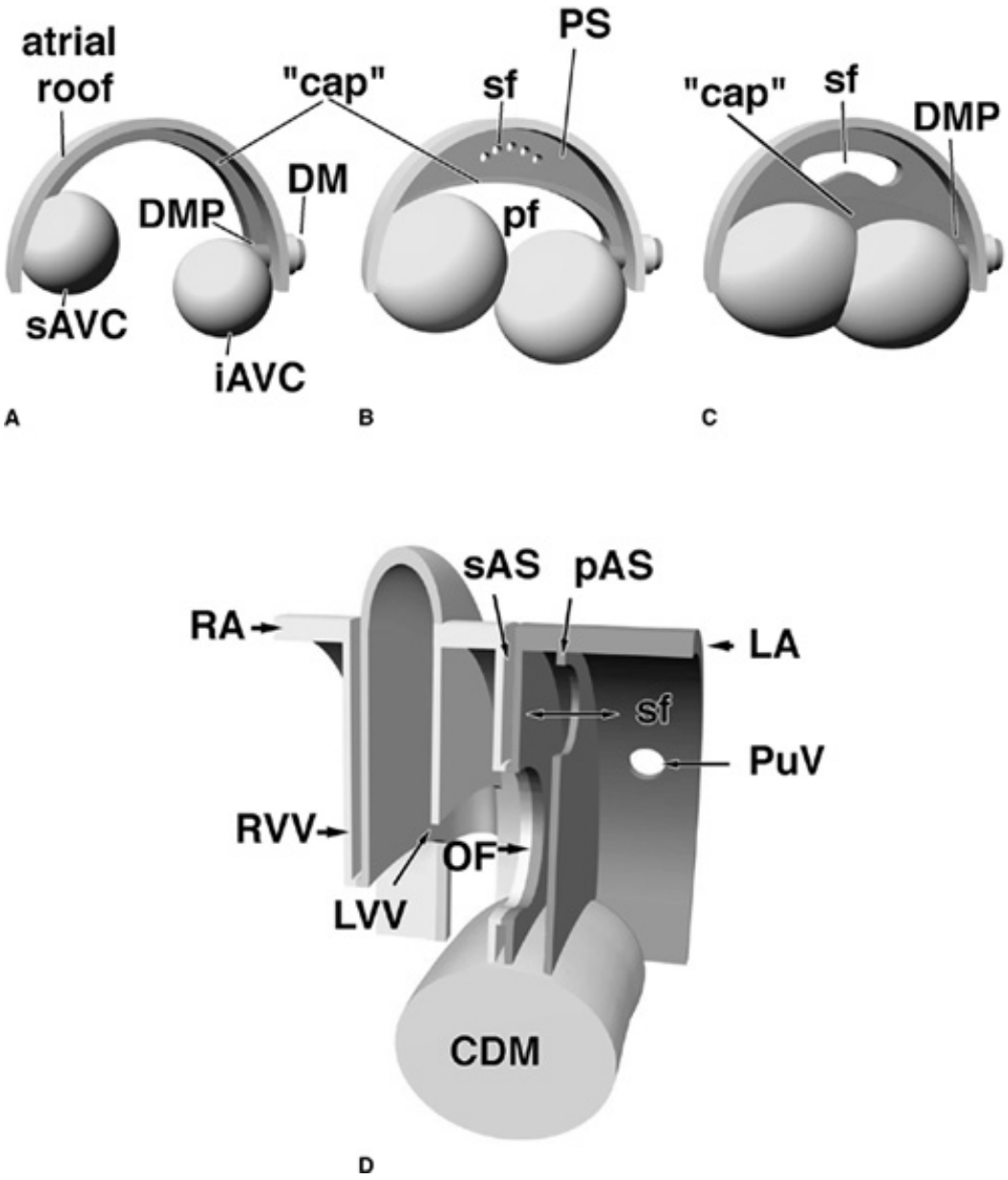

Figure 9-10: A model for the development of the atrial septal complex in the human heart. Panels *A-C* of this cartoon illustrate the key events in the formation of the primary atrial septum (*A-C*). Panel *D* schematically depicts the formation of the atrial septum and venous valves. Panel *A* represents a heart at approximately 4½ weeks of development. The AV cushions can be distinguished but have not yet fused. The leading edge of the primary septum is covered by a mesenchymal cap which is in continuity with the dorsal mesenchymal protrusion of the dorsal mesocardium. Panel *B* represents the situation at approximately 6 weeks of development. The leading edge of the primary atrial septum, covered with a mesenchymal cap, is now approaching the AV cushions, which are in the process of fusing. Within the myocardial portion of the primary septum, multiple fenestrations represent the developing secondary foramen. Completion of fusion of the mesenchymal tissues at 6 to 7 weeks of development (panel *C*) results in the closure of the primary interatrial foramen. At this time, a prominent secondary foramen can be found within the superior portion of the primary septum. The cartoon in panel *D* shows how the secondary atrial septum is formed as a result of infolding of the atrial roof. This occurs at the margin between the myocardium and the left and right atrial expression domain. The myocardium of the primary atrial septum is part of the left atrial expression domain; the orifice of the pulmonary vein also is surrounded by myocardium with a left atrial molecular phenotype. This panel also illustrates that based on the gene expression patterns, the left venous valve develops as a myocardial structure with a right atrial molecular phenotype, whereas the right venous valve (just like the secondary atrial septum) develops by infolding, in this case of the junctional tissue between the right atrium

and the sinus venosus. iAVC = inferior atrioventricular cushion; sAVC = superior atrioventricular cushion; DM = dorsal mesocardium; DMP = dorsal mesenchymal protrusion; pf = primary foramen; PS = primary atrial septum; sf = secondary foramen; LA = left atrium; RA = right atrium; OF = oval fossa; pAS = primary atrial septum; sAS = secondary atrial septum; PuV = pulmonary vein; LVV = left venous valve; RVV = right venous valve (From Wessels et al.[139])

ANOMALIES

Cor Triatriatum Dexter

Complete persistence of the right venous valve of the embryonic heart produces a septum in the right atrium, separating the intercaval part of the right atrium from the atrial body. The remaining opening may be quite small and restrictive.

Persistent Left Superior Vena Cava

Persistence of the left common cardinal vein and left sinus horn results in a left superior vena cava draining into the coronary sinus.

Atrial Septation

Septation of the embryonic common atrium involves two distinct mechanisms.[139] The primary atrial septum (septum primum) forms by active growth of a myocardial septum. Initially, the primordium of this septum can be seen as a ridge in the medical roof of the common atrium. The leading edge of the ridge is covered with a mesenchymal cap which is superiorly continuous with the superior AV cushion and inferiorly with the inferior AV cushion. As the primary septum descends from the roof of the atrium toward the atrioventricular canal, thus decreasing the size of the primary interatrial foramen, the mesenchymal leading edge continues to fuse with the AV cushions, which are also in the process of fusing. These events result in closure of the primary interatrial foramen (or ostium primum) and the formation of the central fibrous body (see Figure 9-12). Concomitantly, perforations appear in the superior aspect of the primary. The perforations coalesce, resulting in the secondary atrial foramen (ostium secundum). Next, the secondary atrial septum develops as an infolding of the atrial roof located between the primary septum and the left venous valve. The foramen ovale is the opening bordered by the free edge of the septum secundum. After fusion of the septum primum with the septum secundum, the foramen ovale becomes the fossa ovalis.

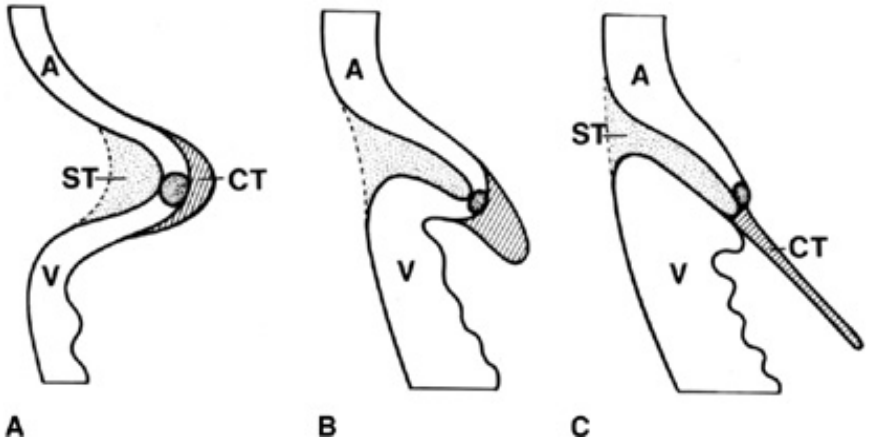

Figure 9-12: Schematic drawings of the formation of the atrioventricular junction in the human

heart. *A*. The situation at the atrioventricular junction at 4 to 5 weeks of development. Myocardial continuity between atrium and ventricle occurs through the myocardium of the atrioventricular canal. The AV junction is sandwiched between the tissues of the AV sulcus at the epicardial side and the AV cushion at the endocardial side. *B*. With progressive remodeling of the AV junction, the sulcus tissues expand toward the midline of the AV canal as the cushion tissue remodels. *C*. With completion of this process, continuity is lost between atrial and ventricular myocardium. A = atrium; V = ventricle; ST = sulcus tissue; AV = myocardium of the atrioventricular canal; CT = cushion tissue. (Adapted from Wessels et al.[148])

Development of the Pulmonary Veins

The so-called pulmonary pit, the future portal of entry for the main pulmonary vein, is recognizable at around 28 days of gestation and is situated in the midline of the inferior portion of the common atrium before atrial septation is initiated. The pulmonary pit is flanked by two myocardial reflections that are referred to as the left and right pulmonary ridges, respectively.[141] This pulmonary pit, actually an invagination of the endocardium into the dorsal mesocardium, can be traced toward the pulmonary mesenchyme as an endothelial strand. Remodeling of the tissues surrounding the pulmonary pit results in incorporation of the ostium of the pulmonary vein in the wall of the left ventricle.

ANOMALIES

Atrial Septal Defect at the Fossa Ovalis

This defect, which often is referred to as a secundum-type atrial septal defect, is due to malformation of the primary atrial septum, resulting in an oversized ostium secundum. Frequently, the atrial defect is further enlarged by a hypoplastic septum secundum. Total absence of both the septum primum and the septum secundum (common atrium) is rare and almost always is associated with a form of persistent AV canal.

Anomalous Pulmonary Venous Connection

The total form of anomalous pulmonary venous connection presumably is due either to lack of development or to a premature involution of the common pulmonary vein. A number of types of pulmonary venous to systemic venous connections occur, depending on which of the early embryonic channels connecting the pulmonary venous bed to the systemic venous circulation remains patent.

Cor Triatriatum Sinister

If incorporation of the common pulmonary vein into the left atrium does not take place and the common pulmonary venous ostium remains narrow, the result is a septum-like structure that may derive from the left pulmonary ridge and divides the left atrium into two components: One receives the pulmonary veins, and the other gives access to the mitral valve and the left atrial appendage.

The Atrioventricular Canal

Division of the AV canal into left-sided and right-sided orifices occurs as a result of fusion of the superior and inferior AV cushions, which are first evident in the 6-mm crown-rump (CR)-length human embryo. At this stage, the common AV canal is located exclusively over the left ventricle. The superior aspect of the developing interventricular septum is continous with the right aspect of the AV junctional myocardium. The communication between the developing right atrium and the

right ventricle is established by the rightward expansion of the AV canal. This expansion, combined with tissue remodeling, brings the right margin of the original AV junction, which still is in continuity with the posterior part of the interventricular septum, toward the posteromedial aspect of the AV junction, where it will form the AV node.[16,125]

Myocardialization

The term *myocardialization* refers to the process of active ingrowth of existing myocardium into mesenchymalized tissues of the heart. In the human heart, it takes place primarily in the conal septum, where it transforms the mesenchymal outlet septum, which is formed as a result of fusion of the conal ridges of the outflow tract, into the muscular outlet septum (Fig. 9-11).[142] It is believed that myocardialization is the driving force for the incorporation of the aortic portion of the outflow tract into the left ventricle and the rightward expansion of the AV junction. Absence or inhibition of myocardialization is associated with structural congenital heart disease in a number of experimental animal models.[143] Most of these malformations involve malalignment of the outlet septum with the muscular interventricular septum, resulting in ventricular septal defects with varying great vessel size disparity.[110]

Meanwhile, the AV canal has enlarged to the right, while the growing endocardial cushions project into the lumen. Smaller cushions appear on the lateral borders of the AV canal. In the 10-mm CR-length embryo, the major cushions reach each other and fuse, resulting in a complete division of the canal into right and left AV orifices. At the same time the cushions also bend, and after fusion they form an arch that is concavely directed anteriorly and toward the left ventricle[143] with its convexity directed anteriorly and toward the atria. The mesenchymal cap on the free margin of the atrial septum primum fuses with the convex atrial side of the fused endocardial cushions. The left limb of the fused AV cushion eventually becomes incorporated into the anterior cusp (aortic leaflet) of the mitral valve. The right half of the fused endocardial cushions comes to lie within the ventricles in a sagittal orientation somewhat to the right of the muscular interventricular septum. Thus, the communication that remains between right and left ventricles, the secondary interventricular foramen, is bordered by the muscular ventricular septum inferiorly and anteriorly, the right extremity of the fused endocardial cushions posteriorly, and the conal septum superiorly. The plane of the secondary interventricular foramen therefore inclines somewhat to the right; that of the primary interventricular foramen, as we have seen, has come to deviate to the left. Both interventricular foramens share the top of the muscular septum as part of their inferior borders.

ANOMALIES

Partial and Complete AV Canal Defect

The several forms of persistent AV canal are due to various degrees of failure of fusion of the superior and inferior AV canal cushions. Total lack of fusion results in a single AV ostium, i.e., the complete form of the anomaly. Since the arch or bay normally formed after the fusion of the endocardial cushions fails to develop, the lower mesenchymal border of the atrial septum cannot fuse with the endocardial cushions. The result is a low-lying large interatrial communication, and the AV part of the cardiac septum is absent. The upper part of the ventricular septum remains deficient to a greater or lesser degree, and there is an interventricular communication. In the partial forms, the endocardial cushions fuse only centrally. The result is an interatrial communication or so-called ostium primum-type atrial septal defect. The upper part of the muscular ventricular septum remains deficient, but this area of the ventricular septum is closed by fibrous tissue. Because the left side of the endocardial cushions does not fuse, the anterior or aortic cusp of the mitral valve is cleft. AV septal defects frequently are associated with trisomy 21 in humans and trisomy 16 in mice.[127] Genetic markers in patients without trisomy 21 also are

under investigation.

Ventricular Septal Defect

Some forms of perimembranous ventricular septal defect may be due to failure of fusion of the right extremity of the fused endocardial cushions, the upper border of the muscular ventricular septum, and the conal septum. Since the endocardial cushions fuse normally, there is no cleft in the anterior mitral valve cusp, and there also is no interatrial communication.

Single Ventricle, Left Ventricular Type with Rudimentary Outflow Chamber, or Double-Inlet Left Ventricle.

If the AV canal becomes divided into two separate ostia (by the fusing AV cushions) but fails to expand to the right, thus retaining its far leftward position, both ostia connect only to the primitive left ventricle. As a result, a communication between the right atrium and the right ventricle does not develop. The communication between the large ventricular chamber (i.e., left ventricle) and the rudimentary outflow chamber (i.e., right ventricle) represents the persistence of the primary interventricular foramen.

The Ventricles

As was mentioned above, the AV canal communicates exclusively with the primitive (or embryonic) left ventricle in the 5-mm CR-length human embryo and blood from the left ventricle reaches the primitive (or embryonic) right ventricle only by way of the primary interventricular foramen. In the developing human heart, the myocardium surrounding the interventricular foramen is characterized by the expression of the GFlN2/HNK antigen and is termed the "primary interventricular ring."[125]

The ventricles enlarge through centrifugal growth of the myocardium. The trabecular myocardium progresses from primary to secondary to tertiary trabeculations, while the compact outer myocardial layer remains relatively thin.[144] Coalescence of the secondary trabeculations into larger tertiary trabeculations occurs after septation, coincident with the formation of the AV valve leaflets.[145] The trabeculae positioned at the border between the developing left and right ventricle coalesce to form the major portion of the muscular ventricular septum.[145] On the right side, a large trabecula, the trabecula septomarginalis,[146] appears early (in embryos about 9 mm in CR length) and runs from the anteroinferior border of the primary interventricular foramen toward the apex.

ANOMALIES

Muscular Ventricular Septal Defect

Failure of compaction and fusion of the trabecular portion of the ventricular septum results in the most common congenital cardiovascular anomaly, the isolated muscular ventricular septal defect.

The Truncus Arteriosus

The embryonic "outflow tract" consists of the conus, truncus, and aortic sac and functions as the conduit between the primitive right ventricle and the aortic arches. Septation of the conotruncal area of the outflow tract begins in embryos about 6 mm in CR length with the appearance of two opposing truncal cushions. One of these cushions is located along the dextrosuperior truncal endocardium (dextrosuperior truncal cushion), and the other on the sinistroinferior wall (sinistroinferior truncal cushion). Coincident with the expansion of the conotruncus, the cushions

rapidly enlarge and fuse to form the truncal septum, thus dividing the truncus into aortic and pulmonary channels. The truncus is the first part of the heart to septate (at the 7-mm CR-length stage). Proximally, the truncal cushions merge with the superior aspects of the conal cushions, which are the comparable mesenchymal masses within the conus. Distally, the undivided portion of the truncus and the aortic sac enlarge to form the truncoaortic sac. Simultaneously, the origin and course of the sixth arches shift leftward, aligning with right ventricular outflow, and the origin and course of the fourth aortic arches shift rightward, aligning with left ventricular outflow. At the same time, a population of cells derived from the cardiac neural crest contributes to the formation of a vertical septum, the aorticopulmonary septum (APS), in the aortic sac.[89] The APS fuses with the truncal septum to complete septation of the aorta and the pulmonary trunk.[127,133,143,146,147]

ANOMALIES

Persistent Truncus Arteriosus

If the truncal cushions remain hypoplastic and fail to fuse, partitioning of the truncus arteriosus does not take place. If, in addition to the hypoplastic truncal cushions, both intercalated valve cushions persist, the result is a quadricuspid truncal valve. Usually, fusion occurs between adjacent valve anlagen, resulting in an apparently tricuspid truncal valve with one larger cusp containing a fused raphe. In the great majority of cases, the aorticopulmonary septum does develop, and a short common pulmonary trunk arises from the persistent trunk. The ductus arteriosus is almost always absent, except when it is associated with interruption of the aortic arch. In experimental models, persistent truncus arteriosus can be produced after selected ablation of neural crest tissue, as was mentioned above.[85]

Aorticopulmonary Septal Defect

This anomaly may be due to malalignment and/or failure of fusion between the distal truncal septum and the aorticopulmonary septum. Both arterial valves are present, but there is a communication of varying size (aorticopulmonary window) between the ascending aorta and the pulmonary trunk.

The Conus

The conal cushions make their appearance at about the same time as the truncal cushions. One is located on the dextrodorsal wall, and the other on the sinistroventral wall of the conus. On the right side, the dorsal conal cushion becomes contiguous with the superior truncal cushion, and on the left, the ventral conal cushion becomes contiguous with the inferior truncal cushion. Fusion of the conal cushion begins proximally and then progresses rapidly, completing the partition of the conal septum by the 14- to 15-mm CR-length stage in the human embryo. Conal septation reduces and then closes the small secondary interventricular foramen, which was bordered by the conal septum, the top of the muscular ventricular septum, and the right extremities of the fused endocardial cushions. The mesenchymal conal septum eventually becomes muscularized by myocardialization, resulting in the muscular outlet septum.[142]

ANOMALIES

Ventricular Septal Defect, Eisenmenger Type

A large basilar septal defect, dextroposition of the aortic valve, and a hypoplastic or absent infundibular septum probably are due to hypoplasia or absence of the conal cushions.

Ventricular Septal Defect, Supracristal Type

The supracristal type of ventricular septal defect probably is due to either simple failure of truncal and conal septal fusion or septal malalignment, which prevents fusion.

Tetralogy of Fallot

The primary anomaly in tetralogy of Fallot probably is an anterior displacement to a varying degree of the conal septum, leading to unequal partitioning of the conus and reduction of the right ventricular infundibulum. A large basilar ventricular septal defect and dextroposition of the aortic valve result from failure of the displaced conal septum to participate in closure of the interventricular foramen. Pulmonary vascular hypoplasia probably is a secondary result of diminished forward blood flow. As was mentioned above, tetralogy of Fallot frequently is associated with 22q11 deletion, particularly in the setting of severe pulmonary atresia or when associated with extracardiac anomalies.

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Chapter 9: MOLECULAR DEVELOPMENT OF THE HEART

DEVELOPMENT OF THE HEART VALVES

The Atrioventricular Valves

Initially, the tubular embryonic heart functions as a peristaltoid pump, relying on endocardial cushions to function as valves and regional variations in conduction velocity to facilitate forward flow. The endocardial cushions develop in the areas characterized by slow contraction and relaxation and, in combination with the specialized myocardium with which they are associated, serve to promote antegrade blood flow. Initially, it is possible to distinguish only two AV cushions: the inferior (iAVC) and the superior (sAVC) cushions. Fusion of these two cushions results in the formation of the two AV orifices. At later stages, the so-called lateral AV cushions appear. Over time, the cushion-derived tissues develop into the thin mature AV valve cusps.[148] The sAVC contributes to the aortic leaflet of the mitral valve, and the iAVC to the septal and posteroinferior leaflet of the tricuspid valve. The right lateral AVC contributes to the formation of the anterosuperior leaflet of the tricuspid valves, and the left lateral AVC is involved in the formation of the parietal leaflet of the mitral valve. Although the cushion-derived tissues form the main component of the leaflets (Fig. 9-12), it is important to note that an essential step in the morphogenesis of the valves is the delamination of the developing leaflets from the underlying ventricular myocardium.[149,150]

ANOMALIES

Tricuspid Valve Atresia and Mitral Valve Atresia

Tricuspid and mitral valve atresias are anomalies that probably are due to abnormal formation and/or premature fusion of the endocardial cushion tissue that borders the AV canal during or shortly after partitioning of the AV canal.

Ebstein's Anomaly of the Tricuspid Valve

Ebstein's anomaly of the tricuspid valve probably is due to an abnormality in the process of myocardial delamination required for AV valve and chordal formation.

The Arterial Valves

The primordia of the semilunar valves become visible as small tubercles on the distal extensions of each truncal cushion after truncal partitioning in the 9-mm embryo. One of each pair is assigned to the pulmonary and aortic channels, respectively. On the walls of both aortic and pulmonary channels, opposite the fused truncus cushions, a third small cushion appears.[146] These two intercalated valve cushions form the third member of each arterial valve primordium. Both the aortic and pulmonary roots, consisting of the sinuses of Valsalva and the semilunar valves, probably are derived from the truncus arteriosus and the truncal and intercalated valve cushions.

ANOMALIES

Bicuspid Arterial Valves

A bicuspid aortic or pulmonary valve is due to a failure of development of an intercalated valve cushion, resulting in a valve with two equal-size cusps, neither containing a raphe, or to fusion of adjacent valve anlagen, in which case the cusps are generally unequal in size, with the larger containing a raphe of varying length.

Arterial Valve Stenosis or Atresia

Fusion of two or all three of the arterial valve anlagen probably results in stenosis or atresia of the valve.

Absent Arterial Valves

Failure of the arterial valve anlagen to develop may explain the rare occurrence of absence of the pulmonary or aortic valve.

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Chapter 9: MOLECULAR DEVELOPMENT OF THE HEART

AORTIC ARCH DEVELOPMENT

Aortic arch development involves the sequential development and then the involution of six arch pairs. The first pair of arches in the 3-mm CR-length embryo is large when the second pair is just forming (Fig. 9-13*A*). Caudally, the dorsal aortas fuse to 0form a single vessel, and then vessel fusion progresses cranially. In a 4-mm embryo, the first and second arches have largely disappeared (Fig. 9-13*B*). The third aortic arch is well developed, and the fourth and sixth arches are being formed as ventral and dorsal sprouts of the aortic sac and dorsal aorta, respectively. The ventral portion of the sixth arch already has as its major branch the primitive pulmonary artery even though the arch itself has not yet been completed. Of note, in mammals the fifth aortic arch is rudimentary. By the 10-mm embryo stage, the first two aortic arches have regressed; the third, fourth, and sixth are present; and the truncoaortic sac has been divided by the formation of the aorticopulmonary septum so that the six arches are now continuous with the pulmonary trunk (Fig. 9-13*C*). Of note, the seventh cervical intersegmental arteries arise from the dorsal aorta near the midline and form the subclavian arteries. In a 14-mm embryo, the dorsal aortas between the third and fourth arches have disappeared and the third arches begin to elongate (Fig. 9-13*D*). At this point, the dorsal portion of the right sixth arch has disappeared, though the left sixth arch persists as the ductus arteriosus. The aortic sac has been broadened to contribute to the brachiocephalic trunk on the right and part of the definitive aortic arch up to the origin of the left third arch (common carotid artery). Finally, by the 17-mm embryo stage, the right dorsal aorta has become atrophic between its junction with the left dorsal aorta and the origin of the right seventh intersegmental artery has become attenuated and later disappears (Fig. 9-13*E*). The remaining components of the right dorsal aorta and right fourth aortic arch form the proximal subclavian artery. After birth, the distal part of the left sixth aortic arch, the ductus arteriosus, normally also involutes to form the ligamentum arteriosum. Thus, most aortic arch anomalies are secondary to abnormal retention or disappearance of various embryonic segments.

Anomalies

PATENT DUCTUS ARTERIOSUS

Persistence of the ductus arteriosus postnatally frequently occurs in permature infants as a result of delayed ductal involution. However, persistence of a large ductus arteriosus also occurs in isolation and in association with a variety of congenital cardiovascular malformations.

DOUBLE AORTIC ARCH

Double aortic arch is a result of persistence and continued patency of the segment of the right dorsal aorta between the origin of the right seventh intersegmental artery and its junction with the left dorsal aorta.

RIGHT AORTIC ARCH

In the right aortic arch anomaly, the right rather than the left dorsal aorta is maintained in its entirety. The branching pattern of the aortic arch therefore will be the mirror image of normal, with the brachiocephalic (innominate) artery arising as the first vessel on the left side rather than

the right side.

ANOMALOUS SUBCLAVIAN ARTERY

The subclavian artery can arise from the aortic arch distal to the left subclavian artery if the right dorsal aorta between the origin of the right seventh intersegmental artery and the junction with the left dorsal aorta is maintained to form the proximal portion of the right subclavian artery.[150]

INTERRUPTED AORTIC ARCH

Interrupted aortic arch anomaly type B results from the disappearance of the left fourth aortic arch (type A is a form of coarctation of the aorta) and has been shown in the mouse embryo to represent a unique population of neural crest cells.[150] The ascending aorta terminates as the brachiocephalic and left common carotid arteries and is isolated from the descending aorta, which is perfused by the pulmonary trunk by way of a patent ductus arteriosus. In the setting of an interrupted aortic arch, an anomalous right subclavian artery is frequently present because of comparable unique neural crest patterning of this vessel.[150]

ABSENT LEFT PULMONARY ARTERY

The left pulmonary artery is almost always absent in that it arises from a left-sided ductus arteriosus (or ligamentum arteriosum). This anomaly results from disappearance of the proximal left sixth arch. If in this anomaly the aortic arch is on the left side, the ductus arteriosus that feeds the intrapulmonary part of the left pulmonary artery arises from the usual position on the underside of the arch. If the aortic arch is on the right, the ductus arteriosus usually arises from the brachiocephalic trunk with the left common carotid and left subclavian arteries as a trifurcation or, rarely, from a diverticulum of the descending aorta. Usually the left subclavian artery in such cases also arises from the diverticulum.

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CORONARY ARTERY DEVELOPMENT

Endothelial Cell Origin

Coronary vascular endothelial maturation closely parallels the development of the embryonic epicardium.[151] A series of cell-fate studies has revealed that the coronary endothelial cells as well as coronary smooth muscle cells derive from the so-called proepicardium, a cluster of cells attached to the ventral wall of the sinus venosus. As cells from the proepicardium spread out and cover the surface of the heart, a subpopulation of epicardially derived cells (EPDCs) transdifferentiate and migrate into the myocardial cell layers,[152-155] where they contribute to the formation of the coronary network. A part of this network reaches the mesenchymal border of the aortic annulus.[151] Initially, multiple connections between the coronary vascular plexus and the aortic root are present; however, only two connections persist. It is interesting to note that the heart begins to pump blood before perfusion by the coronary vasculature occurs, indicating that in these early stages, local diffusion of nutrients is sufficient for the early trabecular myocardium.

Vascular Smooth Muscle Cell Origin

Antibodies to smooth muscle alpha-actin document that the maturation of coronary smooth muscle precedes the maturation of the outflow vessels.[156] Several studies have demonstrated that coronary smooth muscle is derived from the epicardially derived cells. Interestingly, the orderly development of the coronary arterial branching pattern and elastic lamina is dependent on the presence of the neural crest (NC), demonstrating that the pertubation in the development of one subpopulation of extracardiac cells (neural crest-derived cells) can lead to the abnormal development of another subpopulation (epicardially derived cells). After experimental neural crest ablation in the chick embryo, persistent truncus arteriosus associated with a single origin of the coronary arterial three occurs.[156] The distribution and symmetry of the coronary vascular are distinctly abnormal after injury to the neural crest. In addition, the elastic lamina and collagen organization of the great vessels are markedly abnormal after NC ablation, as has been noted in some congenital cardiovascular anomalies.[157]

Vasculogenesis and Adaptation

It is important to note that the maturation of the coronary vasculature, as is the case with the systemic vasculature, represents both angiogenesis (sprouting of existing vessels) and vasculogenesis (fusion of precursor cells).[158] After increased ventricular pressure loading in the chick embryo, myocardial vasculogenesis increases to match increased ventricular mass.[159] This finding is consistent with the investigation of children with pressure-overload LV hypertrophy, in whom capillary density remains unchanged.[160]

ANOMALIES

Anomalous Origin of the Left Coronary Artery

Occasionally, the left coronary artery is found to arise from the pulmonary artery, and rarely from other aortic arch vessels. The developing coronary vessels perforate the aortic annulus in

association with specific immunohistochemical markers, and so it is likely that when this patterning event is altered, anomalies occur.

Abnormal Origin and Course of Coronary Arteries

Numerous variations in the architecture and course of the coronary arteries occur in association with structural cardiovascular malformations. For example, an anomalous origin of the left anterior descending coronary artery from the right coronary artery occurs in association with tetralogy of Fallot. Unfortunately, the mechanisms for these associations have not been defined.

Coronary Arterial Fistulas

Coronary arterial fistulas occasionally occur in isolation and also occur in association with pulmonary valve atresia with an intact ventricular septum. The mechanics responsible for these anomalies are unknown.

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CONDUCTION SYSTEM DEVELOPMENT

The development of the conduction system has fascinated cardiovascular embryologists from the moment it became clear that a subpopulation of specialized myocytes is responsible for the regulation of the cardiac impulse in the heart.[161] During the last decade, several studies have revealed new aspects regarding the development of the conduction system. Immunohistochemical studies have shown that the developing conduction system in humans and other vertebrates is characterized by the expression of a unique set of antigens and genes, some of which also are expressed in the nervous system, sometimes referred to as neuromuscular markers (Fig. 9-14).[125,162,163] Retroviral cell-targeting and -tracing methods have defined subpopulations of cardiomyocytes that differentiate into Purkinje's cells within the trabecular myocardium.[125,164,165] Altered patterns of ventricular depolarization have been recognized in association with structural heart defects, such as the pattern of depolarization noted with endocardial cushion defects, and conduction abnormalities associated with atrial septum defects, as has been observed in patients with mutations in the *Nkx2.5* and *TBX5* (Holt Oram syndrome) genes.[166]

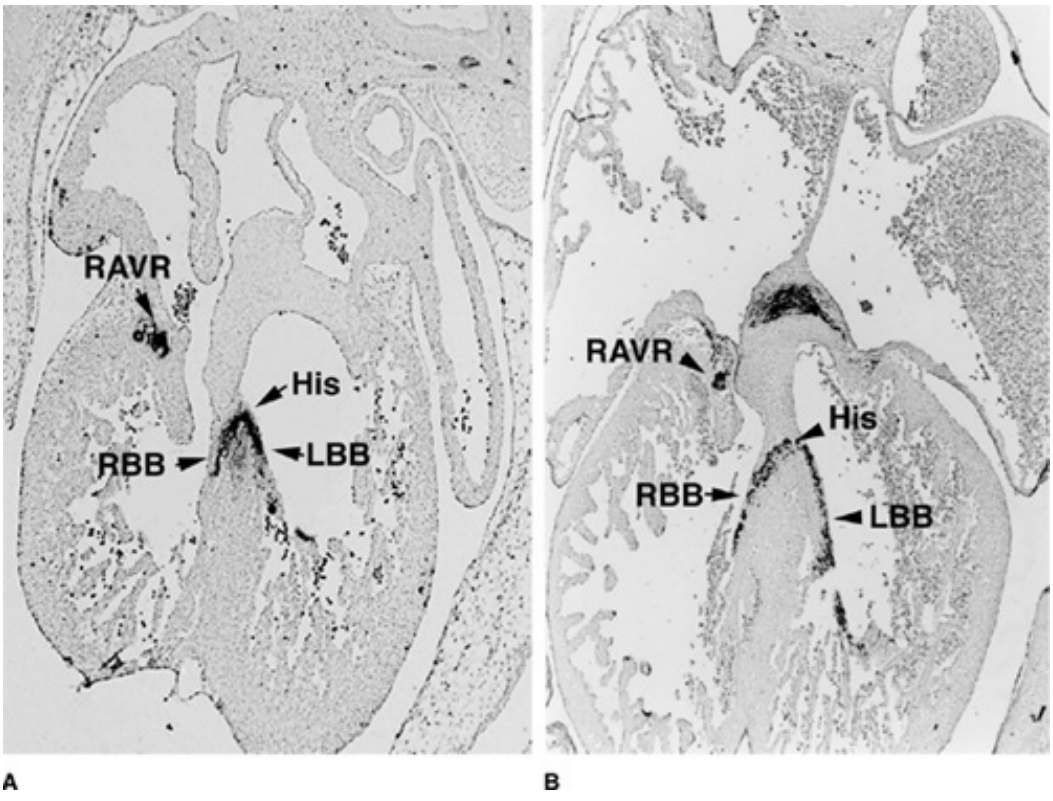

Figure 9-14: Expression of neuromuscular markers in the developing vertebrate heart. Panel *A* shows a transverse section of a human heart at 6 weeks of development immunohistochemically stained for the presence of a carbohydrate moiety recognized by the monoclonal antibody GlN2 (see also Wessels et al.[125]). The section shown in panel *B* is from a rabbit embryo at 15 days of development and is immunohistochemically stained for the presence of neurofilaments (Wessels et al.[139]). RAVR = right atrioventricular ring bundle; His = bundle of His; LBB = left bundle

branch; RBB = right bundle branch.

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CARDIOVASCULAR INNERVATION

Despite numerous descriptive studies regarding the location of cardiac ganglia, little is known regarding the immunohistochemical cues required for the patterning of myocardial innervation. NC cell migration is critical for this process, as NC cells serve as precursors for the cardiac nerves and ganglia.[85] Cardiac ganglia and nerves are present in the 7-week gestation human embryo.[167] The density of cardiac innervation exhibits a gradient of decreasing density from the atrium to the ventricle. It is interesting to note that functional adrenergic receptors are present on the embryonic heart before histologic evidence of autonomic nerves.[168] The differential appearance and distribution of peptide-containing nerves indicate that there is a maturational order to the autonomic and sensory components of the developing human heart.[167]

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FUNCTIONAL MATURATION OF THE EMBRYONIC HEART

Obviously, cardiovascular morphogenesis is influenced directly by the dynamic mechanical environment of the pulsatile embryonic heart. An overview of functional maturation, while critical, is beyond the scope of this chapter. The reader is referred to reviews of embryonic functional maturation in vertebrate and invertebrate species.[167,170]

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Figure 9-6: Schematic representation of the location of the so-called primary ring (characterized by the expression of the antigen GlN2) in different stages of human development. The drawings illustrate the development of the conduction system as a derivative of the primary ring but also show that the changes in the topography of the ring tissue reflects (1) the rightward expansion of the atrioventricular canal and (2) the leftward shift ("wedging") of the developing aorta. 1 = "primary ring"; 2 = right atrioventricular ring; 3 = atrioventricular nodal area; 4 = penetrating His bundle; 5 = crest of interventricular septum; 6 = septal branch; 7 = retroaortic branch. Areas indicated with an asterisk have lost their expression. The Carnegie stages of development presented in the drawings a to d are a = stage 14; b = stage 15; c = stage 17; d = stage 18-19. (Adapted from Wessels et al.[125])

Figure 9-7: Schematic representation of the localization of remnants of the primary ring in the neonatal human heart. The ring is projected on a superior view of the aortic mitral fibrous unit of the adult heart. The black dots indicate the areas in which remnants of the ring are detected in a series of neonatal hearts. 1 = anterolateral part of the right atrioventricular ring; 2 = posteromedial part of the right atrioventricular ring; 3 = "dead-end" tract of the conduction axis; 4 = lateral part of the retroaortic rootbranch; 5 = posterior part of the retroaortic rootbranch. AVN = atrioventricular node; AoV = semilunar valve of the aorta; LBB = left bundle branch; mi = mitral valve; PuV = semilunar valve of the pulmonary trunk; Rbb = right bundle branch; SB = septal branch; tri = tricuspid valve. (Adapted from Wessels et al.[126])

Figure 9-8: Schematic representation of myocardial trabecular development in the chick embryo. *A*. At the onset of ventricular trabeculation [around Hamburger-Hamilton (HH) stage 17], the process is limited to the primitive ventricle (V), while the inner curvature of the cardiac loop remains smooth. *B*. Transverse and frontal sections that show the distribution of secondary trabeculae (around HH stage 28). *C*. Mature tertiary trabecular pattern (HH stage 45). Only two of the principal bundles are shown in the left ventricle for clarity. In both ventricles, the trabeculae are arranged in a counterclockwise apicobasal spiral (viewed from base to apex). Differences between the right and left ventricles relate primarily to geometric differences (cone/crescent versus cylinder/prolate ellipsoid). Ct = conotruncus; At = primitive atrium. (Adapted from Sedmera et al.[144])

Figure 9-9: Posterior view of the atria and sinus venosus in embryos. *A*. 3-mm CR length; *B*. 5-mm CR length; *C*. 12-mm CR length. *D*. Newborn. Diagrammatic. A(C)CV = anterior (common) cardinal vein; AV = azygos vein; CS = coronary sinus; IVC = inferior vena cava; PCV = posterior cardinal vein; PV = pulmonary vein; SH = sinus horn; UV = umbilical vein; VM = vein of Marshall; VV = vitelline vein. (From Van Mierop LHS, Wiglesworth FW. Isomerism of the cardiac atria in the asplenia syndrome. *Lab Invest* 1962; 11:1303. Copyright by U.S. and Canadian Academy of Pathology.)

Figure 9-10: A model for the development of the atrial septal complex in the human heart. Panels *A*-*C* of this cartoon illustrate the key events in the formation of the primary atrial septum (*A*-*C*). Panel *D* schematically depicts the formation of the atrial septum and venous valves. Panel *A* represents a heart at approximately 4½ weeks of development. The AV cushions can be distinguished but have not yet fused. The leading edge of the primary septum is covered by a mesenchymal cap which is in continuity with the dorsal mesenchymal protrusion of the dorsal mesocardium. Panel *B* represents the situation at approximately 6 weeks of development. The leading edge of the primary atrial septum, covered with a mesenchymal cap, is now approaching the AV cushions, which are in the process of fusing. Within the myocardial portion of the primary septum, multiple fenestrations represent the developing secondary foramen. Completion of fusion of the mesenchymal tissues at 6 to 7 weeks of development (panel *C*) results in the closure of the primary interatrial foramen. At this time, a prominent secondary foramen can be found within the superior portion of the primary septum. The cartoon in panel *D* shows how the secondary atrial septum is formed as a result of infolding of the atrial roof. This occurs at the margin between the myocardium and the left and right atrial expression domain. The myocardium of the primary atrial septum is part of the left atrial expression domain; the

orifice of the pulmonary vein also is surrounded by myocardium with a left atrial molecular phenotype. This panel also illustrates that based on the gene expression patterns, the left venous valve develops as a myocardial structure with a right atrial molecular phenotype, whereas the right venous valve (just like the secondary atrial septum) develops by infolding, in this case of the junctional tissue between the right atrium and the sinus venosus. iAVC = inferior atrioventricular cushion; sAVC = superior atrioventricular cushion; DM = dorsal mesocardium; DMP = dorsal mesenchymal protrusion; pf = primary foramen; PS = primary atrial septum; sf = secondary foramen; LA = left atrium; RA = right atrium; OF = oval fossa; pAS = primary atrial septum; sAS = secondary atrial septum; PuV = pulmonary vein; LVV = left venous valve; RVV = right venous valve (From Wessels et al.[139])

Figure 9-11: Schematic drawing of some of the developmental events involved in the septation of the outflow tract. Panel *A* depicts the stage in which the endocardial cushion tissues in the outflow tract (conal cushions and truncal swellings) and the aorticopulmonary septum have not yet fused. Panel *B* illustrates that the truncal swellings contribute to the formation of the semilunar valves of the aorta and the pulmonary trunk, whereas the fusing conal cushions are forming the mesenchymal outlet septum. At this stage, the conal myocardium starts to myocardialize the outlet septum. Panel *C* shows one of the final stages. The aorticopulmonary septum has now completely separated the aorta and pulmonary trunk above the level of the semilunar valves, while below the valves the outlet septum divides the outlet segment of the heart in a subaortic and subpulmonary outlet.

Figure 9-12: Schematic drawings of the formation of the atrioventricular junction in the human heart. *A*. The situation at the atrioventricular junction at 4 to 5 weeks of development. Myocardial continuity between atrium and ventricle occurs through the myocardium of the atrioventricular canal. The AV junction is sandwiched between the tissues of the AV sulcus at the epicardial side and the AV cushion at the endocardial side. *B*. With progressive remodeling of the AV junction, the sulcus tissues expand toward the midline of the AV canal as the cushion tissue remodels. *C*. With completion of this process, continuity is lost between atrial and ventricular myocardium. A = atrium; V = ventricle; ST = sulcus tissue; AV = myocardium of the atrioventricular canal; CT = cushion tissue. (Adapted from Wessels et al.[148])

Figure 9-13: Development of the aortic arch system. Embryos of (*A*) 3 mm, (*B*) 4 mm, (*C*) 10 mm, (*D*) 14 mm, (*E*) 17 mm, (*F*) neonate. (Adapted from Congdon ED. Transformation of the aortic arch system during the development of the human embryo. *Contrib Embryol* 1922; 14:47.)

Figure 9-14: Expression of neuromuscular markers in the developing vertebrate heart. Panel *A* shows a transverse section of a human heart at 6 weeks of development immunohistochemically stained for the presence of a carbohydrate moiety recognized by the monoclonal antibody GlN2 (see also Wessels et al.[125]). The section shown in panel *B* is from a rabbit embryo at 15 days of development and is immunohistochemically stained for the presence of neurofilaments (Wessels et al.[139]). RAVR = right atrioventricular ring bundle; His = bundle of His; LBB = left bundle branch; RBB = right bundle branch.

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 10:

THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

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In the assessment of patients with definite or suspected heart disease, relevant information can be acquired from the history, physical examination, chest roentgenogram, electrocardiogram, and other routine laboratory tests. These data, when integrated properly, result in an accurate diagnosis and appropriate decisions regarding therapy in many patients. In other patients, more information is necessary, and additional, more technical, and usually more expensive noninvasive cardiac tests such as echocardiography or radionuclide studies are needed. In some patients, the general assessment indicates the need for cardiac catheterization and contrast angiography, with or without additional noninvasive cardiac testing. For example, the proper approach to certain patients with symptomatic coronary artery disease may include both coronary arteriography and cardiac catheterization (anatomy and hemodynamics), as well as myocardial perfusion imaging with thallium or technetium sestamibi (extent of inducible ischemia).

Not all patients need every test, and the skillful use of low-technology approaches, including the history and general examination, may preclude the need for additional studies or may determine which of a wide variety of available sophisticated tests should be chosen for a particular patient. This chapter is divided into three sections. The first section concerns the proper application of the history and its use to delineate the differential diagnosis in patients who present with certain common cardiovascular symptoms. The second section details the essential components of the *physical examination* and their usefulness in establishing a likely diagnosis when specific abnormal findings are detected. Finally, the third section focuses on cardiac auscultation.

THE HISTORY

Elements of Accurate History Taking

A carefully obtained history is the cornerstone in the evaluation of a patient with known or suspected cardiac disease.[1,2] A deliberate, compassionate interview forms the basis for a patient-physician relationship that may continue for days, months, or years. Unfortunately, the interview may result in adversary roles for physician and patient if the interviewer appears hurried, demands exact answers, shows impatience, insists on exploring areas that are uncomfortable to the patient, fails to establish eye contact, accepts multiple interruptions during the discussion, seems to treat dreaded diseases casually, gives nonverbal signs of personal unhappiness, or appears to be unsympathetic.[2] When the medical interview is unsatisfactory due to poor communication and lack of rapport, inaccurate information often will be obtained.[2] Also, important facts not revealed during a meticulous initial history usually are not detected later as workup progresses and the patient and physician become focused on high-technology studies and more aggressive therapeutic interventions.[1]

The patient's chief complaint, which requires further elaboration and investigation, may not identify the patient's most serious problem. Symptoms other than the patient's chief complaint must be defined.[2] Rather than focusing entirely on the patient's present illness, the interviewer should note all existing symptoms and establish a present illness for each of these.[2]

A medical questionnaire given to the patient well in advance of the interview is useful. The patient can then record important data more accurately because of the time available for reflection and the checking of details.[2] Any abnormalities indicated on the questionnaire must be defined more completely during the interview, and related areas should be discussed.[2]

A proper interpretation of the past history is important, and the physician should not accept a past event as a fact when the evidence is not well established. Knowledge obtained from family members about the patient's symptoms and his or her response to the illness is extremely important.[2]

Importantly, serious heart disease can occur in patients with mild or no symptoms. Also, knowing the sensitivity, specificity, and predictive value of an answer to a question and of the presence or absence of a physical sign provides the physician with a better perspective. The physician must determine whether or not the history obtained is sufficient to support a decision-making process about the patient.[2] While many patients with severe heart disease have no symptoms, others have many symptoms associated with minor or no disease.

Some patients deny the presence of symptoms because they cannot accept the reality of the situation, whereas others may purposefully withhold information because they may lose their jobs if the truth were revealed.[2] Still other patients may overstate their symptoms for personal gain. Elderly patients, sedentary patients, and patients whose physical activity is limited by another illness may have no symptoms because they do not perform adequate physical effort to produce them.[2]

Past and Family History

The past history may provide important clues to the presence of cardiovascular disease. A definite history of rheumatic fever may be useful in defining the cause of a heart murmur, whereas a negative history of rheumatic fever does not exclude it.[2] A history of hypertension in a family member increases the likelihood that the patient has essential hypertension.[2] Previous trauma may be the cause of constrictive pericarditis, a thoracic aortic aneurysm, an arteriovenous fistula, and other types of cardiac lesions. A detailed history of the use of medications, addicting drugs, and alcohol, each of which may cause heart disease, is essential. A past history of pulmonary embolism, thrombophlebitis, or systemic embolism should be ascertained.

A history of dental work, some other diagnostic or therapeutic procedure, or recent infection suggests the possibility of infective endocarditis in a patient with valvular heart disease. Patients often give a history of having had a "heart attack," which, in fact, may have been an episode of unstable angina, heart failure, or arrhythmia. The "heart attack" history often becomes "myocardial infarction" in the patient's medical record unless more information about the episode is obtained or documentation of the event is reviewed.[1]

Many patients are referred who have had several catheterizations, percutaneous coronary interventions, angioplasties, and one or more coronary bypass operations in addition to multiple noninvasive tests. A thorough and often time-consuming review of records from other institutions, operative notes, cineangiographic films, and noninvasive studies often will provide an accurate assessment of the patient's current status without the unnecessary repetition of expensive and potentially risky procedures.[1]

Past and present therapeutic regimens must be reviewed carefully. Various treatment programs may have been inappropriate or suboptimal. The drugs currently used for the treatment of cardiovascular diseases have a larger number of potential side effects that can result in both cardiovascular and noncardiovascular symptoms (see Chap. 81).

Multiple risk factors for developing coronary artery disease (CAD) have been identified, including age, male sex, hypertension, hypercholesterolemia, low high-density lipoprotein (HDL) cholesterol, cigarette smoking, diabetes, and a family history of premature atherosclerosis (see Chap. 38). The presence or absence of risk factors can increase or decrease the statistical likelihood that an individual patient has CHD.

Patients should be questioned about previous health evaluations. In addition to being examined at the time of routine physicals or in association with other medical treatment, patients often have been examined for the military service, for athletics, or for insurance, and they may have been told of a heart murmur or hypertension on those occasions.[2] Rejection by the military or an insurance company is often due to a cardiovascular abnormality. Many patients have not seen a physician in the recent past or ever had a careful examination of the cardiovascular system.

The increasing hemodynamic burden of pregnancy may cause an otherwise marginally compensated

cardiac patient to become symptomatic. Specific inquiry should be made about heart failure, edema, dyspnea, or prescribed prolonged periods of bed rest during pregnancy.[1] Many normal women have had a murmur detected during pregnancy (see Chap. 82). A history of illicit parenteral drug use should raise the suspicion of infective endocarditis, especially in a febrile patient (see Chap. 73). Cocaine can cause coronary artery vasospasm and also raise myocardial oxygen demand by increasing heart rate and blood pressure. Angina, myocardial infarction, and sudden cardiac death have been well documented after cocaine use (see Chap. 71).

A history of moderate to excessive alcohol consumption, an enlarged heart on prior chest roentgenogram, periods of rapid weight gain or loss, and other illnesses may provide important information, as may questions concerning prior diagnoses made by the patient or by medical personnel.[1]

A family history of congenital heart disease indicates a higher risk of a congenital heart lesion (see Chap. 63). The patient's mother may give a history of rubella during the first few months of pregnancy; this increases the likelihood that the patient has patent ductus arteriosus, pulmonic valve stenosis, coarctation of the pulmonary arteries, or atrial septal defect.

Although most of the common cardiovascular diseases are sporadic, there are several examples in which genetic transmission can occur (see Chap. 62). These include mitral valve prolapse and the hypertrophic or dilated cardiomyopathies. Other genetically determined disorders include some of the inborn errors of metabolism, muscular dystrophies, Ehlers-Danlos syndrome, Marfan's syndrome, and the long Q-T syndromes with or without deafness (see Chaps. 62 and 63).

Symptoms Associated with Cardiovascular Disease

CHEST PAIN

Chest pain or chest discomfort is the foremost manifestation of myocardial ischemia and results from a disparity between myocardial oxygen demand and coronary blood flow in patients with CAD.[3] The most common causes of myocardial ischemia are coronary atherosclerosis, coronary vasoconstriction, and coronary artery thrombosis, the latter occurring particularly in patients with acute coronary syndromes such as acute myocardial infarction and unstable angina (see Chaps. 41 and 42). An increase in myocardial oxygen demand ($MV(r)O_2$) or demand ischemia, a decrease in or inadequate blood flow (supply ischemia), or their combination may be responsible for anginal chest pain (see Chap. 40).

The mechanism responsible for cardiac pain is not clearly understood. Nonmedullated small sympathetic nerve fibers that parallel the coronary arteries are thought to provide the afferent sensory pathway for angina; these enter the spinal cord in the C8-T4 segments.[4] Impulses are transmitted to corresponding spinal ganglia and then through the spinal cord to the thalamus and cerebral cortex. Angina pectoris, like other pain of visceral origin, is often poorly localized and is commonly referred to the corresponding segmental dermatomes.

The differential diagnosis of chest pain is extensive.[5] In addition to angina pectoris and myocardial infarction, other cardiovascular diseases, gastrointestinal diseases, psychogenic diseases, neuromuscular diseases, and diseases of the pulmonary system must be considered (Table 10-1; see also Table 40-6). An accurate interpretation of the etiology and significance of chest discomfort is critically dependent on a carefully taken history. Important clinically relevant information may be missed if the *overenthusiastic use of noninvasive or invasive diagnostic methods* replaces rather than augments direct physician-patient communication (see Chap. 40).

Table 10-1: Differential Diagnosis of Chest Pain

1. Angina pectoris/myocardial infarction
2. Other cardiovascular causes
    a. Likely ischemic in origin
        (1) Aortic stenosis
        (2) Hypertrophic cardiomyopathy
        (3) Severe systemic hypertension
        (4) Severe right ventricular hypertension
        (5) Aortic regurgitation
        (6) Severe anemia/hypoxia
    b. Nonischemic in origin
        (1) Aortic dissection
        (2) Pericarditis
        (3) Mitral valve prolapse
3. Gastrointestinal
    a. Esophageal spasm
    b. Esophageal reflux
    c. Esophageal rupture
    d. Peptic ulcer disease
4. Psychogenic
    a. Anxiety
    b. Depression
    c. Cardiac psychosis
    d. Self-gain
5. Neuromusculoskeletal
    a. Thoracic outlet syndrome
    b. Degenerative joint disease of cervical/thoracic spine
    c. Costochondritis (Tietze's syndrome)
    d. Herpes zoster
    e. Chest wall pain and tenderness
6. Pulmonary
    a. Pulmonary embolus with or without pulmonary infarction
    b. Pneumothorax

c. Pneumonia with pleural involvement
7. Pleurisy

The original subjective description of angina pectoris by William Heberden[6] in the late eighteenth century has not been surpassed. It is quoted in Chap. 40.

Angina pectoris is defined as chest pain or discomfort of cardiac origin that usually results from a temporary imbalance between myocardial oxygen supply and demand. It may occur only with exertion or spontaneously at rest; various subtypes are defined in Chap. 40. The quality of the chest discomfort is usually described as "tightness," "pressure," "burning," "heaviness," "aching," "strangling," or "compression." Usually the patient is able to describe a deep rather than a superficial origin of the pain. Since the qualitative description of the pain is greatly influenced by the patient's intelligence, education, and social/cultural background, a definition of other characteristics of the chest discomfort is often extremely important in evaluating the symptoms appropriately. The most important of these characteristics are the *precipitating factors* for the onset of pain, its *mode of onset and duration*, its *pattern of disappearance*, and its *location*. Classically, the discomfort is induced by exercise, emotion, eating, or cold weather.

A recognizable pattern of reproducibility of chest pain by certain activities is an important characteristic of angina. Often, patients develop pain with exertion after meals, and there is a greater tendency for arm work, which involves a greater element of isometric exercise than isotonic leg exercise, to produce distress.[7-9] Occasionally, angina will dissipate despite continued exercise (the walk-through phenomenon) or will not occur when a second exercise effort is undertaken that previously produced chest discomfort (warm-up phenomenon).

Both circumstances may be attributed to the opening of functioning coronary arterial collaterals during the initial myocardial ischemia. Angina commonly occurs after the patient has eaten a heavy meal or when the patient is excited, angry, or tense. Cold showers increase blood pressure and heart rate, whereas hot showers cause an augmented cardiac output in response to vasodilation. Either may precipitate angina after exercise. The chest pain during any type of activity is often made worse by the use of tobacco. All the hemodynamic changes resulting from the use of nicotine increase the myocardial oxygen demand.

Angina pectoris characteristically has a crescendo pattern at onset and "builds up." Pains, often described as "shooting" or "stabbing," that reach their maximum intensity virtually instantaneously are often not angina but are of musculoskeletal or neural origin. Angina is usually relieved within 5 to 20 min by rest, with or without the use of vasodilator drugs such as nitroglycerin, although nitroglycerin characteristically hastens relief. Failure to obtain relief with rest or nitroglycerin suggests another cause of pain or actual impending myocardial infarction. The reproducible relief of chest pain in an appropriate time frame (within 10 min) can be strong evidence favoring ischemia. A trial of nitroglycerin can be a useful diagnostic strategy. Patients with angina pectoris usually are classified functionally from class I to class IV (Table 10-2), depending on the amount of activity necessary to induce chest pain.[10]

Table 10-2: Canadian Cardiovascular Society Functional Classification of Angina Pectoris

I.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina results from strenuous or rapid or prolonged exertion at work or recreation.
II.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and under normal conditions.
III.	Marked limitations of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight under normal conditions.
IV.	Inability to carry on any physical activity without discomfort-anginal syndrome may be present at rest.

SOURCE: Modified from Campeau L. Letter to the editor. *Circulation* 1976; 54:522. Reproduced with permission from the American Heart Association, Inc., and the author.

Localizing the site of chest discomfort provides additional information in determining its cause. Anginal pain is ordinarily retrosternal or felt slightly to left of the midline, beside or partly under the sternum. It is rarely isolated to the cardiac apex in the inframammary region. The chest pain of myocardial ischemia tends to radiate bilaterally across the chest into the arms (left more than right) and into the neck and lower jaw. Occasionally, radiation to the back or occiput is noted. In the arms, the pain passes down the ulnar and volar surface to the wrist and then only into the ulnar fingers, rarely into the thumb or down the outer (extensor) surface of the arm, which has a different dermatome pattern. Pain occasionally may be felt only in the arm or may start in the arm and radiate to the chest. Attention to the gestures that the patient uses in characterizing and localizing the site of pain may be useful in determining its etiology. One or two clenched fists held by the patient over the sternal area (Levine's sign) is much more indicative of ischemic pain than is a finger pointed to a small, circumscribed area in the left inframammary region. The latter more likely represents chest pain of psychogenic origin.

As indicated earlier, the *duration* of chest pain also may be a useful differentiating feature. Angina pectoris rarely lasts less than 1 min or more than 20 min in the absence of myocardial infarction or persistent arrhythmias. Most patients with angina report prompt relief in less than 5 min after cessation of activity or with the use of sublingual nitroglycerin. Delayed relief of chest pain by sublingual nitroglycerin may be ascribed to a placebo effect. Since nitrates are generalized smooth muscle relaxants, pain due to diffuse esophageal spasm or biliary colic also may be relieved by these same agents. Carotid sinus massage by the physician frequently will relieve anginal chest pain because of the resulting reflex bradycardia and the decrease in systolic blood pressure, thus reducing myocardial oxygen demand.[11] Carotid sinus massage should be performed only in the absence of extracranial occlusive cerebrovascular disease as manifest by carotid bruits or decreased carotid arterial pulsations and with careful auscultatory monitoring of the heart rate. The Valsalva maneuver also may relieve anginal pain by decreasing myocardial wall tension as a result of the reduced venous return and left ventricular volume accompanying the increase in intrathoracic pressure. *Associated symptoms*-such as nausea, vomiting, faintness, fatigue, or diaphoresis-often accompany severe episodes of myocardial ischemia in both men and women.[12] Severe myocardial ischemia often produces marked dyspnea due to a large increase in left ventricular (LV) diastolic filling pressure, sometimes producing an "angina equivalent" in the absence of chest discomfort.

Linked angina is a term applied to definite episodes of angina in patients with established CAD caused by gastrointestinal factors not related to an increase in cardiac work.[13] Episodes typically are induced by stooping or occur after eating; they can be mimicked by esophageal acid stimulation, which can reduce coronary blood flow (CBF).[13]

No consideration of myocardial ischemia as a likely cause of chest discomfort is complete without carefully considering the chest pain in the context of known risk factors for CAD (see above).

Angina pectoris should be considered a symptom and not a specific disease. Coronary arteriographic

studies have demonstrated that more than 90 percent of patients with chest pain precipitated by exercise and relieved by rest have angiographic evidence of significant CAD. However, other diseases may be associated with classic angina pectoris (see below).

Several reports have described certain patients with typical exertional chest discomfort and arteriographically normal coronary arteries.[14,15] These patients are more likely to be females, have fewer coronary risk factors, have variable responses to various antianginal agents, and less commonly, have more relief of pain by sublingual nitroglycerin than patients with occlusive CAD. Although the underlying cause of this condition remains unsettled, the life expectancy of these patients appears no different from that of an age- and sex-matched population without chest discomfort (see Chap. 40).

There is some evidence that abnormal function of small coronary arteries may cause limited CBF responses to stress or pharmacologic vasodilators in a subset of patients with anginal chest pain despite angiographically normal coronary arteries (*microvascular angina*).[16-22] In the past, investigators arguing for or against the existence of this syndrome often have used the term *syndrome X* to describe their patient cohort.[23] Syndrome X appears to include a heterogeneous group of patients with a wide spectrum of chest pain and a variety of vascular and smooth muscle hypersensitive constrictor responses. Multiple research studies continue in an effort to explain syndrome X.[24-30] It should be distinguished from the *metabolic syndrome X* of insulin resistance (glucose intolerance), hypertension, hyperlipidemia, and upper body obesity (see Chaps. 40 and 78).

Some patients with CAD experience angina at rest as a complication or an isolated clinical manifestation of ischemic heart disease.[11] Myocardial ischemic pain at rest more likely results from an acute reduction in CBF than from an increase in $MV(r)O_2$. Possible causative factors include isolated coronary artery spasm or embolism, coronary artery spasm superimposed on coronary atherosclerosis, and coronary thrombosis with spontaneous thrombolysis.[31-34] In patients with progressive coronary atherosclerosis, however, ischemic rest pain also may result from intermittent arrhythmias that increase $MV(r)O_2$ or decrease CBF or from labile hypertension with its increased wall stress. Chest pain at rest may occur only as nocturnal angina. In addition to the preceding mechanisms, nocturnal angina, also known as *angina decubitus*, may be produced by the increase in wall stress and thus $MV(r)O_2$ secondary to redistribution of the intravascular blood volume in the recumbent position.

The relative hypercapnia and acidosis that occur during sleep also may contribute to nocturnal angina. This condition also has been accompanied by concomitant rapid eye movement sleep patterns on the electroencephalogram, which may be associated with augmented sympathetic discharge increasing $MV(r)O_2$ or causing coronary constriction[8-11] (see Chap. 40).

Despite the more malignant natural history observed in many patients with rest angina, particularly associated with ST-T-wave changes, the predictive value of the history alone is not as accurate as with exertional angina. The quality of pain is usually similar to that of exertional angina, but the discomfort may be more severe and its duration longer. In addition, angina at rest is commonly associated with nausea, vomiting, and diaphoresis. The onset of shortness of breath during or after the beginning of chest discomfort suggests that the pain is due to extensive myocardial ischemia and usually results from an acute elevation of LV filling pressure secondary to the development of a large, transiently ischemic myocardial segment. Such patients are commonly found to have multivessel occlusive CAD on arteriography.

Chest pain or discomfort resulting from *myocardial infarction* (MI) is qualitatively similar to angina at rest. Differentiation between the pain resulting from ischemia and that due to MI is usually impossible based on the history alone.[7-9] Pain associated with transmural Q-wave MI is usually more severe and longer lasting than anginal pain and is often associated with nausea, vomiting, and diaphoresis. In addition, MI is frequently accompanied by symptoms of sustained LV dysfunction (dyspnea, orthopnea) and evidence of autonomic nervous system hyperactivity (tachycardia, diaphoresis, bradycardia).[7-9] Painless or atypical presentations of MI, however, occur in up to 30 percent of patients, particularly in diabetic patients and the elderly. Thus determination of serial serum enzymes, isoenzymes, and other serum markers (e.g., troponin I), providing evidence of myocardial necrosis, and serial electrocardiograms (ECGs), indicating myocardial

injury, are necessary to establish the diagnosis in most patients (see Chaps. 42 and 43).

There are two groups of *cardiovascular diseases causing chest pain that is not due to coronary atherosclerosis* (see Table 10-1). The first group consists of cardiac diseases causing myocardial ischemia-related angina in the absence of CAD; ischemia is due to hemodynamic changes associated with an inadequate CBF in relation to a normal or increased myocardial oxygen demand. Among these are *aortic valve stenosis* (see Chap. 56), *hypertrophic cardiomyopathy* (see Chap. 67), and *systemic arterial hypertension* (see Chap. 51), in which LV systolic pressure and LV wall tension are greatly increased or LV hypertrophy is present.[7-9] Chest pain due to myocardial ischemia also can occur with severe aortic regurgitation (see Chap. 56). The large ventricular volume load and increased ventricular dimensions result in increased $MV(r)O_2$, and the reduced diastolic perfusion pressure of the coronary arteries results in a relatively inadequate CBF. Occasionally, very severe anemia or hypoxia also may produce myocardial ischemia by an inadequate oxygen blood supply even in the absence of associated CAD as well as increases in angina in the presence of obstructive coronary artery disease.[7-9] In addition, severe right ventricular (RV) systolic hypertension, as often occurs with pulmonic stenosis or pulmonary hypertension, may cause exertional angina, presumably on the basis of RV subendocardial ischemia.[35]

A second group of cardiac diseases causing chest pain that is not usually due to myocardial ischemia includes *pericarditis* (see Chap. 72), aortic dissection (see Chap. 88), and mitral valve prolapse (see Chap. 58). Pericarditis is a relatively common cause of chest pain.[36] The chest pain of pericarditis is most often sharp and penetrating in quality, and patients often obtain relief by sitting up and bending forward (see Chap. 72). The cardinal diagnostic feature of pericardial pain is its frequent worsening by changes in body position, during deep inspiration, and occasionally, on swallowing. The chest discomfort may radiate to the shoulders, upper back, and neck because of irritation of the diaphragmatic pleura, which is innervated through the phrenic nerve by fibers originating in cervical sympathetic ganglia C3-C5. Therefore, the chest discomfort associated with pericarditis is due predominantly to parietal pleural irritation. Occasionally, the pain of acute benign, presumptive viral pericarditis may mimic that observed in acute MI. Importantly, the most common cause of pericarditis in middle-aged or older people is acute MI. The pericarditis usually occurs several days after the myocardial necrosis and must be distinguished from recurrent infarction or ischemia. Pericarditis also may be a cause of chest pain after cardiac surgery and may be a complication of aortic dissection, with leakage into the pericardium.

Aortic dissection (see Chap. 88) may be misdiagnosed on initial presentation as an acute MI; indeed, MI is a recognized complication of aortic dissection. The pain with dissection, however, is usually of sudden onset as compared with the pain of myocardial ischemia, which builds in intensity with time.[37] Patients frequently characterize the pain as excruciating, the most severe discomfort that they have ever experienced, and as having a tearing quality, commonly localized to the interscapular area. The discomfort may radiate widely into the neck, back, abdomen, flanks, and legs and may migrate, depending on the location and progression of the aortic dissection and the amount of arterial luminal compression. Neurologic symptoms and signs may occur when dissection involves the cerebral arteries. With the exception of patients with Marfan's syndrome (see Chaps. 66 and 76) or idiopathic cystic medial necrosis, most patients with aortic dissection have a history of long-standing systemic arterial hypertension or evidence of it on physical examination.

Psychogenic chest discomfort is a common type of recurrent chest pain that may be difficult to separate from angina pectoris, particularly when it occurs in patients with multiple risk factors for CAD or in otherwise asymptomatic patients with well-documented CAD. The most common psychogenic cause of chest discomfort is anxiety[38] (see Chap. 80). Psychogenic chest pain is often described as sharp or stabbing, is commonly localized to the left inframammary area, and is usually sharply circumscribed. Descriptors such as "stabbing" or "lightning-like" may be used to describe extremely short (<1 min) episodes of pain. At times, the pain may persist for many hours or several days. Patients often note psychogenic pain at rest. Also, nonvocal communication, such as a flat or worried facial expression, retarded motor activity, and hand wringing, may indicate underlying depression. Observation of the patient during pain that occurs spontaneously or during exercise testing often provides insight into a potential psychogenic etiology. Patients with anxiety often have multiple complaints such as breathlessness, giddiness, and palpitations. Associated symptoms, such as air hunger, circumoral paresthesias, globus hystericus, and multiple somatic

complaints, may suggest a neurasthenic personality or hyperventilation syndrome.

Pain originating in the gastrointestinal tract, particularly that of esophageal origin, is commonly confused with ischemic chest pain.[39] Diffuse esophageal spasm, a neuromuscular motor disorder of the esophagus characterized by chest pain, is the extracardiac condition most frequently confused with angina pectoris. Esophageal spasm may occur at any age but is more common in individuals in the fifth decade. The pain is usually retrosternal; may be burning, squeezing, or aching in quality; and often radiates to the back, arms, and jaw. It usually begins during or after a meal and can last minutes or hours. In some patients, the pain may be precipitated or exacerbated by exercise, and relief may be obtained with nitroglycerin, which also relaxes esophageal smooth muscle. A useful feature in the differentiation of diffuse esophageal spasm from ischemic chest discomfort is its frequent association with pain as a result of swallowing, dysphagia, and the regurgitation of gastric contents. Episodes of pain frequently are precipitated either by extremely hot or cold drinks or by an emotional upset. The diagnosis of diffuse esophageal spasm is based on the history, the exclusion of cardiac and musculoskeletal causes of chest pain, and the demonstration of abnormal esophageal motility on cineesophagograms or by esophageal manometry.

Reflux esophagitis results from mucosal irritation produced by failure of the lower esophageal sphincter to prevent regurgitation of highly acidic gastric contents into the distal esophagus.[40-42] The pain is usually epigastric or retrosternal, burning in quality, and frequently precipitated by the recumbent position or by bending over. "Heartburn" and regurgitation often occur after meals or ingestion of coffee or after postural changes. Patients are often awakened by chest discomfort due to acid reflux occurring in the recumbent position. Many of these patients are obese and report relief of discomfort from food, antacids, or elevation of the head of the bed. Dysphagia may result from stricture formation secondary to long-standing esophageal reflux. An upper gastrointestinal series may demonstrate hiatal hernia, but this does not establish the diagnosis of esophagitis or esophageal reflux. Esophagoscopy and esophageal biopsy may demonstrate mucosal lesions and are useful for assessing the severity of inflammation and for excluding malignancy. Sphincter incompetence may be documented by the use of esophageal manometry. Esophageal acid perfusion testing (Bernstein test) often will provoke the patient's characteristic symptoms, and distal esophageal pH monitoring will detect gastroesophageal reflux.[41]

Acute esophageal rupture, a serious and often rapidly lethal event, causes severe retrosternal pain secondary to the chemical mediastinitis produced by acidic gastric contents.[7-9] Spontaneous rupture usually results from a prolonged bout of vomiting or retching after a heavy meal. Rupture is a recognized iatrogenic complication of esophageal instrumentation. The pain varies in location depending on the rupture's site and position. The diagnosis is based on symptoms and signs of mediastinal air following vomiting or esophageal instrumentation.

Although peptic ulcer disease and biliary colic are less commonly confused with chest pain of cardiac origin, myocardial ischemic pain occasionally may be described as burning in character and located near the epigastrium.

Diseases involving the neuromuscular-skeletal systems may cause pain affecting dermatome patterns similar to those occurring with angina pectoris.[7-9] The thoracic outlet syndromes, in which various neural and vascular structures are compressed, may produce symptoms that are sometimes confused with cardiac chest pain. Although compression of the neurovascular bundle by a cervical rib or the scalenus anterior muscle may cause discomfort radiating to the head and neck, the shoulder region, or the axilla, most patients experience pain in the upper extremity resulting from somatic nerve compression, usually in the distribution of the ulnar nerve.[8-11] The presence of associated paresthesias, the presence of pain unrelated to physical exercise, the worsening of discomfort, and its aggravation by certain body positions are useful differentiating characteristics. The diagnosis of thoracic outlet syndrome can be confirmed in many patients by careful physical and neurologic examination.

Tietze's syndrome, or idiopathic costochondritis, is an occasional cause of anterior chest wall pain that is aggravated by movement and deep breathing. The reproduction of the chest pain syndrome by direct pressure over the involved costochondral junction or the relief of pain after local infiltration with lidocaine is a helpful diagnostic maneuver.[43] Degenerative arthritis of the cervical and thoracic vertebrae may cause bandlike pain confined to the chest, neck, or back that often radiates to the arms.[7-9] Radiologic evidence of degenerative changes involving the cervical and thoracic vertebrae is often found in asymptomatic elderly

patients. The production or exacerbation of pain by various postures, movement, sneezing, or coughing is more useful in the diagnosis of chest discomfort due to vertebral disease.[7-9]

The *preeruptive stage of herpes zoster* may be characterized by bandlike chest pain over one or more dermatomes. The advanced age of the patient, additional symptoms of malaise, headache and fever, the presence of hyperesthesia of the involved area on physical examination, and the eventual eruption of typical lesions 4 or 5 days after the onset of symptoms will result in the correct diagnosis. Chest wall pain and tenderness may occur for unknown reasons.[44] The discomfort may be reproduced by pressure over the painful area and by movements of the thorax such as bending, twisting, or turning. The variable duration of the pain and the absence of relief by nitroglycerin distinguish it from angina.

The syndrome of acute massive *pulmonary embolism* with its associated acute pulmonary hypertension and low cardiac output occasionally may simulate acute MI, since myocardial ischemia may be present in both conditions. The quality of chest pain may be identical to that observed in patients with nonradiating ischemic chest pain or may be pleuritic, as described below. The associated signs of severe dyspnea, tachypnea, and intense cyanosis, accompanied by profound anxiety and agitation, however, favor the diagnosis of pulmonary embolism[8-11] (see Chap. 54). The clinical setting may suggest the diagnosis because of the known increased likelihood of pulmonary embolism in the postpartum or postoperative state, during long trips, in patients with congestive heart failure and peripheral edema, and in those with deep-vein thrombophlebitis. Measurements of arterial blood gases, abnormal pulmonary perfusion-ventilation scans, and if needed, pulmonary arteriography will establish the correct diagnosis.[7-9]

Other pulmonary conditions associated with chest discomfort, such as pneumothorax, are rarely confused with ischemic chest pain because of additional characteristic clinical features. Spontaneous pneumothorax usually occurs in otherwise healthy males in the third and fourth decades. The clinical presentation is usually characterized by the abrupt onset of agonizing unilateral pleuritic chest pain associated with severe shortness of breath. The plain or expiratory chest film provides the definitive diagnosis. Chest pain associated with pneumonias of various etiologies, as well as pulmonary infarctions as a consequence of pulmonary embolus, may result from pleural irritation. The discomfort is sharp, varies acutely with breathing, and frequently is accompanied by a reduced inspiratory effort. Associated signs of pulmonary parenchymal infection or infarction usually indicate the underlying diagnosis.

EXTRATHORACIC PAIN

Intermittent claudication of the lower extremities due to peripheral atherosclerosis (see Chap. 90) may present as discomfort during exercise in the arch of the foot, calf of the leg, thighs, hips, or gluteal region.[7-9] Acute arterial occlusion in the lower extremities due to systemic embolism may cause the sensation of hypesthesia.[2] Intermittent claudication of the upper extremities or masseter muscles is usually due to nonatherosclerotic causes of arterial disease, such as arteritis.[2] The pain of Raynaud's disease may be noted in the fingers after exposure to cold, with pallor of the fingers prior to the sensation of pain. Pain and swelling of lower extremities may be caused by thrombophlebitis (see Chap. 90).

Head pain secondary to myocardial ischemia may be felt in the jaw, hard palate, cheek, and sometimes deep in the ear canals. The pain of temporal arteritis, commonly localized to the temporal area, often is associated with abnormal vision and polymyalgia rheumatica.[76] Migraine headache, frequently accompanied by nausea, scotoma, and intolerance to light, is vascular in origin and may be incapacitating.[2] A severe headache may be present in patients with uncontrolled hypertension (see Chap. 51).

Pain in the abdomen, often localized to the midabdomen and lower portion of the back, may be produced by an expanding or rupturing atherosclerotic abdominal aneurysm. Abdominal angina due to vascular disease of the mesenteric arteries is discussed in Chap. 88. The liver is often painful and tender in severe right-sided heart failure, with worsening of the pain during activity.[2]

Various types of *joint pain* may be associated with heart disease. Rheumatic fever, rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, gonococcal arthritis, Reiter's syndrome, and Lyme disease may be associated with valvular, myocardial, or pericardial disease.[2]

RESPIRATORY SYMPTOMS

Dyspnea is defined as difficult or labored respiration or the unpleasant awareness of one's respiration. It has many causes. A clue to the etiology is obtained from the factors that precipitate or relieve it.[1] Chronic dyspnea can be caused by heart failure, pulmonary disease, anxiety, obesity, poor physical fitness, pleural effusions, and asthma.[2] Acute dyspnea may occur with acute pulmonary edema, hyperventilation, pneumothorax, pulmonary embolism, pneumonia, and airway obstruction.[2]

Dyspnea on effort, a frequent symptom, is usually due to congestive heart failure, chronic pulmonary disease, or physical deconditioning (see Chap. 20). The amount of activity necessary to produce dyspnea needs definition. A recent or dramatic increase in the dyspnea is more likely to be due to the development of heart failure than to lung disease. When heart and lung disease coexist, however, the determination of the relative contribution of pulmonary and cardiac dysfunction to dyspnea can be very difficult.

Cheyne-Stokes respiration is a form of periodic breathing characterized by cycles beginning with shallow respirations that increase in rate and depth to significant hyperpnea, followed by decreasing rate and depth of respiration, and then a period of apnea that may last 15 s or longer.[1] This form of respiration occurs in advanced congestive heart failure and in some forms of central nervous system disease. Cheyne-Stokes respiration often occurs during sleep without the patient's awareness and is often reported by others.

Orthopnea results from an increase in hydrostatic pressure in the lungs that occurs with assumption of the supine position. It consists of cough and dyspnea in some patients with LV failure or mitral valve disease and necessitates the use of two or more pillows on lying down. The patient with severe obstructive lung disease, especially acute asthma, also cannot lie flat comfortably.

Paroxysmal nocturnal dyspnea (PND) is the occurrence of dyspnea during sleep, commonly 2 to 3 h after going to bed, that is relieved by assuming the upright position. Dyspnea usually does not recur after the patient goes back to sleep. Episodes can be mild, or they can be severe with wheezing, coughing, gasping, and apprehension.[1] Some episodes will progress to pulmonary edema. The probable mechanism for this *relatively specific symptom* of left-sided heart failure is the increase in central blood volume in the supine position.

A dry, nonproductive cough, occurring with effort or at rest, may be related to the pulmonary congestion associated with heart failure (see Chap. 20). Although dyspnea is usually present, cough may dominate the clinical picture. The cough that accompanies acute pulmonary edema is often associated with frothy, pink-tinged sputum, whereas the sputum associated with chronic bronchitis is usually white and mucoid.[2] The sputum associated with pneumonia is often thick and yellow, and that due to pulmonary infarction may be bloody, as may the sputum associated with cancer of the lung or bronchiolectasis. Cough also may be caused by angiotensin-converting enzyme inhibitors, which are often prescribed for heart failure or hypertension.

Recurrent coughing due to heart failure is often thought to be due to bronchitis, and patients with chronic bronchitis may cough more when heart failure ensues.[2] Patients with a high pulmonary blood flow due to congenital left-to-right shunts are subject to pulmonary infection. Patients with a high pulmonary venous pressure are more vulnerable to the development of pulmonary edema when they have viral pneumonitis than are patients with normal pulmonary venous pressure. This particularly applies to patients with mitral stenosis.

Hemoptysis occurs in many cardiac disorders. Posterior epistaxis due to systemic hypertension may cause blood-streaked sputum; patients on anticoagulants may have epistaxis that mimics hemoptysis. Epistaxis, however, is usually easily differentiated from bloody sputum. Bright red pulmonary venous blood from rupture of submucosal pulmonary venules may be expectorated by patients with pulmonary venous hypertension due to mitral stenosis or severe LV failure.[2] Darker blood or clots often occur with pulmonary emboli.

Pink, frothy sputum may be produced during acute pulmonary edema. Blood-streaked sputum is a feature of the "winter bronchitis" of mitral stenosis.[2] Massive hemoptysis with exsanguination or death from

asphyxiation can follow rupture of an aortic aneurysm or one of the cardiac chambers into the bronchial tree.[2] Rupture of a pulmonary artery by the balloon of an indwelling pulmonary artery catheter can cause abrupt, severe hemoptysis in hospitalized patients.

Wheezing associated with dyspnea may be due to lung or heart disease. If the symptoms have developed recently in an adult over age 40, other clues indicating heart disease should be sought. Wheezing due to heart disease is termed *cardiac asthma*.

EDEMA AND ASCITES

Edema is a common symptom or finding in patients with right- or left-sided heart failure. Fluid retention in heart failure results from increased venous pressure and abnormal activity of salt-retaining hormones (see Chap. 20). In an average-sized person, 5 to 10 lb of excess fluid is required for edema to become apparent; a history of recent weight gain often will correlate with a deterioration in clinical status. The amount of weight loss in response to treatment for heart failure in the past will relate to the severity of the problem. Minor degrees of edema are evident only after a period of dependency of the legs and will decrease after rest. Presacral edema may be most obvious when the patient has been at bed rest. Although edema of cardiac origin may progress to anasarca, cardiac edema rarely involves the face or upper extremities. Edema mainly affecting the face and arms is more likely to be due to venous or lymphatic obstruction by clot or neoplasm. Facial edema is a feature of the nephrotic syndrome, angioneurotic edema, and glomerulonephritis. Swelling or "puffiness" of the hands and fingers is not usually a symptom of cardiac disease. Persistent edema in the legs from which veins were harvested at the time of bypass surgery is common. Other causes of edema-such as varicosities, obesity, tight girdle, renal insufficiency, or cirrhosis with hypoproteinemia-must be considered.[1] A patient with chronic congestive heart failure may detect edema of the ankles and lower legs during the day and note that it diminishes during the night. It is important to ascertain whether edema of the extremities preceded or followed dyspnea on effort. The calcium antagonists may produce bilateral edema of the lower legs. Edema may occur in one or both legs following the harvesting of veins for conduits in patients undergoing coronary artery bypass graft (CABG) surgery.

Patients will be aware of ascites because of increased abdominal girth. Previously comfortable trousers or skirts may no longer fit. Bending at the waist is uncomfortable, with ill-defined abdominal fullness. Patients with severe edema due to congestive heart failure may develop ascites; however, ascites is particularly common in patients with constrictive pericardial disease, sometimes occurring before peripheral edema becomes obvious (see Chap. 72). Ascitic fluid is formed when elevated venous pressure leads to transudation of fluids from the serosal surfaces. Other causes of ascites-such as cirrhosis, nephrosis, and tumor-must be excluded.

FATIGUE AND WEAKNESS

Fatigue and *weakness* may be due to many causes and therefore are not specific symptoms for heart disease. The most common cause of these symptoms is anxiety and depression. Anemia, thyrotoxicosis, and other chronic disease states may be associated with fatigue and weakness.

When a patient with heart disease is volume overloaded, or when there is pulmonary congestion due to heart disease, the patient is likely to complain of dyspnea. With vigorous diuretic therapy, this complaint may be replaced by symptoms of fatigue and weakness,[2] probably related to inadequate cardiac output (see Chap. 21). The heart fails in its prime objective of nourishing all the tissues and organs of the body, including the skeletal muscles. As congestive heart failure worsens, fatigue may replace dyspnea as the major symptom. Beta blockers used to treat angina or hypertension often cause fatigue and lethargy. Hypotension or hypokalemia caused by diuretics can result in fatigue and weakness, as can relative hypovolemia due to the use of angiotensin-converting enzyme inhibitors.

Severe fatigue related to effort may result from transient global myocardial ischemia in patients with extensive CAD. Dyspnea and hypotension also may occur at the same time as the severe fatigue as *angina equivalents*.[2]

PALPITATION

Most normal individuals are intermittently aware of their heart action, particularly at the time of physical and emotional stress. When the heart action is more vigorous than usual or its perception is unpleasant, the term *palpitation* is appropriate.[1] The patient may complain of a "pounding," "stopping," "jumping," or "racing" in the chest. Palpitation is frequently a benign symptom without any serious cardiac disease present; at other times it may indicate a potentially life-threatening condition. Simple premature beats may be perceived as a "floating" or "flopping" sensation in the chest due to the more forceful beat that occurs after the pause following the premature beat. Sometimes a transient feeling of fullness in the neck (due to cannon a waves) is perceived with premature beats. Certain patients perceive almost every premature beat, whereas others are totally unaware of frequent or advanced arrhythmias. A report of skips or irregularity during uninterrupted sinus rhythm is not uncommon. Generally, thin, tense individuals are likely to be more aware of their cardiac activity than others. Individuals with and without arrhythmias often are aware of their cardiac activity when they first lie down on their side to sleep, especially if they lie on their left side.[1]

Rapid heart action of a paroxysmal tachycardia usually begins and terminates abruptly and causes a pounding sensation in the chest.[1] Patients often will indicate whether the tachycardia is regular or irregular and may be able to tap out the rate and rhythm of the episode (see Chap. 24). Chest pressure suggesting angina may occur with an episode of tachycardia even in young, healthy patients without CAD. Patients with CAD, however, often develop severe angina with a sustained arrhythmia because of increased $MV(r)O_2$. Depending on the rate and mechanism of the arrhythmia, faintness and syncope may be described during questioning. Nevertheless, sustained ventricular tachycardia can occur in the setting of serious underlying cardiac disease without a significant compromise in hemodynamics (see Chap. 24). Syncope due to tachyarrhythmias may occur without the patient being aware of palpitations.

SYNCOPE

Cardiac *syncope* (fainting) is defined as the transient loss of consciousness due to inadequate cerebral blood flow secondary to an abrupt decrease in cardiac output (see Chap. 32). *Near syncope* refers to the clinical situation in which the patient feels dizzy and weak and tends to lose postural tone but does not lose consciousness. In assessing the patient with syncope, one determines if there were precipitating factors, premonitory symptoms, injury with the episode, seizure activity or incontinence, or a postictal state.[1] Injury during an episode suggests a sudden profound loss of body tone and increases the likelihood of more serious causes. Brief, unsustained seizure activity can occur with syncope due to a cardiac arrhythmia.

The patient may be incontinent during cardiogenic syncope, but an aura, sustained tonic-chronic movements, tongue biting, and confusion or drowsiness after the event are more characteristic of syncope due to central nervous system disease. In contrast, return of consciousness to the alert state is prompt after reversal of the arrhythmia causing cardiac syncope.[1] The common faint (*vasovagal syncope*) results from bradycardia and hypotension caused by excessive vagal discharge. It is often associated with some precipitating event such as a "heavy" meal in a warm room and has brief premonitory signs and symptoms such as nausea, yawning, diaphoresis, and sometimes the feeling of decreased hearing or vision.[1] There is frequently sufficient warning that the patient does not fall abruptly. The results of head-up tilt-table testing indicate a vasovagal mechanism in some patients with syncope who do not have premonitory symptoms (see Chap. 32). Following a fainting episode, the patient may be pale and diaphoretic and have a slow heart rate. Syncope occurring in the setting of any gastrointestinal symptoms is likely to be vagal in origin. A history of similar episodes during the preceding several years is common in patients with vagal syncope.

A hypersensitive carotid sinus can cause syncope. A history of episodes during an activity such as shaving, wearing of a tight collar, or extreme turning of the head may occur but is unusual even when a sensitive carotid sinus is shown to be the cause of syncope. Syncope following urination (micturition syncope) may occur at the time of rapid decompression of a distended bladder, which typically occurs after a period of sleep. Paroxysms of coughing, usually in patients with underlying pulmonary disease, can result in syncope. Very fast or slow arrhythmias may decrease the cardiac output enough to cause alterations in consciousness, ranging from abrupt profound syncope to mild light-headedness. Stokes-Adams syncope is caused by intermittent complete heart block, sinus arrest, or ventricular tachyarrhythmias[77] (see Chap. 32). It is characterized by abrupt loss of consciousness without warning, a variable period of unconsciousness

(seconds to minutes), and then a rapid return of normal mental status without amnesia or a postictal state.

In the presence of several LV outflow obstruction (aortic stenosis or hypertrophic cardiomyopathy), loss of consciousness with effort may occur. Syncope can be due either to the heart's inability to increase its output in response to the peripheral vasodilatation that occurs during exercise or to a tachyarrhythmia. Intermittent obstruction of a cardiac valve by an intracavitary tumor or thrombus is a rare cause of syncope that occasionally may be precipitated when the patient changes position (see Chap. 77).

Many normal subjects experience transient light-headedness with rapid changes in position. This is more common in older patients, since the ability of the peripheral vasculature to respond is attenuated with aging (see Chap. 86). Postural hypotension is a well-defined cause of fainting or dizziness that usually occurs when the individual is upright and often just after rising from a supine or sitting position. Possible causes include peripheral neuropathy, autonomic dysfunction, volume depletion, or drug side effects.

OTHER CEREBRAL SYMPTOMS

Patients with decreased cardiac output secondary to heart failure may become mentally confused and disoriented. Such symptoms also may be due to hypoxia, to drugs that are invariably prescribed for such patients, and to renal or hepatic failure.[2] A completed stroke may be caused by a lacunar infarct, cerebral hemorrhage, cerebral arterial thrombosis, or a cerebral embolus (see Chap. 89). A transient cerebral ischemic attack is commonly due to an embolus. The embolus may originate in an atheromatous ulcer in the carotid artery system or the aortic arch; be related to infective endocarditis, a recent MI, atrial fibrillation, or clots on a prosthetic valve; or originate in the leg veins and pass through a patent foramen ovale to the brain (see Chap. 89).

The patient with cardiogenic shock or with a severe tachyarrhythmia who also has considerable intracranial or extracranial vascular disease may develop such severe cerebral hypoxia that coma occurs. Hypoxic encephalopathy may follow cardiac resuscitation and occasionally occurs after cardiopulmonary bypass for cardiac surgery. A cerebral abscess may occur in patients with congenital heart disease and a right-to-left shunt.[2]

FEVER, CHILLS, AND SWEATS

Patients with rheumatic fever usually do not have chills. Chills are common in patients with bacterial endocarditis. Symptoms of fever, chills, or sweats in any patient with a heart murmur should lead one to suspect infective endocarditis (see Chap. 73). A history of valvular heart disease is not a prerequisite for a diagnosis of endocarditis, since previously normal valves become infected. A history of recent dental work, genitourinary surgery, or illicit drug use increases the suspicion of infective endocarditis. Fever may accompany pericarditis. Myalgia, chills, and fever on rare occasions may be related to MI, presumably because of some form of immunologic response to the necrotic myocardial tissue. An intracardiac tumor (myxoma) may produce systemic symptoms in the absence of infection. Low-grade fever in a patient with heart failure may be a sign of pulmonary emboli.[2] A profuse "cold sweat" mediated by sympathetic discharge often accompanies early stages of acute MI. Excessive sweating may occur in patients with severe aortic regurgitation. Diaphoresis is often a sign of congestive heart failure in infants.

HOARSENESS

Although usually unrelated to cardiovascular disease, *hoarseness* can occur in patients with an aortic aneurysm that involves the left recurrent laryngeal nerve. Mitral stenosis occasionally may produce hoarseness due to the pressure of a large pulmonary artery on the recurrent laryngeal nerve. Pericardial effusion may be related to myxedema, which may be associated with a coarse, low-pitched voice. Hoarseness and loss of voice may occur following the use of an endotracheal tube during cardiac surgery.

INDIGESTION, HICCUPS, AND DYSPHAGIA

Many patients with angina pectoris due to CAD erroneously attribute their symptoms to *indigestion* or heartburn. Also, patients with heartburn, esophageal reflux, and esophageal spasm may believe they have

angina pectoris. *Hiccups* occasionally may occur in patients with MI and are common during the postoperative period after cardiac surgery. *Dysphagia* may occur in patients with progressive systemic sclerosis, an aortic arch anomaly, or an extremely large left atrium.

GASTROINTESTINAL SYMPTOMS

Anorexia, nausea, and vomiting may occur as a result of digitalis excess. Hepatomegaly associated with tricuspid valve disease or severe right-sided heart failure may cause right-upper-quadrant epigastric pain and fullness as well as anorexia. Abdominal pain due to visceral ischemia or infarction may occur in a patient who has had a period of very low cardiac output. The pain of some gastrointestinal diseases may be referred or extend to the chest or back and lead to confusion with myocardial ischemia.

ABNORMAL SKIN COLOR

Although *cyanosis* is a sign rather than a symptom, patients or family members may describe cyanosis during the history. *Cyanosis* is a bluish color of the skin or mucous membranes caused by excess amounts of reduced hemoglobin. About 4 g of reduced hemoglobin is required for cyanosis to be apparent (see Chap. 63). Severely anemic patients will not exhibit cyanosis. A distribution of cyanosis involving the mucous membranes as well as the periphery (central cyanosis) is caused by the admixture of venous blood at the level of the heart or great vessels. A patient or a family member may detect that the cyanosis is more intense in the feet than in the hands. This differential cyanosis suggests a right-to-left shunt through a patent ductus arteriosus in a patient with Eisenmenger physiology (see Chap. 63). Peripheral cyanosis does not involve the mucous membranes but is the result of slow peripheral flow with accumulation of excess reduced hemoglobin in the setting of circulatory failure, shock, or peripheral vasospasm.

Jaundice may be detected by a patient or by a member of the family. As a rule, hepatic congestion due to heart failure will not produce jaundice. When jaundice does occur in a patient with heart failure, it is appropriate to consider pulmonary infarction in addition to hepatic congestion or cirrhosis of the liver. Hemolysis of red blood cells may occur in patients with prosthetic valves and can produce jaundice.[2]

A history of flush of face and trunk, sometimes accentuated by alcohol, should lead one to search for the other signs and symptoms of carcinoid heart disease[2] (see Chap. 77). Cardiomyopathies due to hemochromatosis should be considered in the patient with diabetes whose skin color has changed from normal to bronze.[2] A slatelike color of the skin, hands, and nose may develop in patients who take amiodarone.

EMBOLIZATION

The entry of a blood clot, vegetation, or tumor fragment from the heart into the systemic circulation results in arterial embolus. Clots may occur in the left atrium behind a stenotic mitral valve, within a ventricular aneurysm, or in the left ventricle of a patient with cardiomyopathy. While many emboli originate in the heart, arteriosclerotic material in the ascending and descending aorta often embolizes to the periphery.[1] Many emboli are asymptomatic. Symptoms of a stroke occur with emboli to the cerebral vessels. MI can result from an embolus to a coronary artery. Hematuria, flank pain, and hypertension can result from embolization to a renal artery. The abrupt development of a cold, painful extremity follows embolic obstruction of an arm or leg artery.[1] Emboli from the vegetations of acute endocarditis may produce characteristic areas of vascular necrosis in the fingers or toes (see Chap. 77). Severe atherosclerosis in the abdominal aorta and iliac vessels can be responsible for showers of peripheral emboli with multiple small, reddish blue lesions on the lower extremities sometimes causing small areas of gangrene. An embolic event may be the presenting manifestation of previously unrecognized cardiac disease.

INSOMNIA

The most common causes of insomnia are mental conflict, emotional disturbances, and depression. Heart failure, however, also may cause insomnia. The patient with Cheyne-Stokes respirations (see above) may sleep during the apneic phase and wake during the hyperpneic phase of the condition. Occasionally, patients with pulmonary congestion due to heart failure have insomnia before they develop nocturnal

dyspnea.

Classification of Cardiac Disability

Several classifications have been proposed and used for many years for the systematic and reproducible grading of disability due to cardiac disease. Although the complete New York Heart Association method of classifying cardiac diagnoses, originally proposed many years ago, is not widely used now, the portion of the classification that concerns functional capacities[45] is still commonly used (Table 10-3). Although the Canadian Cardiovascular Society's grading system for angina (see Table 10-2) is more widely used for patients with chest pain, both classifications continue to be used in the medical literature and in clinical practice, particularly as criteria for the inclusion of heart patients in multicenter clinical trials.

Table 10-3: The Old New York Heart Association Functional Classification

Class 1	No symptoms with ordinary physical ac-tivity.
Class 2	Symptoms with ordinary activity. Slight limitation of activity.
Class 3	Symptoms with less than ordinary activity. Marked limitation of activity.
Class 4	Symptoms with any physical activity or even at rest.

SOURCE: The Criteria Committee of the New York Heart Association. *Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis of the Heart and Great Vessels.* 6th ed. New York: New York Heart Association/Little, Brown; 1964. Reproduced with permission from the New York Heart Association, Inc., and the publisher.

NEXT

Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

THE PHYSICAL EXAMINATION

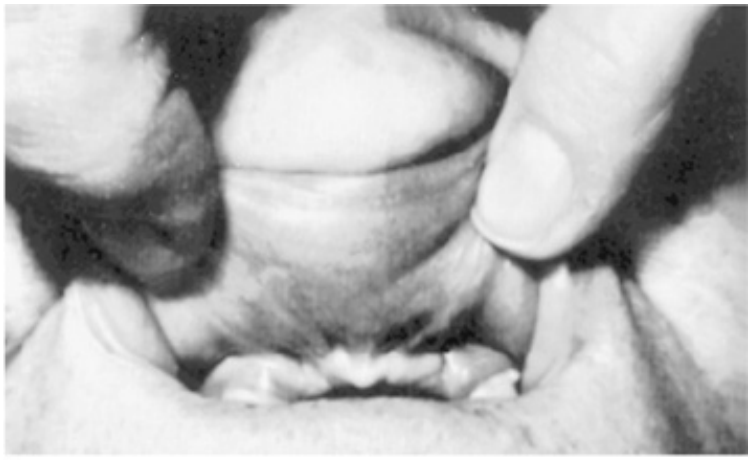
Important information concerning the patient with definite or suspected heart disease is often obtained by a careful and deliberate physical examination, which includes a general inspection of the patient, an indirect measurement of the arterial blood pressure in both arms and one or both lower extremities, an examination of central and peripheral arterial pulses, an evaluation of the jugular venous pressure and pulsations, palpation of the precordium, and cardiac auscultation. Based on the results of this rather inexpensive evaluation, a definite diagnosis often is made, and selected noninvasive and invasive testing is ordered only when appropriate.

General Inspection of the Patient

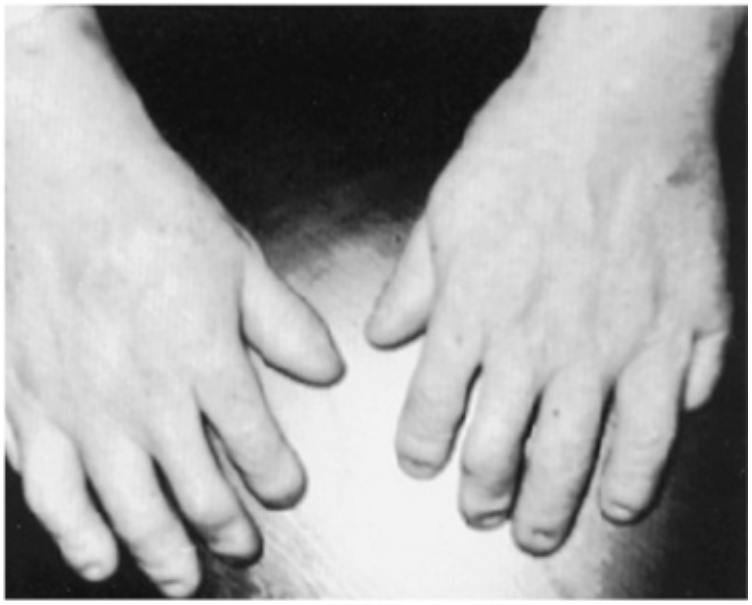
The art of bedside medicine begins with a careful overall appraisal of the patient. This visual approach is of great advantage in seeking clues to the etiology of cardiovascular disease. Since this discussion is organized according to the specific type of heart involvement, diseases that cause several problems are mentioned more than once. Each disorder is italicized, and its major manifestations are described the first time it is named.

Syndromes Associated with Congenital Heart Disease

Congenital heart disease syndromes may be classified into heritable disorders, connective tissue disorders, inborn areas of metabolism, chromosomal abnormalities, sporadic disorders, and teratogenic disorders (see also Chaps. 62, 63, 64 and 76). Occasionally, a particular syndrome falls into more than one category. In the first category, the *Ellis-van Creveld syndrome,* a common disorder in the Amish population, is a heritable form of dwarfism characterized by short extremities, polydactyly, dysplastic teeth and nails, and multiple frenula binding the upper eyelid to the alveolar ridge (Fig. 10-1). Over half the patients have heart disease, usually a large atrial septal defect or a single atrium.[46]



A



B

Figure 10-1: *Ellis-van Creveld syndrome. A.* Typical "lip tie" due to multiple frenulum. *B.* Polydactyly. This patient has a large septal defect.

The *thrombocytopenia-absent radius* (TAR) *syndrome* includes bilateral radial aplasia with a persistent thumb and thrombocytopenia and may be associated with an ostium secundum atrial septal defect (ASD) and/or tetralogy of Fallot. The Holt-Oram syndrome, an autosomal dominant trait, combines an ASD or other congenital heart disease with a thumb[47] (Fig. 10-2) that may be absent, hypoplastic, bifid, triphalangeal, or unusually long. *Tabatznik's syndrome* (heart-hand syndrome type II) is characterized by hypoplastic deltoids, skeletal anomalies of the forearm, bradydactyly, and atrial fibrillation. In the *Laurence-Moon-Bardet-Biedl syndrome*, mental retardation, polydactyly, obesity, retinitis pigmentosa, and hypogonadism occur with a variety of congenital heart diseases.[48]

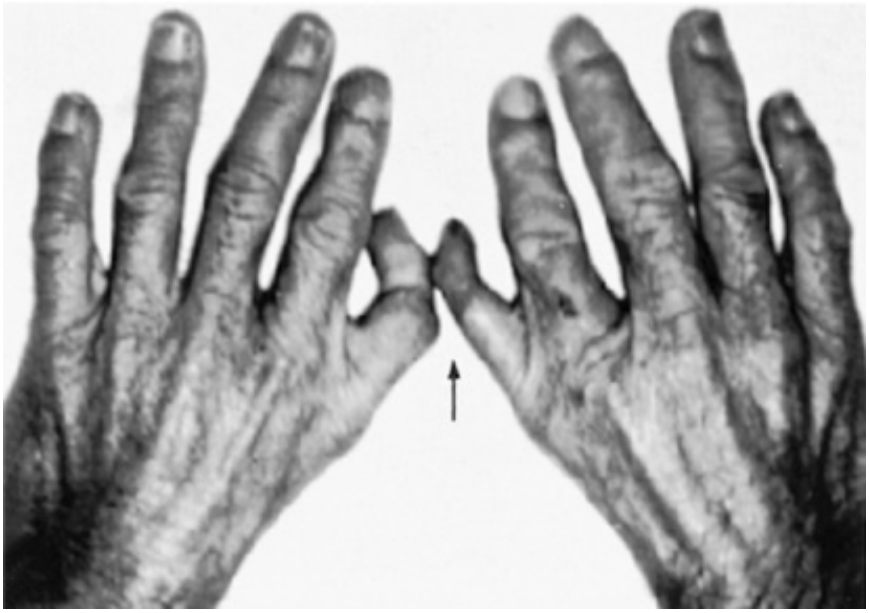


Figure 10-2: *Holt-Oram syndrome:* fingerized thumb (arrow) associated with an atrial septal defect.

Arteriovenous fistulas involving the lung, liver, and mucous membranes are associated with multiple telangiectasias in patients with the hereditary hemorrhagic telangiectasis (*Osler-Weber-Rendu syndrome*).[49] *Cornelia de Lange's syndrome* is characterized by bushy, confluent eyebrows, downward-slanting eyes, a small mandible, low-set ears, hirsutism, long eyelashes, a broad, flat, upturned nose, severe growth and mental retardation, and a peculiar "chicken wing" extremity with a single thumblike digit (Fig. 10-3). A ventricular septal defect (VSD), patent ductus arteriosus, pulmonic stenosis, anomalous venous return, or ASD may be present.

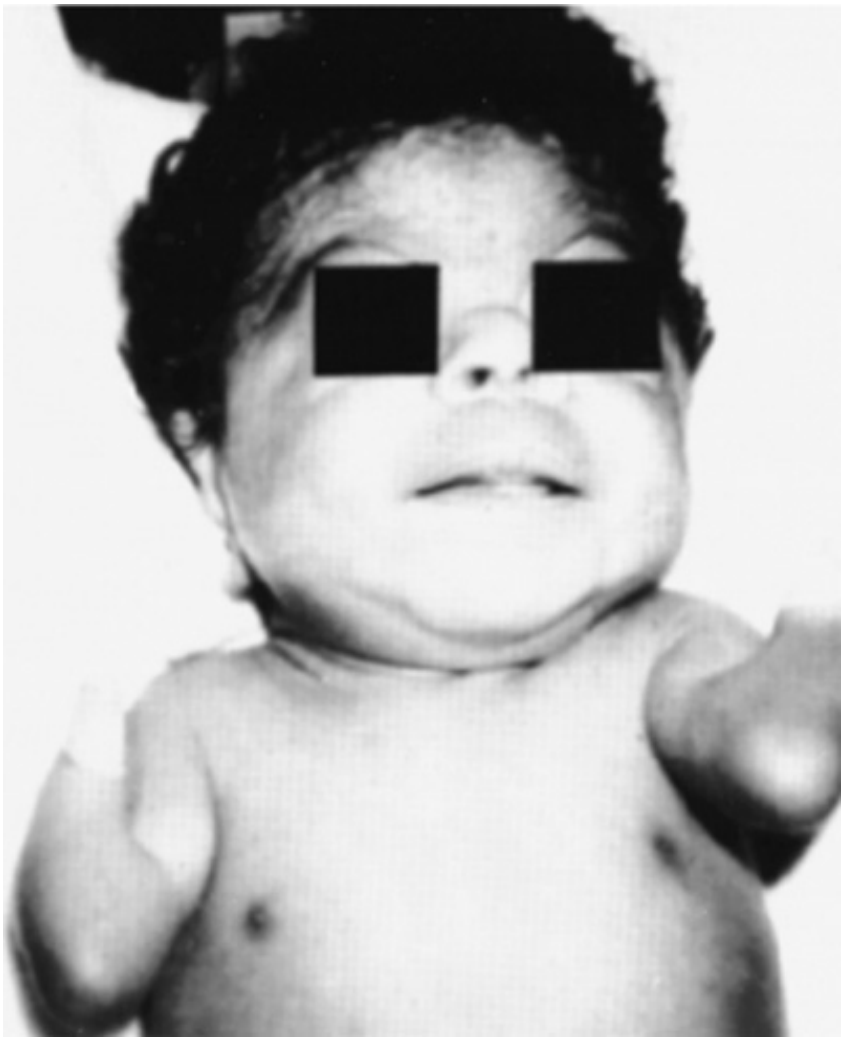


Figure 10-3: *Cornelia de Lange's syndrome:* low hairline, hirsutism, bushy brows, phocomelia, and a single thumblike digit. May be associated with ventricular septal defect.

There appears to be an increased incidence of congenital heart disease in children with a cleft palate or lip.[50] In the *Pierre Robin syndrome,* the cleft palate is associated with a hypoplastic mandible causing a "shrewlike" face (Fig. 10-4). A cleft palate, micrognathia, low-set ears, and truncus arteriosus may be present in the familial *third and fourth pharyngeal pouch syndromes*.

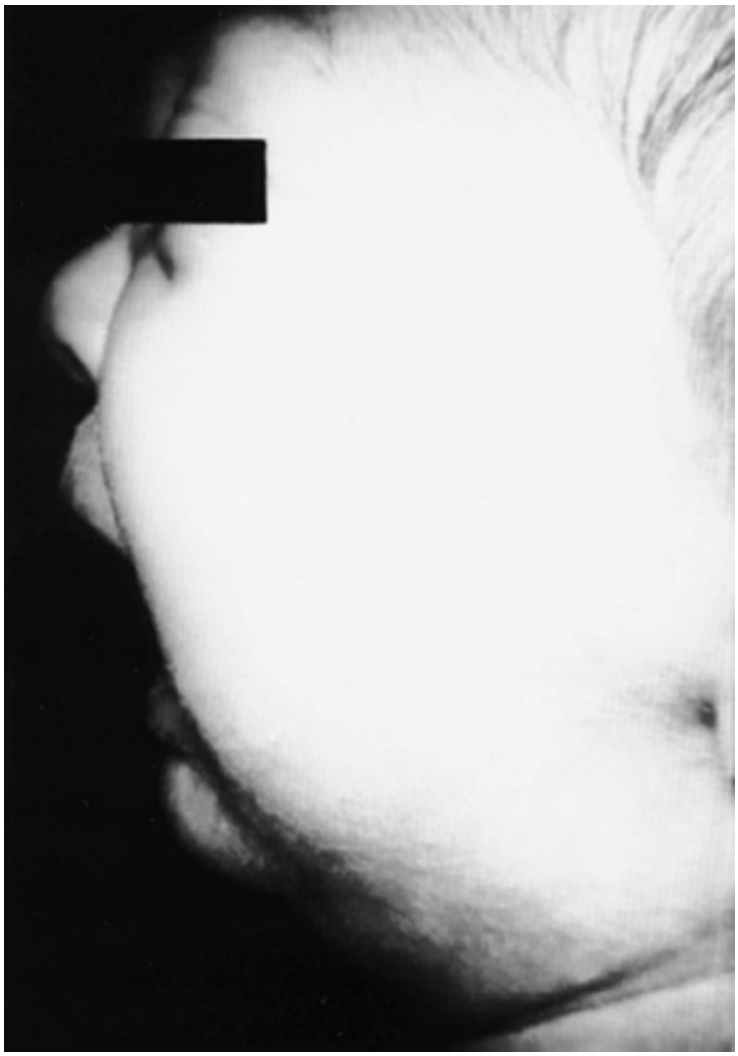
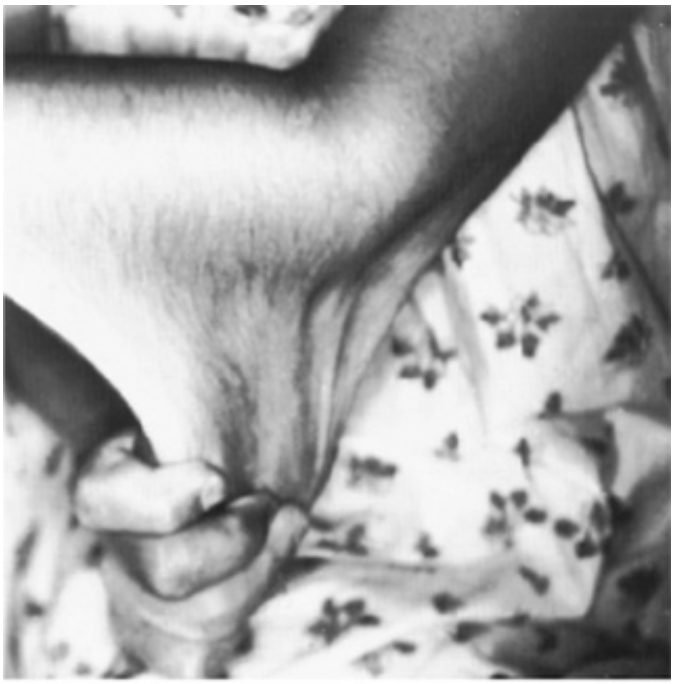


Figure 10-4: *Pierre Robin syndrome*: hypoplastic mandible associated with a ventricular septal defect.

Cutis laxis is a generalized disruption of elastic fibers with diminished skin resilience, frequent hernias, and pulmonary artery branch stenosis.[51] Patients with the *Ehlers-Danlos syndrome* (Fig. 10-5*A, B*) have hyperextensible joints and hyperelastic and friable skin that is often associated with arterial dilatation and rupture, aortic regurgitation, or mitral valve prolapse.[52] Patients with osteogenesis imperfecta have brittle bones, blue sclera, and short legs and have an increased incidence of aortic and mitral regurgitation.[53] Patients with pseudoxanthoma elasticum (see Chap. 76), who have degeneration of dermal elastic fibers and retinal angioid streaks, can develop aortic regurgitation and CAD (Fig. 10-6).



A

B

Figure 10-5: *Ehlers-Danlos syndrome. A.* Hyperextensible skin. *B.* Lax joints. Redundant chordae tendineae and arterial rupture may occur.

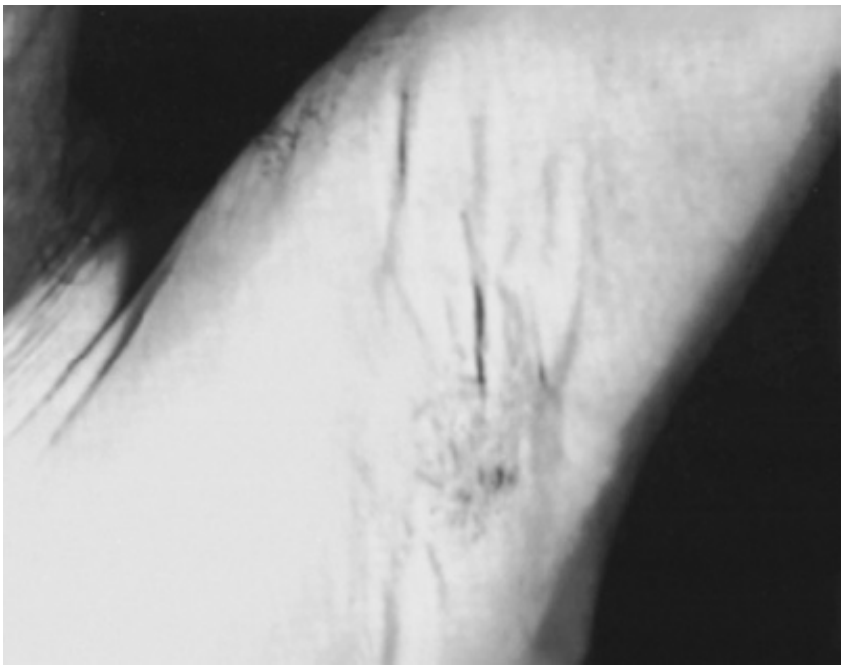


Figure 10-6: *Pseudoxanthoma elasticum*: grooved skin in a typical location. Arterial calcification may occur.

Marfan's syndrome, an autosomal dominant trait, is suggested by skeletal features such as increased height, long fingers, narrow palms, lax joints, kyphoscoliosis, pectus excavatum or carinatum, an elongated face, high-arched palate, and flat feet[54] (Fig. 10-7*A-C*). The legs are disproportionately long, resulting in an abnormal ratio of the upper-to-lower segments of at most 0.85. The arm span many exceed the height. When a patient with Marfan's syndrome clenches the hand around a flexed thumb, the thumb protrudes past the ulnar side of the hand. Such a patient also can easily encircle the wrist by grasping it with the fifth finger and thumb of the other hand (see Fig. 10-7*B*). Other signs include bilateral subluxation of the lens, severe myopia, and blue sclera (see Fig. 10-7*D*). Subcutaneous tissue is sparse. Valvular disease is common; patients with Marfan's syndrome usually have mitral valve prolapse (see Chap. 58), minimal to severe mitral regurgitation, a dilated and often calcified mitral annulus, and eventual chordal rupture. Aortic regurgitation is a consequence of a dilated aortic root, prolapse of the aortic cusps, or aortic dissection (see Chap. 76).

Aortic regurgitation also has been described in patients with inborn errors of metabolism including *Morquio's syndrome* (mucopolysaccharidosis IV) and *Scheie's syndrome* (mucopolysaccharidosis V).[55] Patients with Morquio's syndrome are identified by their short stature, short neck, barrel chest, broad mouth, short nose, widely spaced teeth, and cloudy cornea. In Scheie's syndrome, growth retardation, sternal protrusion, facial abnormalities, and cloudy cornea are present. In *Fabry's disease*, angiokeratomas identified as purplish pinpoint skin lesions occur on the lips, underarm, buttocks, scrotum, and penis (Fig. 10-8). Cardiomyopathy, ischemic heart disease, and conduction defects beginning in the third decade are associated with this sex-linked recessive disorder, in which there is a genetic deficiency of the enzyme α-galactosidase A.[56]

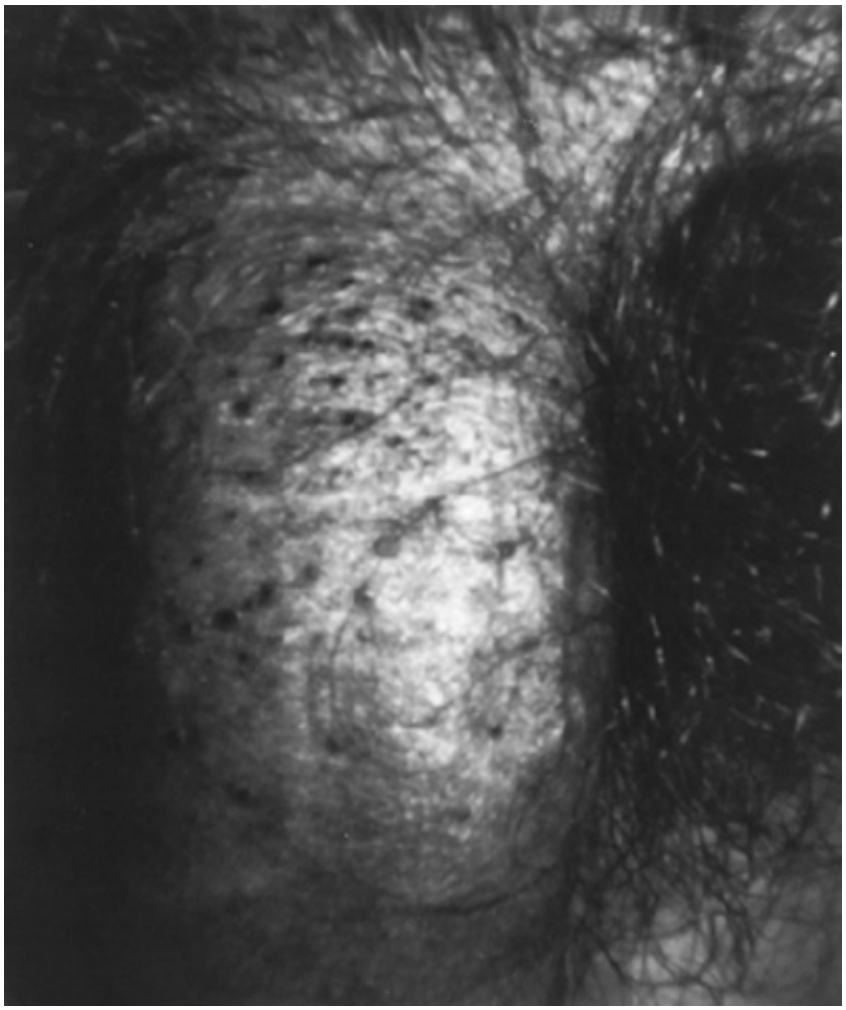


Figure 10-8: *Fabry's disease*: dark-red angiokeratomas on the penis may be linked with coronary artery disease.

Many chromosomal abnormalities have been associated with congenital heart disease. The well-recognized characteristics of *Down's syndrome* (trisomy 21) include a small head, shallow orbits, epicanthal folds, low-set ears, widely spaced eyes (hypertelorism), Brushfield's white spots of the iris, protruding tongue, transverse palmar creases, and mental retardation (see Chap. 64). Congenital heart disease occurs in 40 to 60 percent of patients; a VSD or endocardial cushion defect is the most frequent.[57] Less commonly, tetralogy of Fallot, secundum ASD, patent ductus arteriosus, and other abnormalities are present.[58,59]

Klinefelter's syndrome is characterized by gynecomastia, small testicles, a eunuchoid appearance, tall stature, and long extremities. Associated ASD's have been described.[58]

Patients with abnormalities involving chromosomes 1, 9, 11, and 22 often have congenital heart disease.[59] The findings with *chromosome 1 abnormalities* include a peaked nose, micrognathia, and long, tapering fingers. Children with *chromosome 9 abnormalities* have a prominent forehead, hypertension, anteverted nostrils, a long upper lip, a short neck, mental retardation, and external ear malformations. A child with a *chromosome 11 abnormality* shares similar features plus retraction of the lower lip. Psychomotor retardation, coloboma, hypertelorism (widely spread eyes), downward slanting of the eyes, and preauricular tags or fistulas are clues to a *chromosome 22 defect*.

Congenital heart disease, primarily patent ductus arteriosus, has been associated with the *49*

XXXXY syndrome. This unusual disorder should be suspected when a child has psychomotor retardation, hypoplastic genitals, prognathism, clinodactyly (inward curving of the fifth finger), and radioulnar synostoses.

Congenital heart disease of varied types is common in *trisomy 13* and *trisomy 18 syndromes*.[60] In *trisomy 13 syndrome*, the child has a cleft palate and lip; the ocular tissue and the nose may be missing. Polydactyly in combination with retroflexible thumbs, transverse creases, hyperconvex narrow nails, and flexion of the fingers and hands are characteristic of this syndrome. The features of the trisomy 18 syndrome are a small, triangular mouth with receding chin, small mandible, webbed neck, and tightly clenched fists with the index finger overlapping the third finger and the fifth finger over the fourth (Fig. 10-9).

Figure 10-9: *Trisomy 18 syndrome*: tightly clenched fist with overlapping index and fifth fingers. A ventricular septal defect was present.

Low hairline, low-set ears, deafness, small jaw, and short, webbed neck are physical findings common to both *Turner's syndrome* and the *Klippel-Feil syndrome*. Turner's syndrome also includes short stature, broad chest with widely spaced nipples, epicanthal folds, widely spaced eyes, pigmented moles, ptosis, clinodactyly, and a shortened fifth finger[61] (Fig. 10-10). Coarctation of the aorta, aortic stenosis, and hypertrophic cardiomyopathy are the usual cardiovascular considerations. The Klippel-Feil syndrome may cause facial asymmetry, cleft palate, torticollis, scoliosis, deafness, strabismus, and hydrocephaly. VSD is the most common associated cardiac disorder.[62]

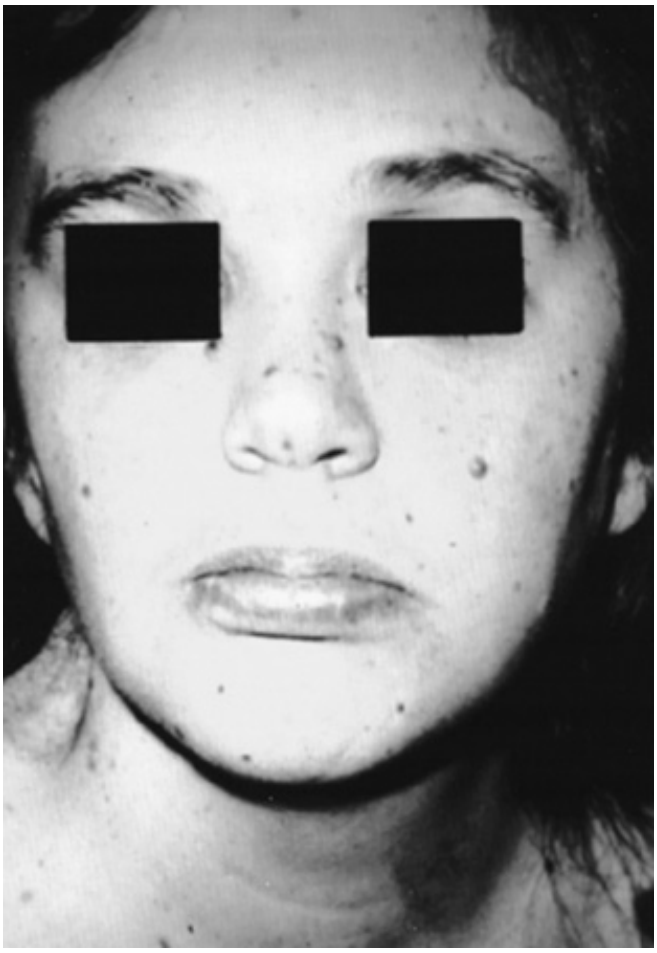


Figure 10-10: *Turner's syndrome:* epicanthal folds, pigmented moles, hypertelorism, and scars on the neck where webs have been removed. May be associated with coarctation of the aorta.

There are many sporadic disorders associated with congenital heart disease. An imperforate anus may be associated with a cardiovascular malformation.[63] This may occur as an isolated finding or as a component of the *VATER association*,[64] the *asplenia syndrome*,[65] the *CHARGE syndrome*[66] (*coloboma, heart disease, atresia choanae, retarded growth, genital hypoplasia, ear anomalies*), or *cat's-eye pupil*[67] (a fissure of the iris and choroid associated with a cardiac defect). The VATER association includes vertebral defect, tracheoesophageal fistula, and radial and renal dysplasia. A ventricular defect occurs in 80 percent of these patients. The asplenia syndrome is associated with a high incidence of complex congenital heart disease. Cardiovascular malformations are found in 15 to 25 percent of newborns with omphalocele.[68]

Teratogenic effects resulting in congenital heart disease may be alcohol-induced, the result of rubella during pregnancy, or induced by phenytoin, thalidomide, or lithium.[69] From 30 to 40 percent of children born to alcoholic mothers are affected with the *fetal alcohol syndrome*.[70] These children have an undeveloped-appearing central face because of maxillary hypoplasia, a small and upturned nose, an indistinct or smooth philtrum, micrognathia, and a thin upper lip and vermilion (Fig. 10-11). ASDs and VSDs are most common, but many other cardiac defects also can be found. The teratogenic effects of the rubella syndrome include cataracts, deafness, and microcephaly. The most frequent congenital cardiac disorders are patent ductus arteriosus, pulmonic valvular and/or arterial stenosis, and ASD.[71]

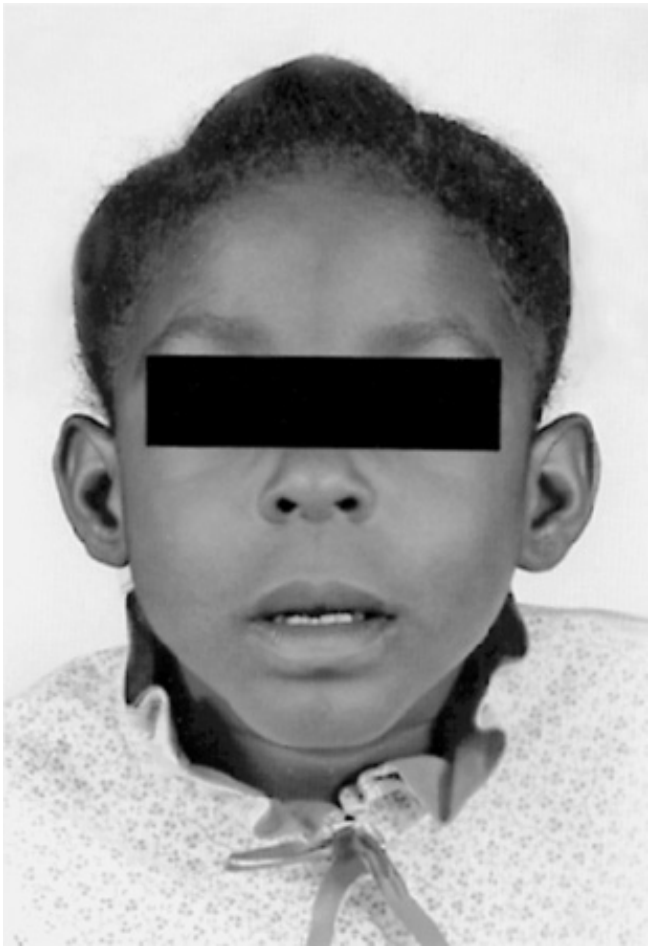


Figure 10-11: *Fetal alcohol syndrome:* midface hypoplasia, absent philtrum, and microcephaly associated with a ventricular septal defect.

Important clues to the diagnosis of underlying congenital heart disease may be obtained from careful observation of the thorax and extremities. Bilateral prominence of the anterior chest with bulging of the upper two-thirds of the sternum is commonly present in children with a large VSD. A unilateral bulge at the fourth and fifth intercostal spaces at the lower left sternal border often is found in adults with VSDs. A bulge in the area of the second and third intercostal spaces at the left sternal border may result from an underlying ASD. Scoliosis is commonly present in cyanotic congenital heart disease. Underdeveloped musculature of the lower extremities compared with the upper extremities occurs with coarctation of the aorta. Clubbing of the digits and cyanosis of the skin or nails suggest congenital heart disease with right-to-left shunting of blood (Fig. 10-12, Plate 29).

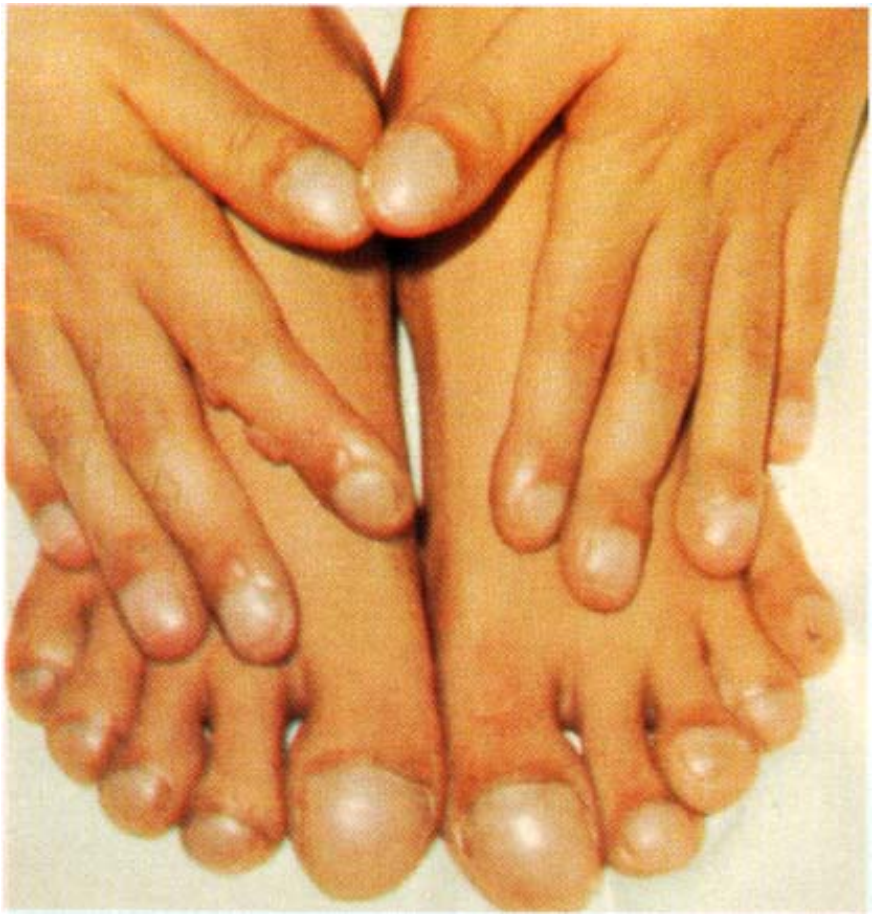


Figure 10-12: (Plate 29) *Symmetric cyanosis*. Equal cyanosis and clubbing of hands and feet due to transposition of great vessels and a ventricular septal defect without patent ductus arteriosus.

Differential cyanosis often provides a clue to exact pathologic anatomy.[72] Cyanosis and clubbing of the toes associated with pink fingernails of the right hand and minimal cyanosis and clubbing of the left hand are due to pulmonary hypertension with normally related great vessels and a reversed shunt, with the patent ductus arteriosus bringing unoxygenated blood to the left arm and lower extremities (Fig. 10-13, Plate 30). The same pattern results from interruption of the aortic arch and a patent ductus arteriosus delivering desaturated blood to the legs. If the right subclavian artery arises proximal to the aortic obstruction, the right hand may be pink and the left hand cyanotic. When an anomalous right subclavian artery originates from the descending aorta, however, both hands are cyanotic. Cyanosis of the fingers greater than that in the toes suggests complete transposition of the great vessels with preductal coarctation or complete interruption of the aortic arch, pulmonary hypertension, and a reverse shunt through a patent ductus arteriosus delivering oxygenated blood to the lower extremities (Fig. 10-14, Plate 31). In this anomaly, the presence of aortic coarctation can be distinguished from complete interruption of the aortic arch. Slightly less cyanosis of the left arm when compared with the right arm favors aortic coarctation, whereas intense symmetric cyanosis of both arms is seen with complete aortic interruption. Red fingertips ("tuft erythema") may signify a small, intermittent right-to-left shunt with only slight reduction in arterial oxygen saturation (Fig. 10-15, Plate 32).

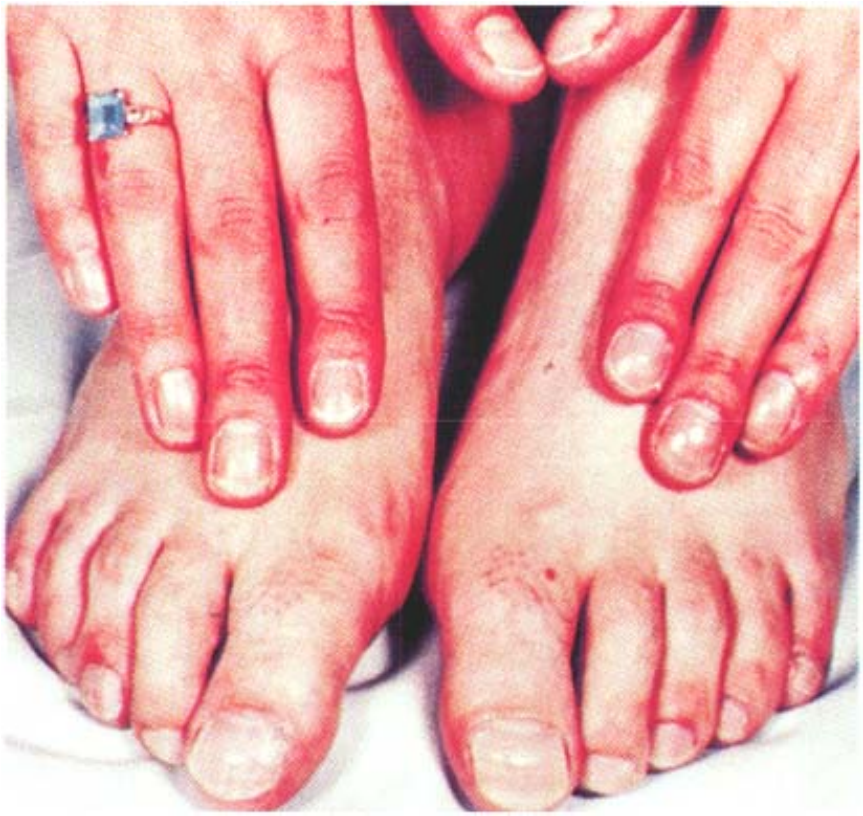


Figure 10-14: (Plate 31) *Differential cyanosis*. Clubbing of left hand (compare thumbs) and cyanosis of left hand and all toes due to patent ductus arteriosus with pulmonary hypertension and normally related great vessels. (Courtesy of Dr. Joseph K. Perloff, University of California, Los Angeles.)

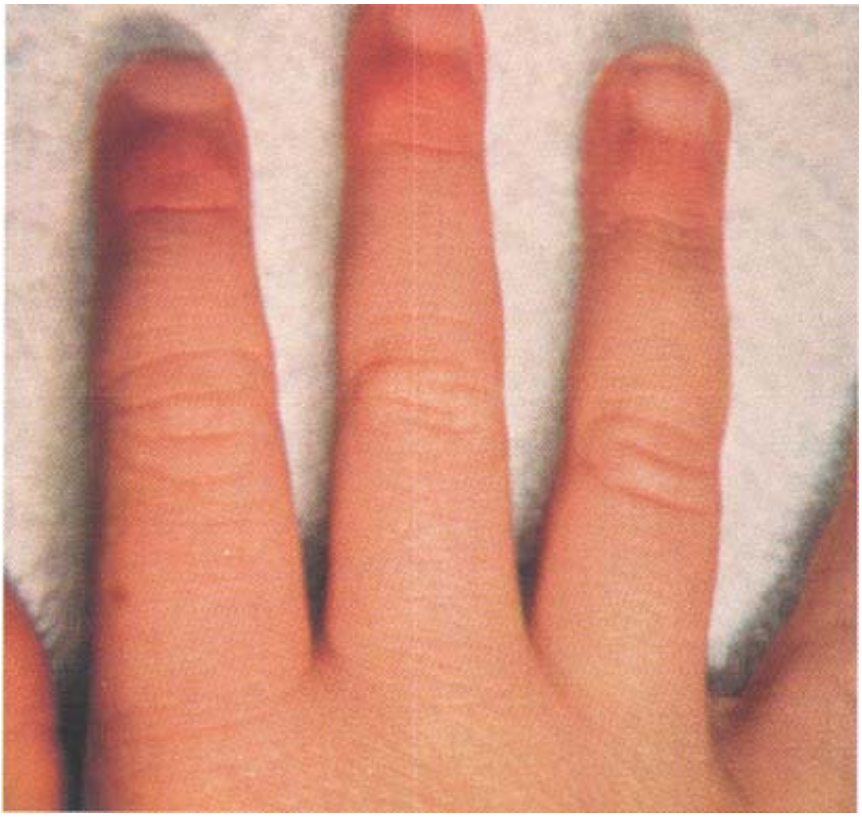


Figure 10-15: (Plate 32) *Tuft erythema*. Erythema of fingertips due to small right-to-left shunt from AV canal defect.

Anotia (congenital absence of the pinna) and facial paralysis may be signs of an underlying VSD and pulmonic stenosis.[73] The presence of any congenital somatic abnormality always should prompt a search for congenital heart disease. Extracardiac anomalies were found in 25 percent of infants seen during the first year for significant cardiac disease in one study.[74] The defects were commonly found in the musculoskeletal system and were associated with specific syndromes.

Disorders Affecting the Valves

The cutaneous lesions of *infective endocarditis* (see Chap. 73) include Osler's nodes, Janeway lesions, clubbing of the fingers (Fig. 10-16, Plate 33), splinter hemorrhages of the nails, and petechiae.[75,76] *Osler's nodes* are reddish purple, tender nodules typically found in the distal pad of the finger or toe (Fig. 10-17, Plate 34). By contrast, *Janeway lesions* are hemorrhagic but nontender and involve the palms or soles. Splinter hemorrhages are linear and black and affect the distal third of the fingernail. They are also present in many unrelated diseases and may result from trauma in otherwise healthy people.

Certain features suggest primary valvular heart disease (see Chaps. 56, 57, and 59). Pulmonic stenosis may be part of Noonan's syndrome, Turner's syndrome (previously discussed), Rubinstein-Taybi syndrome, rubella syndrome (see above), the multiple-lentigines syndrome, pulmonary valve dysplasia, or Watson's syndrome. In *Noonan's syndrome*,[77] the characteristic findings include ptosis, low-set ears, downward-slanting eyes, webbed neck, hypertelorism, low posterior hairline, short stature, mental retardation, and normal chromosomes (Fig. 10-18). Broad toes and thumbs, a slanting forehead, a thin, beaked nose, and large, low-set ears are seen in *Rubinstein-Taybi syndrome*[78] (Fig. 10-19). Café-au-lait spots and mental retardation are linked to pulmonic valve stenosis in *Watson's syndrome*.

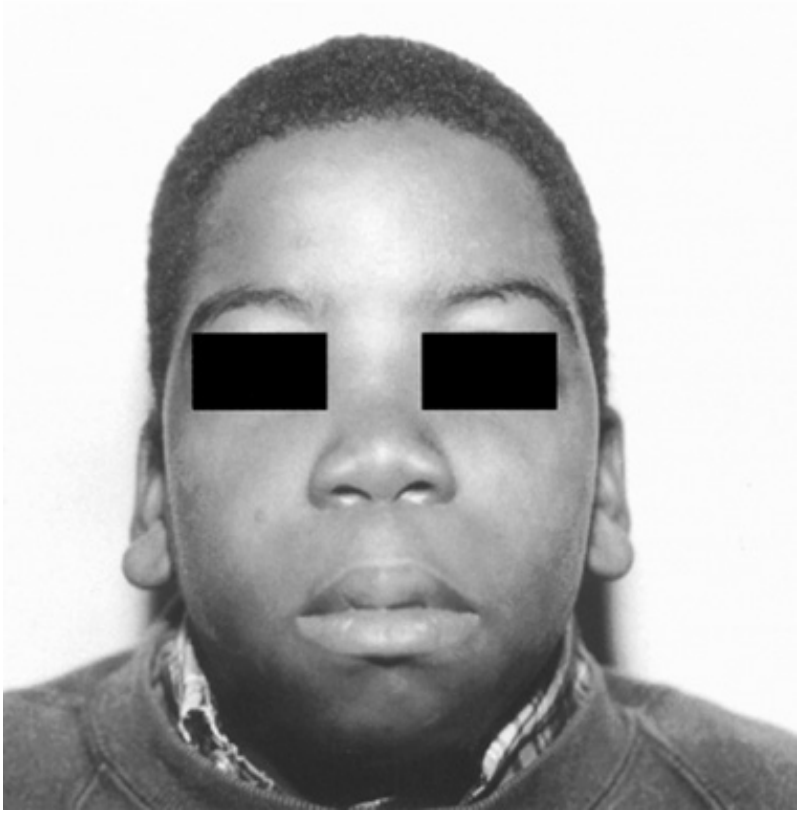


Figure 10-18: *Noonan's syndrome:* ptosis, hypertelorism, and low-set ears associated with valvular pulmonic stenosis.

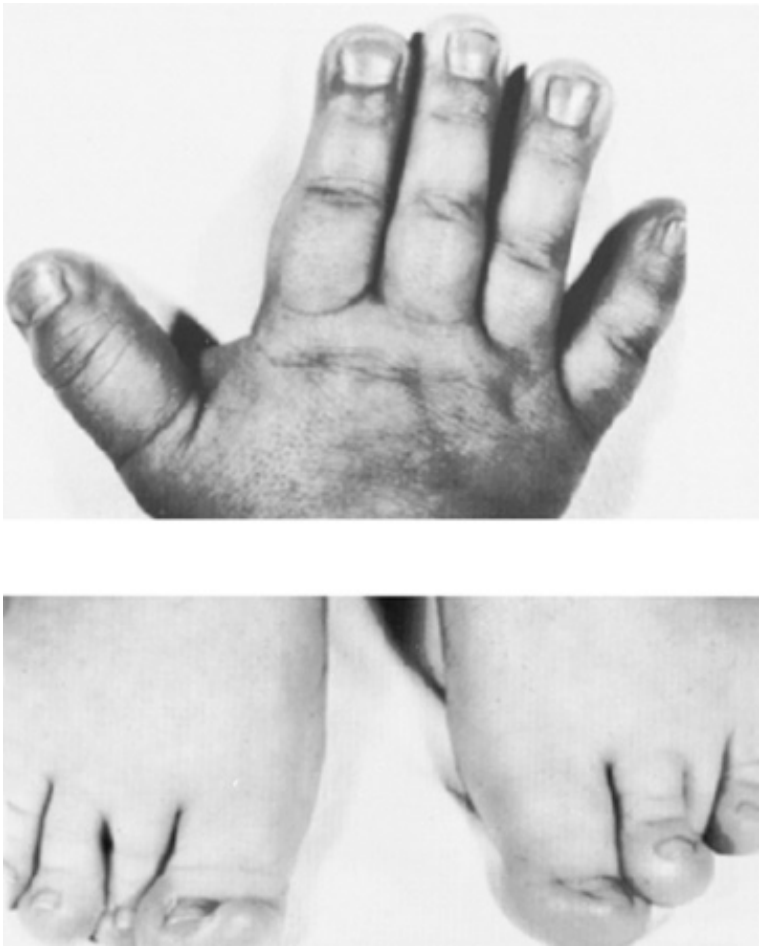


Figure 10-19: *Rubinstein-Taybi syndrome* may be associated with a variety of congenital heart defects. (From Silverman ME, Hurst JW. The hand and heart. *Am J Cardiol* 1968; 22:718. Reproduced with permission from the publisher and authors.)

The *multiple-lentigines syndrome* is identified by the presence of multiple tan to brown macules varying in size from pinpoint to 5 cm in diameter (Fig. 10-20). These cutaneous lesions may affect the entire body but are most heavily concentrated on the neck and upper thorax. Other findings in this syndrome include hearing loss, short stature, hypertelorism, ptosis, prognathism, pectus excavatum or carinatum, kyphoscoliosis, café-au-lait spots, and other skeletal defects.[79]

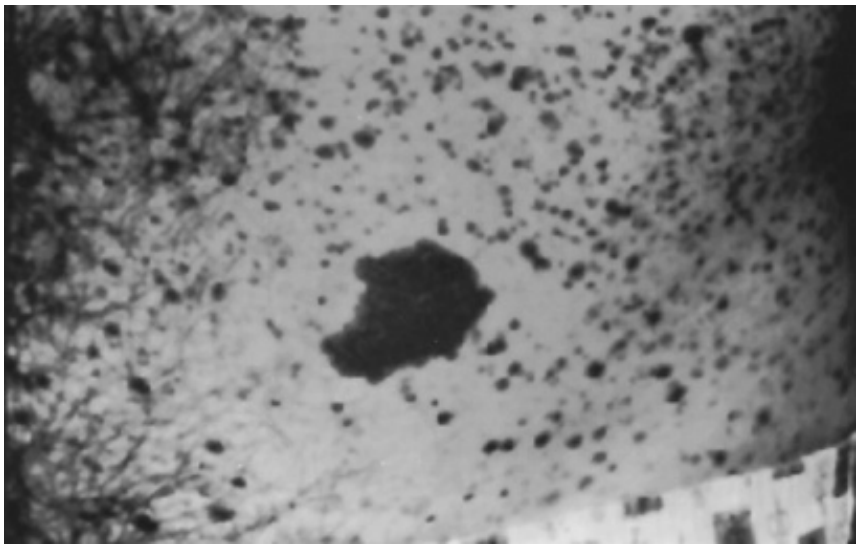


Figure 10-20: *Multiple lentigines syndrome:* dark-brown macular lesions of the abdomen associated with hypertrophic subaortic stenosis. (From Silverman ME. Visual clues to diagnosis. *Primary Cardiology*, October 1986. Reproduced with permission from the publisher and author.)

The *carcinoid syndrome* (see Chap. 77) may present as intense flushing of the face; a chronic cyanotic hue and telangiectasia may be present. Stenosis and/or regurgitation of the tricuspid and/or pulmonic valves often results when hepatic metastases are present.[80] When a patent ductus arteriosus, lung metastases, or a patent foramen ovale is present, the left-sided heart valves can be affected.

In *progressive systemic sclerosis* (scleroderma), tightening of the skin on the fingers and then the hands, forearms, upper chest, and face is associated with hair loss and disappearance of subcutaneous tissue and skin creases (Fig. 10-21). Flexion contractures on the fingers may cause a clawlike hand deformity. Raynaud's phenomenon is an early manifestation. The *CREST syndrome (calcinosis, Raynaud's esophageal involvement, sclerodactyly,* and *telangiectasia*) is a variant of scleroderma (Fig. 10-22). Although valvular changes include thickening of the edges of the mitral, aortic, and tricuspid valves, as well as thickening and shortening of the mitral chordae, the resulting valve disease is rarely significant.[81]

Figure 10-21: *Scleroderma:* clawlike hand deformity and shiny, tight skin. May be linked with myocardial fibrosis.

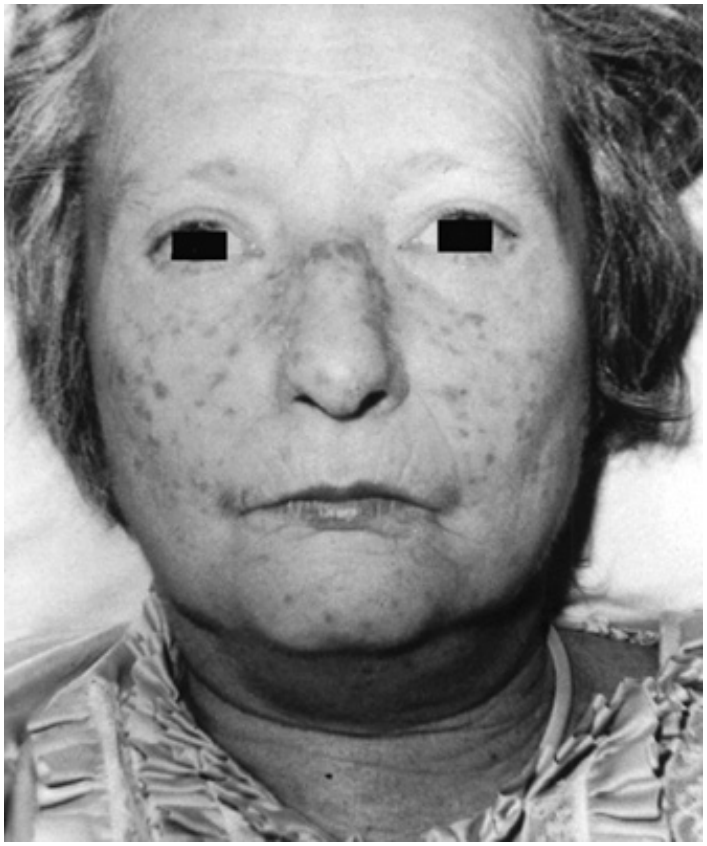


Figure 10-22: *CREST syndrome*. Telangiectasia of the face in a patient with Raynaud's phenomenon and sclerodactyly.

Joint disease associated with cardiac valvular disease is frequent with systemic lupus erythematosus, rheumatoid arthritis, rheumatic fever, polychondritis, ankylosing spondylitis, alkaptonuria, and Whipple's disease. In systemic lupus erythematosus, the joint inflammation is usually symmetric and nondeforming. Typical skin lesions include an erythematous, scaling eruption over the cheeks and bridge of the nose, circumscribed reddish purple plaques, telangiectasia, and patchy hair loss (Fig. 10-23). Verrucous endocarditis may involve any of the four cardiac valves; however, severe valvular dysfunction is unusual.[82,83] Sessile, small, nonbacterial vegetations and valvular thickening causing regurgitation rather than stenosis may be more common in patients with antiphospholipid antibodies[84] (see Chap. 76).

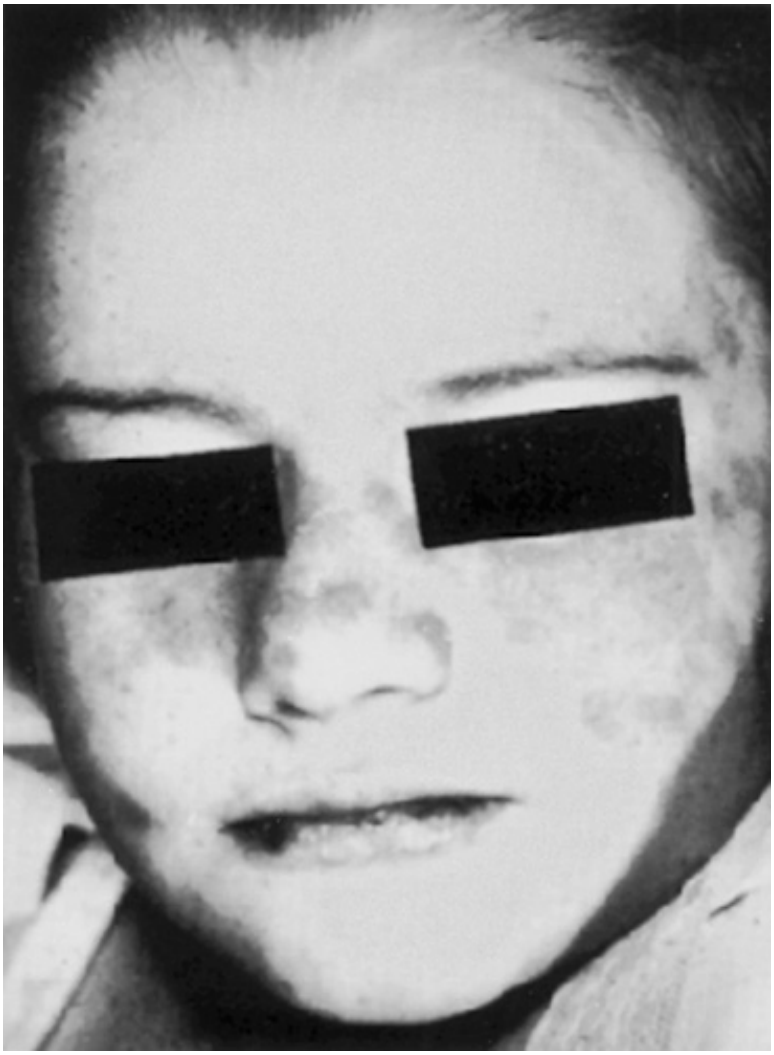


Figure 10-23: *Systemic lupus erythematosus:* butterfly rash associated with pericardial, myocardial, and endocardial disease.

In patients with *rheumatoid arthritis,* the metacarpophalangeal joints, proximal interphalangeal joints, wrists, metatarsophalangeal joints, shoulders, knees, ankles, and elbows are involved with inflammation and subsequent destruction. Advanced disease results in ulnar deviation of the fingers and flexion of the distal interphalangeal joints with hyperextension of the proximal interphalangeal joints, producing a "swan neck" deformity and a Z-shaped configuration of the

thumb (Fig. 10-24, Plate 35). Subluxation of the metacarpophalangeal joints with interosseal muscle wasting and thickening of the wrists are common. Granulomatous aortic or mitral valve disease with regurgitation is most common in patients who are seropositive and have subcutaneous nodules or classic rheumatoid deformities.[85] Rheumatic fever, often with cardiac involvement, should be suspected in patients with erythema marginatum, urticaria, and migratory polyarthritis involving the large joints (see Chap. 55). Subcutaneous nodules are found less frequently. Marked ulnar deviation at the metacarpophalangeal joints, suggesting rheumatoid arthritis, can be due to repeated attacks of rheumatic fever and is known as *Jaccoud's* or *post-rheumatic fever arthritis*. In contrast to rheumatoid arthritis, the fingers can be moved freely into a correct alignment, and x-rays of the hands are normal. It also occurs in systemic lupus erythematosus (SLE).

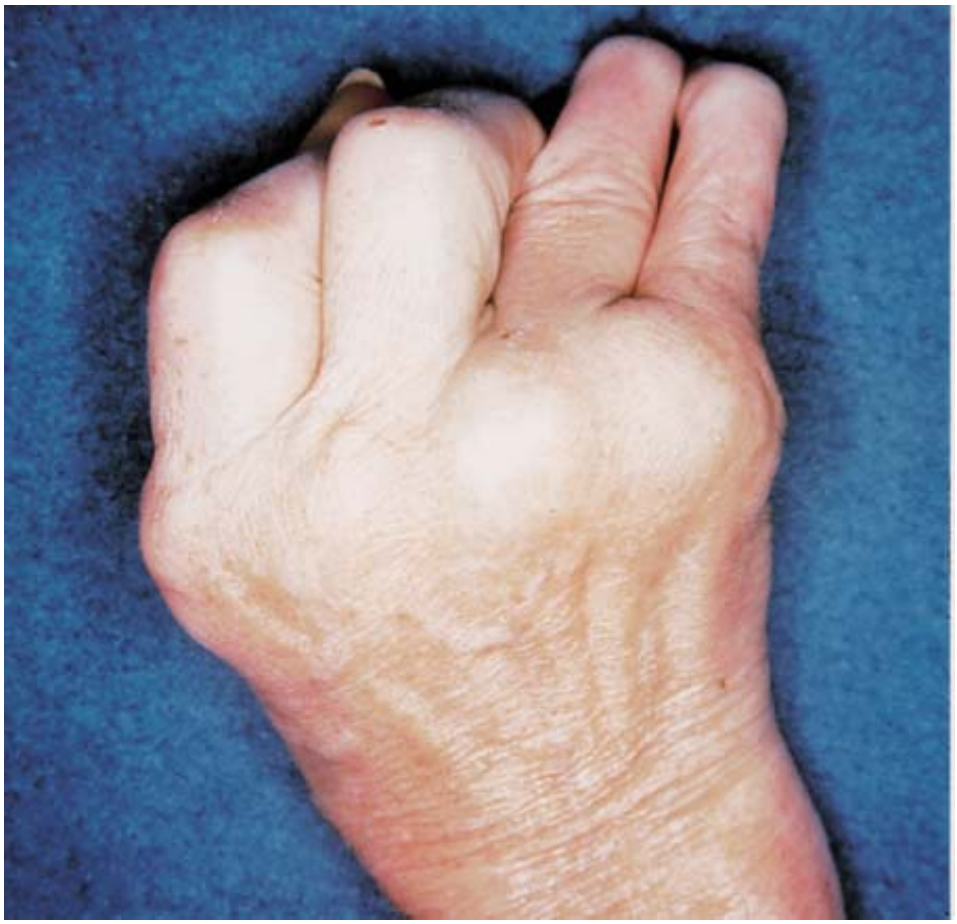


Figure 10-24: (Plate 35) *Rheumatoid arthritis:* with ulnar deviation of the fingers, flexion of the distal interphalangeal joints with hyperextension of the proximal interphalangeal joints.

Polychondritis causes an inflammatory destruction of the cartilage of the face, resulting in a saddle-shaped collapse of the nose or a cauliflower ear. Aortic regurgitation, aortic aneurysm, and rarely aortic root dissection are associated[86] (Fig. 10-25).

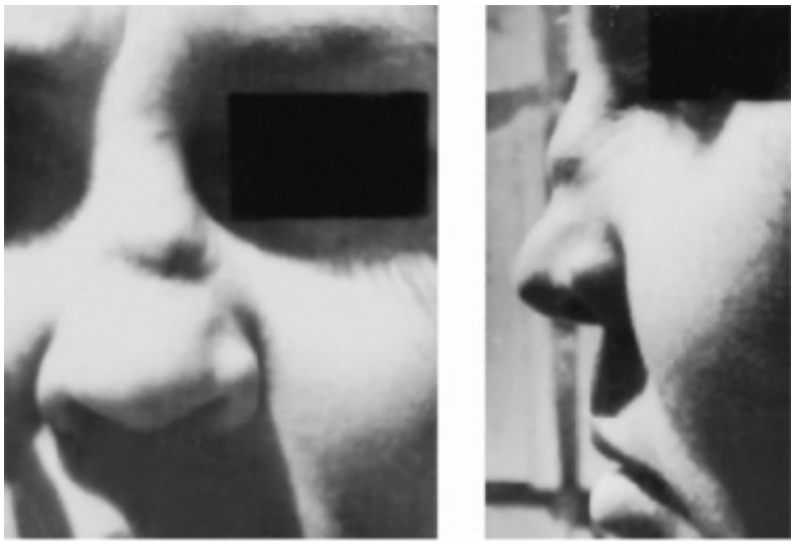


Figure 10-25: *Polychondritis. A,B.* Destruction of cartilage of the nose, producing a "saddle nose" in association with aortic regurgitation. (Courtesy of Dr. Warren Sarrell, Anniston, AL.)

Chronic synovitis involving the fibrocartilaginous joints of the spine occurs in patients with ankylosing spondylitis. The disease may be confined to a sacroiliac area or spread slowly upward. The patient with advanced disease is bent forward, is unable to stand upright, and must walk with a stiff and halting gait (Fig. 10-26). Aortic regurgitation due to thickening and shortening of the aortic cusps from perivascular inflammation and fibrosis occurs in up to 10 percent of patients.[87] Mitral regurgitation and complete heart block also may occur. Cogan's syndrome, consisting of ophthalmic inflammation and audiovestibular symptoms, is another cause of vasculitis involving the aortic root and leading to aortic regurgitation and coronary disease.[88]

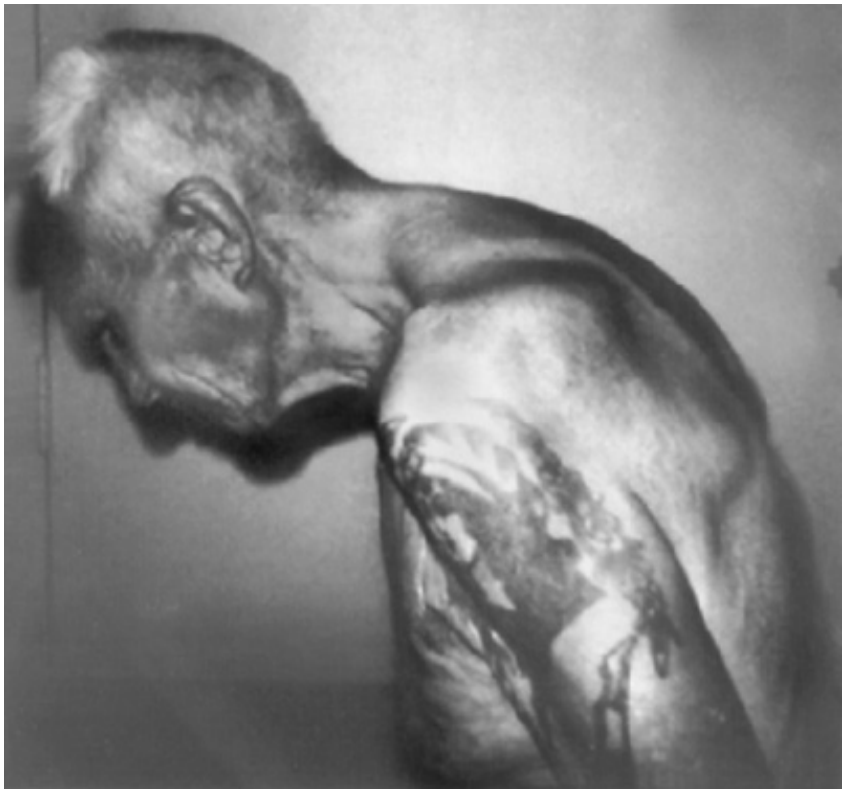


Figure 10-26: *Ankylosing spondylitis:* immobile, curved spine with forward jutting of head. May be seen with AV block or aortic regurgitation. (From Silverman ME. Visual clues to diagnosis. *Primary Cardiology*, June 1987. Reproduced with permission from the publisher, author, and patient.)

Whipple's disease is suggested by the combination of polyarthritis, abdominal pain, and diarrhea. Aortic and mitral regurgitation and endocarditis are known complications.[89] Aortic or mitral valvular disease also may be due to an accumulation of homogentisic acid in *alkaptonuria*. Blue-black, stiff pinnae and joints are important clues to this inherited disorder of tyrosine metabolism.

External signs of mitral valve prolapse (see Chap. 58) include a straight thoracic spine, pectus excavatum, scoliosis, hypomastia, joint laxity, and various neuromuscular disorders. Systolic and rarely diastolic murmurs have been described with chest wall deformities due to *straight-back syndrome* and *pectus excavatum* (Fig. 10-27, Plate 36) that may impinge on or displace the heart.

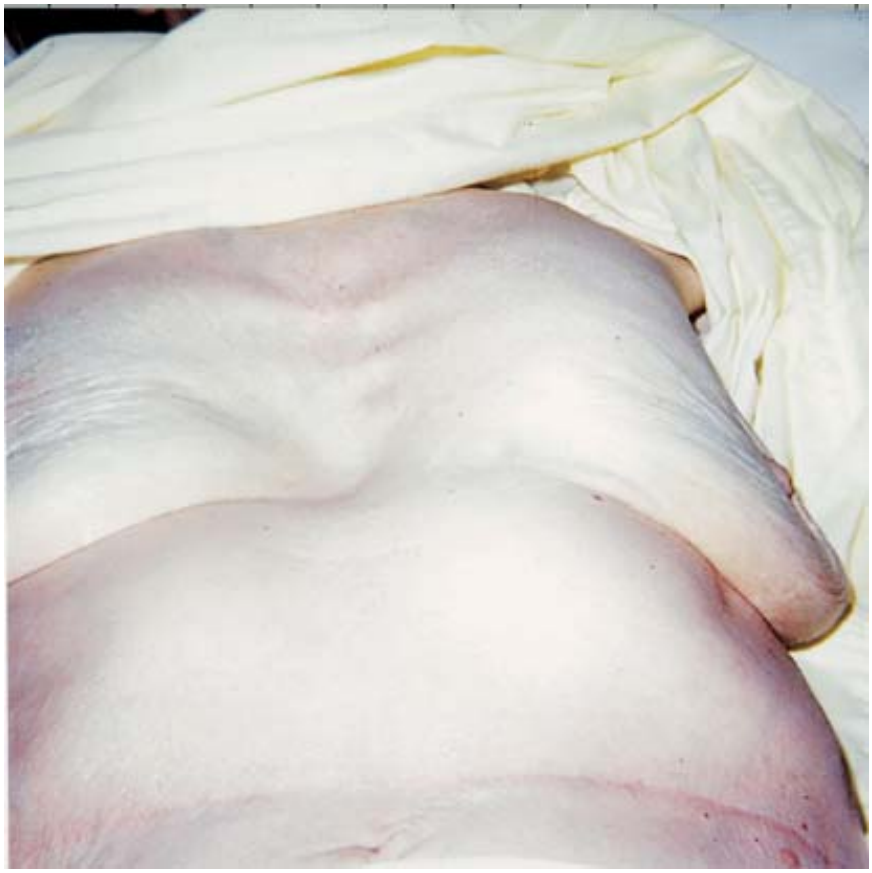


Figure 10-27: (Plate 36) Marked pectus excavatum.

Disorders Associated with Cardiomyopathy

Hypertrophic cardiomyopathy (see Chap. 67) has been associated with *Friedreich's ataxia*, Turner's syndrome, Noonan's syndrome, Fabry's disease, neurofibromatosis, and the multiple-lentigines syndrome. Friedreich's ataxia is a spinocerebellar degenerative disorder that results in a broad-based, lurching gait, impaired vibration, position, and joint sense, and incoordination. Kyphoscoliosis and pes cavus (high instep, retraction of the toes at the metatarsophalangeal joints, and hammer toes) are two important physical signs (Fig. 10-28). Concentric and asymmetric LV hypertrophy that may evolve into a dilated cardiomyopathy have each been described.[90]

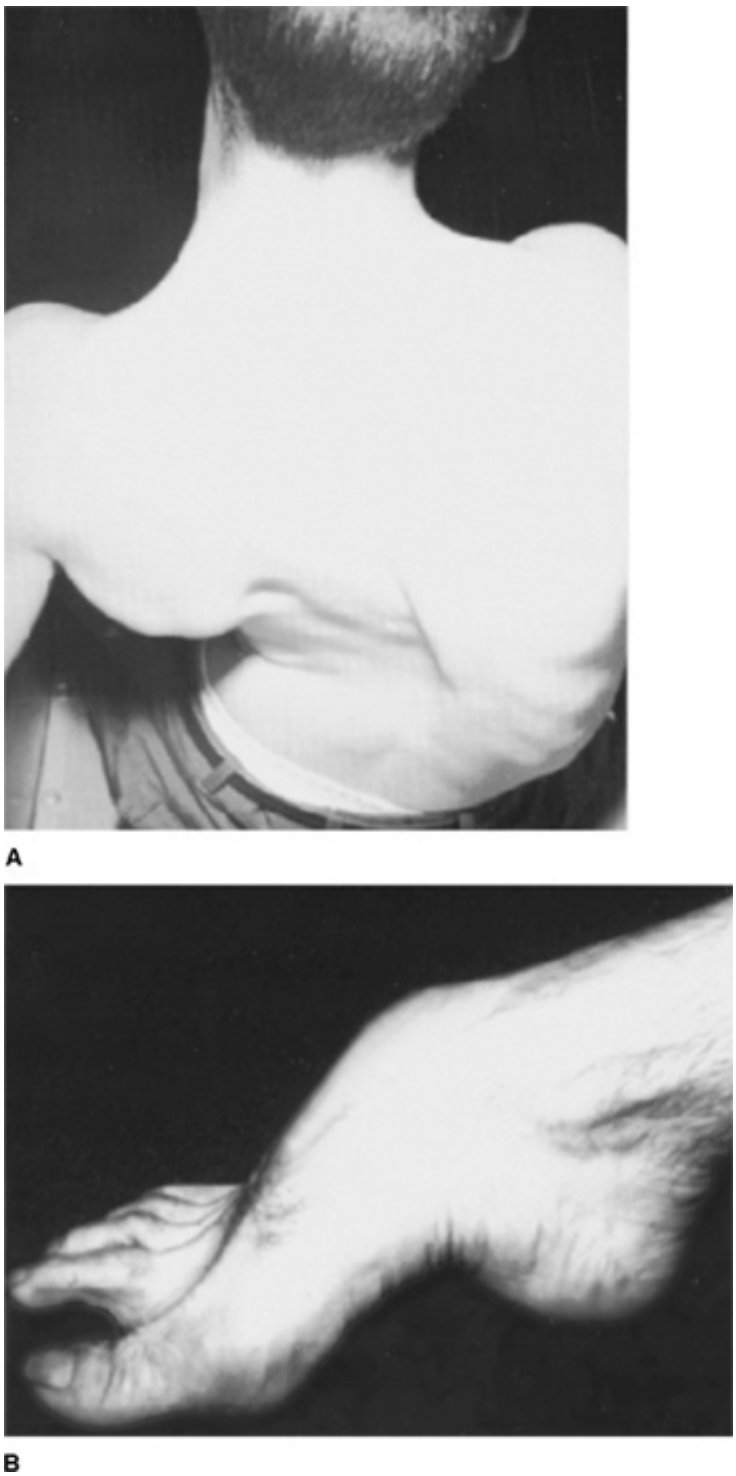


Figure 10-28: *Friedreich's ataxia* (photographs from different patients). *A.* Kyphoscoliosis. *B.* Pes cavus. Myocardial fibrosis and hypertrophy are often present. (From Silverman ME. Visual clues to diagnosis. *Primary Cardiology*, June 1987. Reproduced with permission from the publisher and authors.)

Myocardial hypertrophy may be secondary to extreme obesity or acromegaly. With acromegaly, the broad forehead, thickened skin, and enlarged nose, lip, and tongue produce coarsened facial features (Fig. 10-29), whereas elongation of the mandible leads to prognathism and overbite. The large, sausage-shaped fingers and spadelike configuration of the hands are typical.[91]

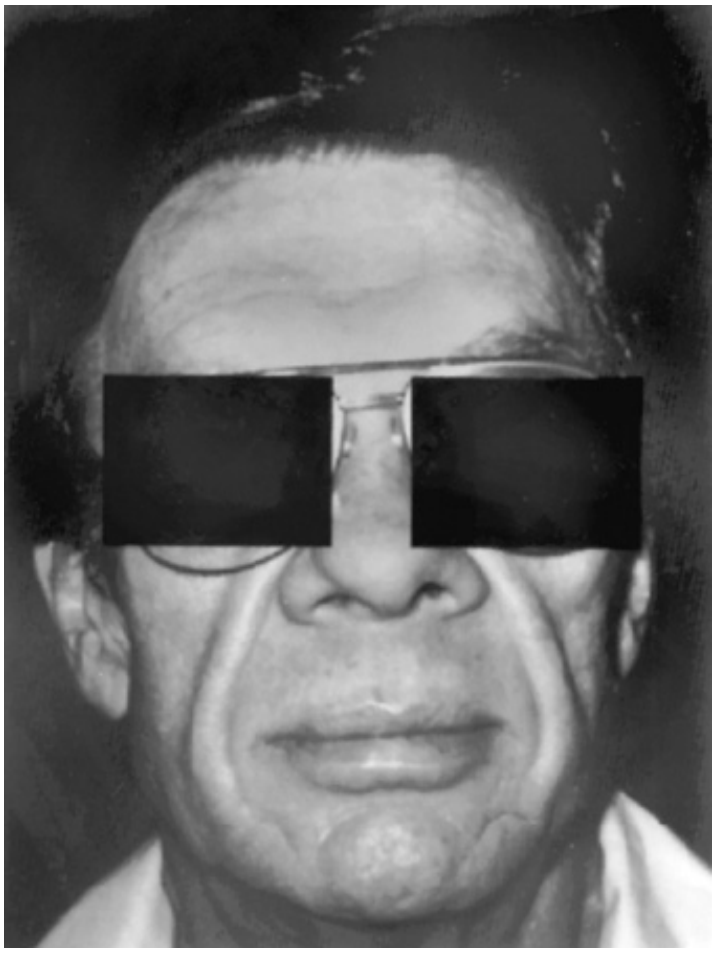


Figure 10-29: *Acromegaly*. Coarse facial features, folds of skin, and prognathism are associated with myocardial hypertrophy and fibrosis. (From Silverman ME. Visual clues to diagnosis. *Primary Cardiology*, February1987. Reproduced with permission from the publisher, author, and patient.)

Cor pulmonale and RV hypertrophy may be secondary to pulmonary hypertension caused by *kyphoscoliosis, restrictive lung disease, progressive systemic sclerosis, upper airway blockade* by enlarged tonsils[126] and adenoids, or the *sleep apnea syndrome* associated with extreme obesity.[92,93]

Myocarditis (see Chap. 69) occurs with SLE, rheumatic fever, Reiter's syndrome,[94] Kawasaki's disease,[95] Lyme arthritis,[96] and occasionally, Whipple's disease. Reiter's syndrome is characterized by conjunctivitis and hyperkeratotic coalescing lesions encrusted on the soles and palms, associated with arthritis and urethritis (Fig. 10-30, Plate 37). Kawasaki's disease begins with fever, nonexudative conjunctivitis, dry, fissured lips, cervical adenopathy, and a strawberry tongue. Later, the palms and soles become indurated and purplish red and then peel. A widespread erythematous rash may appear and then desquamate. *Lyme arthritis*, caused by the spirochete *Borrelia burgdorferi*, begins with a red macule or papule and then develops into an expanding erythematous rash with a bright red border known as *erythema migrans* (Fig. 10-31). The center of the rash may clear, indurate, blister, or become necrotic. Multiple annular lesions may develop.

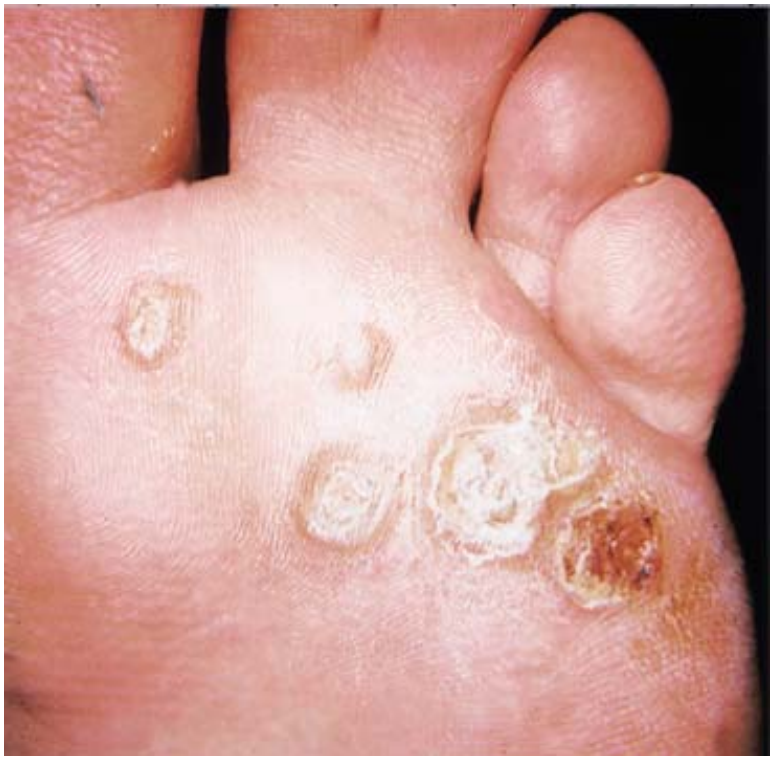


Figure 10-30: (Plate 37) *Hyperkeratotic lesions* encrusted on the soles of the feet in Reiter's syndrome.

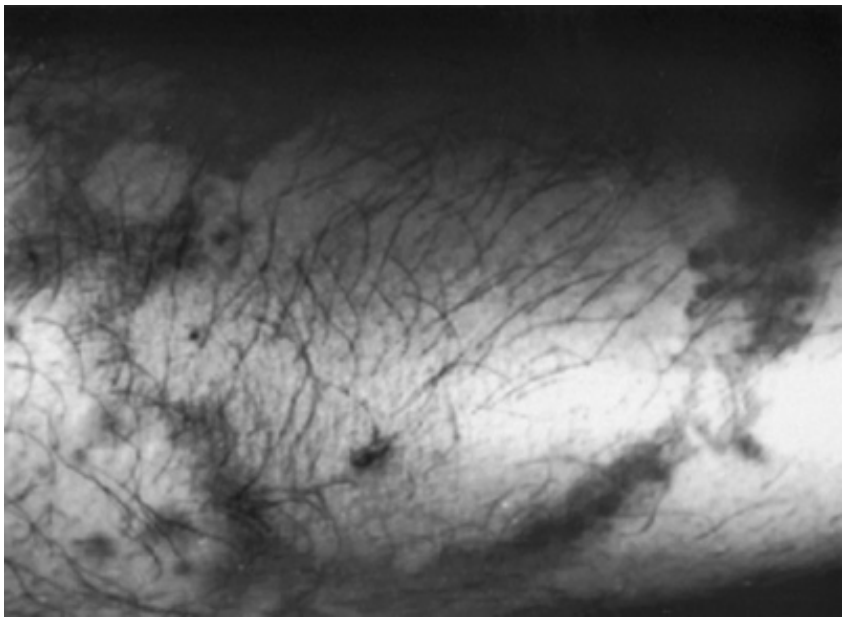


Figure 10-31: *Lyme arthritis:* annular expanding rash with a clear central area. May be associated with pericarditis and AV block. (From Silverman ME. Visual clues to diagnosis. *Primary Cardiology*, December 1986. Reproduced with permission from the publisher and author.)

Diseases that cause myocardial fibrosis include dermatomyositis, Duchenne's and Becker's muscular dystrophy, myotonic muscular dystrophy, Kearns-Sayres syndrome, Friedreich's ataxia, sarcoidosis, and progressive systemic sclerosis (see Chaps. 62 and 76). With dermatomyositis, an erythematous eruption and periorbital heliotropic discoloration affects the face (Fig. 10-32, Plate

38), and a scaly, erythematous rash may cover the knuckles, sparing the interphalangeal region.[97] A waddling gait and pseudohypertrophic calves are characteristic of Duchenne's muscular dystrophy. The ECG is commonly consistent with fibrosis of the posterior left ventricle.[98] In *myotonic dystrophy*, drooping eyelids, cataracts, a receding hairline, and a masklike expression are present.[99] The *Kearns-Sayre syndrome* is a form of ocular muscular dystrophy in which external ophthalmoplegia, ptosis, and retinitis pigmentosa occur.[100] The skin manifestations of sarcoidosis include erythema nodosum, lupus pernio (a red or violet plaque with a predilection for the nose, cheeks, eyelids, and ears), and waxy translucent papules found on the cheeks, periorbital area, ears, nasolabial folds, and elsewhere.[101] Uveitis, bilateral parotid and lacrymal gland enlargement, and arthritis are other signs (see Chap. 68).

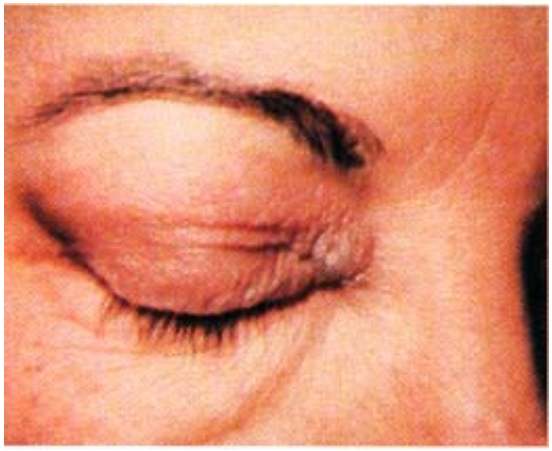


Figure 10-32: (Plate 38) *Dermatomyositis*. A violaceous hue and edema of upper eyelid may be associated with myocardial disease.

Isolated noncompaction of the LV myocardium is characterized by numerous, prominent ventricular trabeculations, deep intertrabecular recesses, arrhythmias, and a distinctive facial dysmorphism.

Infiltrative diseases of the myocardium include Wilson's disease, Cori's disease, Fabry's disease, hemochromatosis, amyloidosis, glycogen storage disease, and sarcoidosis (see Chap. 68). *Wilson's disease* is an autosomal recessive disorder in which copper accumulates in tissues, including the myocardium.[102] Arrhythmias, autonomic dysfunction, and cardiomyopathy have been reported. Kayser-Fleischer rings, usually golden-brown in color and circling the edge of the cornea, provide a major clue to the correct diagnosis.

Cori's disease (type III glycogenosis) is suspected when a patient has xanthomas and a yellowish skin. In *hemochromatosis*, the skin has a bronze or slate-gray coloration; myocardial infiltration with iron deposits often causes a dilated or rarely a restrictive cardiomyopathy associated with arrhythmias and heart failure.[103] Macroglossia and waxy nodules of the skin and eyelids, which may hemorrhage when pinched, are clues to the diagnosis of *amyloidosis*[104] (Fig. 10-33) (see Chap. 68). Glycogen storage disease and myxedema also can enlarge the tongue.

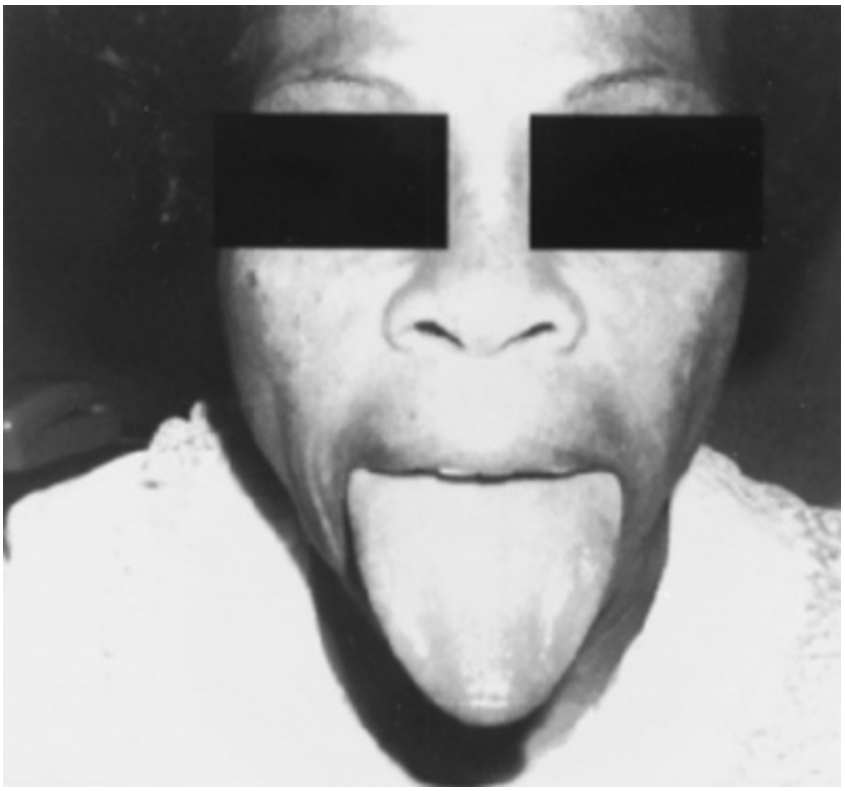


Figure 10-33: *Amyloidosis*. Enlarged tongue may be a sign of an infiltrative cardiomyopathy. (From Silverman ME. Visual clues to diagnosis. *Primary Cardiology*, November1987. Reproduced with permission from the publisher, author, and patient.)

Disorders Associated with Pericardial Disease

Pericarditis may be a result of Reiter's syndrome, Whipple's disease, Kawasaki's disease, SLE, rheumatoid arthritis,[105] rheumatic fever, sarcoidosis, scleroderma, dermatomyositis, hemochromatosis, Behçet's disease, Degos' disease, uremia, mulibrey nanism, polychondritis, hypothyroidism, or metastatic disease among others (see Chap. 72). The components of *Behçet's disease* include erythema nodosum, superficial phlebitis, oral and genital ulcers, and iritis.[106] Patients with *Degos' disease* (malignant atrophic papulosis) present with painless, oval cutaneous lesions that have a white center and surrounding erythema. In this rapidly fatal disease, occlusive fibrosis of small and medium-sized arteries produces pleuritis and pericarditis. In far-advanced renal disease, urochrome pigmentation of the skin and uremic frost are cutaneous manifestations. The term *mulibrey nanism* describes a syndrome involving muscle, liver, brain, and eyes.[107] These patients have a triangular face, bulging forehead, low nasal bridge, growth retardation, pigmentary changes in the fundus, hemangiomas, and constrictive pericarditis. Hypothyroidism, a cause of often massive pericardial effusions, thickens the face and causes dry hair, puffy eyelids, and an enlarged tongue.

Disorders Causing Conduction System Disease

Acquired causes of atrioventricular (AV) block or bundle-branch block include sarcoidosis,[101] rheumatic fever, gout, Reiter's syndrome,[108] dermatomyositis, amyloidosis, Kawasaki's disease,[95] ankylosing spondylitis,[109] SLE,[83] and Lyme arthritis.[96] In gout, uric acid crystals may form nodules affecting the conduction system. AV block may be an early cardiac manifestation of ankylosing spondylitis.

Inherited or congenital disorders associated with conduction defects include SLE, Fabry's disease,

Friedreich's ataxia, Kearns-Sayre syndrome, multiple-lentigines syndrome, muscular dystrophy, myotonic dystrophy, tuberous sclerosis, and Refsum's disease. Maternal lupus is an important cause of congenital complete AV block in the newborn.[82] In *Refsum's disease,* a lipidosis and genetically determined neuropathy characterized by high levels of phytanic acid, cerebellar ataxia, night blindness, deafness, ichthyosis, cataracts, and polyneuropathy have been associated with myocardial disease and conduction abnormalities.

Syndactyly (webbing of the hands or feet) has been found with a long QT interval-a syndrome with a high risk of sudden death.[110]

Disorders Affecting the Vascular System

Aortic aneurysms and dissection (see Chap. 88) are frequent cardiovascular complications of Marfan's and Ehlers-Danlos syndromes. Aneurysms of other vessels and arterial rupture also may occur. A progressive looseness of skin producing pendulous folds and droopy eyelids can be due to cutis laxa, a generalized destruction of elastic tissue that can cause dilatation of the aorta or pulmonary artery and aortic rupture.[51]

Coronary artery stenosis from atherosclerosis can be associated with hyperlipidemia,[111] cerebrotendinous xanthomatoses, Werner's syndrome, uremia, progeria, acromegaly, and diabetes mellitus. *Hyperlipidemia* may be suspected when xanthomas or arcus senilis are present. Xanthelasma usually involve the upper eyelid. When they occur before age 50, there is a strong association with familial hypercholesterolemia and premature CAD. Eruptive xanthomata are recognized as papules with yellow centers surrounded by an erythematous halo. They often appear with a sudden outbreak of discrete 1- to 4-cm lesions on the buttocks, back, thighs, and exterior surfaces of the knees and elbows. They indicate a very high level of triglycerides and are associated with hyperlipidemia, diabetes mellitus, pancreatitis, myxedema, and the nephrotic syndrome. Tendon xanthomata are firm, painless nodules that thicken the exterior tendons of the hand, the Achilles tendons, and sometimes the tendons of the knees and elbows (Fig. 10-34). *Cerebrotendinous xanthomatosis* is a rare disorder in which tendon xanthomata, cataracts, dementia, ataxia, neuropathy, and accelerated atherosclerosis are present. Tuberous xanthomata are yellow to deep-orange papules erupting over the elbows, knees, buttocks, and heels. They may coalesce or be pedunculated and are a manifestation of hyperlipidemia, myxedema, and liver disease. Large, orange, lobulated tonsils are a finding in *Tangier disease,* in which there is deficiency of high-density lipoprotein.

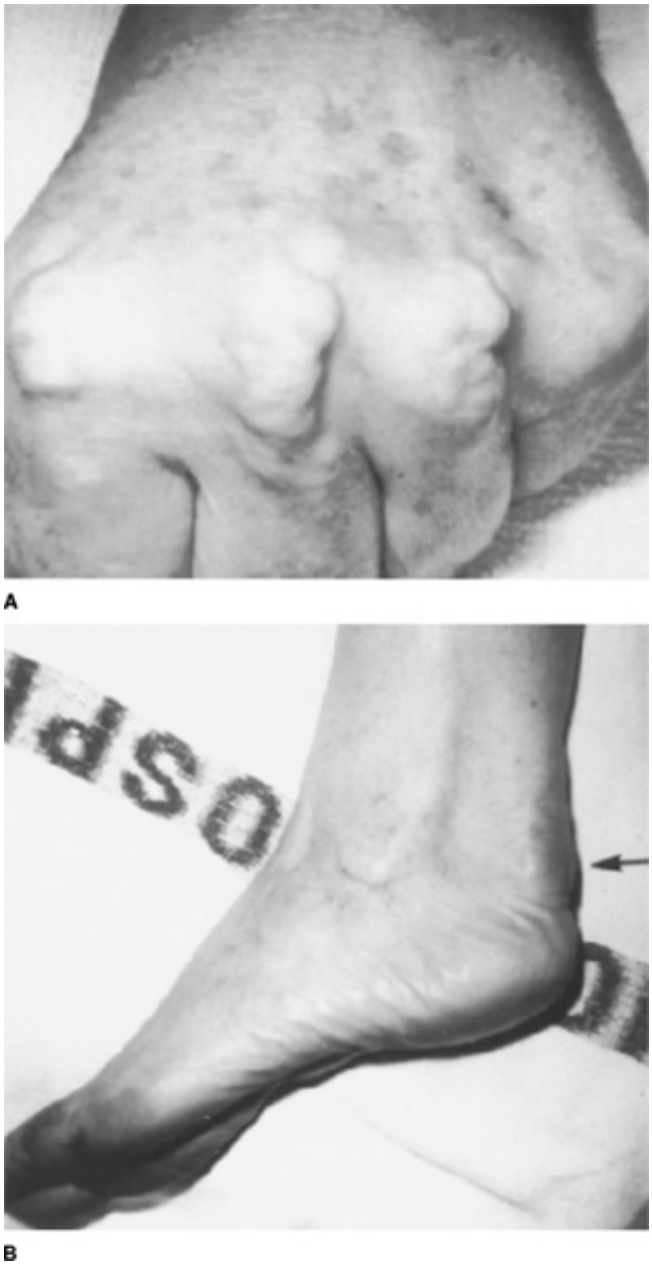


Figure 10-34: *Hyperlipidemia:* xanthomata associated with coronary artery disease. *A*. On the extensor tendons of the hand. *B*. On the Achilles tendon (arrow).

In *Werner's syndrome*, the skin is tightly stretched over the underlying bones.[112] There is marked loss of subcutaneous tissue, and ulcerations occur over the legs. Severe coronary atherosclerosis often results in MI at an early age. Physical findings in diabetes mellitus may include tight skin and necrobiosis diabeticorum, an atrophy of the skin of the lower extremities characterized by ovoid plaques with central telangectasia and a violet, undurated perimeter. *Progeria* is a rare disorder in which the face is small and prematurely aged, the eyes bulge, and the nose is beaked. Severe atherosclerosis with early MI is a common cause of death in early life.[113] A diagonal earlobe crease and short tufts of ear-canal hair curiously have been associated with coronary artherosclerosis.[114] There is a modest correlation between male-pattern baldness involving the vertex of the scalp in men under 55 years of age and an increased risk of MI.[115] Patients resemble those with Marfan's syndrome because they have long extremities, pectus carinatum, and kyphoscoliosis. Pseudoxanthoma elasticum has been associated with fibrosis of the coronary artery and calcification of peripheral arteries[116] (see Chap. 76). A glycosphingolipid is deposited in the arterial endothelium of patients with Fabry's disease and may result in angina pectoris or MI. Patients with Hurler's syndrome have mental retardation, a large, boat-shaped head, a broad

nose, large lips, small, widely spaced teeth, and a large, protuberant tongue. Glycosaminoglycan deposition in the coronary arteries is present.[117] Myocardial fibrosis due to repeated coronary small-vessel spasm has been postulated to be a result of progressive systemic sclerosis.[81]

Vasculitis may be due to SLE, rheumatoid arthritis, Behçet's disease,[108] Kawasaki's disease, and polyarteritis. Cutaneous infarction, nodules, petechiae, livedo reticularis, gangrenous digits, MI, heart failure, and hypertension may be due to polyarteritis[118] (see Chap. 76).

Arteriovenous shunts may be found in extensive skin disease, hereditary *hemorrhagic telangiectasia,* and the Klippel-Trenaunay-Weber syndrome. *Kaposi's sarcoma* or exfoliative dermatitis due to psoriasis may divert the blood supply through shunts in the skin to produce high-output cardiac failure. Clues to underlying arteriovenous fistula as a cause of high-output failure include a barely discernible scar from a knife wound or a surgical incision. Telangiectasias of the fingertips, face, palate, lips, and tongue, as well as pulmonary and hepatic arteriovenous fistulas, are components of *hereditary hemorrhagic telangiectasia*.[44] The triad of anomalies that Klippel-Trenaunay-Weber syndrome comprises are vascular nevus, large varices, and bony or soft tissue hypertrophy.[119] Marked enlargement of a limb(s) and facial hemihypertrophy are features of this disorder, in which part or all of the deep venous system is absent and arteriovenous malformation is often present. Hemangiomas of the skin also may indicate multinodular hemangiomatosis of the liver, a cause of high-output heart failure in infancy (Fig. 10-35).

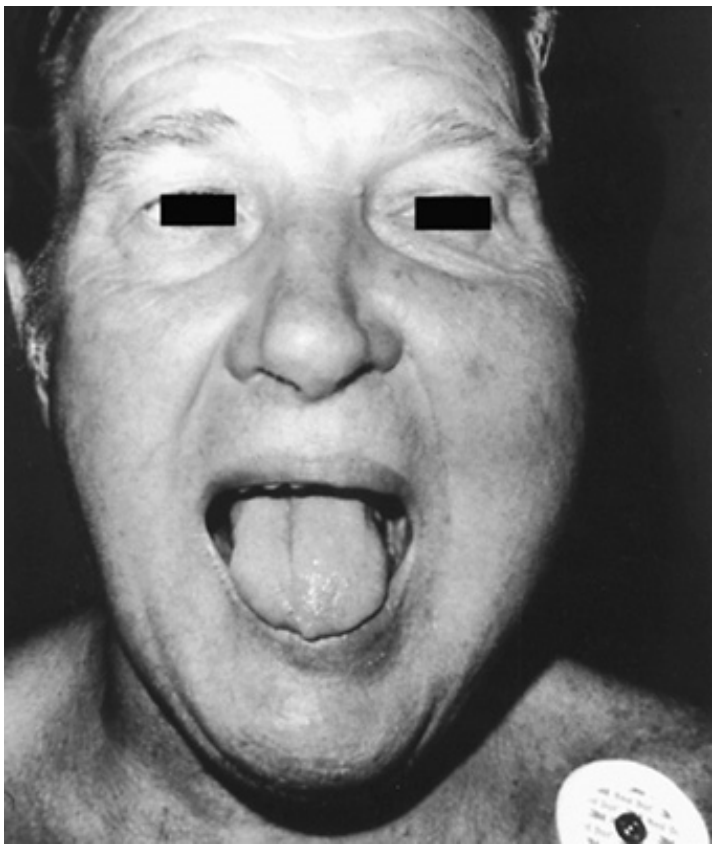


Figure 10-35: *Klippel-Trenaunay syndrome:* hypertrophy of left side of face and tongue in a patient with port-wine stains, gigantism of digits, and varicose veins.

Stenosis of large arteries may occur with supravalvular aortic stenosis, rubella syndrome, Turner's syndrome, and neurofibromatosis. The face of a child with supravalvular aortic stenosis (Williams syndrome) is almost diagnostic (Fig. 10-36). The head is small, with an elflike appearance; the

cheeks are full and baggy; and the mouth is large.[120] Thick lips and peg-shaped, widely spaced teeth are typical findings. The forehead is prominent and broad. Mental retardation is often present. The supravalvular aortic stenosis may be a localized ridge or a diffuse narrowing of the aorta beginning just above the sinuses of Valsalva. Pulmonic artery branch stenosis is frequently present. Coarctation of the aorta is a common cardiac lesion in Turner's syndrome,[61] and neurofibromatosis has been associated with renal artery stenosis.

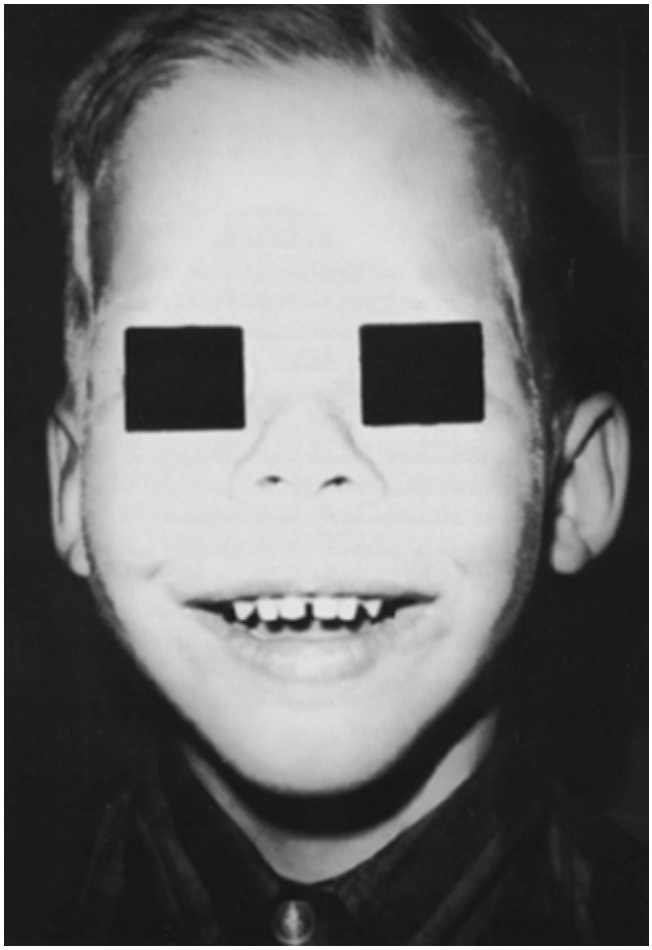


Figure 10-36: *Supravalvular aortic stenosis:* turned-up nose, broad cheeks, large mouth with peg-shaped teeth, and large ears.

Facial swelling and jugular venous distention may be early signs of *superior vena caval obstruction* from clot or tumor.

Miscellaneous Disorders

Multiple lentigines, cutaneous myxomas, myxoid fibroadenomas of the breast, and various endocrine abnormalities are features of a recently described inherited disorder in which single or multiple cardiac myxomas occur.[121] Telangiectasia of the tongue and lips or under the fingernails may be associated with a pulmonary arteriovenous fistula (Figs. 10-37 and 10-38, Plates 39 and 40). A susceptibility to atrial fibrillation and atrial flutter has been documented in patients who have facioscapulohumeral muscular dystrophy.[122] Sinus node dysfunction, elbow contractures, and humeroperoneal weakness are manifestations of Emery-Dreifuss muscular dystrophy.[123]

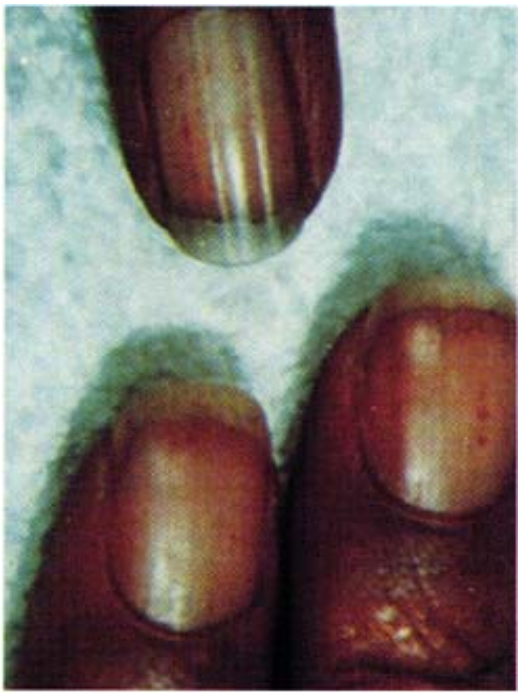


Figure 10-37: (Plate 39) Hereditary hemorrhagic telangiectasia. Telangiectasia under nails. (From Silverman ME, Hurst JW. The hand and the heart. *Am J Cardiol* 1968; 22:609. Used with permission from the publisher.)

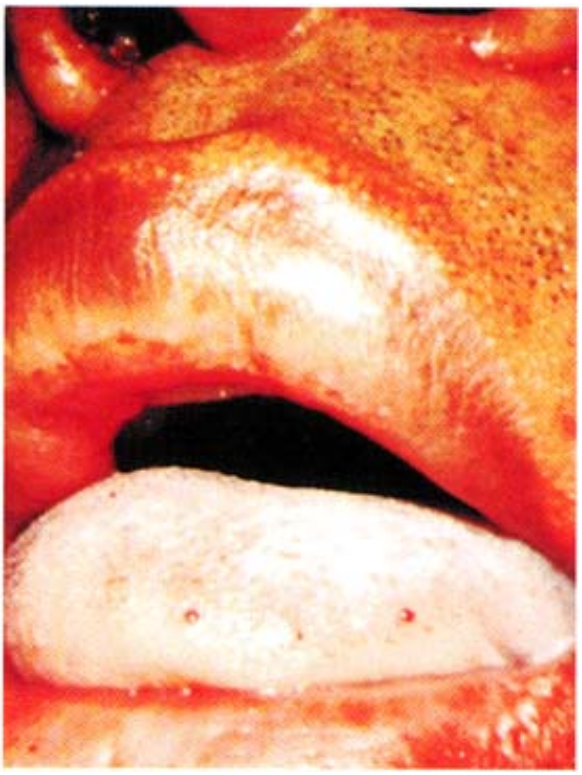


Figure 10-38: (Plate 40) Hereditary hemorrhagic telangiectasia. Telangiectasia of tongue and lips may be associated with a pulmonary arteriovenous fistula.

Single or multiple rhabdomyomas may develop within the myocardium and cause heart failure,

valvular obstruction, or arrhythmias in patients with tuberous sclerosis[124] (Fig. 10-39, Plate 41). The diagnosis is suggested by the presence of yellow-brown angiofibromas (adenoma sebaceum) on the face, subungual fibromas around the fingernail, café-au-lait spots, and subcutaneous nodules. Finally, horizontal ear creases often are associated with the presence of extensive CAD (Fig. 10-40, Plate 42).

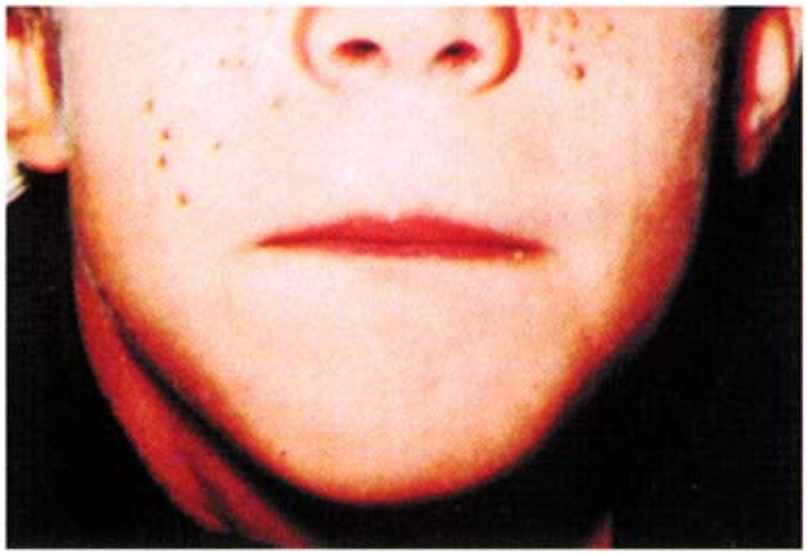


Figure 10-39: (Plate 41) Tuberous sclerosis. Adenoma sebaceum may be associated with rhabdomyomas of the myocardium.

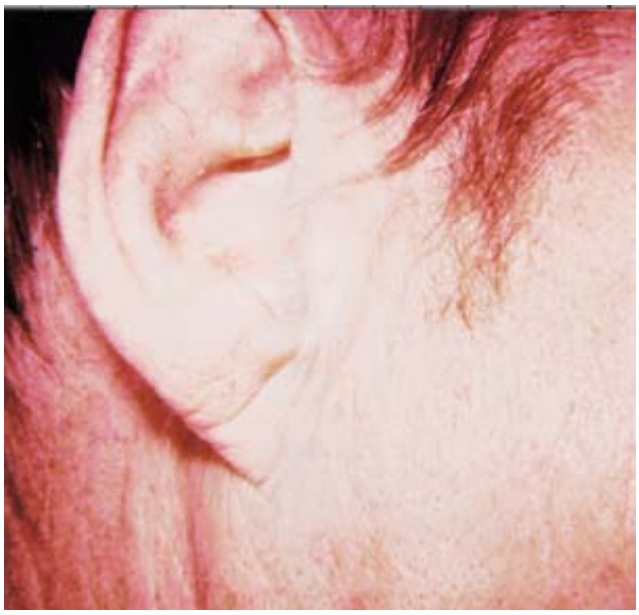


Figure 10-40: (Plate 42) Horizontal ear creases often are associated with the presence of extensive CAD.

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

MEASUREMENT OF ARTERIAL BLOOD PRESSURE

A pneumatic cuff with a mercury or aneroid manometer for the noninvasive assessment of arterial blood pressure is the most commonly used method for determining the status of the circulation and the interaction between the heart and arterial system. Blood pressure deviations from normal often provide important diagnostic information in patients with a variety of cardiac and noncardiac diseases. Accordingly, the blood pressure is best recorded by the physician during his or her *initial* physical examination.

Physical Determinants of the Arterial Pressure

The arterial blood pressure, a measure of lateral force per unit area of vascular wall, is quantitated as millimeters of mercury or dynes per square centimeter. The factors responsible for the peak systolic blood pressure include the volume and velocity of LV ejection, the peripheral arteriolar resistance, the distensibility of the arterial wall, the viscosity of the blood, and the end-diastolic volume in the arterial system.[125] The subsequent diminution in pressure during diastole is, in turn, determined by blood viscosity, arterial distensibility, peripheral resistance to flow, and length of the cardiac cycle.[125] Important physical factors affecting arterial distensibility include (1) the elastic modulus of the arterial wall, the ratio of stress (force acting to deform the wall) to strain (the proportional deformation produced), and (2) the geometry of the arterial wall, i.e., the internal radius (r) and wall thickness (h), which govern wall tension (T) according to the modified Laplace equation $T = Pr/h$, where P is intravascular pressure. A decrease in elasticity or an increase in radius results in diminished distensibility and a greater rise in pressure per unit volume of blood.[126]

The mean arterial pressure is the product of the cardiac output and the total peripheral resistance, the latter often being increased by many mechanisms, including α-adrenergic stimulation, the renin-angiotensin system, or other circulating hormonal or humoral factors.[127]

Methods for Measuring the Arterial Pressure

DIRECT METHODS

In 1733, Stephen Hales recorded the arterial pressures in animals by cannulation and use of a blood-filled glass column.[128] Current techniques for the direct and continuous measurement of arterial pressure use the electromanometer, a transducer that converts mechanical energy into an electric signal suitable for amplification, display, and recording. The artery is cannulated with a saline-filled catheter or needle that mechanically couples the circulation to the arterial manometer. Pressures are recorded using atmospheric pressure as the "zero" reference level, and intravascular pressures are further referenced to the level of the heart by addition or subtraction of a gravitation factor. The gravitation factor is expressed by the formula pgh, where p is the density of blood (in grams per milliliter), g is the acceleration due to gravity (980 cm/s), and h is the transducer height (centimeters) above or below the horizontal plane of the heart.

The strain-gauge manometer is commonly used for the precise and accurate measurement of the arterial pressure. However, error may originate in the catheter or coupling system, in which the

properties of inertia, friction, and elasticity interact to produce damping of the frequency response. Systems may be overdamped or underdamped, both of which can result in signal distortion. Nevertheless, the appropriate combination of an inelastic cardiac catheter and connecting tube filled with bubble-free fluid produces "critical" damping in which the system response is constant to some desirable frequency level and adequate for the clinical recording of intravascular pressures.[125]

Measurement errors also occur when an end-hole catheter is positioned axial to flow in a vessel and may become especially important during high arterial flow, when kinetic energy may exceed 10 percent of the total fluid energy. Also, pressure transients due to catheter whip can falsely elevate the measured arterial pressure.[125]

Miniature, self-flushing strain-gauge manometers attached directly to an intravascular catheter or needle eliminate many of the problems related to transducer mounting and flushing and overdamping by connective tubing. The most satisfactory method for reducing measurement errors, however, is the use of intravascular electromanometers mounted on cardiac catheters or surgically implanted in the vascular wall.

INDIRECT METHODS

The invention of the pneumatic cuff manometer (Riva-Rocci, 1896) and the subsequent discovery and use of the arterial sounds (Korotkoff, 1905) permitted indirect measurement of the arterial pressure. The mercury manometer is the "gold standard," and the more fragile aneroid manometer should be calibrated against the mercury manometer at least every 6 months. Semiautomatic electronic devices, if used, should be validated according to Association for the Advancement of Medical Instrumentation (AAMI) guidelines.[129] The most commonly used noninvasive method is based on the auscultatory detection of low-pitched Korotkoff sounds over a peripheral artery at a point distal to cuff compression of the artery. McCutcheon and Rushmer[130] described two major components of these sounds: the initial transient (k_{-i}) and the compression murmur (k_c), which coincide with the opening tap and rumble sounds of Rodbard.[131] The initial sound k_{-i} occurs when cuff pressure reaches arterial pressure and likely results from abrupt arterial opening and vascular distention. The intensity of this initial sound depends on the slope of the pressure pulse and the level of the distal arterial pressure at the time of arterial opening, the sound being louder with vasodilatation and high-velocity flow and softer with arterial constriction or circulatory collapse. The initial transient is probably caused by oscillation of the arterial walls as the occluded segment is suddenly opened by systolic pressure, and the compression murmur is caused by a turbulent jet of flow distal to the partially compressed segment.

The Korotkoff sounds have been divided into five phases occurring in sequence as the occluding pressure declines (Table 10-4). To avoid error, the observer must be prepared to recognize two normal Korotkoff sound variations associated with blood pressure (BP) reading. (1) The *ausculatory gap* is a period of silence occurring during Korotkoff phases I and II. This disappearance of sound is temporary and is usually short, but the gap can occur over a period of 40 mmHg. It seems to be associated with higher BP readings. (2) An absent Korotkoff phase V occurs when sounds are heard to "0." When this is the case, phase IV should be recorded along with phase V. In this case, phase IV is the best reference for diastolic pressure.

Table 10-4: Phases of the Korotkoff Sounds

Phase I
The pressure level at which the first faint, consistent tapping sounds are heard. The sounds gradually increase in intensity as the cuff is deflated. The first of at least two of these sounds is defined as the systolic pressure.
Phase II
The time during cuff deflation when a murmur of swishing sounds are heard.
Phase III
The period during which sounds are crisper and increase in intensity.
Phase IV
The time when a distinct, abrupt, muffling of sound (usually of a soft blowing quality) is heard. This is defined as the diastolic pressure in anyone in whom sounds continue to zero.
Phase V
The pressure level when the last regular blood pressure sound is heard and after which all sound disappears. This is defined as the diastolic pressure unless sounds are heard to zero.

Proper technique is important for obtaining accurate measurements. The inflatable rubber bag within the compression cuff should have a width that is 20 percent greater than the limb diameter and a length adequate to encompass two-thirds the limb. The cuff should be applied snugly, with the inflatable bag positioned over the artery, at the level of the heart. Before auscultation, the cuff is quickly inflated to a pressure 20 mmHg above the systolic, as indicated by obliteration of the radial pulse. The stethoscope is then applied lightly but firmly over the artery, and auscultatory pressure is determined by noting the onset (peak systole) and behavior of the Korotkoff sounds as the cuff is deflated at a rate of about 3 mmHg per second. When the sounds disappear, the bag should be rapidly decompressed and 1 or 2 min allowed to pass before repeat determinations are made. When possible, the blood pressure should be taken with the subject upright as well as supine. Determination of the blood pressure in both arms is recommended, especially in the elderly. An American Heart Association hypertension primer recommends that the systolic pressure be recorded as the point at which the first tapping sounds occur for two consecutive beats (phase I) and that the diastolic pressure in adults be recorded as the point at which sounds become inaudible. In children and in adults with a hyperkinetic circulation, the diastolic pressure should be recorded as the point at which muffling of the sounds occurs (onset of phase IV). The arterial pressures at both the onset of muffling (phase IV) and the disappearance of sound (phase V) should be recorded. The mean blood pressure can be estimated by the addition of one-third the pulse pressure (systolic pressure minus diastolic pressure) to the diastolic pressure.

Patients with atrial fibrillation may have a significant beat-to-beat variation in their arterial pressure. Accordingly, the indirect blood pressure should be measured several times and the average noted.

This indirect method provides several potential sources of error due to improper equipment, inaccurate detection of the Korotkoff sounds, and observer techniques.[125] The standard pneumatic cuff often may be unsatisfactory for pressure measurement in the arms or in the legs of very obese subjects.[132] The arterial pressure may be underestimated if the cuff is deflated too rapidly, particularly when bradycardia or an irregular rhythm is present or if inadequate inflation does not result in complete arterial occlusion. When the cuff is deflated too slowly or is immediately

reinflated for multiple pressure determinations, the resulting venous congestion may elevate the diastolic pressure artificially and falsely decrease the systolic pressure by decreasing the intensity of phase I or phase II sounds to an inaudible level.

Studies correlating direct and indirect blood pressure measurements have been characterized by considerable variability between individual subjects but in general have shown a good correlation between indirect and direct measurements of blood pressure in the arm. The observed trend has been for the indirect method to underestimate systolic pressure by several millimeters of mercury, to overestimate diastolic pressure by several millimeters of mercury when phase IV is used as an end point, and to slightly underestimate diastolic pressure in normal individuals when phase V is taken as the end point.

Home blood pressure recordings using manual or automatic inflation and deflation of the cuff and detection of Korotkoff sounds by a microphone, stethoscope, or ultrasonic transducer are being used with increasing frequency for the ambulatory assessment of patients with hypertension. In general, ambulatory blood pressure devices do not meet the standards for automated devices of the Association for the Advancement of Medical Instrumentation.[129,133-135]

More recently, arterial tonometry has been used as a completely noninvasive method for monitoring the arterial pressure. This probe, with a micromanometer in its tip, operates on the principle of a piezo-resistive transducer of cantilever construction.[136-141]

Normal Arterial Pressure

Normal pressures have been defined on the basis of values included within two standard deviations of the mean of pressures obtained in a large population of apparently healthy individuals. The normal blood pressure range varies with age, sex, and socioracial grouping.[142] In the United States, the pressure increases rapidly during the first few days of life and then increases gradually, with a slightly greater increment in systolic than in diastolic values, throughout life. The pressure tends to be higher in Western, industrialized societies than in Asian, African, and technically undeveloped societies.

With increasing age and into senescence, the aorta undergoes progressive dilatation and elongation, with increasing stiffness of its walls.[143] As a result of this diminished vascular distensibility, there is an increase in systolic arterial pressure with less change in diastolic pressure.[144]

The normal blood pressure limits for adults (below 40 years of age and of mixed sex and race) living in the United States are approximately 100 to 140 mmHg systolic and 60 to 90 mmHg diastolic. In an individual subject, however, baseline pressures above or below these levels do not define a pathologic state, since the physiologic range of normal for an individual may overlap with the statistical range of abnormality.[125] The systolic arterial pressure rises slowly and progressively in most Americans between the ages of 20 and 60 and more rapidly later, increasing by about 20 mmHg between the ages of 60 and 80.[145] Diastolic pressure usually rises very little after age 45.[153] Data from the Framingham Study and then from more recent studies (e.g., MRFIT, SHEP, Syst-Eur) have shown a clear correlation between systolic pressure and cardiovascular events, a reduction in events with reduction of systolic blood pressure,[146-151] or even a negative association between diastolic blood pressure and events.[152]

In mildly to moderately hypertensive persons, the blood pressure "casually" recorded by a physician is significantly higher than the average value of a series of intermittent, indirect determinations or continuous direct recordings made during normal activity.[153] To estimate basal blood pressure, measurements have been obtained during sleep, when the subject first awakens in

the morning while still recumbent, or after several hours of reclining.

Factors contributing to variations in an individual's blood pressure during daily activities include (1) body posture, (2) state of muscular, cerebral, or gastrointestinal activity, (3) emotional or painful stimuli, (4) environmental factors such as temperature and noise level, and (5) the use of tobacco, coffee, alcohol, and other drugs with direct or neurally mediated vasomotor properties.[125,154] Twenty-four-hour pressures, obtained from normal and hypertensive subjects with an automatic recorder, have shown considerable variability with activity and emotional stimuli.[155,156] The average diurnal pattern of blood pressure consists of an increase throughout the day and early evening and a significant, rapid decline to a low point during the early, deep stage of sleep.

With normal respiration, the peak systolic blood pressure is greater during expiration than during inspiration by as much as 10 mmHg. An augmentation of this difference occurs in patients with pericardial tamponade (pulsus paradoxus; see Chap. 72) and during hyperventilation.

Isotonic exercise in both the supine and upright positions produces a moderate increase in blood pressure (systolic pressure greater than mean greater than diastolic pressure). Sustained isometric muscular contractions produce an abrupt increase in systolic, mean, and diastolic blood pressure that depends on the strength of the contraction.[157]

Abnormal Arterial Pressure

INCREASED PULSE PRESSURE

An increase in arterial pulse pressure is commonly observed during routine blood pressure recordings. This usually is due to an increase in stroke volume and ejection velocity, often with a decrease in peripheral resistance. Fever, anemia, hot weather, exercise, pregnancy, hyperthyroidism, or arteriovenous fistulas may produce this change. Several cardiac diseases, such as aortic regurgitation, patent ductus arteriosus, and truncus arteriosus, also can result in a widened pulse pressure. An increased pulse pressure due to a large stroke volume may occur with complete heart block or marked sinus bradycardia.[125]

Atherosclerosis of the large arteries often reduces arterial compliance and results in an elevated systolic pressure with a normal or even decreased stroke volume. The systolic hypertension of the elderly does not necessarily represent a change in arteriolar resistance. Efforts to lower this type of systolic pressure elevation are often appropriate but can result in diminished peripheral perfusion (see Chap. 51). The increased pulse pressure associated with systemic arteriovenous fistulas is less common; a relative tachycardia may be the only clinical clue. Compression of a systemic arteriovenous fistula can produce a prompt slowing of the heart rate (Branham's sign).

REDUCED PULSE PRESSURE

A narrow pulse pressure is uncommon in normal subjects but may result from an increased peripheral resistance (increased circulating catecholamines in heart failure), decreased stroke volume (severe aortic stenosis), and/or markedly decreased intravascular volume (diabetic ketoacidosis).[125]

UNEQUAL PULSE PRESSURES

The diagnostic importance of blood pressure differences between right and left arms has been enhanced in recent years by the recognition of supravalvular aortic stenosis and this "choana effect" in children and of the subclavian steal syndrome in adults.[158] Most patients with the

former have greater than 20 mmHg higher blood pressure in the right arm. The subclavian steal syndrome, often accompanied by symptoms of cerebrovascular insufficiency, usually results in a pronounced lowering or absence of brachial artery pressure in the ipsilateral extremity.[125]

A progressive increase in systolic pressure normally occurs as the point of measurement is moved peripherally from the central aorta (Fig. 10-41), and the increment in systolic pressure is equivalent in the large arteries of the upper arm and the thigh. Direct recordings of femoral and brachial arterial pressures (systolic, diastolic, and mean) in adults[159] and children[160] and indirect measurement of popliteal and brachial artery pressures using appropriate pressure cuffs[161] have demonstrated that mean pressures are equal at these sites. A difference in arm and leg pressures may occur because of coarctation of the aorta or acquired disease such as aortic dissection, aortic arch syndrome, or the subclavian steal syndrome.[125]

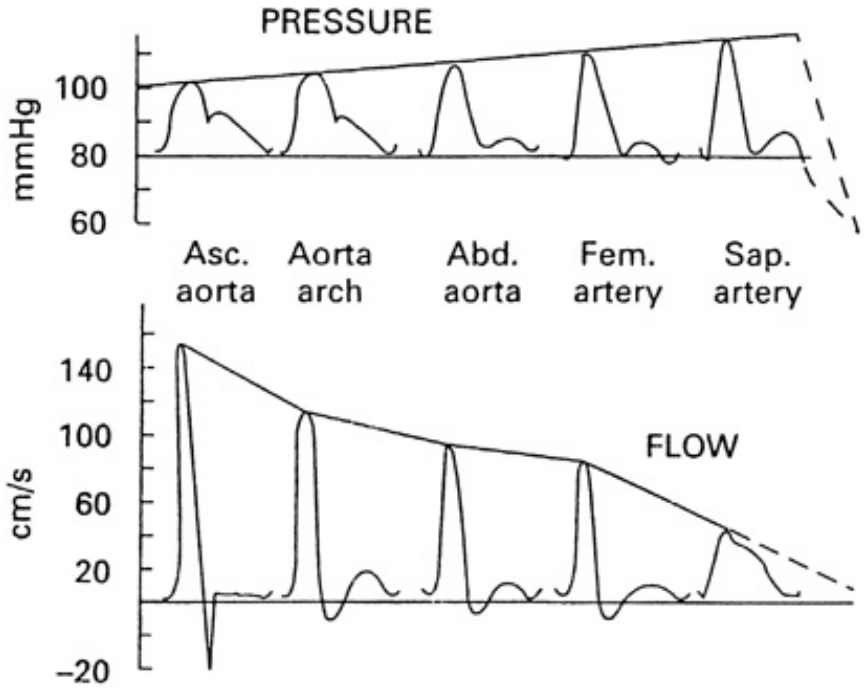

Figure 10-41: Micromanometer and catheter tip flow velocity as change in contour of pressure waves (above) and flow waves (below) between the ascending aorta and the saphenous artery. (From Vlachopoulos C, O'Rourke MF. The arterial pulse. *Curr Probl Cardiol* 2000; 25:296-346.)

Pulsus Alternans

Pulsus alternans may be detected by palpating a peripheral artery. The femoral artery is probably best for this purpose. One must, of course, be certain the heart rhythm is normal. The sphygmomanometer can be used to measure accurately the beat-to-beat variation in pressure that characterizes pulsus alternans.

Pulsus alternans, which is discussed at greater length later in this chapter, occurs in patients with severe heart disease who exhibit impaired LV contraction. It also can occur for a few beats following supraventricular tachycardia in normal persons or when the respiratory rate is half the pulse rate. This may be apparent when pulsus paradoxus is present in patients with cardiac tamponade.

Pulsus Paradoxus

A normal person may exhibit a 10- to 12-mmHg drop in systolic pressure during normal inspiration. A fall in pressure greater than this amount may be identified in patients with acute cardiac tamponade, constrictive pericarditis, severe obstructive lung disease, and restrictive cardiomyopathy.

Pulsus paradoxus is best detected by inflating the blood pressure cuff above systolic pressure and then slowly releasing it. As the cuff pressure is gradually reduced, the blood pressure sounds become audible during expiration. The difference in pressure between the first audible sound heard on expiration and the pressure level at which the sounds are heard during all phases of respiration gives a measurement of magnitude of pulsus paradoxus. The mechanism of pulsus paradoxus is discussed in Chap. 72.

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

THE ARTERIAL PULSE

The arterial pulse is as any periodic fluctuation that is caused by the heart and occurs at the same frequency as the heartbeat. Ejection of blood with every cardiac contraction is converted to *flow* pulsations, *pressure* pulsations, and *dimension* pulsations in arteries throughout the body. While the term *pulse* refers to any such pulsation, the arterial pulse perceived by a clinician is the pressure pulse in a large, accessible artery. Palpation of the arterial pulse is a basic and important element of the physical examination.[162-166] Any discussion of the arterial pulse must include recent advances in measurement of arterial hemodynamics, assessment of the arterial wave contour, and frequency analysis of the pressure pulse.[162-170]

Physical Determinants of the Arterial Pulse

GENESIS OF THE ARTERIAL PULSE

Pressure and blood flow measurements in the ascending aorta result from the interaction between the heart and arterial system. When LV pressure exceeds the aortic pressure, it becomes the driving force for the movement of blood into the ascending aorta.[162] This driving force is dependent on the intrinsic contractility of ventricle muscle, the size and shape of the left ventricle, and the heart rate. It is opposed by several forces that impede the development of flow and are interrelated in a complex manner. Three major determinants of arterial impedance include (1) resistance, (2) inertia, and (3) compliance.

Resistance is related to blood viscosity and the geometry of the vasculature; it opposes flow and is unaffected by changes in heart rate. Inertia, which is related to the mass of the column of blood, opposes the rate of change of arterial blood flow (i.e., acceleration) and depends on the heart rate. Compliance is related to the distensibility of the vascular walls, opposes changes in arterial blood volume, and also depends on the heart rate. The heart rate dependency of inertia and compliance introduces phase shifts between instantaneous pressure and flow in a pulsatile system.[167] Inertia and compliance are important determinants of the character of ventricular ejection, especially in early systole, when flows and pressures are changing rapidly.

The arterial pulse wave begins with aortic valve opening and the onset of LV ejection. Aortic pressure rises rapidly in early systole because the LV stroke volume enters the aorta faster than it flows to distal sites. The rapid-rising portion of the arterial pressure curve is often termed the *anacrotic limb* (from the Greek, meaning "upbeat"). In experimental animals and in humans, peak proximal aortic flow velocity occurs slightly earlier than peak pressure.[167] After its peak, aortic pressure declines as ventricular ejection slows and peripheral blood flow continues. During isovolumic relaxation, a transient reversal of flow from the central arteries toward the ventricle just prior to aortic valve closure is associated with an incisura on the descending limb of the aortic pressure pulse. The subsequent smaller, secondary positive wave has been attributed to the elastic recoil of the aorta and aortic valve but is partially due to reflected waves from more distal arteries. Subsequently, aortic pressure decreases again as further "runoff" in the peripheral circulation occurs in diastole.

The proximal aortic pulse pressure is directly proportional to the ratio of stroke volume to arterial

distensibility, but multiple factors influence this complex relationship.[171] Arterial distensibility diminishes as the distending arterial pressure increases. Accordingly, the pulse pressure for a constant stroke volume will be larger if the mean blood pressure is elevated. In addition, arterial distensibility varies inversely with the rate of rise of intraluminal pressure. When the systolic ejection rate increases, the stiffer arterial wall results in a greater pulse pressure. Finally, the arterial pulse pressure is modified by reflected pressure waves and by the rate of blood flow from arterioles to veins.

CONTOUR OF THE ARTERIAL PULSE

Pulsatile changes in arterial diameter are virtually identical to the pressure pulse, with minor differences explained in terms of nonlinear elasticity and viscosity of the arterial wall. In 1939, Hamilton and Dow defined the pressure wave contour in different arteries in terms of wave reflection between the aortic valve and peripheral sites.[172] The pulse waveform recorded at any site of the arterial tree is the sum of a forward waveform and a backward-traveling one that is the "echo" of the incident wave reflected at peripheral sites. *Wave reflection is an important determinant of LV load and CBF*. A reflected wave occurring at systole increases systolic pressure and thereby increases ventricular afterload. In contrast, occurrence of the reflected wave at diastole is highly desirable because augmentation of pressure during diastole aids coronary perfusion.

Conventionally, the pulse is described in the *time domain,* where it is considered as a change in arterial pressure with time. An alternative approach that has the advantage of being quantitative is to analyze the pulse in the *frequency domain*. Pulse is conceived as a composite wave that can be resolved into component harmonics like a musical wave. Impedance is the measure of the opposition to flow presented by a system and can be approached quantitatively when harmonic analysis is used to relate frequency components of pressure and flow pulses.[173-178] Study of impedance provides valuable insights for several issues of vascular mechanics.

Usually, there is a linear relation between pressure and flow at the same point in an artery and between pressures at different points in the arterial system. From impedance curves, it is possible to identify the factors responsible for the relation between the pulsatile pressure and flow. Furthermore, the coefficient of reflection in peripheral vessels can be calculated from the relation of resistance to the minimal and subsequent values of impedance modulus. The peripheral arterial pressure wave recorded is the summation of the incident (initial) and reflected waves. The systemic circulation has been represented by a simple asymmetric T-tube model that emphasizes the importance of wave reflection at two arteriolar reflecting sites in the upper and lower parts of the body.[169] An important patient study indicates major reflection sites at the aortic level of the renal arteries and at a point distal to the terminal abdominal aorta bifurcation.[170]

PERIPHERAL TRANSMISSION OF THE ARTERIAL PULSE

As the normal aortic pulse wave is transmitted peripherally, significant changes in its contour occur due to (1) distortion and damping of pulse wave components, (2) different rates of transmission of various components, (3) distortion or exaggeration by reflected, resonant, or standing waves, (4) conversion of kinetic energy into hydrostatic or potential energy, (5) differences in distensibility and caliber of the arteries, and (6) changes in the vessel wall due to age and/or disease.[176]

The arterial pressure pulse enters the proximal aorta and travels distally at a velocity many times faster than maximum blood flow. The pressure wave is accompanied by a traveling wave distending the arterial wall, the pulse wave velocity increasing as arterial wall distensibility diminishes.[171] This normally occurs distally, as the arteries branch into smaller channels and their walls become stiffer. With increasing age or with systemic hypertension, however, arterial wall

distensibility diminishes, and pulse wave velocity is correspondingly greater.

The pulse wave arrives progressively later at more peripheral sites when timed from the QRS complex on the ECG. Representative time delays from the central aorta are as follows: carotid, 30 ms; brachial, 60 ms; radial, 80 ms; and femoral, 75 ms.

The arterial pulse wave undergoes a progressive change in shape during its transmission distally (Fig. 10-41). The pulse pressure and systolic amplitude increase, and the ascending limb of the pulse wave becomes steeper. The incisura of the central aorta pulse is gradually replaced by a smoother, somewhat later dicrotic notch that occurs at lower pressure levels. The dicrotic notch and the following positive secondary or dicrotic wave probably result from the summation of the forward pulse wave and reflected waves from the peripheral vessels.[162]

EXAMINATION OF THE ARTERIAL PULSE

All major arterial pulses should be examined bilaterally for both patency and waveform characteristics. The thickness and hardness of the arterial walls often can be assessed by "rolling" the vessel against underlying tissue. A pulse in the foot should not be considered absent unless examined with the foot in a dependent position. Otherwise, the arterial pulses usually are examined with the patient supine and with the trunk of the body slightly elevated.

The examiner uses tactile receptors in the tips of the fingers to sense movement of the arterial wall associated with the pressure pulse as it passes the site of palpation. Measurements in the proximal aorta show cyclic movement in both diameter and length proportional to the pulse pressure. In more peripheral arteries with connective tissue attachments, however, the detectable movement is small and variable, with radial expansion by only about 2 percent of the end-diastolic cross-sectional area.[162]

The usual technique for palpating the arterial pulse is to press with the examining fingers until the maximum pulse is sensed. The pulse is felt as changing displacement superimposed on the "baseline" displacement produced by compressing the artery. The examiner should apply varying degrees of pressure while concentrating on the separate phases of the pulse wave. This method, referred to as *trisection,* is useful for assessing the upstroke, systolic peak, and diastolic slope of the arterial pulse.[176] Controversy exists as to how many fingers should be used to palpate the pulse; the examiner should use whichever method he or she prefers.

Palpation of the carotid artery is preferred for assessing cardiac performance, since the carotid pulse corresponds more closely to the central aortic pressure. In certain cardiac diseases (e.g., aortic regurgitation), however, the abnormalities detected in the carotid pulse are accentuated in the more peripheral pulses. For determining the cardiac rate and rhythm, the radial pulse most often is used, but if it is irregular, cardiac auscultation often provides more reliable information. To evaluate the integrity of the peripheral arterial blood supply and to localize any lesions that exist, the arterial pulses in all four extremities should be examined and compared (see also Chap. 90).

Inspection of the carotid arterial and jugular venous pulsations should be performed at the same time. The carotid pulse is usually best examined with the sternocleidomastoid muscles relaxed and with the head rotated slightly toward the examiner. The carotid pulse may be timed from the first heart sound, which is heard slightly before the pulsation. The carotid pulse should be palpated in the lower half of the patient's neck in order to avoid carotid sinus compression. Occasionally, it is useful to palpate two arteries simultaneously (e.g., radial and femoral) to detect an apparent pulse wave delay, such as occurs in patients with coarctation of the aorta.

The examination of arterial pulses in the abdomen and upper and lower extremities should be

performed carefully in all patients and compared using a scale such as the following: 0 = complete absence of pulsation; 1+ = small or reduced pulsation; 2+ = normal or average pulsation; and 3+ = large or bounding pulsation. Furthermore, auscultation over the major arteries should be performed, since an audible bruit may be a clue to partial occlusion or may indicate transmission (e.g., carotid) of a cardiac murmur.

NORMAL ARTERIAL PULSE

The normal carotid pulse has a smooth, rapid upstroke or ascending limb to a smooth, dome-shaped summit (see Fig. 10-42). Then a downstroke occurs that is somewhat less rapid than the upstroke. The dicrotic notch and secondary diastolic wave usually are not felt but may be palpable in some normal individuals, particularly during fever, exercise, or excitement. The dicrotic notch usually occurs about 300 ms after the onset of the pulse wave when corrected for heart rate.

In arteries distal to the carotid, the pulse wave arrives later and has a steep initial wave that rises to a high peak pressure, whereas the diastolic pressure and the mean pressure are slightly lower. The systolic upstroke time (onset of pulse wave to its peak) tends to be shorter, but the apparent LV ejection time (onset of pulse wave to incisura) is longer in more peripheral arterial pulses. In the brachial artery, the heart rate-corrected systolic upstroke time averages 120 ms (range, 90-160 ms), and the systolic ejection time averages about 320 ms (range, 280-360 ms).

Graphic recordings of the arterial pulses frequently show two positive deflections during systole, the first shoulder being referred to as the *percussion wave* and the second as the *tidal wave*. In the normal proximal aortic pulse, the percussion wave is due to arrival of the impulse generated by LV ejection, the tidal wave may represent its echo from the upper part of the body, and the dicrotic or diastolic wave is a reflection from the lower part of the body.[166] The contour of the distal pulses can be explained in similar terms, with altered time relations between incident and reflected waves at different distances from peripheral reflecting sites.

With aging, there is a relative increase in the second (tidal) systolic wave and the height of the incisura relative to the first systolic wave.[162,177,179,180] The systolic upstroke time is longer, and the amplitude and duration of the diastolic wave tend to be less prominent.

ABNORMAL ARTERIAL PULSES

In hypertension and arteriosclerosis, the pressure pulse amplitude is increased, the tidal wave is prominent, and the diastolic wave is absent. All features of the pulse can be explained by increased wave velocity.[162,177] Reflected waves return to the proximal aorta during late systole, augmenting the tidal wave and increasing systolic pressure. With systemic hypotension, the pulse wave velocity is decreased, and the later tidal and diastolic waves are further displaced from the percussion wave.

Impairment of the pulse of one or both carotid arteries is usually produced by atherosclerosis, but multiple other causes include thrombosis, embolus, arteritis, and diseases of the aortic arch. Kinking of the carotid or brachiocephalic artery is relatively frequent, particularly in hypertensive patients, and may simulate aneurysmal dilatation. Femoral pulses may be diminished in the child or young adult as a result of coarctation of the aorta. In most adults, however, the diminution of the femoral pulsation is caused by atherosclerosis of the abdominal aorta, aortic bifurcation, or ileofemoral arteries (see also Chap. 90).

HYPERKINETIC ARTERIAL PULSE

Large, bounding arterial pulses usually indicate the rapid ejection of an increased volume of blood from the left ventricle (see Fig. 10-42*A*). Commonly, the arterial pulse pressure is increased, and the peripheral arterial resistance diminished. The hyperdynamic arterial pulse is sometimes referred to in terms that describe a particular component of the pulse wave. Thus the *water-hammer pulse,* named after a Victorian toy, refers to an extremely rapid, forceful ascending limb of the arterial pulse wave.[181] By contrast, *collapsing pulse* refers to a quick, marked decrease in the arterial pulse wave following its peak. Hyperkinetic pulses often are more prominent in the brachial, radial, and femoral arteries than in the carotid artery. The term *Quincke pulse* refers to visible small pulsations in the nail bed of patients with hyperdynamic arterial pulses from any cause, including aortic regurgitation.

Hyperkinetic arterial pulses occur in normal subjects with a hyperkinetic circulation (e.g., exercise, fever), patients with cardiovascular diseases associated with increased stroke volume, and subjects with marked bradycardia and an extremely large stroke volume (e.g., athletes). A hyperdynamic arterial pulse also occurs in patients with an abnormally rapid runoff of blood from the arterial system (e.g., patent ductus arteriosus, arteriovenous fistulas). Patients on chronic hemodialysis often have hyperdynamic pulses produced by the combination of a surgical arteriovenous fistula, anemia, and hypertension.

In aortic regurgitation, the rapid-rising, bounding arterial pulse results from increases in both stroke volume and the rate of LV ejection. The early systolic flow often produces palpable vibrations manifest as a thrill on the steep ascending limb. Later in systole, the rate of ventricular ejection and the arterial pulse wave decrease sharply, often resulting in systolic collapse.

BISFERIENS ARTERIAL PULSE

The bisferiens (from the Latin, meaning "twice beating") pulse has a waveform characterized by two positive waves during systole (see Fig. 10-42*B*). The pulse wave upstroke rises rapidly and forcefully, producing the first systolic peak (percussion wave). A brief decline in pressure is followed by a smaller and somewhat slower-rising positive pulse wave (tidal wave). Abnormalities of LV ejection and reflected waves from peripheral arteries contribute to the prominence of the second systolic wave in the bisferiens pulse. The bisferiens pulse, usually felt in the carotid artery, is sometimes more easily palpable in a brachial or radial artery. A bisferiens pulse often occurs in patients with pure aortic regurgitation and in patients with combined aortic stenosis and severe aortic regurgitation.[182] It also can occur in other conditions associated with the rapid ejection of an increased stroke volume from the left ventricle (e.g., exercise, fever, patent ductus arteriosus).

The bisferiens pulse often is present in patients with hypertrophic cardiomyopathy, many of whom have a pressure gradient in the LV outflow tract.[183] In this syndrome, the midsystolic negative wave usually coincides with a marked decrease in the rate of LV ejection. The second systolic wave, or tidal wave, most likely is produced by reflected waves from the periphery. The bisferiens pulse may be elicited by maneuvers that decrease the LV size or increase its contractility. The most characteristic aspect of the arterial pulse in hypertrophic cardiomyopathy is its rapid rate of rise. A physical finding nearly specific for hypertrophic cardiomyopathy is a much smaller arterial pressure pulse in the cardiac cycle following a premature ventricular beat (see Chap. 67).

HYPOKINETIC ARTERIAL PULSE

A small, weak arterial pulse is frequently present in patients with a diminished stroke volume (see Fig. 10-42*C*). Usually, the decreased stroke output is associated with decreased rate and duration of LV ejection, and there is a narrow arterial pulse pressure despite an increased arterial resistance. Common causes include hypovolemia, LV failure, and mitral or aortic valve stenosis.

PARVUS ET TARDUS PULSE

Patients with moderate or severe valvular aortic stenosis often have an arterial pulse that is small and has a delayed systolic peak.[184,186] Occasionally, there may be a detectable shoulder on the upstroke of the carotid pulse, referred to as *anacrotic*[184] (see Fig. 10-42*D*). Palpable coarse vibrations often are present as a systolic thrill over the slowly rising carotid pulse. The parvus et tardus pulse is much easier to detect in the carotid arteries than in more distal arteries.

Most middle-aged patients with uncomplicated severe aortic stenosis have a parvus et tardus pulse, but this pulse also may occur in relatively mild stenosis. Conversely, an apparently normal arterial pulse is not unusual in elderly patients with severe aortic stenosis who have decreased distensibility of the large arteries, which also alters the character of the arterial pulse.[162,164] Severe LV failure often results in a small, weak pulse that may be difficult to distinguish from that of aortic stenosis.

DICROTIC ARTERIAL PULSE

The dicrotic (from the Greek *dikrotos*, meaning "double beating") pulse is a twice-peaked pulse with one peak in systole and the second in diastole, the latter due to an accentuated and palpable dicrotic wave that follows the second heart sound[187] (see Fig. 10-42*E*). It is usually felt best in the carotids, although it also may be palpated over more peripheral arteries. Major abnormalities include a short systolic ejection phase, a low dicrotic notch, a large diastolic wave, a narrow pulse pressure, a diminished rate of rise of the pulse, and the lack of distinct percussion and tidal waves. The dicrotic pulse is most common in young or middle-aged patients with impaired LV performance. It is usually associated with a low cardiac output, markedly diminished stroke volume, elevated LV end-diastolic pressure, and high systemic arterial resistance. In general, the dicrotic wave becomes less prominent with age, hypertension, generalized atherosclerosis, and diabetes. Rarely, the dicrotic wave can be palpated in young, febrile patients in whom none of the other abnormal features of the dicrotic pulse are present.

PULSUS ALTERNANS

In pulsus alternans, beats occur at regular intervals with a regular alternation of the systolic height of the pressure pulses[188,189] (see Fig. 10-42*E*). Rarely, pulsus alternans is so marked that the weaker pulses are not felt at all. When pulsus alternans is noticed first after a premature beat, the extent of the difference in systolic pressure in alternating beats may decline for several cycles until the pulse amplitude is again constant. The initiation of post-premature ventricular beat pulsus alternans is probably related to the increased duration of LV filling after the premature beat, resulting in a greater end-diastolic volume and hence increased contractile force due to the Frank-Starling mechanism.

Sustained pulsus alternans (see Chap. 20) is seen in severe depression of LV performance with an alteration in aortic flow, systolic LV pressure, aortic systolic pressure, LV *dP/dt*, and LV end-diastolic pressure. Sustained pulsus alternans likely is due to alteration of the contractile state of at least part of the myocardium, which may be caused by the failure of electromechanical coupling in some cells during the weaker contraction.[189] A subsequent stronger contraction would then represent contraction of all cells, some of which were potentiated.[190]

Pulsus alternans may be better appreciated when palpating a distal artery, which normally has a slightly wider pulse pressure than the carotid artery. The patient's respiration should be held, since the small changes in arterial pressure caused by normal respiration may obscure the recognition of pulsus alternans. Pulsus alternans can be confirmed by using a sphygmomanometer and is usually

associated with a LV third heart sound.

PULSUS PARADOXUS

A *paradoxical pulse* is defined as a marked decrease in the pulse amplitude during normal quiet inspiration or a decrease in the systolic arterial pressure by more than 10 mmHg. The normal small decline in systolic blood pressure probably is produced predominantly by relative pooling of blood in the pulmonary vessels during inspiration and also may reflect the delayed transmission through the lungs of the preceding expiratory fall in venous pressure and RV cardiac output.[176]

In patients with cardiac tamponade, fluid accumulation in the pericardium increases intrapericardial pressure, and the heart's filling capacity is reduced. During inspiration, the expected augmentation of venous return to the right side of the heart occurs despite the elevated intrapericardial pressure.[191] The diminished thoracic pressure also causes a pooling of blood in the pulmonary veins and capillaries and diminishes pulmonary venous return to the left atrium. Since the high intrapericardial pressure limits flow to the heart and the total cardiac filling capacity is limited, the increase in right-sided heart volume with inspiration causes an obligatory decrease in left-sided heart filling. This, along with the pooling of blood in the pulmonary bed, produces a decline in LV stroke volume and systolic blood pressure during inspiration.[192]

Pulsus paradoxus is common with cardiac tamponade but infrequent with constrictive pericarditis (see Chap. 72). Different hemodynamic mechanisms contribute to the production of a paradoxical pulse in certain patients with superior vena cava obstruction, asthma, or obstructive airways disease; in some patients with pulmonary embolism or shock; and in some patients after thoracotomy.[176]

The extent of pulsus paradoxicus can be quantitated by cuff sphygmomanometry as the pressure difference between the first discernible Korotkoff sound on expiration and the pressure level at which Korotkoff sounds are audible during all phases of respiration.

EFFECTS OF ARRHYTHMIAS ON THE ARTERIAL PULSE

Premature Ventricular Depolarizations

A premature ventricular depolarization may be associated with no pulse, a small-amplitude pulse, or a normal arterial pulse depending on timing and whether or not the LV pressure generated is able to open the aortic valve.[193] The arterial pulse following a premature beat usually is greatly enhanced because of decreased aortic impedance, increased LV filling, and augmented LV contractility. At times, premature ventricular beats are so common as to produce an irregularly irregular pulse. Then the presence of cannon *a* waves in the jugular venous pulse should alert one to the correct diagnosis.

Tachyarrhythmias

The ECG is usually needed for the definitive diagnosis of any abnormality of heart rate or rhythm. On the other hand, careful observation of the arterial and jugular venous pulses frequently leads to the correct diagnosis. Simultaneous cardiac auscultation is also frequently helpful.

Most tachycardias associated with a regular pulse are of supraventricular origin. In sinus tachycardia, the arterial pulse will slow gradually with carotid sinus pressure and then again increase gradually. Paroxysmal atrial tachycardia has an "all or none" response. In patients with atrial flutter, carotid sinus pressure will increase the block at the AV junction, the pulse rate slowing and subsequently returning to its original rate in a "jerky" fashion.

In patients with ventricular tachycardia and AV dissociation, the variation in the atrial ventricular sequence of contraction and resulting variation in pulse amplitude often may be detected by palpation.[194]

An irregularly irregular pulse with a varying pulse pressure is usually the result of atrial fibrillation; however, multifocal atrial tachycardia is also a common cause of this finding in patients with severe chronic obstructive lung disease.

Bradyarrhythmias

An unusually slow heart rate frequently is associated with a decrease in the rate of rise and amplitude of the arterial pressure pulse. Complete heart block often is readily diagnosed by the variability in the arterial pulse amplitude, the changing intensity of the first heart sound, and intermittent cannon *a* waves in the jugular venous pulse, all due to the time-dependent variable contribution of atrial contraction to ventricular filling.

EFFECTS OF DRUG THERAPY ON THE ARTERIAL PULSE

Pulse wave analysis provides important information about the actions of drugs that, most importantly, may not be apparent with conventional methods.[162] *Nitrates* decrease central systolic pressure substantially while they have no or minimal effect on peripheral systolic pressure (Fig. 10-43).[162a] *Beta-blocking* agents have variable effect depending on their intrinsic properties. Nonselective agents tend to increase late systolic pressure augmentation; in contrast, those agents with vasodilating properties have the opposite effect. Both angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers have significant effects on the arterial pulse by reducing late systolic pressure augmentation. These actions can be explained on the basis of wave reflection. Reduction of wave reflection is an important advantage in the logical treatment of hypertension and heart failure.

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

THE VENOUS PULSE

An accurate assessment of the venous pulse is an integral part of the physical examination because it provides information concerning both the mean right atrial pressure and the hemodynamic events in the right atrium.[165] Factors influencing the right atrial and central venous pressure (CVP) include the total blood volume, thedistribution of blood volume, and the strength of right atrial contraction.

Venous blood returning from the systemic capillaries is nonpulsatile. Changes in volume flow created by skeletal muscles and the respiratory pump are nonsynchronous with the pulsatile activity of the heart. Changes in flow and pressure caused by right atrial and ventricular filling, however, produce pulsations in the central veins that are transmitted toward the peripheral veins, opposite to the direction of blood flow. With the possible exception of the *c* wave, which is the combined result of carotid arterial impact and an upward movement of the tricuspid valve, the pulsations observed in the neck are produced by right atrial and ventricular activity.[195]

Examination of the Jugular Venous Pulse

The two main objectives of the bedside examination of the neck veins are estimation of the CVP and inspection of the waveform.[197] Usually, the right internal jugular vein is superior for both purposes. In most normal subjects, the maximum pulsation of the internal jugular vein is observed when the trunk is inclined by less than 30°. In patients with an elevated venous pressure, it may be necessary to elevate the trunk further, sometimes to as much as 90°. When the neck muscles are relaxed, shining a beam of light tangentially across the skin overlying the internal jugular vein often exposes its pulsations. Simultaneous palpation of the left carotid artery aids the examiner in deciding which pulsations are venous.

Measurements of Venous Pressure

The difference between venous distention and venous pressure elevation must be considered. Veins may be markedly dilated with minimal increase in pressure or may not be visibly distended despite a very high venous pressure.[196] Venous pressure may be estimated by examining the veins on the dorsum of the hand. With the patient sitting or lying at a 30° elevation or greater, the arm is slowly and passively raised from a dependent position. When the venous pressure is normal, the veins collapse when the dorsum of the hand reaches the level of the sternal angle of Louis. Unfortunately, local venous obstruction or augmented peripheral venous constriction may diminish the accuracy of estimating CVP by this method.

The external or internal jugular veins also may be used to estimate venous pressure.[196] Because of its more direct route to the right atrium, the internal jugular vein is superior for the estimation of venous pressure and assessment of the venous waveform. The patient is examined at the optimal degree of trunk elevation for visualization of venous pulsations. The vertical distance from the top of the oscillating venous column to the level of the sternal angle is generally less than 3 cm. Greatly elevated venous pressure may be missed by failing to elevate the patient's head adequately. It may be necessary to actually have the patient sit upright. If the "pulsating meniscus" is very high, pulsations may not be apparent in the lower neck. When venous engorgement is

marked, the patient's earlobe may pulsate, and even the veins on the top of the head may be distended.

In patients suspected of RV failure but having a normal resting venous pressure, the abdominojugular test is useful.[196] With the patient breathing normally, firm pressure is applied with the palm of the hand to the upper right quadrant of the abdomen for 10 s or more. The patient should be instructed to continue to breathe normally during the test. In most subjects, the jugular venous pressure is not altered significantly. In some normal patients there is a transient increase in jugular venous pressure with a rapid return to or near baseline in less than 10 s. The dysfunctioning right ventricle, however, is unable to accept the increment in blood volume due to enhanced venous return without a marked increase in its filling pressure, which is transmitted to the neck veins. In patients with RV failure, which often results from left-sided heart failure, the venous pressure either rises rapidly and then partially declines slowly during continued abdominal compression or remains elevated by 4 cm of blood or more until the abdominal pressure is released (Fig. 10-44). Ducas et al.[198] also studied the abdominojugular test and confirmed its clinical value.

Analysis of Venous Waveforms

Again, the patient's trunk should be inclined to whatever elevation is necessary to reveal the top of the oscillating venous column.[199] Slow, deep inspiration will increase the amplitude of the presystolic *a* wave while decreasing the mean right atrial pressure. This is a useful technique for identifying the site at which the pulsations will be best visualized. Simultaneous palpation of the left carotid artery and cardiac auscultation aid the examiner in relating the venous pulsations to the timing of the cardiac cycle.

Normal Venous Pulse

The normal *jugular venous pulse* (JVP) reflects phasic pressure changes in the right atrium and consists of three positive waves and two negatives troughs (Fig. 10-45). It is useful to refer to the events of the cardiac cycle (Plate 2). The positive presystolic *a* wave is produced by right atrial (RA) contraction and is the dominant wave in the JVP, particularly during inspiration. During atrial relaxation, the venous pulse descends from the summit of the *a* wave. Depending on the PR interval, this descent may continue until a plateau (*z* point) is reached just prior to RV systole. More often, the descent is interrupted by a second positive venous wave, the *c* wave, that is produced by bulging of the tricuspid valve into the right atrium during RV isovolumic systole and by the impact of the carotid artery adjacent to the jugular vein.[200] Following the summit of the *c* wave, the JVP contour declines, forming the normal negative systolic wave, the *x* wave. The *x* descent is due to a combination of atrial relaxation, the downward displacement of the tricuspid valve during RV systole, and the ejection of blood from both ventricles (see Chap. 3).

The positive, later systolic *v* wave in the JVP results from the increase in blood volume in the venae cavae and right atrium during ventricular systole when the tricuspid valve is closed. After the peak of the *v* wave is reached, the RA pressure decreases because of the diminished bulging of the tricuspid valve into the right atrium and the decline in RV pressure that follows tricuspid valve opening. In the JVP, the latter occurs at the peak of the *v* wave. Following the summit of the *v* wave, there is a negative descending limb, referred to as the *y* descent or diastolic collapse, which is due to the tricuspid valve opening and the rapid inflow of blood into the right ventricle. The initial *y* descent corresponds to the RV rapid-filling phase. The trough of the *y* wave occurs in early diastole and is followed by the ascending limb of the *y* wave, which is produced by the continued diastolic inflow of blood into the right side of the heart. The velocity of this ascending pressure curve depends on the rate of venous return and the distensibility of the chambers of the right side of the heart. When diastole is long, the ascending limb of the *y* wave is often followed

by a small, brief, positive wave, the *h* wave, that occurs just prior to the next *a* wave. At times, there is a plateau phase rather than a distinct *h* wave. With increasing heart rate, the *y* trough and *y* ascent are followed immediately by the next *a* wave.

Usually, there are three visible major positive waves (*a*, *c*, and *v*) and two negative waves (*x* and *y*) when the pulse rate is below 90 beats per minute and the PR interval is normal. With faster heart rates, there is often fusion of some of the pulse waves, and an accurate analysis of the waveform is more difficult.

Abnormal Venous Pulse

ELEVATED VENOUS PRESSURE

The most common cause of an elevated jugular venous pressure is an increased RV pressure such as occurs in patients with pulmonic stenosis, pulmonary hypertension, or RV failure secondary to left-sided heart failure or RV infarction. The venous pressure also is elevated when obstruction to RV inflow occurs, as with tricuspid stenosis or RA myxoma, or when constrictive pericardial disease impedes RV inflow. It also may result from vena cava obstruction and, at times, an increased blood volume. Patients with obstructive pulmonary disease may have an elevated venous pressure only during expiration.

KUSSMAUL'S SIGN

Normally, during inspiration, there is an increase in the *a* wave of the JVP but a decrease in the mean jugular venous pressure as a result of the increased filling of the right-sided chambers associated with the decrease in intrathoracic pressure. *Kussmaul's sign* denotes an inspiratory increase in the venous pressure, which may occur in patients with severe constrictive pericarditis when the heart is unable to accept the increase in RV volume without a marked increase in the filling pressure. Although Kussmaul's sign was first described in patients with constrictive pericarditis, its most common cause is severe right-sided heart failure, regardless of etiology. The presence of Kussmaul's sign is also useful in the diagnosis of RV infarction[201] (see Chap. 72).

ABNORMALITIES OF THE *a* WAVE

The *a* wave in the JVP is absent when there is no effective atrial contraction, such as in atrial fibrillation (see Fig. 10-45*E*). In certain other conditions, the *a* wave may not be apparent. In sinus tachycardia, the *a* wave may fuse with the preceding *v* wave, particularly if the PR interval is prolonged. In some patients with sinus tachycardia, the jugular *a* wave may occur during the *v* or *y* descent and may be small or absent. In the presence of first-degree AV block, a discrete *a* wave with ascending and descending limbs is often completed prior to the first heart sound, and the *ac* interval is prolonged (see Fig. 10-45*F*).

Large *a* waves are of considerable diagnostic value (see Fig. 10-45*B*). When giant *a* waves are present with each beat, the right atrium is contracting against an increased resistance. This may result from obstruction at the tricuspid valve (tricuspid stenosis or atresia, right atrial myxoma) or conditions associated with increased resistance to RV filling.[200] A giant *a* wave is more likely to occur in patients with pulmonic stenosis or pulmonary hypertension in whom both the atrial and ventricular septa are intact.

Cannon *a* waves occur when the right atrium contracts while the tricuspid valve is closed during RV systole.[200] Cannon *a* waves may occur either regularly or irregularly and are most common in the presence of arrhythmias (see Fig. 10-45*G*).

ABNORMALITIES OF THE *x* WAVE

The most important alteration of the normally negative systolic collapse (*x* wave) of the JVP is its obliteration or even replacement by a positive wave. This is usually due to tricuspid regurgitation. Although atrial relaxation may contribute to the normal *x* descent, the development of atrial fibrillation does not obliterate the *x* wave except in the presence of tricuspid regurgitation. Accordingly, the occurrence of a positive wave in the JVP during ventricular systole is strong evidence of tricuspid regurgitation (Fig. 10-46*A*). Mild tricuspid regurgitation lessens and shortens the downward *x* wave as the regurgitation of blood into the right atrium produces a positive wave that diminishes the usual systolic fall in venous pressure. In some patients with moderate tricuspid regurgitation, there is a fairly distinct positive wave during ventricular systole between the *c* and *v* waves. This abnormal systolic waveform is usually referred to as a *v* or *cv* wave, although it has also been referred to as an *r* (regurgitant) or an *s* (systolic) wave. In patients with constrictive pericarditis, the *x* descent wave during systole is often more prominent than the early diastolic *y* wave (see Fig. 10-45*C* and Chap. 72).

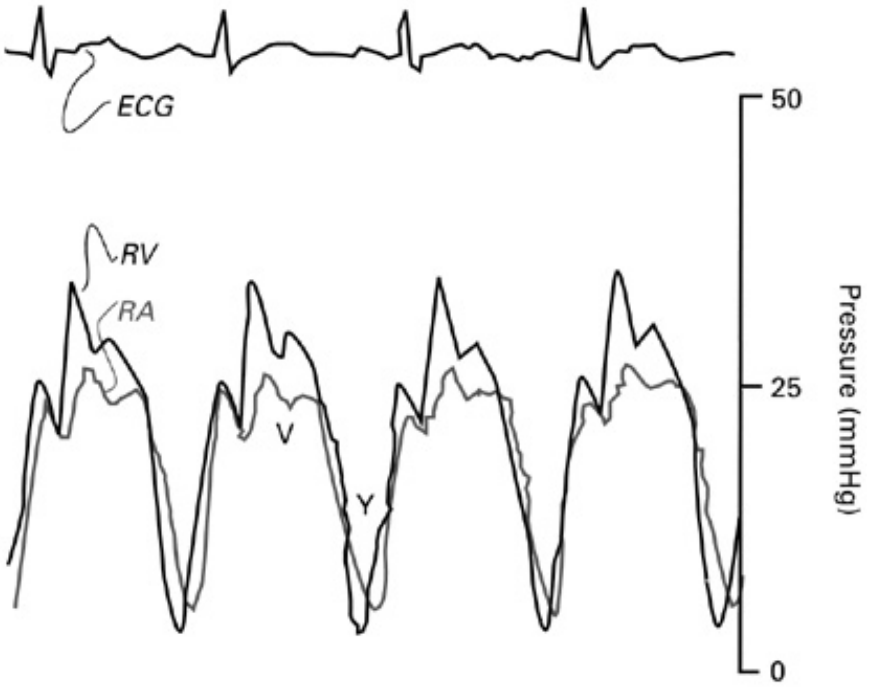

Figure 10-46: Right ventricular (RV) and right atrial (RA) pressure curves and simultaneous ECG from a patient with severe tricuspid regurgitation. Note ventricularization of the RA pressure curve.

ABNORMALITIES OF THE *v* WAVE

The positive, late systolic *v* wave results from the increasing RA blood volume during ventricular systole when the tricuspid valve normally is closed. With mild tricuspid regurgitation, the *v* wave and the obliteration of the *x* descent result in a single, large positive systolic wave (ventricularization) (see Figs. 10-45*A* and 10-46).

Normally in the JVP the *v* wave is lower in amplitude than the *a* wave. In patients with an ASD, however, the *a* and *v* waves are often equal in the right atrium and the JVP (see Fig. 10-46*D*). In patients with constrictive pericarditis and sinus rhythm, the RA *a* and *v* waves also may be equal,

but the venous pressure is increased, which is unusual with isolated ASD. In patients with constrictive pericarditis who are in atrial fibrillation, the *cv* wave is prominent and the *y* descent rapid.

ABNORMALITIES OF THE *y* TROUGH

The *y* descent, or diastolic collapse, is produced mainly by the tricuspid valve opening and the rapid inflow of blood into the right ventricle. A rapid, deep *y* descent in early diastole occurs with severe tricuspid regurgitation (see Fig. 10-45*A*). A venous pulse characterized by a sharp *y* descent, a deep *y* trough, and a rapid ascent to the baseline is seen in patients with constrictive pericarditis or with severe right-sided heart failure. A slow *y* descent in the JVP suggests an obstruction to RV filling and may be the only abnormal finding in patients with tricuspid stenosis or right atrial myxoma (see Fig. 10-45*B*). In both constrictive pericarditis and severe right-sided heart failure, the venous pressure is elevated with a sharp *y* dip in the JVP (see Chap. 72). The presence of a large positive systolic venous wave favors the diagnosis of severe heart failure.

Effects of Arrhythmias on the Venous Pulse

Large *a* waves in the JVP during arrhythmias are present when the *P* wave (atrial contraction) occurs between the onset of the QRS complex and the termination of the T wave (see Fig. 10-46*G*). Such cannon *a* waves may occur regularly in junctional rhythm. More commonly, they occur irregularly when AV dissociation accompanies premature ventricular beats, ventricular tachycardia, or complete heart block. The *a* wave is absent in patients with atrial fibrillation, and flutter *a* waves at a regular rate of 250 to 300 per minute occasionally are observed in patients with atrial flutter and varying degrees of AV block. Patients with multifocal atrial tachycardia often have prominent and somewhat variable *a* waves in the JVP. In these patients, many of whom have pulmonary hypertension secondary to lung disease, the *a* waves are often very large.

PREVIOUS | NEXT

Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

EXAMINATION OF THE RETINA*

Inspection of the smaller vessels of the body is possible in only three areas: the retina, the conjunctiva, and the nail beds. The ophthalmoscope has made the retina by far the easiest and most rewarding site.[201] Viewing this two-dimensional vascular display is generally much easier if the pupils are dilated. Pulse and blood pressure determinations should be made prior to the instillation of rapidly acting mydriatics, since both may increase after absorption of the drops. The pupils are left undilated in patients in whom the iris seems closely apposed to the cornea and in those with a history of closed-angle glaucoma. Examination of the retina should proceed methodically. Best pupillary dilatation is maintained if the optic disk is observed first. Assess for evidence of edema and blurred margins and for cupping with sharp contours. Rule out neovascularization or the pallor of optic atrophy. Next, scan along the superior temporal arcade, inspecting the arteries carefully for embolic plaques at each bifurcation. Observe the arteriovenous crossing for obscuration of the vein and for pronounced nicking and banking of the vessels. The lower arcade and the nasal vessels may be inspected next. Avoid the macular area until all else has been viewed because the pupil constricts most intensely when this area is illuminated. To discover diabetic microaneurysms early, look just temporal to the fovea, along the horizontal raphe. To find cotton-wool infarcts, look circularly around the disk two disk diameters out. Using this method, the retina can be efficiently searched for evidence of cardiovascular disease[201] (Table 10-5).

Table 10-5: Retinal Topography

Finding	Most Common Location
Arteriovenous crossings	Upper temporal quadrant
Cotton-wool spots	Around optic disk
Hard exudates	Between disk and fovea
Microaneurysms	Temporal to fovea
Emboli	Arterial bifurcations
Diabetic new vessels	Nerve head and arcades

Alterations in retinal caliber along the course of a single artery or vein are more important than estimates of arteriovenous ratios or absolute vascular diameter. Determining the degree of tortuosity of straightening are of little value where the veins are large, dark, and tortuous.

Variations in the caliber of a single vessel are more important than determinations of arteriovenous ratios. These changes may take the form of focal narrowing, sometimes called *beading* or *spasm*.

Thickening of the Vascular Wall

Normally, only the blood column is visible when the retinal vessels are viewed. When changes in the walls do occur, they are most visible along the sides of the vessels, since the location of the tangential line of sight presents a greater thickness to the viewer. Fatty exudate (hard exudate) may collect along venous walls (never arteries), particularly in diabetic exudative retinopathy.

Arteriosclerosis

In arteriosclerosis, medial smooth muscle (which may hypertrophy in chronic hypertension) becomes hyalinized with the deposition of collagen. As the wall thickens, the vessel takes on a burnished coppery luster; with further thickening, this may transmute to silver.

Arteriovenous Compressions

Arteriovenous compressions or "nicking" results from the sharing by the artery and vein of a common adventitial sheath at their crossings. Arteriosclerotic thickening impedes venous outflow at these locations, with venous tortuosity, engorgement, and darkening of the flood column distal to the compression.[201]

Atherosclerosis

Retinal atheromata have a predilection for the bifurcation and bends within the first two branches of the central retinal artery, appearing as segments of irregular yellowish sheathing and having the crystalline knobbiness of a salted pretzel stick.[210]

Cotton-Wool Spots

Cotton-wool spots are generally a sign of serious systemic disease. They may be seen in patients with severe hypertension, blood dyscrasias, collagen diseases, or hemorrhagic shock. Cotton-wool spots also are seen frequently in patients with acquired immunodeficiency syndrome (AIDS) (Fig. 10-47, Plate 43). Cotton-wool "exudates" are not exudates but consist of a cluster of cell-like swollen ends of fragmented axons (cytoid bodies) in an area of edematous retina.[201]

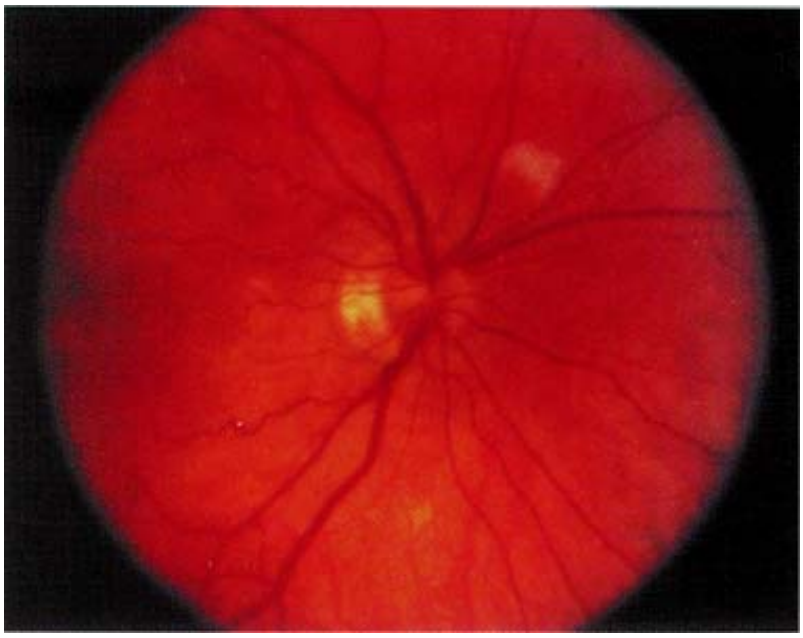

Figure 10-47: (Plate 43) Retinal cotton-wool spot. Cotton-wool spots are most frequently found close to the optic disk. Although they occur in acute uncontrolled systemic hypertension, the more common cause now, in younger patients, is infection with the human immunodeficiency virus (HIV). This normotensive 37-year-old man had no visual symptoms and no other retinopathy. There is a myopic crescent at the temporal disk edge, which is not abnormal. He died of complications related to the acquired immunodeficiency syndrome (AIDS) 2 years later.

Hard Exudates

Hard exudates are most likely residues of edema. They occur in situations where the vessels become leaky, and as the more watery component of the extravasation is resorbed, the lipid residue forms a hard, yellow, waxy deposit. These deposits may surround the leaking vessel in a circinate ring or may accumulate in the macula, radiating from the fovea in the spokes of a macular "star" (Fig. 10-48, Plate 44).

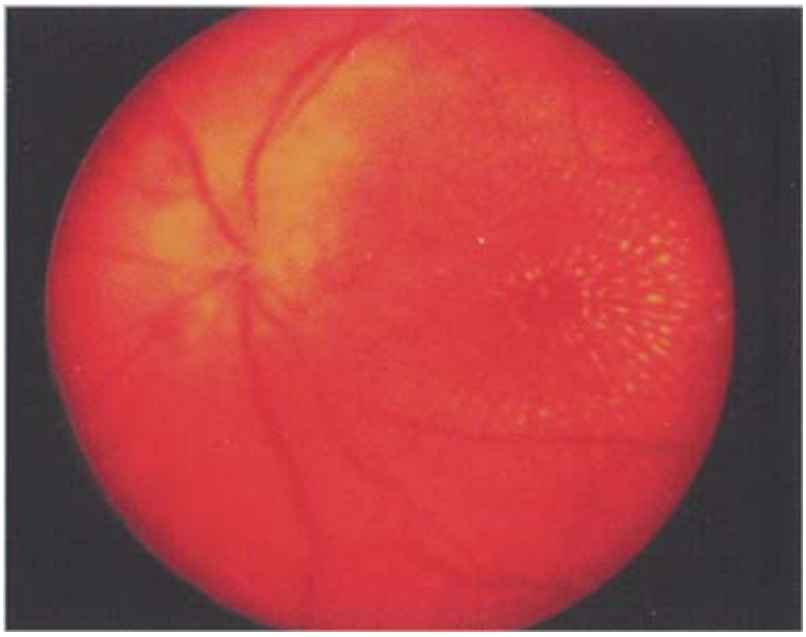

Figure 10-48: (Plate 44) Disk swelling and hard exudate in a macular "star" pattern. In this hypertensive patient with periarteritis nodosa, vascular leakage has led to the deposit of hard exudates around the fovea. Radial perifoveal connective tissue results in the star pattern of the exudate. Note also that the optic disk is edematous, with blurred margins, secondary to hypertension.

Microaneurysms

Microaneurysms are not unique to diabetes but occur in many disease states, including retinal venous obstructive disease, sickle cell disease, the dysproteinemias, Behçet's disease, sarcoidosis, and other forms of uveitis. They may represent abortive attempts at revascularization of compromised capillary bed (Fig. 10-49, Plate 45).

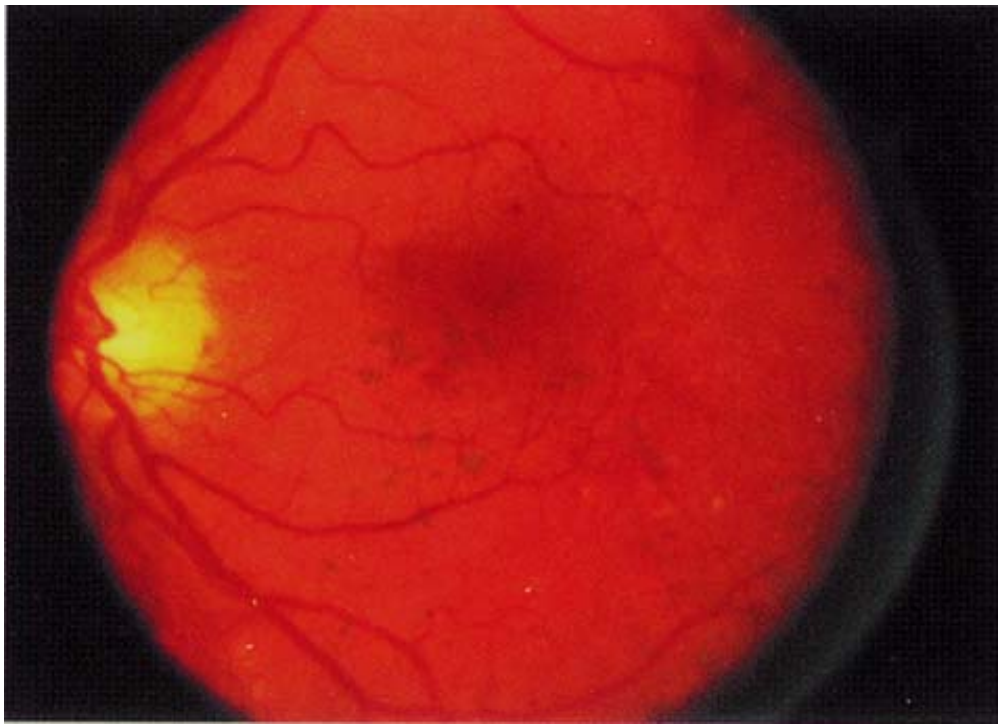

Figure 10-49: (Plate 45) Background diabetic retinopathy. Retinal microaneurysms, dot-and-blot hemorrhages, and a few fine upper temporal hard exudates are diagnostic of early diabetic retinopathy. The patient had no visual symptoms, but retinopathy of this magnitude can often be seen in patients with insulin-requiring diabetes of 15 or more years' duration.

Neovascularization

In neovascularization the new vessels generally originate from capillaries from the venous side of the circulation and are associated with greater or lesser degrees of fibrosis. In all cases, however, the new vessels are incorporated in an associated fibrous membrane (Fig. 10-50, Plate 46; Fig. 10-51).

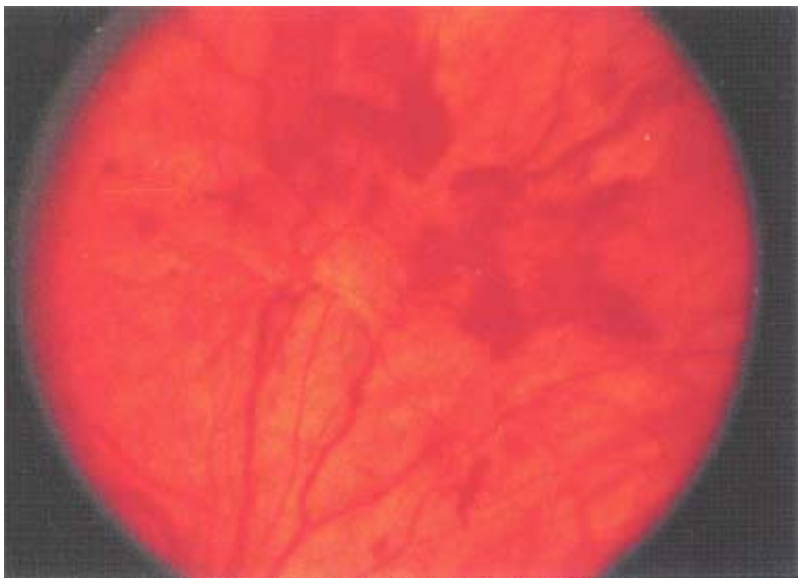

Figure 10-50: (Plate 46) Proliferative diabetic retinopathy with preretinal hemorrhage. When neovascularization develops, preretinal and vitreous hemorrhages are much more likely to occur.

Easily visible neovascularization either in the periphery of the retina, as in this diabetic patient, or at the disk is an indication for immediate panretinal laser photocoagulation.

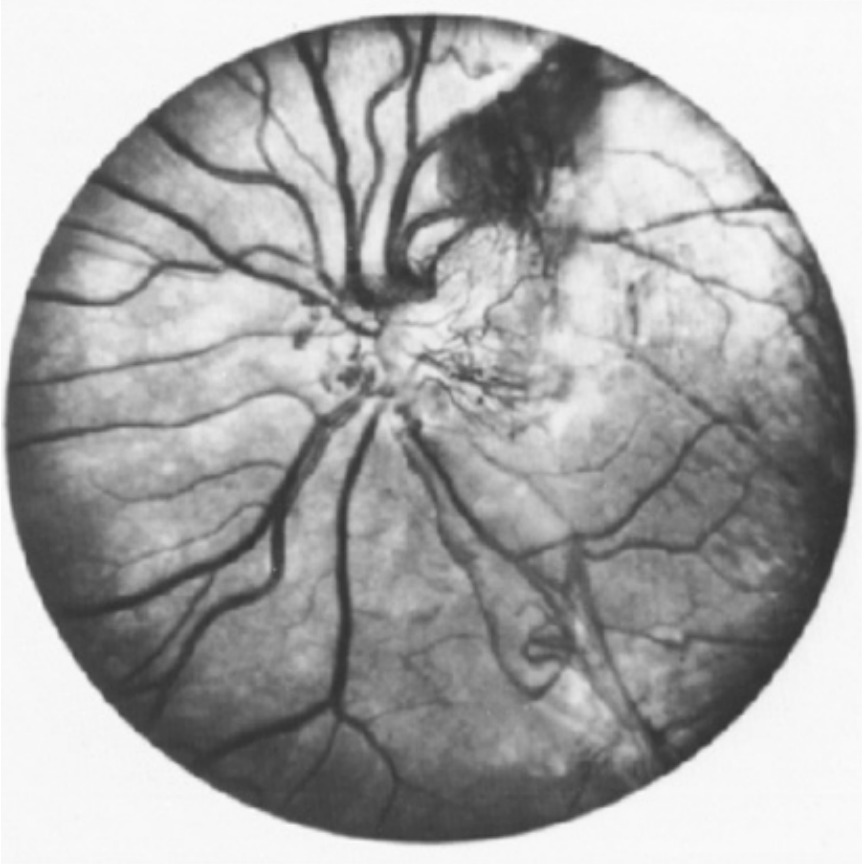

Figure 10-51: Proliferative diabetic retinopathy, left eye. There is extensive neovascularization of the disk with an associated small intravitreal hemorrhage that obscures the upper temporal vessels. Along the inferior temporal arcade is another area of neovascularization. These new vessels are incorporated in fibrous membranes that may tent up the vessels and cause traction detachments of the retina, as at the lower right edge of the photograph.

Retinal Hemorrhage

Hemorrhage into the retina indicates further breakdown in the integrity of the vascular wall. When the hemorrhage occurs in the inner retina, as in hypertension, it assumes a feathery flame shape as it is molded and dispersed by the nerve fibers coursing toward the disk. In obstruction of the central retinal vein, the fundus may be splattered with blood (Fig. 10-52, Plate 47).

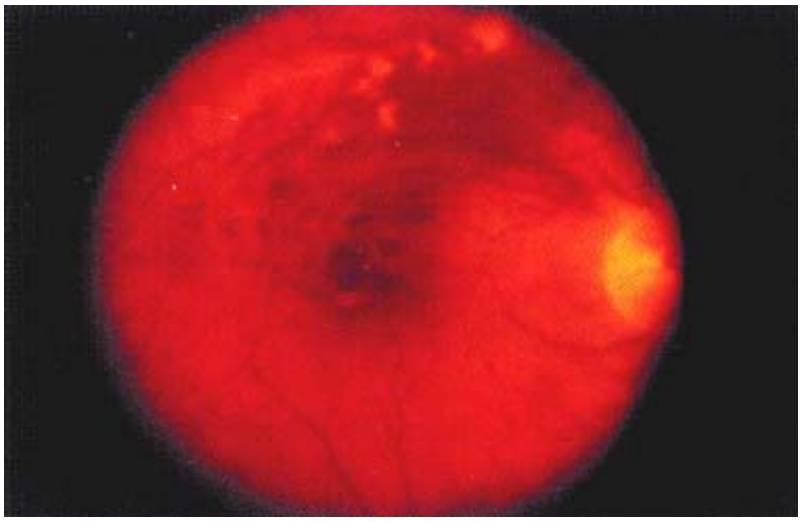

Figure 10-52: (Plate 47) Branch retinal vein obstruction. Thickening of the retinal arterial wall in diabetes and hypertension may compromise the lumen of the vein, where they share a common adventitial sheath at an arteriovenous crossing. The resulting obstruction produces hemorrhage retinopathy in the drainage area of the affected vein. Note here how the flame-shaped pattern of blood outlines the arcuate pattern of the nerve fibers as they run toward the optic disk.

Vascular Occlusion

When the central artery or one of its branches is occluded, the nonperfused retinal area becomes cloudy in a matter of minutes. At the fovea, where the retina is one cell layer thick and nourished by the choroid, the normal color and transparency persist. By contrast with the surrounding pallor, the fovea then has a cherry-red appearance (Fig. 10-53, Plate 48). Occlusions of branches of the central vein produce edema and hemorrhage in the drained area. As collateral drainage channels develop (see Fig 10-52 and Plate 47), the edema and hemorrhagic retinopathy subside, leaving white-walled veins, neovascularization, and microaneurysms in the affected area (Fig. 10-54, Plate 49).

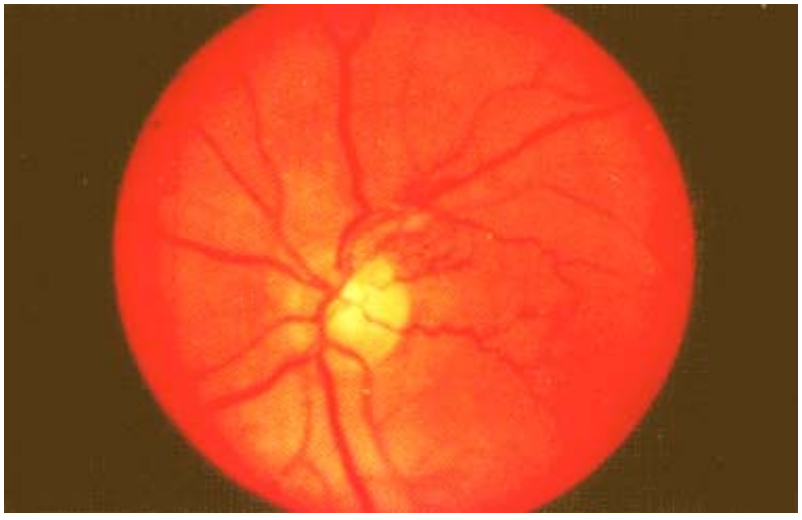

Figure 10-54: (Plate 49) Neovascularization after branch retinal vein obstruction. New vessels may develop late after obstruction of a branch of the central retinal vein. These most often serve to shunt flow around the obstructed vessel site and are thus not as exuberantly proliferative as those seen in diabetic retinopathy.

Optic Disk Edema

The term *papilledema* is reserved for the form of disk edema that is the result of increased intracranial pressure. It therefore has an etiologic connotation and is not used generally to mean optic disk edema. *Papillitis* is the term applied to inflammatory disk edema. Patients with anterior ischemic optic neuropathy commonly have a pale, edematous disk with an altitudinal field effect.

Embolism

Table 10-6 lists the characteristics of retinal emboli of cardiovascular significance. Of these, platelet emboli are at once the most common and the most evanescent. Hollenhorst cholesterol plaques may be identified at the same bifurcations for months to years after the embolic shower. Platelet emboli, Hollenhorst plaques (see Fig. 10-53, Plate 48; Fig. 10-55, Plate 49), and calcium emboli (Fig. 10-56, Plate 50) are usually seen along the course of a retinal artery. Roth spots (Fig. 10-57, Plate 51) and fat emboli may not appear to be intravascular and may not be associated with a vessel that is ophthalmoscopically visible (see Table 10-6).[201]

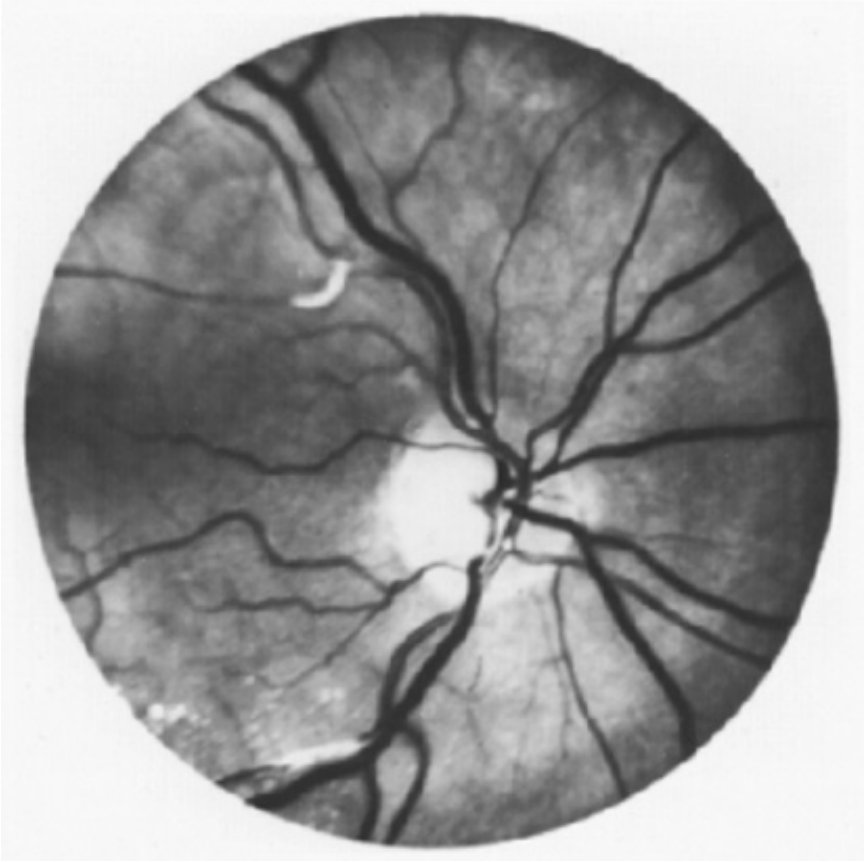

Figure 10-55: Retinal emboli often lodge at bifurcations, as in this patient with carotid atherosclerosis. Note that the embolic material often seems larger than the containing vessel, as in the embolus at the lower left edge of the photograph. Emboli may damage the vessel wall and cause leakage, as can be seen by the exudate deposited about the inferior embolus. Hollenhorst cholesterol plaques rarely obstruct arterial flow completely, and this patient maintained vision.

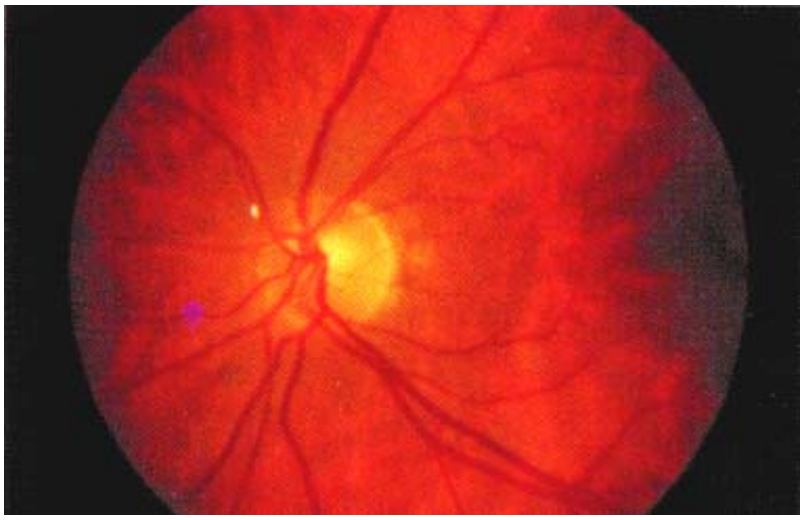

Figure 10-56: (Plate 50) Calcific retinal embolus associated with aortic valvular disease. Calcific aortic valvular disease and valve replacement surgery may result in retinal emboli. Like cholesterol emboli, these calcific flecks lodge at arterial bifurcations but seldom obstruct flow completely. They are white and glitter in the ophthalmoscope beam. Somewhat similar emboli may be seen after the intravenous injection of illicit drugs expanded with talc.

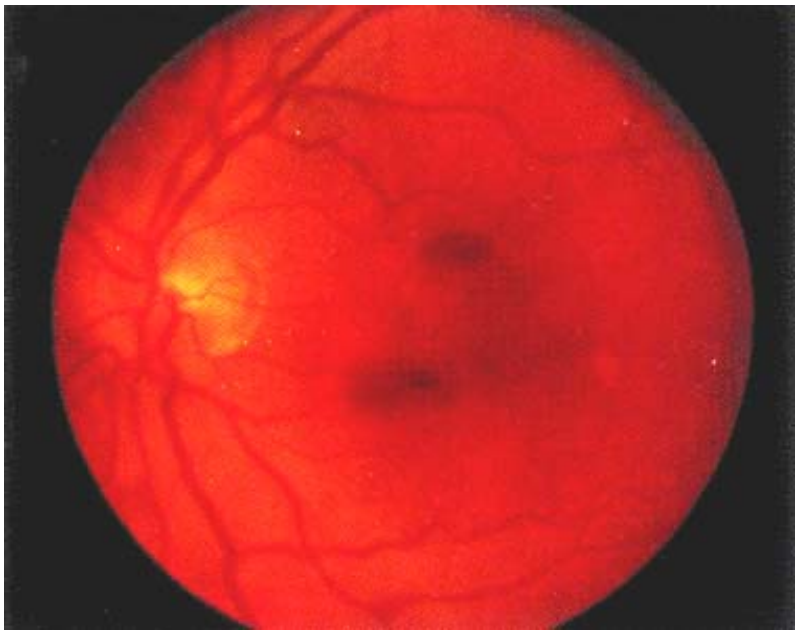

Figure 10-57: (Plate 51) Retinal hemorrhages after cardiac catheterization. Following cardiac catheterization, symptomatic and asymptomatic retinal hemorrhages may occur. The latter are more common. Presumably, these are the result of embolic events. Note, in this recently catheterized patient, the two oval hemorrhages and a small area of cloudy swelling just inferior and temporal to the fovea.

Table 10-6: Emboli of Cardiovascular Significance

Type	Appearance	Significance
Platelet	Dull pink to gray often with associated fibrin	Downstream vegetations, mural thrombi
Hollenhorst plaque	Glistening yellow-orange plaques at bifurcations	Downstream atheroma (containing cholesterol)
Calcium plaque	Glistening white plaques	Calcific aortic stenosis
Roth spot	Hemorrhage with gray-white center (see Plate 51, Fig. 10-57)	Blood dyscrasia or septic embolus as in subacute bacterial endocarditis
Fat embolus	Fuzzy-bordered gray-white spot without hemorrhage	Severe trauma with long bone fractures
Myxoma	Disk edema, retinal edema in arterial supply zone	Life-threatening atrial myxoma

Diabetes Mellitus

In diabetes mellitus, focal loss of a portion of the capillary bed is followed by microaneurysm formation and vascular dilatation around the borders of the area of capillary dropout (see Fig. 10-49 and Plate 45). Vascular leakage occurs with dot and blot hemorrhages and deposits of hard exudate (Fig 10-58). New blood vessels develop along the vascular arcades and at the optic nerve head (see Figs. 10-50 and 10-51 and Plate 50).

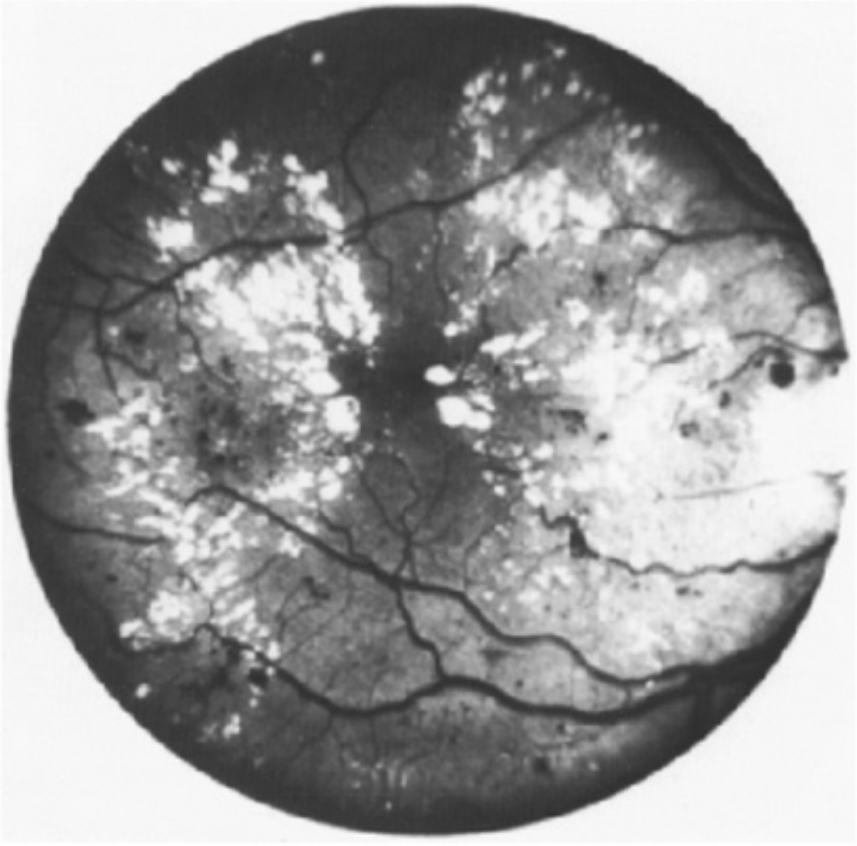

Figure 10-58: Exudative diabetic retinopathy, right eye, illustrating microaneurysms, dot-and-blot hemorrhages, and venous engorgement with extensive deposits of hard, yellow exudate.

Vasoconstriction of the arterial tree and thickening of the arterial vessel walls with consequent reduction in lumen diameter are homeostatic responses to hypertension. Arteriosclerotic narrowing of the vessels acts to insulate the capillary bed from the elevated pressure of the arterial supply. These arteriosclerotic changes are visible as narrowing, increases in central light reflexes, and copper and silver "wiring" of the arteries (Fig. 10-59, Plate 52). Radial arrangement of such exudate deposits in the macula produces a "star" (see Fig 10-48 and Plate 48). Hemorrhage may occur in the retinal layers in a characteristic flame pattern, and focal ischemia in the nerve fiber may result in cotton-wool microinfarcts. In severe hypertensive decompensation, the optic nerve head becomes swollen and edematous (see Fig. 10-48 and Plate 48).

Hypertensive patients should be classified as to whether or not their retinal circulation is compensated or has decompensated with observable edema, cotton-wool spots, flame hemorrhages, or swelling of the optic disk.[201]

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

PHYSICAL EXAMINATION OF THE CHEST, ABDOMEN, AND EXTREMITIES

Physical examination of the lungs is an important noninvasive technique requiring only a stethoscope.[202] Wheezing and a pleural friction rub are detected only by the clinical evaluation. The pleural friction rub may be a clue to the diagnosis of pulmonary infarction. Pleural fluid due to heart failure is usually located in the right pleural space. When pleural fluid is localized predominately to the left, a cause other than or in addition to heart failure, such as pulmonary infarction, should be considered.

A pneumothorax may develop as a consequence of spontaneous mediastinal emphysema or may be iatrogenic, due to procedures.[202] Hyperresonance and diminished breath sounds may be due to pulmonary emphysema. Signs of pulmonary consolidation may be due to pneumonia or pulmonary infarction. Wheezing and rales may be due to bronchial disease. Heart failure may be associated with rales in the lung bases, wheezing, and pleural fluid. Importantly, heart failure frequently is not associated with rales, since interstitial pulmonary edema usually does not produce rales.[202]

The diameter of the *abdominal* aorta should be determined in every patient[202] (see Chap. 88). An abdominal aortic aneurysm may be missed if the examiner fails to assess the area above the umbilicus.

Specific abnormalities of the abdomen may be secondary to heart disease. A large, tender liver is common in patients with heart failure or constrictive pericarditis. Systolic hepatic pulsations are frequent in patients with tricuspid regurgitation. A palpable spleen is a common but late sign in patients with severe heart failure and is also often present in patients with infective endocarditis.

Although hepatic cirrhosis is the most common cause of ascites, the latter may occur with heart failure alone, although it is less common with the use of diuretic therapy. Severe tricuspid regurgitation, as caused by infective endocarditis in drug addicts, may produce prominent systolic pulsation of the internal jugular veins in the neck, a large, moving, and pulsating liver, and ascites. Constrictive pericarditis should be considered when the ascites is out of proportion to peripheral edema. In many such patients, the heart is normal in size or only slightly enlarged, a pericardial "knock" is heard, and there is a rapid *x* and/or *y* descent in the internal jugular vein pulsation.[202] Restrictive cardiomyopathy can mimic constrictive pericarditis, but the heart is usually moderately large in patients with restrictive cardiomyopathy. When there is an arteriovenous fistula in the abdomen, a continuous murmur may be heard over the abdomen. Fistulas due to trauma and surgery may occur.

A systolic bruit may be heard over the kidney areas and may signify renal artery stenosis, particularly in patients with systemic hypertension. A systolic bruit often is auscultated over the abdominal aorta, but its presence does not indicate the severity of disease of the aorta.[202]

Examination of the upper and lower extremities may provide important diagnostic information (see Chap. 90). The clinical detection of arterial disease and thrombophlebitis is important. Atherosclerosis of the peripheral arteries may produce intermittent claudication of the buttock, calf, thigh, or foot, with severe disease resulting in tissue damage of the toes. Peripheral

atherosclerosis is an important risk factor for ischemic heart disease, and its presence increases the likelihood of coronary atherosclerosis. Thrombophlebitis often causes pain in the calf or thigh or edema, and its presence should raise the consideration of pulmonary emboli as well. Edema is a late sign of heart failure, and its predictive value as a diagnostic sign is poor. It frequently involves the right leg prior to the left. Considerable heart failure and a resulting weight gain may be present without edema being present. Edema of the lower extremities may be secondary to local factors such as varicose veins or thrombophlebitis or the removal of veins at CABG surgery. Under such circumstances, the edema often occurs in only one leg.

Edema may result from restrictive garments, and venous stasis often is secondary to a long trip in a car or airplane.[202] Edema may be due to salt and water retention in patients with primary renal disease. In the differential diagnosis of edema, local factors should be considered first. If local factors can be excluded, the cause of the salt and water retention should be determined with an assessment for evidence of primary renal disease. Rarely, peripheral edema can be an early sign of lymphatic obstruction produced by metastatic disease in the pelvis or abdomen.

Since the invention of the stethoscope by Laennec in 1826, cardiac auscultation has played a key role in the evaluation of patients with cardiovascular disease. New diagnostic techniques developed in recent years have led to a better understanding of the relationship between intracardiac pressure, flow, and valve motion and the resulting sound phenomena on the other. The analysis of heart sounds and murmurs by phonocardiography, together with information obtained by cardiac catheterization, angiography, echocardiography, and cardiac surgery, has made cardiac auscultation a precise discipline based on firm physiologic principles.[203]

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

INSPECTION AND PALPATION OF THE PRECORDIUM

Inspection and palpation of the cardiac pulsations of the anterior chest have been practiced by physicians since ancient times and have a solid scientific basis. The results of precordial inspection and palpation have been correlated with noninvasive studies, hemodynamic data, and surgical and autopsy studies[202,203] and remain an important part of the cardiovascular examination. Their usefulness depends on an understanding of cardiovascular physiology, the proficiency of the examiner, and his or her ability to integrate findings with history, the information obtained by other portions of the physical examination, the ECG, the chest roentgenogram, and other diagnostic tests.

Precordial Pulsations Due to the Heartbeat

Precordial pulsations, reflecting underlying movement of the heart and great vessels, occur principally in seven areas of the anterior chest[204,205] (Fig. 10-60):

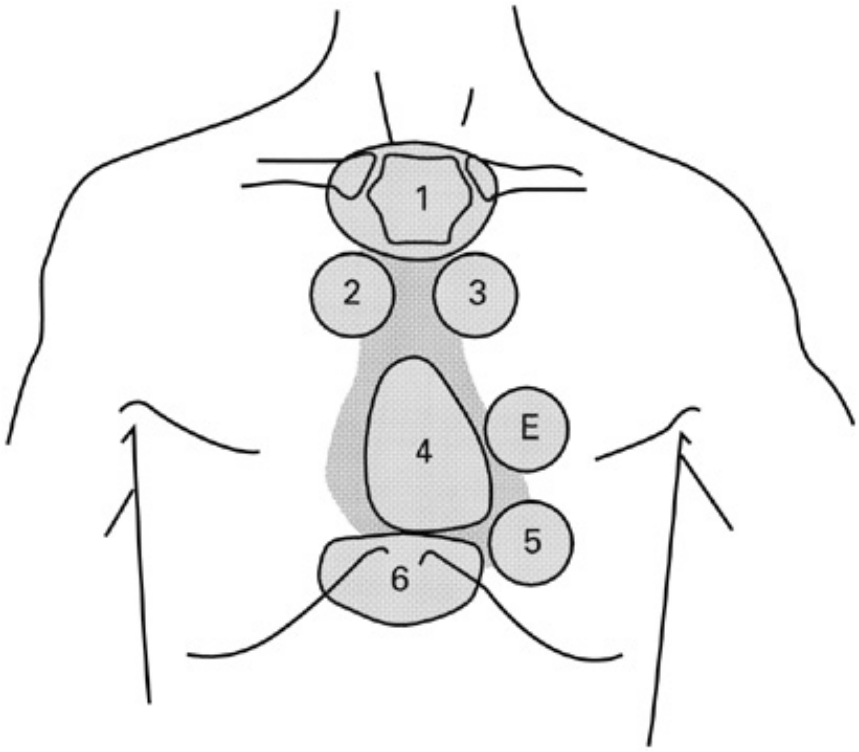


Figure 10-60: Seven areas to be examined for abnormal cardiovascular pulsations by inspection and palpation. (From Schlant RC, Hurst JW. *Examination of the Precordium: Inspection and Palpation.* New York: American Heart Association; 1990:1-28. Used with permission from the publisher and authors.)

1. The sternoclavicular area

2. The aortic area
3. The pulmonic area
4. The RV (left parasternal) area
5. The LV (apical) area
6. The epigastric area
7. Ectopic (variable-location) areas

While the cardiac apex is usually produced by the left ventricle, it is sometimes produced by an enlarged right ventricle that displaces the left ventricle laterally and posteriorly. Occasionally, the cardiac position is abnormal due to dextroposition, dextroversion, dextrocardia, or other changes in intrathoracic structures. Although the cardiac apex impulse is commonly referred to as the *point of maximal impulse* (PMI), the two terms are not necessarily synonymous, since the maximal precordial pulsation may be produced by an enlarged or hypertrophied right ventricle, a dilated aorta or pulmonary artery, or a LV wall-motion abnormality. Therefore, precordial pulsations should be described by their location, timing, contour, and duration.

Inspection of the Precordium

The examiner should first inspect the thorax from the foot of the bed with the subject supine, the legs horizontal, and the head and trunk elevated to approximately 30°.[205] The patient may have a barrel-shaped chest with an increased anteroposterior diameter, a straight-back syndrome, pectus excavatum, pectus carinatum, kyphoscoliosis, or ankylosing spondylitis. Each may produce or be associated with cardiac abnormalities. Asymmetry of the thorax due to convex bulging of the precordium suggests the presence of heart disease since childhood. Exaggerated movements of the cardiac apex often can be detected from this observation point.

Next, the examiner should move to the patient's right side and observe the patient's chest tangentially rather than from above. A light beam directed across the precordium may enhance subtle findings.[205,206] Precordial movements frequently can be recognized more easily if the tip of an applicator stick, tongue blade, or light pencil is held against the impulse as a fulcrum. Motion of the underlying chest wall is transmitted to the free end of the instrument and exaggerated, making the movements more obvious.

In patients with an abnormally prominent apical impulse and in some thin, normal individuals, the apical impulse or apex beat can be seen. The presystolic apical motion associated with the atrial contribution to ventricular filling (a fourth heart sound) sometimes may be visualized, as may the diastolic waveform due to rapid ventricular filling (a third heart sound). A late systolic bulge either at the apex or in an ectopic area, usually located either medial and superior or lateral to the apical impulse, may be observed in patients with a large dyskinetic ventricular aneurysm.[203] When precordial pulsations are exaggerated, they become visible as well as palpable. In general, however, outward movements are best discerned by palpation, whereas inward movements usually are seen more easily than felt.[202,203]

Palpation of the Precordium

With Tietze's syndrome, pain, sometimes with swelling and tenderness, may affect the costochondral, chondrosternal, or xiphosternal joints and may be reproduced by touching. Palpation also may reveal tender superficial veins on the anterior chest (Mondor's disease), a rare etiology of chest discomfort.[206] Collateral vessels in the posterior intercostal spaces may be palpable in patients with aortic coarctation.[206]

Palpation of the precordium is also best performed from the right side, with the patient supine and the upper trunk elevated 30°. Palpation with the right hand usually provides more information. Patients with suspected cardiovascular disease also should be examined in the left lateral

decubitus position, rotated 45 to 90°.[207] In this position, the normal LV impulse may be displaced several centimeters leftward and may appear more prominent and sustained. The size of the apex impulse rather than its distance from the midsternal or midclavicular line determines its normality.[207] Often, the apex impulse and other palpable events such as a LV rapid filling wave (S_3) or presystolic *a* wave (S_4) may be felt only in this position.

The location and size of the cardiac apex impulse should be defined, its contour characterized, and any abnormal precordial pulsations identified. The palm of the hand, ventral surface of the proximal metacarpals, and fingers should all be used for optimal appreciation of specific movements. The fingers appear to be particularly insensitive to movements of relatively large amplitude and very low frequency. This is consistent with the clinical observation that an examiner's hand occasionally can be seen to move up and down with precordial motion, although the same movements are imperceptible by palpation alone. By contrast, higher-frequency events, such as the vibrations associated with abnormally loud aortic or pulmonic components of the second heart sound, are easily palpable, even though the amplitude of their movement is not readily visible.[204]

The pads of the fingers are most useful for detecting LV and normal RV motion, whereas the palm and proximal metacarpals are usually best used for palpating larger, low-frequency movements such as the parasternal systolic lift of RV hypertrophy.[204] Varying pressure with the hand is often quite useful. High-frequency movements such as ejection sounds, valve closure sounds, and mitral opening snaps are detected more easily with the hand held firmly against the chest, whereas low-frequency movements such as ventricular diastolic filling events are best recognized with light pressure with the fingertips.

Thrills are palpable vibrations from murmurs or bruits ordinarily associated with grade 4/6 murmurs or louder. The location of a thrill often helps identify its origin. Thrills are palpated most easily with the fingertips or with firm pressure, using either the palm of the hand or the proximal metacarpals. Sometimes thrills are felt better during a held end-expiration with moderate pressure applied from the right hand on top of the left hand, which is placed on the chest. Occasionally, palpable murmurs are more readily detected with the right palm placed over the anterior chest and the left hand supporting the posterior thorax with equal force.[205]

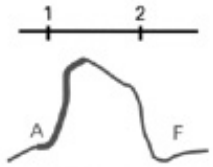
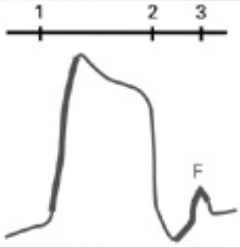
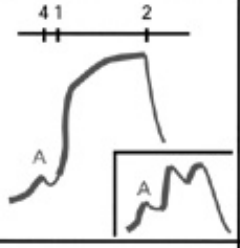
To detect abnormal RV motion, the heel of the hand should be placed over the lower half of the sternum with the patient's breath held at end-expiration. The parasternal lift due to RV hypertrophy is often better visualized than actually felt. In patients with chronic obstructive pulmonary disease, subxiphoid and epigastric palpation with the patient's breath held at end-inspiration is useful for assessing RV motion.

Proper patient positioning is important. The location of the apex impulse is usually described in terms of its distance from the midsternal or midclavicular line and the intercostal space in which it is located. Although heart size is commonly estimated based on the size and location of the apex impulse with the patient supine, this is not always a reliable indicator of LV end-diastolic volume. The apex impulse is often faint or not palpable with the patient supine because of the distance of the ventricular apex from the chest wall. Palpation of the cardiac apex with the patient in the left lateral position, however, permits optimal assessment of the size (diameter) and contour of the systolic outward movement at the apex; diastolic movements are also best appreciated with the patient in this position. Since the apex impulse may shift several centimeters laterally when the patient rotates to the left lateral position, however, the location of the apex impulse may be incorrect in this position. Palpation with simultaneous cardiac auscultation often is useful for identifying the systolic or diastolic timing of precordial pulsations. Simultaneous palpation of the apical impulse and carotid pulse may be helpful in assessing the severity of aortic stenosis. An appreciable lag time between the onset of the apex impulse and carotid pulse usually indicates

severe aortic stenosis.

Physiology of Precordial Motion

Although only the apical impulse is palpable normally, a brief RV systolic motion can be felt at the left sternal edge in asthenic individuals. With the onset of isovolumic LV contraction, there is anterior movement of the left ventricle toward the chest walls (**see** Fig. 10-61). Counterclockwise rotation of the left ventricle along its longitudinal axis occurs as the cardiac apex moves anteriorly and makes contact with the chest wall in early systole.[208] The maximal outward movement occurs coincident with or just after aortic valve opening. After rapid early ejection, the left ventricle moves away from the chest wall, and the apex retracts during latter systole and returns to baseline well before the second heart sound.[204] The outward apex movement in early systole normally is palpable, but the later systolic inward movement is only visible (Fig. 10-61). Palpable movements of the apex in diastole result from LV filling. The early diastolic outward movement due to rapid ventricular filling (F wave), which corresponds to the normal S_3, is occasionally palpable in normal children and young adults (**see** Fig. 10-61). Later diastolic filling due to left atrial contraction (*a* wave) is not normally palpable. Precordial motion is modified by age, chest wall thickness, lung disease, and pleural or pericardial effusion.

Type of movement and associated clinical condition	Graphic Representation (palpable features in heavy line)	Location and accompanying features
NORMAL ADULT APEX IMPULSE		Cardiac apex; moderate systolic thrust; A and F waves usually imperceptible
HYPERKINETIC APEX IMPULSE "Normal Child "Hyperdynamic states "Ventricular septal defect "Patent ductus arteriosus "Mitral regurgitation "Aortic regurgitation		Exaggerated thrust at cardiac apex; F wave may be palpable, coincident with third heart sound
HYPERKINETIC RIGHT VENTRICULAR IMPULSE "Atrial septal defect "Pulmonary regurgitation	Same as above	Maximal at left sternal edge in third and fourth intercostal spaces
SUSTAINED APEX IMPULSE "Left ventricular hypertrophy, ""as in: "Aortic stenosis "Hypertension "Insert: a variation that ""may occur in hypertrophic ""cardiomyopathy		Maximal at cardiac apex; A wave may be visible and palpable coincident with fourth heart sound
SUSTAINED RIGHT VENTRICULAR IMPULSE "Right ventricular ""hypertrophy, as in: "Pulmonary hypertension "Pulmonary stenosis	Same impulse as in Sustained above	Maximal at left sternal edge in third and fourth intercostal spaces
ECTOPIC LEFT		

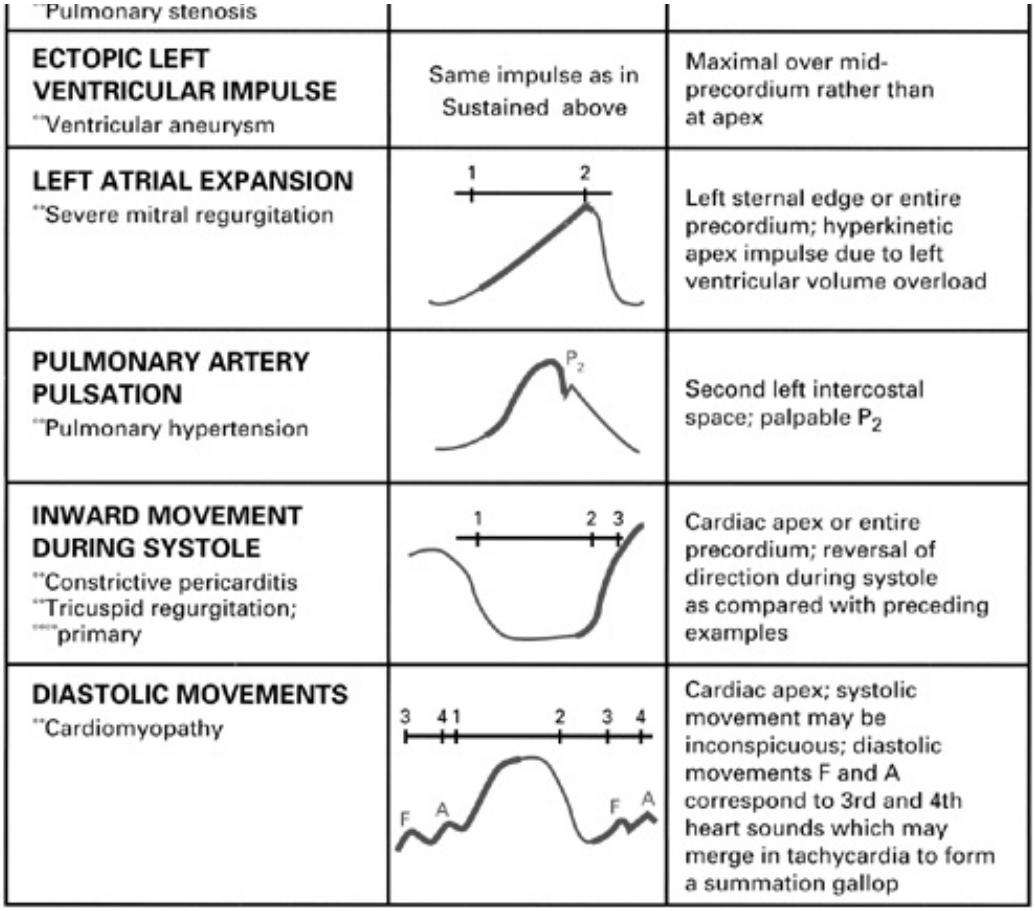


Figure 10-61: Graphic representation of apical movements in health and disease. Heavy line indicates palpable features. P_2, pulmonary component of second heart sound; A, atrial wave, corresponding to a fourth heart sound (S_4) or atrial gallop; F, filling wave, corresponding to third heart sound (S_3) or ventricular gallop. (From Willis P IV. Inspection and palpation of the precordium. In: Hurst JW, ed. *The Heart*, 7th ed. New York: McGraw-Hill; 1990:164. Reproduced with permission from the publisher and author.)

AREA 1: STERNOCLAVICULAR AREA PULSATIONS

The sternoclavicular area (**see** Fig. 10-60) includes the right and left sternoclavicular joints, the manubrium, and the upper sternum. Usually, no pulsation is noted in this area. A slight, brief systolic pulsation of a sternoclavicular joint or the manubrium may be due to aortic regurgitation. Abnormal pulsations and movements in the sternoclavicular area are commonly produced by enlargement, dilatation, or diseases of the aorta, particularly aortic dissection, atherosclerotic aneurysm, or syphilitic aneurysm. An abnormal pulsation of a sternoclavicular joint in patients with chest pain may be an early clue to diagnosis of aortic dissection. A slight pulsation in the right sternoclavicular area may suggest a right-sided aortic arch in patients with cyanotic heart disease, particularly tetralogy of Fallot.[204] A kinked, tortuous right carotid artery or dilatation and tortuosity of other brachiocephalic vessels may produce visible and palpable pulsations in the suprasternal notch or the supraclavicular areas.

AREA 2: AORTIC AREA PULSATIONS

Vibrations of the aortic component (A_2) of the second heart sound may be palpated when they are accentuated, as in arterial hypertension. With valvular aortic stenosis, a systolic thrill is present frequently in the second and less commonly in the first and third right intercostal spaces near the sternum (see Fig. 10-60). It often radiates upward toward the right side of the neck and to the

suprasternal notch and right supraclavicular area. Less frequently, the thrill is palpable at the second or third left interspaces next to the sternum or at the apex. A systolic thrill in the aortic area and in the right carotid artery also can occur in patients with severe aortic regurgitation without stenosis. Abnormal systolic pulsations in the aortic area may be due to dilatation of the ascending aorta due to aneurysm and/or chronic aortic regurgitation.

AREA 3: PULMONIC AREA PULSATIONS

Vibrations associated with a loud pulmonic component of S_2 (see Fig. 10-60) often are palpable in patients with pulmonary hypertension from any cause. During simultaneous palpation of the carotid pulse, a palpable P_2 or A_2 coincides with the early downslope of the carotid pulse. A systolic thrill in the second and third left intercostal spaces near the sternum often occurs with pulmonic valve stenosis. The thrill often radiates toward the left side of the neck, in contrast to the thrill with aortic stenosis, which radiates upward and to the right.

Pulsations of a dilated pulmonary artery may be seen or felt in the second or third left intercostal space near the sternum. In normal infants and children or anxious adults with thin chest walls, a slight, brief, early systolic pulsation may be present in this area. This pulsation is accentuated by conditions that cause an increased cardiac output (e.g., fever, pregnancy). Idiopathic dilatation of the pulmonary artery also may cause a palpable systolic impulse in the same area.[205]

The common causes of an accentuated and sustained systolic pulsation in the pulmonary artery area are pulmonary hypertension, increased pulmonary blood flow, and their combination. In general, pulmonary hypertension causes a relatively slow, sustained, and forceful pulmonary artery pulsation, whereas a large pulmonary blood flow (e.g., ASD) produces an extremely active, more vigorous, but less sustained pulsation. Valvular pulmonary stenosis with poststenotic dilatation of the pulmonary artery may be associated with a palpable, sustained pulsation in this area, often with a slow rise of the initial phase.

AREA 4: LEFT PARASTERNAL-RIGHT VENTRICULAR OR TRICUSPID AREA PULSATIONS

A systolic thrill in the third, fourth, or fifth intercostal space in the parasternal area to the left of the sternum (see Fig. 10-60) is characteristic of VSD, although tricuspid regurgitation also can produce a thrill here.

Normally, the lower left parasternal region retracts very slightly during systole, and RV activity is not palpable. Slight, gentle outward pulsations of the lower sternum and left parasternal area may be recorded in normal children and young adults, in thin adults with a small anteroposterior thoracic diameter, or in patients with pectus excavatum. Sometimes, these pulsations can be palpated in the subxiphoid area and are increased by hyperdynamic cardiac function.

Abnormal pulsations of the sternal and left parasternal areas most commonly are due to RV hypertrophy or dilatation. The pulsation associated with RV hypertension is usually more sustained throughout systole and tends to rise more gradually than the pulsation produced by a RV volume load, which usually is more vigorous but often briefer.[203,208]

A predominant RV pressure load occurs with pulmonic stenosis and pulmonary hypertension due to LV failure, mitral valve disease, a left-to-right shunt, or pulmonary vascular disease. The sustained anterior precordial pulsation associated with isolated valvular pulmonic stenosis may not occur with tetralogy of Fallot because the thick right ventricle is not excessively dilated. ASD and VSD are two congenital lesions frequently associated with a RV volume load.

Moderate or severe mitral regurgitation may produce an abnormal late systolic anterior left parasternal pulsation even in the absence of pulmonary hypertension.[209] This precordial lift is brisk, and its greatest force coincides with the accentuated *v* wave in the left atrial pressure wave. It likely is due to the large volume of blood regurgitated into the expanding left atrium, which is located centrally behind the right ventricle and anterior to the spine. While expansion of the left atrium may contribute somewhat to the anterior motion of the heart, it is likely that most of the anterior motion and force is the result of a jet or squid effect.

Conditions associated with a decrease in RV compliance, such as RV hypertrophy secondary to pulmonary hypertension, may be associated with a palpable "right sided" S_4 in this area or, occasionally, in the epigastric area. Although a palpable S_3 in this area may reflect a large RV volume load, it usually indicates RV dysfunction or failure. RV S_3 and S_4 vibrations may be augmented during inspiration and may be attenuated or even disappear during expiration (see below).

AREA 5: APICAL AREA PULSATIONS

As mentioned earlier, the apex impulse (see Fig. 10-60) is not synonymous with maximum impulse or point of maximum impulse (PMI). The location, size, and character (duration, contour or shape, amplitude, and apparent force) of the apex impulse should be determined.[207] The examiner should focus on one phase of the cardiac cycle at a time and correlate the findings with other cardiovascular events.

The normal apex (apical) impulse usually is located within 10 cm of the sternal midline, at or within the left midclavicular line in the fifth intercostal space, when the patient is supine. It may be located lateral to the midclavicular line when associated with a high diaphragm, pregnancy, marked pectus excavatum, or other conditions that displace a normal heart to the left. The normal apex impulse is less than 3 cm in diameter and in most instances is considerably smaller. The early systolic outward movement of the apical area (Fig. 10-61) begins at about the same time as that of the S_1, just before the upstroke of the carotid pulse. Peak outward motion normally occurs with or just after blood is ejected into the aorta; then the apex normally moves inward. The outward movement of the apical impulse is normally not excessively forceful and is felt only during the first third of systole.

The apex impulse may be hyperkinetic or hyperdynamic with increased amplitude in normal individuals who have a thin chest wall, a flat chest, or a depressed sternum. Lying on the left side may cause a normal apical impulse to move laterally and to have increased amplitude and duration[207]; however, it still should not exceed a diameter of greater than 3 cm. A hyperdynamic apex impulse also may be found in anxious children, in patients with high cardiac output states, and in patients with a mild to moderate LV volume load from mitral or aortic regurgitation. The apex impulse is more sustained when mitral or aortic regurgitation is more severe or when LV systolic function is decreased.[204] In general, a greatly sustained apex impulse indicates either marked LV hypertrophy or depressed LV systolic function, whereas LV dilatation displaces the apex impulse laterally and inferiorly[207,210] (see Fig. 10-61).

Concentric LV hypertrophy without an increase in LV cavity size may occur in systemic hypertension, valvular aortic stenosis, and hypertrophic cardiomyopathy. Characteristically, the apex impulse is not displaced but is both abnormally forceful and sustained.[204,205] An S_4 vibration may be palpable or visible or both.

Severe LV dilatation-whether due to volume load or ventricular failure-may displace the apex impulse laterally and inferiorly and cause a marked increase in size. The duration of the apex

impulse is more sustained in patients with LV systolic dysfunction, particularly when associated with marked LV dilatation.

Important information about relative amounts of ventricular hypertrophy and dilatation often can be obtained from the apex impulse. Thus, in valvular aortic stenosis, with marked concentric LV hypertrophy but little or no dilatation, the apex impulse characteristically is small, forceful, and sustained but not displaced. A presystolic S_4 often is palpable at the apex. By contrast, in severe aortic regurgitation with marked dilatation of the left ventricle plus considerable eccentric hypertrophy, there is a diffuse apex impulse with increased force, duration, and amplitude, and it is displaced laterally and inferiorly.[205]

In some patients with acute MI, a sustained apex impulse may simulate that due to LV hypertrophy.[201] Those developing mitral regurgitation secondary to MI (papillary muscle dysfunction) may manifest LV dilatation and hypertrophy by a displaced and sustained, forceful, large apex impulse.[211] A late systolic bulge at the cardiac apex may be due to a functional LV aneurysm, occasionally resulting in a bifid apex impulse. In other patients, a late systolic bulge may be palpable in an ectopic area between the apex impulse and the left parasternal area.

A bifid apex impulse during systole also may be due to marked LV dilatation and hypertrophy in patients with both aortic stenosis and regurgitation or in patients with hypertrophic cardiomyopathy.[212] Infrequently, a faint systolic notch or vibration is palpable in the apex impulse of patients with mitral valve prolapse at the moment of a nonejection midsystolic click. Systolic retraction of the apical impulse usually indicates either constrictive pericarditis or severe tricuspid regurgitation with marked RV dilatation (see Fig. 10-61). An apical systolic thrill most commonly is produced by mitral regurgitation and often is diffuse, whereas a diastolic thrill is usually produced by mitral stenosis and is localized to a small, discrete periapical area.

Diastolic Events: Palpable Third and Fourth Heart Sounds

During early diastole, brief outward chest wall movement corresponding to a LV filling or a third heart sound (S_3) occasionally may be seen or felt, even if it is not audible with a stethoscope (see Fig. 10-61). In children and young adults, the presence of an early diastolic ventricular filling sound (S_3) and movement is usually normal. On the other hand, the presence of such a movement or sound in a sedentary adult or a patient with heart disease usually indicates an elevated LV diastolic pressure and volume and likely ventricular decompensation, often with a decreased ejection fraction. Patients with acute MI or transient myocardial ischemia during angina pectoris frequently develop a transient palpable and audible ventricular filling S_3, which reflects the acutely decreased ventricular compliance. A palpable ventricular rapid filling wave (S_3) may be present in patients with LV failure from any cause; however, hemodynamic systolic ventricular failure is often not always present when a ventricular filling wave or sound occurs in the presence of volume loading and dilatation of the left ventricle, as with mitral regurgitation or aortic regurgitation.

The presystolic left atrial contribution to the apical impulse (referred to as the *atrial impulse* or *a* wave) may be detected during late diastole, just prior to S_1 (see Fig. 10-61). Usually, a palpable atrial impulse coincides with an audible fourth heart sound and is associated with an increased LV end-diastolic pressure and decreased compliance. In general, an S_4 is not normally palpable but may be felt at the apex with its associated S_4 in some normal adults if the PR interval is long and circulation is hyperdynamic.[202] In some patients with ischemic heart disease, a palpable apical S_4 may develop or become more prominent during an episode of angina pectoris or even during exertion without chest pain. A palpable presystolic impulse, S_4, or both occur frequently in

patients with acute MI, and these are also frequently present in other conditions producing a decrease in LV compliance and increased end-diastolic pressure.

In a patient with mitral valve disease, the presence of a palpable left-sided atrial impulse or S_4, a palpable left-sided ventricular filling sound or S_3, or an abnormally sustained apical impulse is evidence against the diagnosis of isolated important mitral stenosis and suggests the presence of coincident LV disease.

A double, or bifid, apical impulse may be present in various circumstances, most commonly in the combination of an outward movement during ventricular systole and a second outward pulsation during diastole.[205] The diastolic impulse may occur either in early diastole (S_3) or in late diastole or presystole (S_4).

A bifid apical impulse with two systolic impulses may be present in patients with hypertrophic obstructive cardiomyopathy, complete left bundle branch block (LBBB), or MI. If these patients also develop a palpable impulse during either early (S_3) or late (S_4) diastole, a triple or trifid apical impulse may occur. When such patients develop both a palpable S_3 and a palpable S_4, it is occasionally possible to see and feel a quadruple apical impulse.

AREA 6: EPIGASTRIC AREA PULSATIONS

Some normal and many hyperkinetic individuals have visible or palpable pulsations of the aorta in the epigastric area (see Fig. 10-61). Abnormally large pulsations of the aorta may be due to an aortic aneurysm or aortic regurgitation. Hepatic movements may be identified in the epigastric area, particularly in patients with tricuspid regurgitation, tricuspid stenosis, or marked RV dilatation, hypertrophy, and hyperactivity.

In some patients with pulmonary hypertension due to chronic lung disease, the detection of RV hypertrophy by precordial palpation is difficult because the shape of the chest often conceals the enlarged right ventricle. To detect abnormal RV pulsations in patients with emphysema, the palm of the right hand should be placed on the epigastric area and moved cephalad while gently sliding the fingers under the rib cage. Aortic pulsations can be detected by the palmar surface of the fingers, and pulsations due to RV hypertrophy can be felt in the fingertips.

AREA 7: ECTOPIC AREA PULSATIONS

Occasionally, cardiac pulsations are encountered in areas other than those described previously, i.e., between the pulmonary and apical areas (see Fig. 10-61). Ischemic heart disease is the most common cause of an ectopic systolic pulsation, which may occur transiently during an episode of angina pectoris. A similar paradoxical systolic outward movement may be detected after acute MI and may persist; more commonly, it disappears within a few weeks. A persistent paradoxical ectopic pulsation also may be found in patients who develop a ventricular aneurysm after MI. Ectopic pulsations on the anterior chest wall also can be found in patients with cardiomyopathies of varying etiologies. In patients with severe mitral regurgitation and a giant left atrium that extends to the right, an ectopic systolic pulsation of the atrium occasionally may be felt in the right anterior or lateral chest or in the left axilla.[205]

Percussion versus Inspection and Palpation of the Precordium

When performed by a skilled examiner, percussion of the heart can provide an estimate of cardiac size and shape. Percussion of the heart only gives information about the location of the borders of cardiac dullness, whereas precordial inspection and palpation provide both information about the

location of the outer limits of cardiac pulsations and a determination of the size and character of the pulsations. Although percussion has been used in the diagnosis of pericardial effusion, it has limited value when the results are objectively correlated with the diagnosis as determined by more sensitive and specific noninvasive and invasive testing.

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

CARDIAC AUSCULTATION

The Stethoscope

The physician must choose a stethoscope that fits the ears comfortably with the right angulation, has as short a segment of flexible tubing as possible, and is equipped with a diaphragm and a bell. Selection of the proper earpieces for comfort and the best transmission of sound is based on individual preference and is best evaluated by trial and error. A snug, comfortable fit depends on the size of the earpieces as well as the angle at which they enter the ear canal; the angulation of the rigid metal tubing therefore must be chosen to suit the comfort of the individual. The rubber tubing should be as short as feasible; experience indicates that tubing about 12 in (30 cm) long is the best compromise. Rapaport and Sprague[213] have shown that thick-walled tubing about 3 mm in diameter is best suited to transmit sounds and murmurs.

The human ear is most sensitive to auditory vibrations that occur in the frequency range between 1000 and 4000 to 5000 Hz; the sensitivity falls off sharply when the frequency of vibration is below 1000 Hz. This is particularly true of low-frequency sounds, which must be of considerably greater amplitude to reach the threshold of audibility than sounds of higher frequency. Most cardiovascular sounds and murmurs of diagnostic importance are between 30 and 1000 Hz, thereby placing the auscultator at considerable disadvantage.[214] Therefore, a stethoscope requires *both a diaphragm and a bell*, and each must be applied to the chest wall with optimal pressure. The diaphragm, which is fairly rigid, brings out the high frequencies and attenuates the lows. When the diaphragm is used to accentuate high-pitched sounds, it should be pressed very firmly against the skin. This technique will make a high-frequency murmur, such as the faint diastolic blowing murmur of aortic valve regurgitation, audible along the left sternal border when it would otherwise be missed. The bell tends to accentuate the low-frequency sounds and to filter out the high-pitched tones. Often, low-frequency sounds are more easily appreciated by palpation than by auscultation; in these situations, the stethoscope should be placed very lightly on the skin, with just enough pressure to seal the edge at the point of maximal impulse. With very light pressure of the bell, the low-pitched sounds are accentuated; however, with firm pressure of the bell against the skin, the skin itself becomes a relatively tight diaphragm, and the low-frequency sounds are suppressed. Although this technique can be very helpful, the stethoscope always should be equipped with a valve system that permits one to switch from the diaphragm to the bell with ease.

Examination of the Patient

The examination should take place in a quiet room that is well lighted and comfortably heated. The patient should be properly gowned, with adequate exposure to the waist. The examining table should be large enough that the patient can be instructed to lie flat, sit up, or roll to one side with complete ease. Usually, the physician will examine from the right side, and it is equally important that the physician be comfortable.

Prior to auscultation, the clinician should take advantage of the information obtained from the history as well as from the examination of the arterial, venous, and cardiac pulsations. When abnormalities are found, their auscultatory counterparts should be pursued diligently. For example, prominent *a* waves in the jugular venous pulse should alert the clinician to search

carefully for a low-pitched, right-sided fourth heart sound (S_4) or the subtle presystolic murmur of tricuspid stenosis, whereas large *v* waves that augment with inspiration should suggest tricuspid regurgitation. The presence of pulsus alternans always should demand a careful search for third and fourth heart sounds (S_3, S_4), as well as for the presence of functional mitral or tricuspid regurgitation, often present in severe cardiac decompensation. A rapid, jerky rise of the carotid pulse may be the clue to the diagnosis of hypertrophic cardiomyopathy, which can be confirmed by manipulating the systolic murmur with maneuvers that change the pre- and afterloading conditions of the heart.

There are four primary areas of cardiac auscultation: (1) the primary and secondary aortic areas in the second right interspace and the third left interspace adjacent to the sternum, respectively, (2) the pulmonary area in the second left interspace, (3) the tricuspid area in the fourth and fifth interspaces adjacent to the left sternal border, and (4) the mitral area at the cardiac apex. This does not mean to imply that auscultatory events arising from each valve are heard only in their respective areas. The murmur of aortic stenosis in the elderly is often heard best (and at times only) at the apex, whereas the murmur of a flail posterior mitral leaflet may radiate to the base and simulate the murmur of aortic stenosis. Ejection sounds arising from the stenotic aortic valve are usually most prominent at the apex, whereas the opening snap of mitral stenosis is heard best midway between the tricuspid and mitral areas. The murmur of tricuspid regurgitation may be appreciated best at the classic mitral area if the right ventricle occupies the apex. Furthermore, cardiac auscultation should not be restricted to just these four areas. For example, the murmur of aortic regurgitation secondary to abnormalities of the aortic root may be heard best to the right of the sternum, whereas the murmur of tricuspid regurgitation in the emphysematous patient with pulmonary hypertension may be heard best in the epigastrium. The continuous murmur of a patent ductus arteriosus is heard just below the left clavicle, whereas the murmur of large bronchial collaterals may be most prominent in the posterior thorax. Again, the overall clinical presentation will guide one to the appropriate area to auscultate.

During auscultation, one listens both specifically and selectively for heart sounds and then for murmurs, first during systole and then during diastole. As described by Levine and Harvey,[215] the physician should adopt a systematic approach to listening. The patient should be lying on his or her back, and each area should be surveyed with both chest pieces. In each area examined, the physician listens specifically for the first heart sound (S_1), noting its intensity, constancy, presence of splitting, and variation with respiration. This is followed by selective listening for the second heart sound (S_2), noting the same characteristics. Then extra sounds are searched for and carefully listened to, first in systole and then in diastole, with mental notations as to their time of appearance, pitch, and other characteristics that may identify them as gallop sounds, ejection sounds, or valve-opening sounds. Whether the examination is initiated at the base by listening to S_2 or at the apex by listening to S_1 depends on the physician's preference. Of greater importance is that the examination be performed in a methodical, systematic way, with the physician listening intently for one event at a time. Attention is then first turned to systole and then to diastole for the presence of murmurs. After this general survey, the physician listens selectively for certain sounds and murmurs. With the bell applied lightly to the skin at the apex, the patient is instructed to roll onto the left side, and the clinician selectively "tunes in" to diastole and the low-frequency range. This allows the physician to determine the presence or absence of diastolic filling sounds or diastolic rumbles arising from the AV valves. The examination is continued with the patient in the sitting position. While the patient leans slightly forward during quiet respiration, the clinician can optimally appreciate splitting of S_2. With the patient's breath held in deep expiration, the physician examines the aortic and pulmonic areas with the diaphragm firmly pressed against the chest wall, selectively "tuning in" to the high-frequency range in an effort to hear the faint blowing diastolic murmur of aortic regurgitation or, if the clinical situation warrants, the presence of a pericardial friction rub. Sounds and murmurs such as these are discovered only when they are searched out carefully with intent listening and concentration.

Auscultation of the heart should be considered a dynamic exercise. In addition to being auscultated in the left lateral ducubitus position, the patient should, when possible, also be examined while standing, squatting, and during the Valsalva maneuver and following its release. This type of dynamic examination changes the pre- and afterloading conditions of the heart and may yield diagnostic information because of the typical response of heart sounds and murmurs to these maneuvers.

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

HEART SOUNDS

Heart sounds are of two types: high-frequency transients associated with the abrupt terminal checking of valves that are closing or opening and low-frequency sounds related to early and late diastolic filling events of the ventricles. Sounds related to closing and opening of the AV valves include mitral and tricuspid closing sounds (M_1, T_1), nonejection sounds, and the opening snaps; sounds related to closing and opening of the semilunar valves include aortic and pulmonic closure sounds (A_2, P_2) and early valvular ejection sounds or clicks. Low-frequency sounds include the physiologic heart sound (S_3) and the pathologic S_3 gallop associated with early ventricular filling events and the presystolic atrial S_4 gallop associated with late diastolic events resulting from the atrial contribution to ventricular filling. With tachycardia, these sounds may fuse, producing a summation gallop.[216,217]

The First Heart Sound

The first heart sound (S_1) as recorded by high-resolution phonocardiography consists of four sequential components: (1) small, low-frequency vibrations, usually inaudible, that coincide with the beginning of LV contraction and felt to be muscular in origin, (2) a large, high-frequency vibration, easily audible, related to mitral valve closure (M_1), (3) a second high-frequency component, following closely, related to tricuspid valve closure (T_1), and (4) small, low-frequency vibrations that coincide with accelerated flow of blood into the great vessel. The two major components normally audible at the left lower sternal border are the louder M_1 followed by T_1. They are separated by only 20 to 30 ms, and at the apex in the normal subject, and only a single sound (M_1) is usually appreciated. Splitting of the first heart sound is less evident with the tachycardia following coughing or with sustained handgrip exercises

ECHOCARDIOGRAPHIC CORRELATES AND SPLITTING OF S_1

The first high-frequency component of S_1 coincides with the complete coaptation of the anterior and posterior leaflets of the mitral valve. This sound is due to the sudden deceleration of blood setting the entire cardiohemic system into vibration when the elastic limits of the closed, tensed valves are met. It is unlikely that complete coaptation of the complex valve leaflets and final tensing are simultaneous; presumably it is the latter event that is associated with vibrations perceived as M_1. When T_1 is more widely separated from M_1, however, identical echocardiographic correlates have been demonstrated in patients with wide splitting of S_1 due to Ebstein's anomaly of the tricuspid valve.[216] This exaggerated T_1, or "sail sound," and its wide separation from M_1 have been a helpful sign in the diagnosis of this entity.[217] Wide splitting of S_1 with normal sequencing (M_1, T_1) is also present in right bundle branch block of the proximal type as well as in LV pacing, ectopic beats, and idioventricular rhythms originating from the left ventricle due to a delayed contraction of the right ventricle. In a similar manner, pacing from the right ventricle and ectopic beats and idioventricular rhythms originating from the right ventricle will produce reversed splitting of S_1 (T_1, M_1) due to delay in LV contraction. Reversed splitting of S_1 also may be present in patients with hemodynamically significant obstruction of the mitral valve, since mitral valve closure is delayed due to the increased left atrial pressure, which must be overcome by the rising LV pressure before closure can occur. Similar delay in M_1 also may be found in mitral obstruction secondary to left atrial myxoma.

HEMODYNAMIC CORRELATES OF S_1

Figure 10-62 illustrates the sound and pressure correlates of M_1. The first high-frequency component of M_1 coincides with the downstroke of the left atrial *c* wave and is delayed from the left ventricular-left atrial

pressure crossover by 30 ms. In the past, these findings have caused considerable confusion regarding the origin of both M_1 and T_1, since it was assumed that these sounds occurred at AV pressure crossover. However, the elegant studies of Laniado et al.[218] established that forward flow continued for a short period following left ventricular-left atrial pressure crossover due to the inertia of mitral flow, with M_1 occurring 20 to 40 ms later, coincidentally with cessation of mitral flow and closure of the valve. An even greater delay between the occurrence of T_1 and right ventricular-right atrial pressure crossover has been shown,[219] and O'Toole et al.[220] have shown that T_1 also coincides with the downstroke of the right atrial *c* wave. These hemodynamic data, together with the echocardiographic correlates of M_1 and T_1, confirm the prime role played by the AV valves in the genesis of S_1.

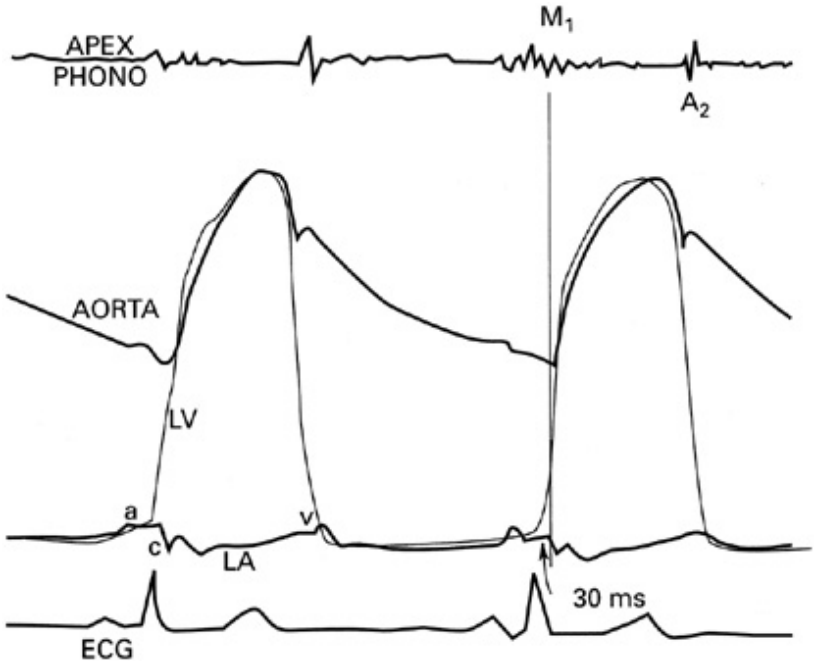

Figure 10-62: The apex phonocardiogram is displayed simultaneously with the cardiac cycle, as recorded by high-fidelity catheter-tipped micromanometers in the central aorta, left ventricle (LV), and left atrium (LA). The first high-frequency component of M_1 is coincident with the downstroke of the left atrial *c* wave and is separated from left ventricular-left atrial pressure crossover by an interval of 30 ms. (From Shaver JA, Saderni R, Reddy PS, et al. Normal and abnormal heart sounds in cardiac diagnosis: I. Systolic sounds. *Curr Probl Cardiol* 1985; 10:10-53. Reproduced with permission from the publisher and authors.)

INTENSITY OF S_1

The primary factors determining intensity of S_1 are (1) integrity of valve closure, (2) mobility of the valve, (3) velocity of valve closure, (4) status of ventricular contraction, (5) transmission characteristics of the thoracic cavity and thorax, and (6) physical characteristics of the vibrating structures.

Integrity of Valve Closure

In rare situations, usually in the setting of severe mitral regurgitation, there is inadequate coaptation of the mitral leaflets to a degree that valve closure is not effective. As a result, abrupt halting of the retrograde blood column during early ventricular contraction does not occur, and S_1 may be markedly attenuated or absent. Such may be the case in severe mitral regurgitation due to a flail mitral leaflet, as shown in Fig. 10-63.

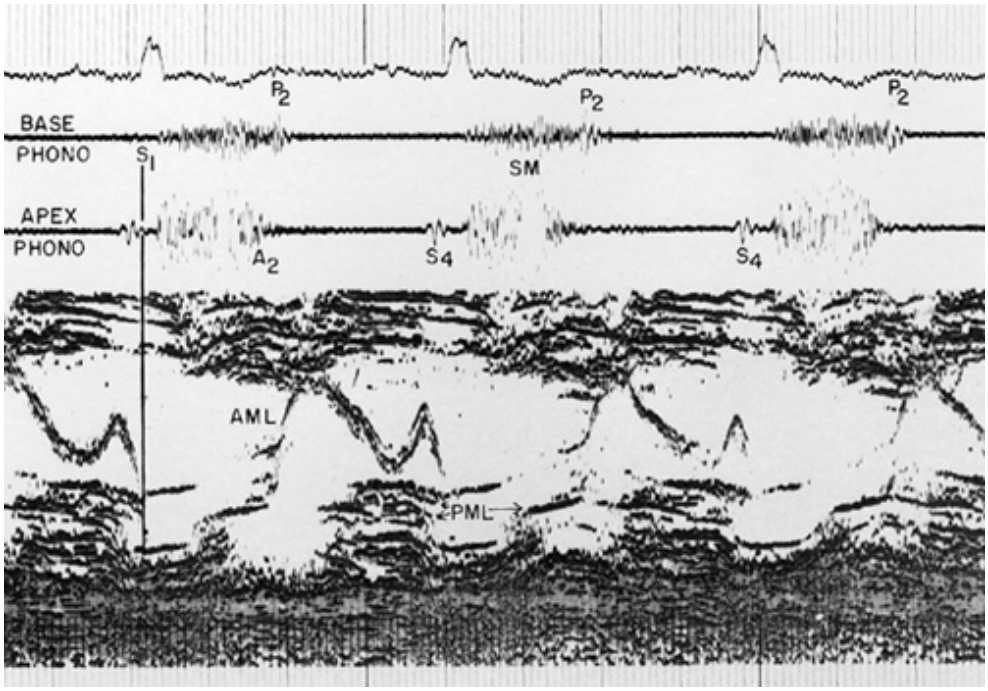

Figure 10-63: Base and apex phonocardiograms are recorded simultaneously with the mitral valve echocardiogram in a 62-year-old man who developed acute mitral regurgitation secondary to rupture of the chordae tendinae of a myxomatous valve. During diastole, multiple echoes arise from the flail posterior mitral leaflet (PML), and during early ventricular systole, effective mitral valve closure does not occur, resulting in an inaudible low-frequency vibration on the apex phonocardiogram. During systole, there is separation of the anterior (AML) and posterior mitral leaflets, resulting in severe mitral regurgitation. The murmur has a crescendo-decrescendo contour simulating the murmur of aortic stenosis ending prior to A_1. Wide physiologic splitting of S_1 is present. The prominent S_4 present on the apex phonocardiogram was associated with an apical presystolic impulse. (From Shaver JA. The physical examination in cardiac diagnosis. *Cardiol Consult* 1985; 6:3. Reproduced with permission from the publisher and author.)

Mobility of the Valve

Severe calcific fixation of the mitral valve with complete immobilization will cause a markedly attenuated M_1. This is seen most commonly in the setting of long-standing mitral stenosis.

Velocity of Valve Closure

The velocity of valve closure is the most important factor affecting the intensity of S_1 and is determined by the timing of mitral valve closure in relation to the LV pressure rise in early systole.[221] The relative timing of left atrial and LV systole may vary this relationship. As the PR interval progressively decreases from 130 to 30 ms, there is a progressive increase in the intensity of M_1 and progressive delay in M_1 relative to the onset of LV contraction. When left atrial and LV systole occur almost simultaneously at a PR interval of 10 ms, however, S_1 again becomes soft. At short PR intervals (30-70 ms), the mitral valve leaflets are maximally separated by atrial contraction at the onset of LV systole. With LV contraction, the mitral valve closes at a high velocity with a large excursion. This results in a loud, late M_1 occurring on a steeper part of the LV pressure curve when the retrograde blood column is suddenly decelerated at the moment the elastic limits of the mitral valve are met. At longer PR intervals, there is less separation of the mitral valve leaflets, which have already begun to close with atrial relaxation. When LV systole begins, there is less excursion of the mitral valve until tensing occurs, and S_1 occurs earlier relative to the onset of LV contraction at a lower LV pressure. Thus less force is applied to the mitral valve, its closing velocity is decreased, and less energy is generated when a column of retrograde blood is abruptly halted, resulting in a softer M_1.

The clinical finding of marked variation in the intensity of S_1 in a patient with a slow heart rate often will

alert the clinician at the bedside to the diagnosis of complete heart block with AV dissociation. Other conditions in which there are beat-to-beat variations in the intensity of S_1 include Mobitz type I heart block and ventricular tachycardia with AV dissociation. Variations in the intensity of S_1 also occur with atrial fibrillation with both normal and stenotic AV valves. The loud S_1 occurs at short RR intervals, whereas a softer S_1 occurs at longer RR intervals when the valve leaflets have closed partially.[222]

The position of the mitral valve at the onset of ventricular systole may be altered not only by the relative timing of atrial and ventricular systole but also by altering the rate of LV filling during atrial systole. Leonard et al.[221] have shown that the timing and intensity of both S_1 and S_4 in hypertensive patients can be influenced by variations in venous return. It is suggested that the mitral leaflets have a greater separation when venous return is decreased to the noncompliant hypertensive left ventricle because there is more effective atrial volume transport into a relatively underfilled ventricle. This results in a softer S_4 that migrates toward an increased S_1. When venous return is increased, the atrial contribution of ventricular filling is now operating on the steeper portion of the LV pressure volume curve. The S_4 becomes louder and earlier, and S_1 is decreased in amplitude due to partial atriogenic closure of the mitral valve. This is the most likely explanation of a soft S_1 frequently noted in hypertensive patients with normal PR intervals.

Status of Ventricular Contraction

The status of ventricular contractility is also an independent factor determining the amplitude of S_1.[221,222] In normal subjects, both exercise and catecholamine infusion have been shown to increase the amplitude of S_1, whereas administration of β-blocking agents decreases it.[221] In both situations, the prime factor in altering the intensity of S_1 is the rate of pressure development in the ventricle. This increased rate of pressure development partially explains why S_1 is increased in patients with anemia, arteriovenous fistulas, pregnancy, anxiety, and fever. It is also likely that these high-output states, often associated with tachycardia, result in wider separation of the AV valves at the onset of ventricular systole due to high flow through a shortened diastolic period. Similarly, the loud T_1 in an ASD is due to high flow through the tricuspid valve, secondary to the left-to-right shunt at the atrial level. A decrease in the intensity of S_1 associated with a decrease in the rate of LV pressure development may be found in myxedema, cardiomyopathy, and acute MI.[223,224] Beat-to-beat variation in the intensity of S_1 (auscultatory alternans) also has been found in patients with pulsus alternans, in whom beat-to-beat alteration in the rate of LV pressure development occurs.

Transmission Characteristics of the Thoracic Cavity and Chest Wall

The degree of attenuation of heart sounds generated by the vibrating cardiohemic system is a function of both sound frequency and the distance of the heart from the chest wall. The higher-frequency heart sounds are attenuated to a greater extent than are lower-frequency sounds. Conditions such as obesity, emphysema, and large pleural or pericardial effusions will decrease the intensity of all auscultatory events, whereas a thin body habitus would tend to increase the intensity.

Physical Characteristics of the Vibrating Structures

Alterations in the physical characteristics of the vibrating structures also may vary the intensity of S_1. Both MI and ischemia induced by pacing have been shown to decrease the intensity of S_1 secondary to these alterations.[224]

S_1 IN PATHOLOGIC CONDITIONS

Careful attention to the intensity of S_1 is an extremely important aspect of cardiac auscultation, often giving clues to the proper diagnosis and degree of abnormality of the involved structures. The following conditions are examples where alterations in the intensity of S_1 play a key role in the correct diagnosis.

S_1 in Mitral Stenosis

A loud, late M_1 is the hallmark of hemodynamically significant mitral stenosis.[225] When M_1 is loud, it is associated with a loud opening snap, and the intensity of both M_1 and the opening snap correlates with valve motility (Fig. 10-64, *left*). When calcific fixation of the stenotic mitral valve occurs, M_1 is soft, and the opening snap is absent. The relationship between sound and pressure and echocardiographic mitral valve motion is shown in Fig. 10-65. Significant scarring of the mitral valve is evident as a result of the rheumatic process. The increased left atrial pressure delays the time of pressure crossover between the left atrium and the left ventricle. As a result, M_1 occurs later and at a much higher than normal LV pressure, at a time when there is a more rapid rate of development of LV pressure. The presystolic gradient between the left atrium and the left ventricle prevents preclosure of the mitral valve leaflets. As a result, the closure of the leaflet begins from a domed position within the LV cavity and takes place over a much greater distance than normal following the onset of LV contraction. Both these factors increase the velocity of mitral valve closure and the momentum of blood directed toward the mitral valve leaflets, resulting in a loud M_1 when the elastic limits of the stenotic mitral valve are met. A similar mechanism is responsible for the booming S_1 with after vibrations in left atrial myxoma (see Fig. 10-65, *center*).

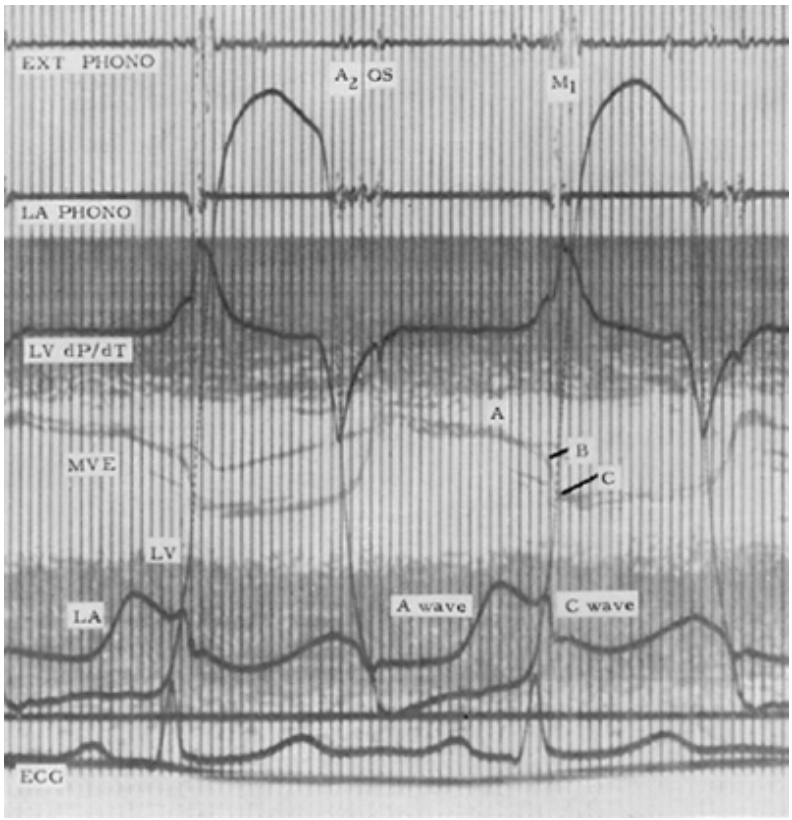

Figure 10-65: External sound, equisensitive LV and left atrial pressures (catheter-tipped micromanometer), LV *dP/dt*, and left atrial sound are recorded simultaneously with the mitral valve echocardiogram in a patient with hemodynamically significant mitral stenosis. A significant presystolic gradient is present due to atrial contraction, and the onset of the rapid closure of the mitral valve (*B*) is delayed until the LV pressure exceeds left atrial pressure. This occurs 40 ms after the beginning of the LV pressure rise at a time when LV *dP/dt* is much higher than normal. Following left atrial-left ventricular pressure crossover, there is rapid ventriculogenic closure of the mitral valve (*BC*), resulting in a very loud M_1 coincident with the *C* point of the mitral valve echocardiogram. Its separation from A_2 is determined by both the level of the left atrial pressure and the rate of LV pressure decline. (From Shaver JA, et al. Normal and abnormal heart sounds in cardiac diagnosis: I. Systolic sounds. *Curr Probl Cardiol* 1985; 10:10-53. Reproduced with permission from the publisher and the authors.)

S_1 in Mitral Valve Prolapse

Tei et al.[226] have reported a loud M_1 heard over the apex in patients with nonrheumatic mitral regurgitation; this is indicative of holosystolic mitral valve prolapse (see Fig. 10-64, *right*). Patients with the more common middle to late systolic prolapse have a normal S_1, whereas a soft or absent S_1 may indicate a flail mitral leaflet (see Fig. 10-65). The increased amplitude of leaflet excursion with prolapse beyond the line of closure explains the loud M_1 associated with holosystolic prolapse. An alternate explanation may be a summation of a normal M_1 and an early nonejection click of valvular prolapse.

S_1 and LBBB

In LBBB, M_1 is decreased in intensity and is frequently delayed, at times resulting in reversal of sequence of S_1.[227] The reason for the delay and the decreased intensity of M_1 in this condition is multifactional, with different mechanisms operative in different patients, depending on the degree of completeness of the LBBB, the site of block (proximal versus peripheral), and especially the status of LV function.[228] The primary factors involved are (1) delay in onset of LV contraction, (2) degree of LV dysfunction, (3) presence of concomitant first-degree heart block, and (4) presence of a noncompliant left ventricle facilitating atriogenic preclosure of the mitral valve. It is likely that more than one factor is operative in most patients with LBBB, with one or two factors predominating.

S_1 in Acute Aortic Regurgitation

One of the important auscultatory findings in acute aortic regurgitation is attenuation or absence of M_1.[222] Severe regurgitation into a left ventricle that has not had time to adapt to the acute volume overload causes a marked increase in the LV end-diastolic pressure, resulting in premature closure of the normal mitral valve in middiastole. With the onset of LV systole, minimal mitral valve excursion occurs, causing a marked reduction in the intensity of M_1.

Systolic Ejection Sounds

Ejection sounds are early systolic ejection events that can originate from either the left or the right side of the heart. These sounds may be classified as valvular, arising from deformed aortic or pulmonic valves, or as vascular, or root events caused by the rapid, forceful ejection of blood into the great vessels. The presence or absence of valvular ejection sounds is of great benefit in defining the level of RV or LV outflow tract obstruction, whereas root ejection sounds give insight into abnormalities of the great vessels with or without systemic or pulmonary hypertension.

AORTIC VALVULAR EJECTION SOUNDS

Aortic valvular ejection sounds are found in nonstenotic congenital bicuspid valves and in the entire spectrum of mild to severe stenosis of the aortic valve. This sound introduces the typical ejection murmur of aortic stenosis, is widely transmitted, and is often heard best at the apex. The aortic valvular ejection sound is delayed 20 to 40 ms after the onset of pressure rise in the central aorta and is coincident with the sharp anacrotic notch on the upstroke of the aortic pressure curve. The sound is coincident with the maximal excursion of the domed valve when its elastic limits are met.[229] The abrupt deceleration of the oncoming column of blood sets the entire cardiohemic system into vibration, the lower-frequency components being recorded as the anacrotic notch and the high-frequency components representing the valvular ejection sound. Inherent in this mechanism of sound production is the ability of the deformed valve to move. With severe calcific fixation of the valve, no excursion or piston-like ascent of the deformed valve is possible; therefore, no sudden tensing of the valve leaflets or abrupt deceleration of the column of blood occurs. Sound and motion correlates identical to those demonstrated by cineangiography have been found with phonoechocardiography, clearly showing the onset of the ejection sound to be coincident with the maximal opening of the valve[230] (Fig. 10-66). The intensity of the ejection sound correlates directly with the mobility of the valve, but there is no correlation between intensity and the severity of the obstruction. In mobile, nonstenotic bicuspid valves, the ejection sound is not only loud but also widely separated from S_1

due to the prolonged excursion of the mobile valve. The presence of an aortic valvular ejection sound is a valuable physical finding at the bedside; it not only defines the LV outflow obstruction at the valvular level but also gives insight into the mobility of the valve (see Fig. 10-66).

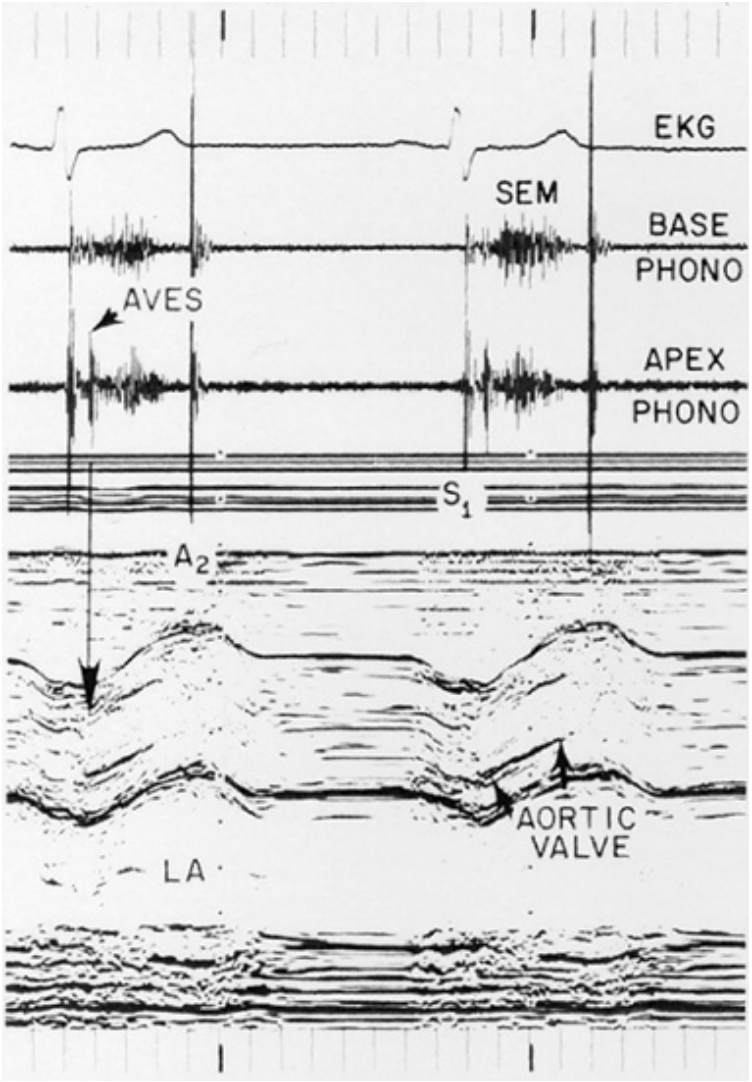

Figure 10-66: Base and apex phonocardiograms are recorded simultaneously with the aortic valve echocardiogram in a young man with valvular aortic stenosis. A prominent aortic valvular ejection sound (AVES) is recorded at the apex and is coincident with the maximal excursion of the aortic valve in early systole. It is followed by a crescendo-decrescendo systolic ejection murmur (SEM) that ends well before a loud A_2.

PULMONIC VALVULAR EJECTION SOUNDS

Pulmonic valvular ejection sounds have identical sound and pressure correlates as aortic valvular ejection sounds.[231] Echocardiographic correlations also have shown that the onset of the pulmonary ejection sound occurs at the maximal excursion of the stenotic pulmonary valve. In contrast to the aortic valvular ejection sounds and to most right-sided auscultatory events, the pulmonic sound or ejection click decreases in intensity or disappears with inspiration in mild to moderate pulmonic stenosis. In very mild valvular pulmonic stenosis, respiratory variation may be absent.[231] In very severe valvular obstruction, a vigorous atrial contraction can completely preopen the pulmonic valve in diastole, causing a crisp preejection sound. In this situation, RV pressure at the time of the atrial kick actually can exceed pulmonary artery end-diastolic pressure.[231] As the severity of the pulmonic stenosis increases, both the excursion of the deformed valve and the RV isovolumic contraction time decrease. The net effect of both these events is migration of

the pulmonary ejection sound toward S_1.

AORTIC VASCULAR EJECTION SOUNDS

Ejection sounds originating from the aortic root are common in systemic arterial hypertension in the setting of a tortuous sclerotic aortic root, a tight, noncompliant arterial tree, and forceful LV ejection. They are coincident with the upstroke of the high-fidelity central aortic pressure and have been interpreted as an exaggeration of the ejection component of the normal S_1. Echocardiographic correlations by Mills et al.,[230] however, have shown that this sound occurs at the moment of complete opening of the aortic valve and always on the pressure upstroke of the high-fidelity aortic pressure curve. These observations have led them to conclude that this sound probably originates from the valve leaflets.

In contrast to the ejection sound of the stenotic aortic valve, these aortic root sounds tend to be poorly transmitted from the aortic area and are not heard well at the apex. It may be difficult to differentiate this sound from the tricuspid component of a widely split S_1, which is best heard at the fourth left parasternal area and often increases with inspiration. In either condition, it should be emphasized that the benign S_1 ejection sound or M_1-T_1 complex is frequently misinterpreted as a pathologic S_4-S_1 sequence. Factors that favor the presence of an S_4-S_1 complex are an associated palpable presystolic apical impulse, optimal audibility of the S_4 with the stethoscope bell applied lightly at the apex, and a change in the intensity of the S_4 with maneuvers that vary venous return.

PULMONARY VASCULAR EJECTION SOUNDS

Vascular or root ejection sounds also may arise from the pulmonary artery, and the common denominator is dilatation of the pulmonary artery.[231] This dilatation can be idiopathic or secondary to severe pulmonary hypertension. Although it has been stated that this sound is louder during expiration, there is no consensus on this point. Unlike splitting of S_1, which is heard best at the mitral or tricuspid area, this sound is louder in the second and third left intercostal spaces.

Echocardiographic correlates of the pulmonary root ejection sound show it to be coincident with complete opening of the pulmonary valve, occurring during the upstroke of the high-fidelity pulmonary artery pressure recording. This has led to the conclusion that these vascular ejection sounds may originate from semilunar valve cusps that have undergone changes in structure in response to increased pressure. Other investigators have found that the pulmonary root ejection sounds in the setting of pulmonary hypertension coincide with the upstroke of the high-fidelity pulmonary artery pressure tracing, whereas in both idiopathic dilatation of the pulmonary artery and ASD, this sound occurs during the upstroke of the pulmonary pressure tracing.[231] In each of these conditions, it has been suggested that this sound is related to sudden checking of the rapidly accelerating blood column by the "tight" or "loose" pulmonary artery when its elastic limits are met.

Nonejection Sounds

The midsystolic click due to prolapse of the mitral or tricuspid valve is the most frequent cause of systolic nonejection sounds and is often associated with a systolic regurgitant murmur. Although originally thought to be extracardiac in origin, confirmation of their valvular origin has been shown by angiographic,[232,233] intracardiac phonocardiographic,[234,235] and echocardiographic studies.[236,237] As originally proposed by Reid,[238] the cause of this sound is due to tensing of the AV valves during systole. As with other high-frequency cardiac sounds, it is produced by vibrations of the entire cardiohemic system when the elastic limits of the prolapsed valve are suddenly reached.

The presence of a nonejection click on physical examination is sufficient to make the diagnosis of mitral valve prolapse (MVP). The sound has a sharp, high-frequency clicking quality and, although often confined to the apex, can be transmitted widely on the precordium. It may be an isolated finding, occurring most often in middle to late systole, or there may be multiple clicks, presumably as a result of different areas of the large, redundant, scalloped mitral leaflets prolapsing at different times. Numerous echocardiographic studies have shown the presence of the characteristic mid- to late-systolic prolapse as well as holosystolic

prolapse in patients with clicks. All these patterns may be seen in the presence of an isolated systolic click, click and late systolic murmur, or a late systolic murmur alone. The click usually occurs at the time of maximal prolapse.

A feature of MVP is the variability of the auscultatory findings from examination to examination and even from beat to beat (Fig. 10-67). The timing of the click or the click and late systolic murmur varies considerably with changes in posture[239] (Fig. 10-68). In the upright posture, the heart becomes smaller due to decreased venous return, and the click moves earlier in systole. Angiographic studies have confirmed an earlier and greater degree of prolapse in the upright posture compared with the supine position. Squatting, which causes an immediate increase in venous return and afterload, increases LV volume, resulting in later prolapse and movement of the click toward S_2. At the bedside, these simple maneuvers are helpful in differentiating the nonejection click from early ejection sounds, a split S_2, or an S_3 (see Chap. 58).

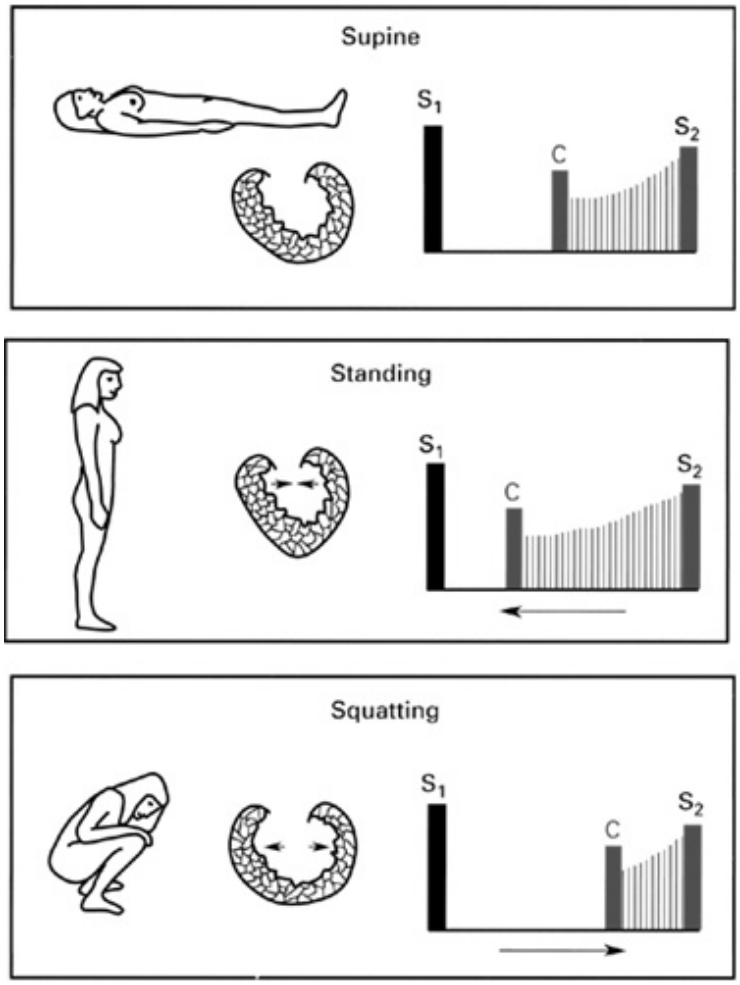

Figure 10-68: A midsystolic nonejection sound (*C*) occurs in mitral valve prolapse and is followed by a late systolic murmur that crescendos to S_1. With assumption of the upright posture, venous return decreases, the heart becomes smaller, the *C* moves closer to S_1, and the mitral regurgitant murmur has an earlier onset. With prompt squatting, both venous return and afterload increase, the heart becomes larger, the *C* moves toward S_2, and the duration of the murmur shortens. (From Shaver JA. *Examination of the Heart*, Part IV: Auscultation. Dallas: American Heart Association; 1990:13. Reproduced with permission from the publisher and the authors.)

In general, maneuvers that decrease LV volume-such as sitting, standing, or strain of the Valsalva maneuver-cause the click to move closer to S_1. Maneuvers that increase LV volume move the click toward S_2 (see Chap. 58).

Although the most common cause of nonejection clicks is prolapse of the AV valves, systolic sounds have been reported in patients with left-sided pneumothorax, adhesive pericarditis, atrial myxomas, LV aneurysm, aneurysm of the membranous ventricular septum associated with a VSD, and incompetent heterograft valves. The presence of these conditions usually can be recognized by the clinical setting and by the absence of the typical changes in the timing of the click associated with physiologic and pharmacologic maneuvers.

The Second Heart Sound

Leatham[240] has emphasized the importance of the S_2 in the cardiac examination by labeling it as the "key to auscultation of the heart." To appreciate the significance of the normal and abnormal S_2, knowledge of its relationship to the hemodynamic events of the cardiac cycle is essential.[241,242] Figure 10-69 records the two components of S_2 simultaneously with the cardiac cycle by high-fidelity catheter-tipped micromanometers. The A_2 and P_2 are coincident with the incisura of the aorta and pulmonary artery pressure trace, respectively, and terminate the LV and RV ejection periods. RV ejection begins prior to LV ejection, has a longer duration, and terminates after LV ejection, resulting in P_2 normally occurring after A_2. RV and LV systole are nearly equal in duration, and the pulmonary artery incisura is delayed relative to the aortic incisura, primarily due to a larger interval separating the pulmonary artery incisura from the RV pressure compared with the same left-sided event. This interval has been called the "hangout" interval, a purely descriptive term coined in our laboratory over 15 years ago. Its duration is felt to be a reflection of the impedance of the vascular bed into which the blood is being received.[243] Normally, it is less than 15 ms in the systemic circulation and only slightly prolongs the LV ejection time. In the low-resistance, high-capacitance pulmonary bed, however, this interval is normally much greater than on the left, varying between 43 and 86 ms, and therefore contributes significantly to the duration of RV ejection. Awareness of this interval is essential for proper understanding of normal physiologic splitting and for the abnormal splitting seen in conditions where significant alterations in pulmonary vascular impedance have occurred.

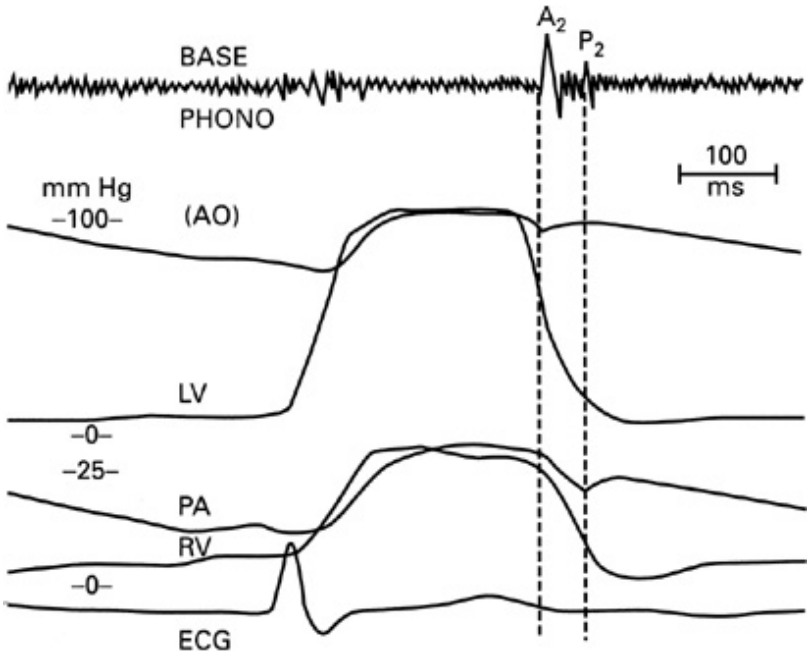

Figure 10-69: The cardiac cycle recorded by high-fidelity catheter-tipped micromanometers. The aortic (A_2) and pulmonic (P_2) closure sounds are coincident with the incisurae of their respective arterial traces. Although the LV and RV mechanical systoles are nearly equal in duration, the RV systolic ejection period terminates after LV ejection because of an increased right-sided "hangout" interval. (From Shaver JA. The second heart sound: Newer concepts: I. Normal and wide physiological splitting. *Mod Concepts Cardiovasc Dis* 1997; 46:7. Reproduced with permission from the American Heart Association and the authors.)

ECHOCARDIOGRAPHIC CORRELATIONS AND MECHANISMS OF SOUND PRODUCTION

Figure 10-70 illustrates the relationship between the aortic and pulmonary valve echocardiogram and A_2 and P_2. The first high-frequency component of both A_2 and P_2 is coincident with completion of closure of the aortic and pulmonic valve leaflets. A_2 and P_2 are not due to the clapping together of the valve leaflets but are produced by the sudden deceleration of retrograde flow of the blood column in the aorta and pulmonary artery when the elastic limits of the tensed leaflets are met. This abrupt deceleration of flow sets the cardiohemic system into vibration; the lower-frequency vibrations are recorded as in the incisura of the great vessels, whereas the higher-frequency components result in A_2 and P_2. This pressure gradient across the valves is the result of both the level of the diastolic pressure in the great vessel and the rate of pressure decline in the ventricle and is consistent with the well-known clinical observation of increased intensity of A_2 and P_2 in systemic and pulmonary hypertension.

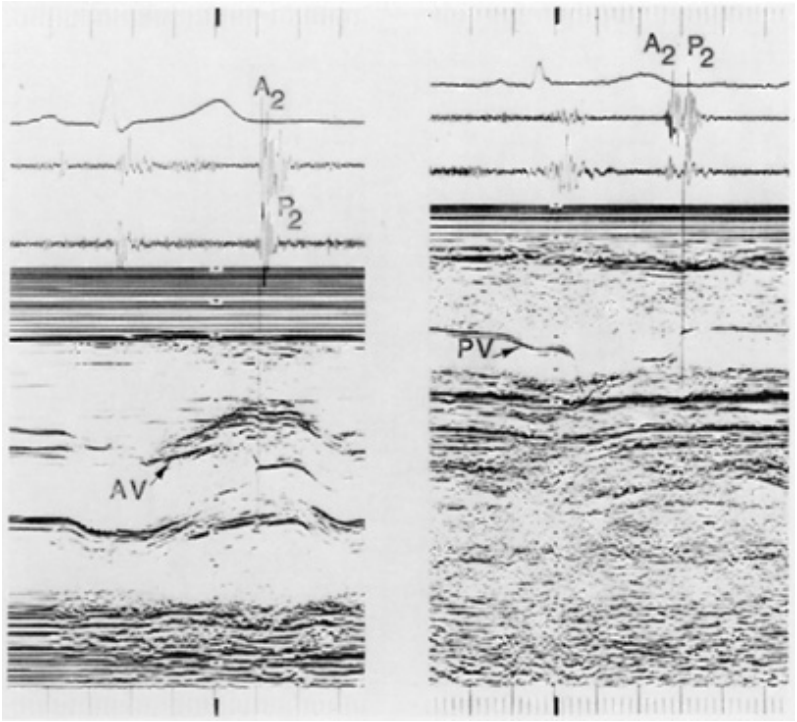

Figure 10-70: (*Left*) The base and apex phonocardiograms are recorded simultaneously with the aortic valve echocardiogram. The first high-frequency component of A_2 is coincident with the completion of closure of the aortic valve. (*Right*) Base and apex phonocardiograms are recorded with the pulmonary valve echocardiogram. The first high-frequency component of P_1 is coincident with the completion of closure of the pulmonic valve. (From Shaver JA, et al. Normal and abnormal heart sounds in cardiac diagnosis: I. Systolic sounds. *Curr Probl Cardiol* 1985: 10:43. Reproduced with permission from the publisher and the authors.)

NORMAL PHYSIOLOGIC SPLITTING

Normally during expiration, A_2 and P_2 are separated by an interval of less than 30 ms and are heard by the clinician as a single sound.[244] During inspiration, both components become distinctly audible as the splitting interval widens, primarily due to a delayed P_2, although an earlier A_2 contributes to a lesser degree[245] (Fig. 10-71). The traditional explanation of normal splitting was that the delayed P_2 during inspiration was secondary to increased venous return, prolonging the duration of RV systole, whereas a concomitant decrease in venous return to the left side of the heart shortened LV systole. More recent studies have shown that the delayed P_2 and early A_2 associated with inspiration are due to a complex interplay

between dynamic changes in pulmonary vascular impedance and changes in systemic and pulmonary venous return.[245]

On auscultation, splitting of S_2 is usually best heard at the second or third left intercostal space; the normal P_2 is softer than A_2 and is rarely audible at the apex. When P_2 is heard at the apex, either significant pulmonary hypertension is present or the apex is occupied by the right ventricle-a situation seen commonly in normotensive ASD. The absolute value of inspiratory splitting varies with age and depth of respiration. In younger subjects, maximal splitting during inspiration averages 40 to 50 ms; with age, this value decreases such that a single S_2 during both phases of respiration may be normal in subjects older than age 40.[246]

ABNORMAL SPLITTING

All conditions in which abnormal splitting of S_2 exists can be identified at the bedside by the presence of audible expiratory splitting (>30 ms)-i.e., the ability to hear two distinct sounds during expiration[246] (see Fig. 10-71). This finding must be present when the patient is auscultated in both the supine and upright positions. There are three causes of audible expiratory splitting: (1) wide physiologic splitting primarily due to delayed P_2, (2) reversed splitting primarily due to delayed A_2, and (3) narrow physiologic splitting as seen in pulmonary hypertension, where A_2 and P_2 are heard as two distinct sounds during expiration at a narrow splitting interval. Tables 10-7 and 10-8 classify the common causes of wide physiologic splitting and reversed splitting of S_2 according to the abnormality of the cardiac cycle responsible for the altered timing of A_2 and P_2. In each table, the cardiac cycle has been divided into three phases (see Fig. 10-69): (1) the electromechanical couple interval, the time from the onset of the Q wave to the rise of ventricular pressure, (2) ventricular mechanical systole, the sum of the isovolumic contraction time plus the ejection period minus the "hangout" interval (abnormalities of this interval exclude those conditions in which prolongation of the "hangout" interval is primarily responsible for the increased ejection time), and (3) "hangout" or impedance interval, the time between the incisura of the arterial trace and the ventricular pressure at the same level as the incisura (includes all conditions in which prolongation of this interval is primarily responsible for the increased ejection time).

Wide Physiologic Splitting of S_2

An example of wide physiologic splitting of S_2 due to delayed electrical activation of the right ventricle secondary to right bundle branch block is shown in Fig. 10-72. Prolongation of RV mechanical systole secondary to severe pulmonary hypertension and pulmonic stenosis are also responsible for a delayed P_2. Classic wide, fixed splitting of S_2 is found in patients with ASD. A composite in Fig. 10-73 documents the role played by decreased impedance of the pulmonary vascular bed in the audible expiratory splitting found in ASD, idiopathic dilatation of the pulmonary artery, and mild pulmonic stenosis with aneurysmal dilatation of the pulmonary artery. In each case, there is a marked increase in the "hangout" interval, as measured by high-fidelity pressure tracings. Wide physiologic splitting secondary to a decreased LV ejection time occurs in patients with acute mitral regurgitation.

Reversed Splitting of S_2

Almost all cases of reversed splitting of S_2 are due to a delay in A_2. As a result, the sequence of closure sounds is reversed, with P_2 preceding A_2. At the bedside, this abnormality is recognized by paradoxical movement of A_2 and P_2 with respiration.[247] During inspiration, P_2 moves toward A_2, and the splitting interval narrows, whereas during expiration, the two components separate, and audible expiratory splitting is present (see Fig. 10-71). The presence of reversed splitting of S_2 almost always indicates significant underlying cardiovascular disease.

Both RV ectopic and paced beats produce a delay in the onset of LV contraction, resulting in reversed splitting of S_2. The mechanism responsible is a delayed activation of the left ventricle, prolonging the Q to LV pressure rise interval. The most common cause of reversed splitting is complete LBBB, which can be

due either to delayed activation of the left ventricle, as seen in isolated proximal block, or to prolonged mechanical systole (primarily isovolumic contraction time), as seen in proximal or peripheral block invariably associated with significant LV dysfunction. Delay often exists in the onset of LV pressure rise when isovolumic contraction time is markedly prolonged, since in most cases of LBBB varying degrees of both mechanisms are present, with one predominating.

Reversed splitting of S_2 may occur in a patient with hypertrophic cardiomyopathy and is due to the large systolic pressure gradient and prolonged LV relaxation.[248] Although both these mechanisms may contribute to the reversed splitting observed in patients with valvular aortic stenosis, an additional mechanism is an exaggerated "hangout" interval.[249]

In hypertensive cardiovascular disease, splitting is usually physiologic, with the intensity of A_2 being increased; however, rare instances of reversed splitting do occur. Reversed splitting of S_2 also has been reported in ischemic heart disease and during episodes of angina pectoris. The latter is extremely uncommon and rarely has been documented by phonocardiography. It is most likely due to a prolonged isovolumic contraction time of the ischemic left ventricle, although during angina it also may be due to an increase in systemic arterial pressure or transient LBBB.[250]

Decreased impedance in the systemic vascular bed also can contribute to the delayed A_2 seen in poststenotic dilatation of the aorta. It also plays a role in the reversed splitting occasionally seen in both chronic aortic regurgitation and patent ductus arteriosus. Reversed splitting of S_2 also has been reported in some cases of type B Wolff-Parkinson-White syndrome, where early activation of the right ventricle through an accessory pathway has caused P_2 to occur prematurely.

Narrow Physiologic Splitting

Narrow physiologic splitting of S_2 is a common finding in severe pulmonary hypertension, as shown in Fig. 10-71.[251] In contrast to the normal situation, where only a single sound is heard during expiration, both A_2 and P_2 are easily heard, even though the splitting interval is less than 30 ms because of the increased intensity and high-frequency composition of P_2. Narrow splitting, although common in severe pulmonary hypertension, is not always the case, and wide splitting with an increased amplitude of P_2 is often present. Wide, persistent splitting becomes a useful sign of abnormal RV performance in patients with primary pulmonary hypertension. In order to reconcile these different responses in S_2 when pulmonary hypertension develops, it is essential to appreciate that normally the duration of RV and LV systole is nearly equal and that a potential interval (the normally wide right-sided "hangout" interval) can be encroached on as the pulmonary hypertension progressively decreases the capacitance and increases the resistance of the pulmonary vascular bed[252] (see Fig. 10-69). Thus a spectrum of the width of splitting may be seen in pulmonary hypertension, depending on the degree of selective prolongation of RV systole, always in the setting of a narrow "hangout" interval. Furthermore, it is clear that varying degrees of splitting may be seen in the same patient during different stages of the disease process producing the pulmonary hypertension. Similar hemodynamic correlates have been found in patients having hyperkinetic pulmonary hypertension secondary to large ASDs. Fixed splitting of S_2 occasionally has been documented in severe RV failure secondary to pulmonary hypertension. This usually has been attributed to the inability of the compromised right ventricle to accept the augmented venous return associated with inspiration.

SINGLE S_2

All conditions listed in Table 10-8 that delay A_2 may produce a single S_2 when the splitting interval becomes less than 30 ms. Also, conditions in which one component of S_2 is either absent or inaudible will produce a single S_2 (e.g., truncus arteriosus, severe tetralogy of Fallot, severe semilunar valve stenosis, pulmonary atresia, and most cases of tricuspid atresia). In Eisenmenger's VSD, the duration of RV and LV systole is necessarily equal, and a loud, single S_2 is appreciated because A_2 and P_2 occur simultaneously. The most common cause of an apparently single S_2 is the inability to hear the fainter of the two components

of the sound (usually P_2) because of emphysema, obesity, or respiratory noise. Another common cause of single S_2 is seen in individuals over age 50. Although this has been attributed to a delayed A_2, a decreased inspiratory delay in P_2 also has been reported. This latter finding has been shown to be due to a decreased right-sided "hangout" interval, most likely related to aging changes in the pulmonary vascular bed.

Opening Snaps

Opening of the normal AV valve is almost always a silent event. With thickening and deformity of the leaflets, usually rheumatic in origin, however, a sound is generated in early diastole in a manner analogous to ejection sounds arising from deformed semilunar valves. The term *opening snap* was first used by Thayer[253] in 1908 to describe the high-frequency early diastolic sound in mitral stenosis. Thayer also recognized that the sound had been absent in those patients who, on autopsy, had markedly thickened and essentially immobile valves. This mechanism was confirmed by hemodynamic and angiographic studies that showed sudden checking of the early diastolic descent of the funnel-shaped stenotic valve when its elastic limits were met.[254] Phonoechocardiography has given an even more precise correlation of the opening snap with the maximum opening motion of the anterior mitral leaflet (see Fig. 10-64, *left*).

The opening snap is a crisp, sharp sound that can be heard in the midprecordial location, usually best in the area from the left sternal border to just inside the apex. Often it is heard well at the base of the heart and frequently is not well heard at the maximal intensity of the diastolic murmur. The diastolic rumble generally follows the opening snap by a short interval. There is no variation in the intensity or timing of the mitral opening snap with respiration.

As with ejection sounds of valvular origin, the intensity of the mitral opening snap correlates well with the mobility of the valve. A loud opening snap is found in mobile stenotic valves with good excursions (see Fig. 10-64, *left*), whereas the opening snap is absent with severe calcific fixation of the valve. The intensity of M_1 parallels the intensity of the opening snap; mobile valves having a loud opening snap have an accentuated M_1, and immobile valves having a decreased or absent opening snap have marked attenuation of M_1. Although the presence of valvular calcification decreases valve mobility and the audibility of the opening snap, the sound is actually found in 50 to 60 percent of patients with calcific valves.

The opening snap follows A_2 by an interval of 0.03 to 0.15 s. In patients with mild mitral stenosis, the interval is usually long, whereas in patients with more severe stenosis, the A_2-opening snap interval is shorter. The A_2-opening snap interval in atrial fibrillation can vary with cycle length. With a short preceding RR interval, the left atrium has not had time to empty, the left atrial pressure remains high, and the A_2-opening snap interval is short. With a longer preceding RR interval, the left atrial pressure falls, and the A_2-opening snap interval widens.

There have been a number of attempts to use the A_2-opening snap interval to predict the level of left atrial pressure and the severity of mitral stenosis.[255] The opening snap occurs at the maximal mitral valve opening shortly after left ventricular-left atrial pressure crossovers. Factors that influence the timing of the opening snap relative to A_2 are (1) the rate of LV pressure decline, (2) the level of the LV pressure at the time of A_2, and (3) the level of the left atrial pressure. Increasing severity of mitral stenosis is usually accompanied by an increasing left atrial pressure and therefore a shortening of the A_2-opening snap interval. Because this interval is multifactorially determined, there is an imperfect correlation between the A_2-opening snap interval and the mitral valve area.[256] Tricuspid valve stenosis also can produce an opening snap.[258] This sound is frequently not detected because the findings of coexisting mitral stenosis, which is almost invariably present, overshadow those of tricuspid stenosis. The maximum intensity of the tricuspid opening snap tends to be found closer to the left sternal border, and unlike the mitral snap, the intensity of the tricuspid snap increases with inspiration. When present, it generally follows the mitral opening snap.[257] An early diastolic sound also can be caused by a right or left atrial myxoma. Although the clinical findings of a left atrial myxoma may be similar to those of mitral stenosis, the echocardiographic picture is classic (see Fig. 10-64, *center*). The tumor "plop" occurs at the maximal diastolic descent of the myxoma.

Although an opening snap is rarely heard with normal valves, it may be heard in situations where high flow exists across the AV valves.[258] An early diastolic sound is frequently present in large ASDs coincident with maximal opening of the tricuspid valve. Other conditions in which functional opening snaps have been found include large VSDs, thyrotoxicosis, and tricuspid atresia with a large ASD. The opening snap must be differentiated from other early diastolic sounds such as the S_3, the pulmonary component of a widely split S_2, and a pericardial knock. At the bedside, differentiation of an opening snap from P_2 is made by noting that the maximal intensity is near the apex rather than at the pulmonary area and that there is lack of movement with respiration. During continuous respiration, it is often possible to appreciate three sounds on inspiration, occurring in rapid sequence in the pulmonary area, and only two components on expiration.

The Third and Fourth Heart Sounds

The third and fourth heart sounds (S_3, S_4) are low-frequency events related to early and late diastolic filling of the ventricles (Fig. 10-74). When they are heard in disease states, they are called *gallop sounds*, and their presence gives valuable information to the clinician regarding the status of ventricular function and compliance.

THE THIRD HEART SOUND

Physiologic S_3

The physiologic S_3 is a benign finding commonly heard in children, adolescents, and young adults, but it is rarely present in adults after age 40 and, when present, is often associated with a thin, asthenic body habitus. This is a low-frequency sound that follows A_2 by 120 to 200 ms and occurs during rapid filling of the ventricle.[259,260] It is best heard at the apex in the left lateral position with the stethoscope bell pressed lightly against the skin and is differentiated from the pathologic S_3 primarily by the "company it keeps."[261]

Pathologic S_3

Most agree that the pathologic S_3 is an exaggeration of the physiologic S_3, with a common mechanism of production.[262] The exact genesis of the S_3 remains controversial. Three major mechanisms of production have been proposed: the valvular theory, the ventricular theory, and the impact theory. The most popular theory has indicated that these sounds have their origins within the left or right ventricle or their walls.[263] The dynamic interplay between the force of delivery of blood into the ventricle and the ability of the ventricle to accept this flow is an important factor in the genesis of this sound. When there is appropriate interaction between these factors, the S_3 occurs when the ventricle suddenly reaches its elastic limits and abruptly decelerates the onrushing column of blood, thereby setting the entire cardiohemic system into vibration. Thus an S_3 may be produced by excessive rapid filling into a ventricle with normal or increased compliance, as with high-output states and mitral regurgitation, or by a normal or less than normal rate of filling into a ventricle with decreased compliance, as in patients with hypertrophic cardiomyopathy. Likewise, decreased rates of filling into overfilled ventricles with large end-systolic volumes, as seen in patients with poor LV function and congestive heart failure, will produce this sound.[264]

Although this mechanism is likely responsible for the sound recorded within the ventricular cavity and on its epicardial surface, Reddy et al.[217,265] have reported convincing data that the sound heard with the stethoscope can be due to the dynamic impact of the heart with the chest wall. The force of the impact and resulting intensity of S_3 depend primarily on the size of the heart, the motion of the heart within the thorax, and the chest wall configuration. This theory explains the S_3 present in hyperdynamic states as well as those with an increased end-systolic volume secondary to LV dysfunction. In the latter, the space between the enlarged heart and the lateral chest wall is diminished, thereby facilitating a more forceful impact in early diastole. This results in an exaggerated rapid filling wave on the apex cardiogram and the prominent S_3 pathognomonic of congestive failure (Fig. 10-75, *lower panel*). Table 10-9 tabulates the major factors responsible for the production of the S_3 as recorded within the left ventricle and on the chest wall.

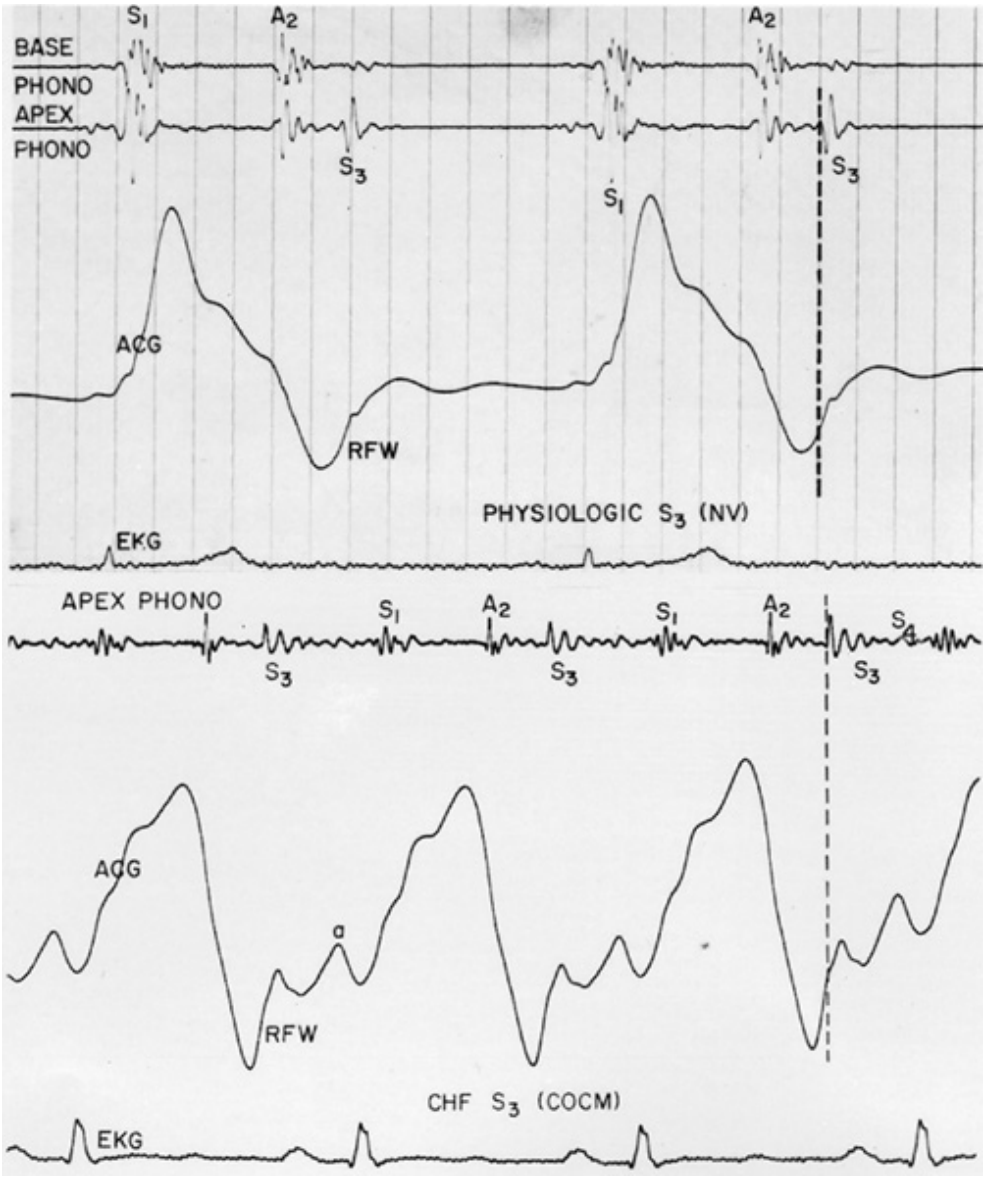

Figure 10-75: (*Top*) A physiologic S_3 (normal variant) recorded in a 24-year-old woman without evidence of cardiovascular disease. The onset of the S_3 occurs during the rapid filling wave (RFW) of the ACG between the *O* and *F* points. The remainder of the cardiovascular examination was entirely within normal limits. (*Bottom*) A very prominent S_3 gallop is recorded in a patient with severe congestive cardiomyopathy (COCM). On physical examination, there was a small-volume carotid pulse and marked engorgement of the neck veins with elevated venous pressure. The ACG shows a very prominent presystolic pulsation (a), and an extremely rapid filling wave is present. The onset of the S_3 occurs during the RFW of the ACG. The first heart sound is soft. (From Shaver JA. Early diastolic events associated with the physiologic and pathologic S_3. *J Cardiogr*. 1984; 14(suppl 5):30. Reproduced with permission from the publisher and the authors.)

Table 10-9: Hemodynamic Determinants of the S_3

Ability of the ventricle to accept flow during the rapid phase of diastolic filling
Rate of relaxation of the ventricle
End-systolic or residual volume of the ventricle
Compliance of the relaxed ventricle
Nonobstructed atrioventricular valve
Atrial pressure head
Atrial blood volume
Atrial compliance
Dynamic impact of the heart with the chest wall
Architecture of the thorax
Cardiac size
Cardiac motion within the thorax
Phase of respiration
Position of the patient

SOURCE: From Shaver JA, et al. Early diastolic events associated with the physiologic and pathologic S_3. *Am J Cardiol* 1984; 14(suppl 5):45. Reproduced with permission from the publisher and authors.

A convenient classification of physiologic and pathologic states with an S_3 is presented in Table 10-10. Both the intensity and timing of the pathologic S_3 associated with LV dysfunction are related to the patient's volume status. With diuresis, the S_3 may decrease in intensity or disappear, and it tends to move away from A_2. A loud, persistent S_3 with cardiomyopathy or acute MI is an ominous sign associated with high mortality, whereas prompt subsidence with therapy suggests a more favorable outlook. LV third heart sounds are heard best at the apex, whereas RV third heart sounds are heard at the lower left sternal edge and may increase in intensity with inspiration.

Table 10-10: Third Heart Sound (S_3), Ventricular Diastolic Gallop, Protodiastolic Gallop, and Pericardial Knock

Physiologic S_3-children and young adults
Decreased prevalence with increasing age
Pathologic S_3
Ventricular dysfunction-poor systolic function, in-creased end-diastolic and end-systolic volume, decreased ejection fraction, and high filling pressures
Idiopathic dilated cardiomyopathy
Ischemic heart disease
Valvular heart disease

Congenital heart disease
Systemic and pulmonary hypertension
Excessively rapid early diastolic ventricular filling
Hyperkinetic states
Anemia
Thyrotoxicosis
Arteriovenous fistula
Atrioventricular valve incompetence
Left-to-right shunts
Restrictive myocardial or pericardial disease
Constrictive pericarditis (pericardial knock)
Restrictive cardiomyopathy
Hypertrophic cardiomyopathy?

In chronic aortic regurgitation, even though end-diastolic volume is increased, end-systolic volume may not be increased until LV dysfunction develops. As LV dysfunction develops, the ejection fraction decreases, resulting in an increased end-systolic volume, and a pathologic S_3 appears in these patients.[266] An S_3 is very common in acute aortic regurgitation and is usually followed by the middiastolic component of the Austin Flint rumble.

A pathologic S_3 resulting from excessive early diastolic filling is common in hyperkinetic states and AV valve regurgitation and often initiates a short flow rumble. It is often present in large left-to-right shunts due to high flow across the mitral valve with VSD or patent ductus arteriosus and with high flow across the tricuspid valve with ASD. The presence of this sound in these conditions does not imply congestive heart failure, and such patients may maintain normal myocardial contractility for years after the S_3 is detected.[267] Pathologic third heart sounds are heard in both restrictive and hypertrophic cardiomyopathy. In constrictive pericarditis, an early prominent sound of a somewhat higher frequency is heard-the *pericardial knock*. The evidence to date points to the simultaneous occurrence of the pericardial knock and the termination of rapid filling of the ventricles. Whether this relationship is causal or coincidental is unclear. The apex cardiac pulsation may show systolic retraction followed by an exaggerated diastolic impulse. The pericardial knock usually increases in intensity with inspiration and occurs near the nadir of the *y* descent of the jugular venous pulse. Atrial fibrillation is commonly present in severe constrictive pericarditis, and at times the loud early knock may be confused with the opening snap of mitral stenosis.

THE FOURTH HEART SOUND

Precordial vibrations resulting from atrial contraction are normally neither palpable nor audible. Under pathologic conditions, forceful atrial contraction generates a low-frequency sound (S_4) just prior to S_1 (also termed the *atrial diastolic gallop* or the *presystolic gallop*). Atrial contraction must be present for production of an S_4. It is absent in atrial fibrillation and in other rhythms in which atrial contraction does not precede ventricular contraction. The S_4 follows the onset of the P wave of the ECG by approximately 70 ms. Audibility of the S_4 depends not only on its intensity and frequency but also on its separation from S_1. The degree of this separation is determined primarily by the PR interval, but it is also somewhat influenced by the PS_4 and the QS_1 intervals. A loud S_1 also may mask the audibility of a preceding softer

S_4. The S_4 is best heard at the apex impulse with the patient turned in the left lateral position. It varies considerably with respiration, usually being heard best during expiration. A left-sided S_4 may radiate to the brachiocephalic and carotid vessel and be best heard in the areas in patients with severe lung disease or who are very obese. A left-sided S_3 may do likewise. A left-sided S_4 and S_3 may also be augmented post-tussively and with sustained handgrip exercise. Both the intensity and timing of the S_4 are closely related to the end-diastolic volume of the ventricle. Maneuvers that increase venous return increase the audibility by increasing the intensity of the sound and by causing it to occur earlier, thereby separating it further from S_1. Decreased venous return does the opposite. Audible fourth heart sounds are usually accompanied by a palpable presystolic apical impulse in the absence of obesity, emphysema, etc., but occasionally, palpable presystolic impulses are not audible. The S_4 generated by a forceful right atrial contraction is usually heard best at the lower left sternal border. Unlike the left-sided S_4, it tends to be accentuated with inspiration. It is also accompanied by prominent *a* waves in the JVP and is occasionally audible over the right jugular vein.[268]

As with the S_3, both the ventricular origin of the S_4 sound due to the abrupt deceleration of the atrial contribution to late diastolic filling and the impact theory have been proposed.[270] It is likely that the former is responsible for the sounds recorded within the ventricular cavities or on their epicardial surfaces, whereas the latter mechanism is responsible for the S_4 auscultated at the chest wall.

The presence of an S_4, particularly when associated with a palpable presystolic apical impulse, is an abnormal finding. Although it is considered to be a normal finding in older subjects by some investigators,[269] others feel strongly that a definite S_4 in a middle-aged or older person is unlikely to be a normal event.[268] Conditions such as obesity, emphysema, or barrel-chest deformity may hinder the clinical detection of both an S_4 and an apical presystolic impulse.

The common pathologic conditions in which S_4 is heard are listed in Table 10-11. A forceful atrial contraction into a hypertrophied, noncompliant ventricle almost always produces an early and easily audible and recordable S_4. The severe LV hypertrophy present in systemic hypertension, severe valvular aortic stenosis, and hypertrophic cardiomyopathy often is responsible for a loud S_4 (Fig. 10-76). In each case, the S_4 is associated with a prominent apical presystolic impulse and is widely separated from S_1.

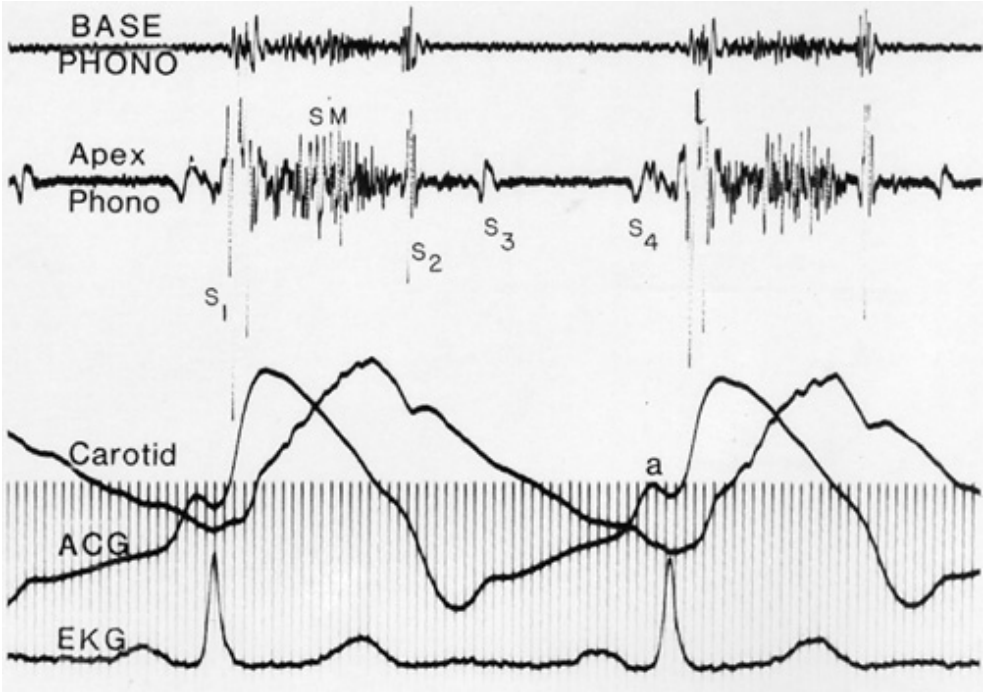

Figure 10-76: Atrial diastolic (ADG) and ventricular diastolic gallops (VDG) are recorded in an adult with severe calcific aortic stenosis. The ADG is associated with a prominent presystolic apical impulse (a), and the VDG occurs during the rapid filling wave of the ACG. The carotid pulse has a very slow rate of rise and a markedly prolonged LV ejection time. The classic diamond-shaped systolic ejection murmur (SM) is present at the base and apex. Note the higher-frequency composition of the SM at the apex but preservation of the crescendo-decrescendo pattern. (From Shaver JA. Current uses of phonocardiography in clinical practice. In: Rapaport E, ed. *Cardiology Update: Reviews for Physicians*. New York: Elsevier; 1981:356. Reproduced with permission from the publisher and author. Copyright 1981 by Elsevier Publishing Co., Inc.)

Table 10-11: Fourth Heart Sound (S_4), Atrial Diastolic Gallop, and Presystolic Gallop

Physiologic-recordable rarely audible
Pathologic
Decreased ventricular compliance
Ventricular hypertrophy
Left or right ventricular outflow obstruction
Systemic or pulmonary hypertension
Hypertrophic cardiomyopathy
Ischemic heart disease
Angina pectoris
Acute myocardial infarction
Old myocardial infarction
Ventricular aneurysm
Idiopathic dilated cardiomyopathy
Excessively rapid late diastolic filling secondary to
Vigorous atrial systole
Hyperkinetic states
Anemia
Thyrotoxicosis
Arteriovenous fistula
Acute atrioventricular valve incompetence
Arrhythmias
Heart block

An audible S_4 with a palpable presystolic impulse is common in patients with ischemic heart disease during an acute episode of angina and in the early phases of transmural MI. Its prevalence is also increased with prior MI; however, audible fourth heart sounds in patients with ischemic heart disease without prior

infarction or hypertension are uncommon.[217] In patients with LV aneurysm or idiopathic or ischemic cardiomyopathy, abnormal fourth heart sounds are commonly present and often associated with an S_3, producing a quadruple rhythm. If tachycardia is present, or if the PR interval is prolonged, S_3 and S_4 may fuse, giving rise to a loud summation gallop (see Fig. 10-74).

Quadruple rhythms are common in hyperkinetic states where the S_3 is due to excessively rapid early diastolic filling and the S_4 results from a forceful atrial contraction into a volume-loaded ventricle. With varying degrees of tachycardia, incomplete summation may occur, simulating a diastolic rumble, or complete fusion may occur, generating a loud summation gallop (see Fig. 10-74). In acute AV valve regurgitation, vigorous atrial contraction into an acutely volume-loaded ventricle can produce an S_4 associated with a presystolic apical impulse. At times it may be difficult to appreciate because of the masking effect of the loud systolic murmur. This contrasts with most patients with chronic mitral regurgitation, who do not have an S_4 but frequently have an S_3.

Presystolic and isolated diastolic fourth heart sounds as well as summation gallops may be heard with varying degrees of heart block. First-degree heart block facilitates audibility of the S_4 because it further separates S_4 from S_1. In 2:1 heart block, an isolated S_4 may be heard in diastole, and a presystolic S_4 may be audible because of the increase in diastolic volume. In complete heart block, S_4 may be heard randomly throughout diastole, and when it occurs simultaneously with rapid early ventricular filling, a loud summation gallop may occur. Fourth heart sounds also have been reported in ventricular systole when atrial contraction occurred during systole in a patient with heart block. The occurrence of an S_4 when the mitral valve is closed excludes its ventricular origin due to either a pressure or volume change and is in keeping with the impact theory of S_4 sound production.[217]

Prosthetic Valve Sounds

The sounds produced by prosthetic valves are varied, depending on the type of valve, its position, and whether or not it is functioning normally. Mechanical valves produce opening and closing clicks that are easily audible and in many patients can be heard even without a stethoscope. Ball-in-cage valves such as the Starr-Edwards produce the loudest and most distinctive opening and closing clicks in any position as long as there is normal valve and ventricular function. In the aortic position, a crisp opening click occurs 0.06 to 0.07 s after S_1 and is coincident with maximal ball excursion, as demonstrated by echocardiography. The metallic ball of the Starr-Edwards valve also produces multiple early systolic clicks when the freely moving ball bounces against the cage during early systolic ejection. These clicks occur during the harsh systolic ejection murmur. Absence or decrease in intensity of these clicks can occur with valve obstruction or LV dysfunction. A decrease in the intensity of the opening and closing clicks, which normally have an intensity ratio of more than 0.5, and the absence of the opening click are also indications of valve malfunction.

In the mitral position, a prominent opening click occurs 0.05 to 0.15 s after A_2. Narrowing of this interval indicates an elevation of left atrial pressure, which may be due to either valvular obstruction or regurgitation. Interference with ball motion also can produce prolongation or significant beat-to-beat variation of this interval. A closing click is also prominent. Just as is seen with the normal S_1, there is variability in the intensity of the closing click, with the changing RR intervals of atrial fibrillation being louder with short RR intervals and softer with long intervals. A decreased intensity with first-degree AV block also occurs due to partial atriogenic closure of the valve, thus reducing the ball excursion and therefore the click intensity. Although a decreased intensity of the valve clicks occurs with valve malfunction, the presence of normal ball motion on an echocardiogram suggests that a nonvalvular cause such as severe LV dysfunction is responsible for the decreased intensity.

The auscultatory findings of disk valve prostheses vary, depending on the type of disk valve. Central occluder valves such as the Beall valve, which was used predominantly in the mitral and tricuspid positions, produce distinct, audible opening and closing sounds. The more commonly used tilting-disk valves do not ordinarily produce audible opening sounds in either the aortic or mitral position.[205] The closing sounds of disk valves are distinct and easily heard in both aortic and mitral positions. LV dysfunction, first-degree AV

block, or another arrhythmia that causes the disk to move to a partially closed position prior to the onset of ventricular contraction will result in a softer sound. This finding must be distinguished from malfunction caused by either fibrosis or thrombus disturbing the disk motion. Auscultation of the bileaflet St. Jude valve is similar to that of the tilting-disk valve.

The sounds produced by tissue prosthetic valves are more like normal heart sounds than the sounds from a mechanical valve.[205] In the aortic position, an opening sound is usually not audible. In the mitral position, an opening sound is audible in about 50 percent of patients at an interval of 0.07 to 0.11 s after A_2.

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

EXTRACARDIAC SOUNDS

Pacemaker Sounds

High-frequency sounds of brief duration are occasionally present in patients with transvenous pacemakers located in the RV apex. They are extracardiac in origin, occurring nearly synchronously (within 6-10 ms) with the pacemaker spike, and are due to stimulation of intercostal nerves adjacent to endocardial electrodes.[270] This stimulus results in contraction of the intercostal muscles, and frequently twitching of the muscle can be observed. The presence of these sounds always should suggest possible myocardial perforation by the endocardial lead, although this is not always present. Stimulation of the pectoral muscles, as well as diaphragmatic stimulation, also has been reported to produce these extracardiac sounds. They also have been observed in patients having transthoracically placed epicardial leads.

Pericardial Friction Rub

Inflammation of the pericardial sac with or without fluid may cause a pericardial friction rub. These friction sounds are very high-pitched, leathery, and scratchy in nature. They seem close to the ear and are auscultated best with the patient leaning forward or in the knee-chest position, holding his or her breath after forced expiration. The pericardial rub may have three components during the intervals of the cardiac cycle when the heart has the greatest excursions within the pericardial sac-at the time of atrial systole, at the time of ventricular contraction, and during rapid early diastolic filling. The usual friction rub occurs during the first two intervals, although three-component rubs may be heard. Triple-component friction rubs are common in uremic pericarditis, particularly when the underlying cardiac disease is hypertension. In this situation, the heart is hyperkinetic due to both pressure and volume overload as well as to the anemia associated with renal failure. Pericardial friction rubs are very common in the acute phase of transmural MI, although they often last for only a few hours. There is a common misconception that friction rubs are not heard when there is a large amount of fluid in the pericardial sac; this is not the case, because usually some portions of the visceral and parietal pericardial surfaces are in contact despite the large amount of fluid (see Chap. 72).

Occasionally, certain midsystolic (ejection) murmurs have a scratchy character and may be misinterpreted as friction rubs. This is particularly true of the short, scratchy pulmonic ejection murmur heard in hyperthyroidism (Means-Lerman sign).[271] Such scratchy sounds should not be considered to be a friction rub unless both systolic and diastolic components are heard.

Mediastinal Crunch: Hamman's Sign

When air is present in the mediastinum, a series of scratchy sounds (Hamman's sign[272]) may occur, related indirectly to both heartbeat and respiratory excursion. These sounds occur most frequently during ventricular systole and in a random fashion. The diagnosis of mediastinal emphysema may be confirmed by crepitation in the neck secondary to subcutaneous air. These crunching sounds due to air in the mediastinum are common following cardiac surgery.

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

HEART MURMURS

A *cardiac murmur* is defined as a relatively prolonged series of auditory vibrations of varying intensity (loudness), frequency (pitch), quality, configuration, and duration.[273] Although the exact physical principles that govern the production of murmurs have been debated for years, most authorities now agree that turbulence is the prime factor responsible for most murmurs. Turbulence arises when blood velocity becomes critically high due to high flow, flow through an irregular or narrow area, or a combination of both. Leatham has attributed the production of murmurs to three main factors: (1) high flow rate through normal or abnormal orifices, (2) forward flow through a constricted or irregular orifice or into a dilated vessel or chamber, and (3) backward or regurgitant flow through an incompetent valve, septal defect, or patent ductus arteriosus. Frequently, a combination of these factors is operative.

While the intensity of a systolic murmur is not always proportional to the hemodynamic disturbance, grading the loudness of a murmur from 1 to 6 as described by Freeman and Levine[274] is generally used. A *grade 1 murmur* is so faint that it can be heard only with special effort. A *grade 2 murmur* is faint but can be heard easily. A *grade 3 murmur* is moderately loud, a *grade 4 murmur* is very loud, and a *grade 5 murmur* is extremely loud and can be heard if only the edge of the stethoscope is in contact with the skin but cannot be heard if the stethoscope is removed from the skin. A *grade 6 murmur* is exceptionally loud and can be heard with the stethoscope just removed from contact with the chest. Experience has shown that systolic murmurs of grade 3 or more in intensity are usually hemodynamically significant.[275] Systolic thrills usually are associated with murmurs of grade 4 or louder. The intensity of the murmur varies directly with the velocity of blood flow across the area of murmur production. The velocity, in turn, is directly related to the pressure head that drives the blood across the murmur-producing area. For example, high velocity of flow through a small VSD produces a loud murmur, whereas a large flow at low velocity through an ASD produces no murmur. The *intensity* of a murmur as auscultated at the chest wall is also determined by the transmission characteristics of the tissues intervening between the source of the murmur and the stethoscope. Obesity, emphysema, and the presence of significant pericardial or pleural effusion will decrease the intensity of a murmur, whereas a thin, asthenic body habitus often will accentuate it.

The frequency of a murmur bears a direct relationship to the velocity of blood flow, as does the intensity of the murmur. The low-velocity flow resulting from a small pressure head across a stenotic mitral valve produces a low-pitched rumbling murmur, whereas the large diastolic pressure gradient across a regurgitant aortic valve causes a high-pitched murmur. A recent study has further demonstrated that the dominant frequencies contained in heart murmurs due to stenotic lesions are directly related to the instantaneous jet velocities distal to the associated obstruction. Occasionally, the frequency composition of the same systolic murmur may vary, depending on the area auscultated. For example, the systolic murmur of aortic stenosis frequently sounds higher-pitched at the apex than at the base.[276] Some murmurs such as the "cooing dove" regurgitant murmur of a ruptured or retroverted aortic cusp, the systolic "whoop" or "honk" of mitral valve prolapse, or the high-pitched systolic murmur of a degenerated bioprosthetic valve-have a very distinctive musical quality.

In addition to the intensity and frequency of murmurs, their *timing* also should be described. There is seldom any difficulty distinguishing between systole and diastole, since systole is considerably shorter at normal heart rates. At rapid heart rates, however, the durations of these two intervals approach each other. Under such circumstances, the examiner usually can time the murmur by simultaneous palpation of the lower right carotid artery or can rely on the fact that the second heart sound (S_2) is usually the louder sound at the base. Once S_2 is identified, murmurs can be located properly in the cardiac cycle as systolic or diastolic. If the murmur in question is at the apex, the proper timing can be ensured by the "inching" technique popularized by Harvey and Levine.[215] This consists of slowly moving the stethoscope down from the base to the apex while repeatedly fixing the cardiac cycle in mind, using S_2 as a reference point. With sinus tachycardia, carotid sinus pressure may temporarily slow the rate and make it possible to differentiate

systole from diastole. Continuous murmurs are heard throughout the cardiac cycle in systole and diastole and usually have their peak intensity around S_2.

The *location* and *radiation* of a murmur are determined multifactorially by the site of origin, intensity, and direction of blood flow, as well as by the physical characteristics of the chest. The duration and time intensity contour (murmur *envelope*) of a specific murmur are intimately related to the instantaneous pattern of blood flow velocity causing the murmur.

Systolic Murmurs

Systolic murmurs may be classified into two basic categories-ejection (midsystolic) murmurs and regurgitant murmurs. This simple classification is attractive because it has a physiologic as well as a descriptive basis. Systolic *ejection* murmurs are due to forward flow across the LV or RV outflow tract, whereas systolic *regurgitant* murmurs are due to retrograde flow from a high-pressure cardiac chamber to a low-pressure chamber.[277]

SYSTOLIC EJECTION (MIDSYSTOLIC) MURMURS

The systolic *ejection* murmur begins shortly after the pressure in the left or right ventricle exceeds the aortic or pulmonic diastolic pressure sufficiently to open the aortic or pulmonic valve. As a result, there is a delay between the S_1, which occurs shortly after AV pressure crossover, and the beginning of the murmur (Fig. 10-77). The murmur then waxes and wanes in a crescendo-decrescendo fashion often described as "diamond shaped" or "spindle shaped" in configuration. The murmur ends before the semilunar valve closure on the side from which it originates. The contour of the time-intensity pattern or *envelope* of the murmur corresponds to the contour of the flow velocity, and the murmur is heard when the sound produced during the peak turbulence exceeds the audible threshold. Thus not only is the overall intensity of the murmur proportional to the rate of ventricular ejection, but also its shape depends on the instantaneous flow velocity during the period of ejection. As can be seen in Fig. 10-78, during normal LV ejection, a disproportionately large volume flow occurs in early systole. If velocity of flow exceeds the murmur threshold, a short midsystolic or ejection murmur results, and its envelope corresponds to the flow velocity pattern. If the stroke volume of the ventricle is increased, this pattern of ejection persists in an exaggerated fashion; the resulting murmur has a tendency to peak early in systole and fade out about halfway through the ejection phase. Such murmurs have been referred to as "kite shaped" and are common in high-output states or conditions such as aortic regurgitation or heart block, where stroke volume is high.

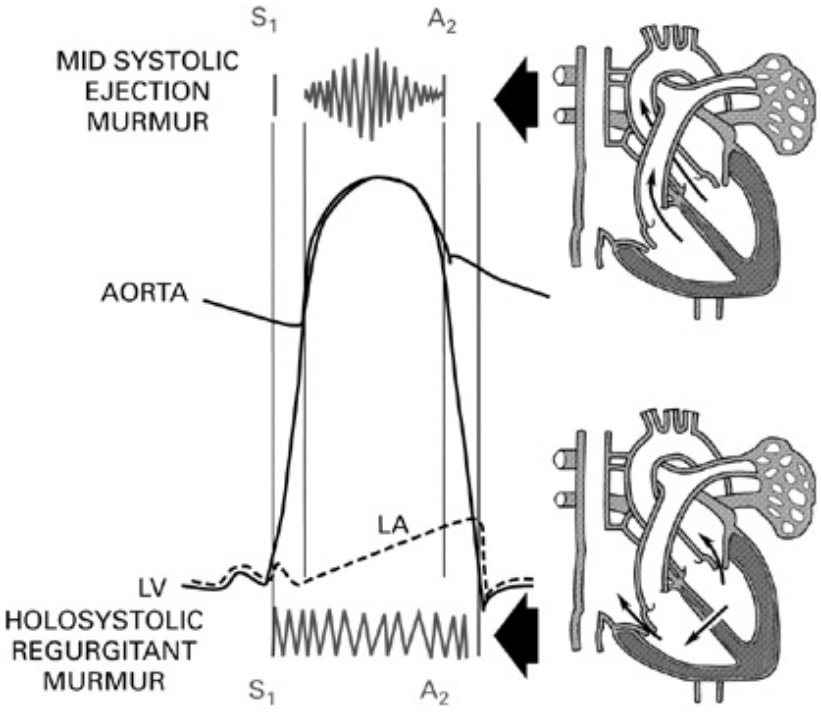

Figure 10-77: Midsystolic ejection murmurs are caused by forward flow across the LV or RV outflow tract, whereas pansystolic regurgitant murmurs are caused by retrograde flow from a high-pressure cardiac chamber to a low-pressure one. (*Left*) Diagrammatic representation of the midsystolic ejection murmur and the pansystolic regurgitant murmur, as related to LV, aortic, and left atrial (LA) pressures. The systolic ejection murmur occurs during the period of LV ejection; the onset of the murmur is separated from S_1 by the period of isovolumic contraction and the crescendo-decrescendo murmur terminates before A_2. The pansystolic regurgitant murmur begins with, or may replace, S_1, and the murmur continues up to and through A_2 as LV pressure exceeds left atrial pressure during the period of isovolumic relaxation. The murmur has a plateau configuration and varies little with respiration. (*Right*) Flow diagram. (Left panel reproduced from Reddy PS, Shaver JA, Leonard JJ. Cardiac systolic murmurs: Pathophysiology and differential diagnosis. *Prog Cardiovasc Dis* 1971; 14:19. Entire figure reproduced with permission from Shaver JA. Systolic murmurs. *Heart Dis Stroke* 1993; 2:10.)

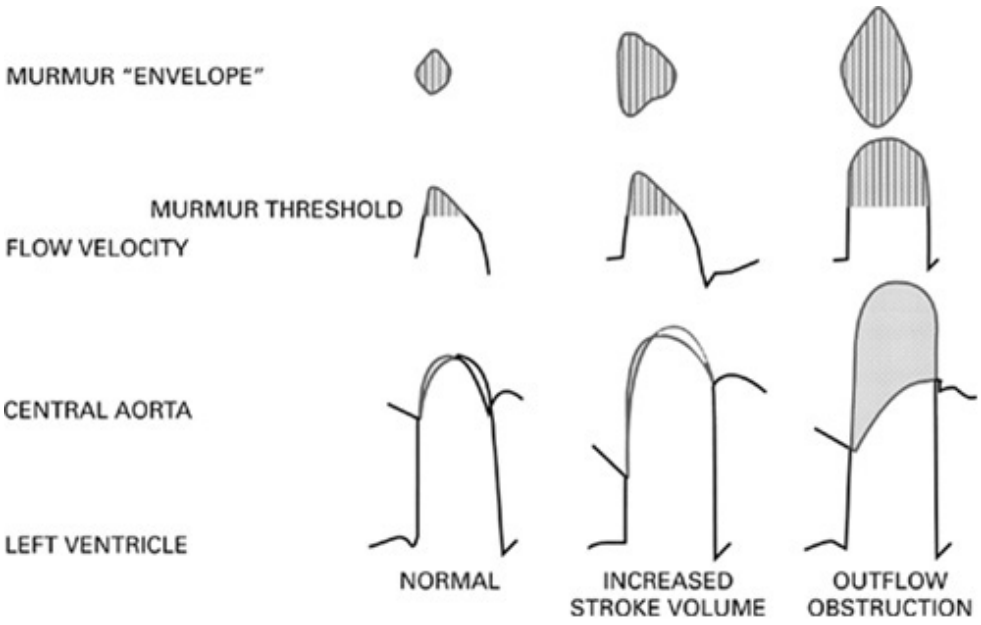

Figure 10-78: The simultaneous time-intensity course of the murmur "envelope," aortic flow velocity, and

LV and central aortic pressure. During normal LV ejection (*left*), peak flow velocity is early, with two-thirds of the ventricular volume ejected during the first half of systole. The murmur threshold may be exceeded during the early peak flow and the corresponding murmur envelope inscribed. (*Center*) Exaggeration of the normal pattern of LV ejection with a high stroke volume, as in high-output states. With critical aortic stenosis (*right*), rapid early ejection is no longer possible; the flow velocity is increased, and the contour becomes rounded and prolonged, producing the typical diamond-shaped murmur of aortic stenosis. (Modified from Reddy PS, et al. Cardiac systolic murmurs: Pathophysiology and differential diagnosis. *Prog Cardiovasc Dis* 1971; 14:4. Reproduced with permission from the publisher and the authors.)

The flow characteristics of normal RV ejection are somewhat different. Early ejection rates are not nearly as high, and the flow curve peaks somewhat later, having a more rounded contour. This flow pattern may well explain some of the long systolic ejection murmurs heard in ASDs and the straight-back syndrome, where only minimal gradients are found across the RV outflow tract.[278] With true valvular obstruction, rapid early ejection is no longer possible; the aortic flow velocity patterns become rounded, resulting in the more symmetric murmur of aortic stenosis. In such cases, the instantaneous flow pattern is determined by the instantaneous pressure head with the resulting high correlation between the contour of the pressure gradient and the murmur envelope. If LV or RV obstruction is severe, systole is prolonged, and closure sound of the semilunar valve is delayed. The murmur, however, always stops before the closure sound on the side from which it originates, although it may envelop the closure sound of the opposite side of the circulation. Because of the high correlation between the shape of the murmur and its underlying flow velocity characteristics, careful attention must be given during auscultation to the shape and duration of the murmur as well as to its intensity.

The intensity of ejection murmurs closely parallels changes in cardiac output. Any condition that increases forward flow-such as exercise, anxiety, fever, or increased stroke volume associated with the long diastolic filling period after a premature beat-increases the intensity of the murmur. Likewise, conditions that decrease cardiac output-congestive heart failure, beta blockade, or other negative inotropic agents-will decrease the intensity of the ejection murmur. This intimate relationship to flow, particularly with beat-to-beat variations, usually will allow the clinician to differentiate a systolic ejection murmur from a systolic regurgitant murmur. Furthermore, definitive diagnosis of the systolic murmur often can be made during auscultation by careful attention to the response of the murmur to various bedside maneuvers that alter the flow and loading conditions of the heart.[279] These maneuvers include respiration, the strain and release phases of the Valsalva maneuver, standing, squatting, passive leg elevation, isometric hand-grip exercise, inhalation of amyl nitrite, and transient arterial occlusion.

Innocent Murmurs

Innocent murmurs are always systolic ejection in nature and occur without evidence of physiologic or structural abnormalities in the cardiovascular system when peak flow velocity in early systole exceeds the murmur threshold.[275] These murmurs are almost always less than grade 3 in intensity and vary considerably from examination to examination and with body position and level of physical activity. They are not associated with a thrill or with radiation to the carotid arteries or axillae. They may arise from flow across either the normal LV or RV outflow tract and always end well before semilunar valve closure.

Innocent murmurs are found in approximately 30 to 50 percent of all children. In young children, especially children aged 3 to 8 years, the vibratory systolic (Still's) murmur is common. It has a very distinctive quality described as "groaning," "croaking," "buzzing," or "twanging." It is heard best along the left sternal border at the third or fourth interspace and disappears by puberty. Considerable controversy exists as to the origin of the vibratory systolic murmur. Regardless of the exact cause, most authorities agree that this murmur originates from flow in the LV outflow tract.

Innocent systolic ejection murmurs also have been attributed to flow in the normal RV outflow tract and have been termed *innocent pulmonic systolic murmurs* because the site of their maximal intensity is auscultated best in the pulmonic area at the second left interspace with radiation along the left sternal border. These are low to medium in pitch, with a blowing quality, and are common in children, adolescents, and young adults. Stein et al.,[280] who used high-fidelity catheter-tipped micromanometers to record

intracardiac sound and pressure in the aorta and pulmonary artery in adults with normal valves, invariably recorded the ejection murmur in the region of the aortic valve. They concluded that these murmurs, despite their precordial location, were aortic in origin.

In adults over age 50, innocent murmurs due to flow in the LV outflow tract are often heard and may be of a higher frequency, with a musical quality, and frequently loudest at the apex. They may be associated with a tortuous, dilated sclerotic aortic root, often in the setting of systolic hypertension. Mild sclerosis of the aortic valve also may be present.

The preceding descriptive breakdown of innocent murmurs is based primarily on age, precordial location, and distinctive acoustic qualities. Since all these murmurs are equally innocent, and because there is considerable overlap among them with respect to origin, transmission, and frequency composition, they are best characterized as systolic ejection murmurs without associated abnormalities of the cardiovascular system. Since both innocent and pathologic ejection murmurs have the same mechanism of production, it is "the company the murmur keeps" that affords the differential diagnosis of the pathologic systolic ejection murmur from the innocent murmur[281] (Fig. 10-79).

For a murmur to be considered innocent, the examination of the cardiovascular system must disclose no abnormalities. Blood pressure and contour of the carotid, femoral, and brachial arteries always should be evaluated carefully. For example, a seemingly innocent murmur in the setting of hypertension, particularly in a younger patient, always should suggest the diagnosis of coarctation of the aorta, which can be diagnosed readily by palpation of weak or nearly absent femoral pulses and confirmed by taking the blood pressure in the lower extremities. There should be no elevation of the jugular venous pulse, and the contour of the jugular pulse should be normal, without exaggeration of either the *a* or *v* wave. Evidence of cardiac enlargement on physical examination should be absent, and palpation of the apex in the left lateral position should show no evidence of a presystolic impulse, sustained systolic motion, or hyperdynamic circulation. On auscultation, normal physiologic splitting should be present. A physiologic S_3 is often present in association with an innocent murmur in children and young adults but should not be heard after age 30. An S_4 is rarely heard in normal children and adults (younger than 50 years) and always should be considered to be abnormal when associated with a presystolic impulse. Systolic ejection sounds of valvular origin as well as midsystolic nonejection sounds should be absent because their presence points to minor abnormalities of the semilunar and AV valves, respectively (see Fig. 10-79). The remainder of the physical examination should show no evidence of a cardiac cause of pulmonary or systemic congestion. In almost all patients with innocent murmurs, the ECG and the cardiac silhouette on chest x-ray should be normal.

The supraclavicular arterial murmur or bruit is a common finding in normal individuals, particularly children and adolescents. These murmurs are maximal in intensity above the clavicles and tend to be louder on the right, although they are often heard bilaterally. The bruit begins shortly after S_1, is diamond-shaped, and is of brief duration, usually occupying less than half of systole. Although the exact mechanism is unknown, it is related to peak flow velocity near the origin of the normal subclavian, innominate, or carotid artery. When particularly prominent, this murmur may transmit to the basal region of the heart and simulate a systolic ejection murmur. However, unlike the cardiac ejection murmur, the supraclavicular murmur is always louder above the clavicles than below them. Complete compression of the subclavian artery may cause the murmur to disappear completely, whereas partial compression occasionally may intensify it. Hyperextension of the shoulders is a simple bedside maneuver that may decrease the intensity of the murmur and cause it to disappear completely. In the adult, the supraclavicular murmur must be distinguished from the murmur of true organic carotid obstruction, this latter murmur being longer, often extending through S_2, and frequently associated with a history suggestive of transient ischemic attacks.

Functional Systolic Ejection Murmurs

Systolic ejection murmurs produced by high cardiac output states are functional and flow-related but are excluded from the category of innocent murmurs because of their associated altered physiologic state. These include the cardiac murmurs of thyrotoxicosis, pregnancy, anemia, fever, exercise, and peripheral arteriovenous fistula, which are best interpreted in light of the total presentation of the patient (see Fig. 10-77). Although these murmurs are often grade 3 and occasionally grade 4 in intensity, they always end well before S_2 and are only rarely confused with obstruction of the LV or RV outflow tract. The large stroke

volume associated with high-degree heart block often produces a functional systolic murmur; when found in the setting of complete heart block, beat-to-beat variations in the intensity of the murmur are present due to the random contribution of atrial systole to LV filling.

The functional systolic murmur in patients with a hemodynamically significant ASD is due to the increased flow in the RV outflow tract secondary to the left-to-right shunt at the atrial level. It is easily diagnosed at the bedside "by the company it keeps." The hallmark of this condition is wide, fixed splitting of S_2. When the shunt is large (more than 2.5:1), a hyperdynamic parasternal impulse is usually present, and a diastolic flow rumble is often heard in the tricuspid area. In addition, the tricuspid closure is loud, and prominent *a* and *v* waves are seen in the JVP. An important condition to be differentiated from an ASD is narrowing of the anteroposterior diameter of the bony thorax. Prominent systolic murmurs-often grade 3 or 4-are heard in patients having the straight-back syndrome and/or pectus excavatum.[282] Audible expiratory splitting is frequently present and, coupled with a prominent pulmonary artery on the chest x-ray (secondary to the narrow anteroposterior diameter), can lead to additional unnecessary procedures to rule out an ASD. Careful attention at the bedside to the physical examination of the spine, thoracic cage, and sternum should be part of the routine evaluation of any patient with a murmur. Often, confirmation of the thoracic abnormality with a lateral chest film is all that is necessary for definitive evaluation. Similar systolic murmurs from the RV outflow tract are also present in patients having significant left-to-right shunting at the ventricular level.

Prominent systolic ejection murmurs are the rule in patients with significant aortic regurgitation secondary to the large forward stroke volume. Although no significant LV outflow gradient is found in these patients, the intensity of such murmurs may be grade 4 or 5, and occasionally they are associated with a thrill. They always end well before aortic closure and are clearly separated from the early regurgitant murmur. Such a murmur is rarely confused with significant valvular obstruction because of the peripheral findings of wide-open aortic regurgitation. When true valvular obstruction is present (mixed stenosis and regurgitation of the aortic valve), the longer systolic ejection murmur is often associated with a prominent thrill. Systolic ejection murmurs due to large RV stroke volume are also seen in severe organic pulmonic valvular regurgitation.

Ventricular ejection into a dilated great vessel is commonly associated with a systolic ejection murmur. In the elderly, such murmurs are due to ejection into a dilated, sclerotic aorta and often are best appreciated at the apex. Frequently, degenerative changes of the aortic valve are also present, and the clinician is faced with a difficult decision as to whether or not true obstruction exists. The presence of significant calcification on fluoroscopic examination favors true obstruction and can be confirmed when a significant gradient is demonstrated by Doppler studies. A systolic ejection murmur due to RV ejection into a massively dilated pulmonary artery is frequently present in idiopathic dilatation of the pulmonary artery (see Fig. 10-73), which is often confused with an ASD due to the wide auditory expiratory splitting present in this condition. The prominent pulmonary ejection sound also may be confused with a loud tricuspid closure sound of a patient with an ASD. Short systolic ejection murmurs, frequently associated with a prominent late pulmonary ejection sound, are also seen in dilated pulmonic arteries secondary to severe pulmonary hypertension of any cause. Physical findings of severe pulmonary hypertension are always present, including a prominent parasternal impulse and increased intensity of the pulmonic component of S_2, which is well heard at the apex. Prominent *a* waves in the neck and a right-sided S_4 that increases with inspiration are present if the ventricular septum is intact. If the pulmonary hypertension is associated with intracardiac shunting, cyanosis frequently is present. A high-pitched, early diastolic murmur of pulmonic regurgitation secondary to severe pulmonary hypertension often is present.

LV Outflow Tract Murmurs

Obstruction to LV outflow may be congenital or acquired and may be located at the valvular, supravalvular, or subvalvular level. Stenosis is occasionally present at more than one level. In the clinical evaluation, one should attempt to define the severity and the level of obstruction. A summary of this differential diagnosis can be found in Table 10-12 (see Chap. 56).

The murmur of fixed stenosis of the LV outflow tract, regardless of the site, is crescendo-decrescendo, and

its contour closely parallels the instantaneous pressure gradient. As long as cardiac output is maintained, there is an excellent correlation between the intensity and length of the murmur with severity of obstruction. Although there is a tendency toward late peaking of the murmur with increasing severity of the obstruction, this delayed peaking has not been found to correlate as well with the severity of valvular obstruction in aortic stenosis as it has in pulmonic stenosis.[283] The murmur of significant fixed LV outflow tract obstruction usually is best heard in the second right and second and third left interspaces near the sternum. It radiates widely into the neck and along the great vessels. With radiation to the apex, particularly in the elderly patient, the high-frequency components of the murmur predominate, and the apical murmur has a high pitch and often a musical quality. This characteristic change in the pitch between the proximal and distal radiation of the murmur is a repeated source of confusion on auscultation. There is an almost overpowering urge to call it a separate murmur of mitral regurgitation; however, observations repeatedly demonstrate that this murmur, regardless of its timbre or harmonics, retains a spindle-shaped configuration whenever it is heard or recorded. The murmur of aortic stenosis varies directly with the length of the preceding diastole; the longer the preceding ventricular filling period, the louder is the systolic murmur (Fig. 10-80). In contrast, the apical murmur of mitral regurgitation is associated with little or no variation in intensity with varying cycle lengths. This observation is useful in patients with atrial fibrillation or frequent premature contractions and helps to identify whether an apical murmur is due to radiation of an ejection murmur or is an additional regurgitant murmur of mitral regurgitation. Beat-to-beat variations in the intensity of the murmur of aortic stenosis have been noted in both pulsus alternans and AV dissociation.

A loud early systolic valvular ejection sound or click is the hallmark of congenital valvular aortic stenosis, and its presence defines the obstruction at the valvular level (**see** Fig. 10-66). As discussed earlier in this chapter, its intensity correlates well with the motility of the valve, and there is little correlation with the severity of the obstruction. It disappears when the valve becomes immobile due to calcific fixation and is absent in fixed subaortic stenosis. With progressive increase in the severity of the outflow obstruction, the duration of LV ejection is prolonged, resulting in narrow, single, or reversed splitting of S_2. Reversed splitting of S_2 in aortic stenosis in the absence of LBBB is always associated with severe obstruction (see Chap. 56).

Regardless of the site of obstruction, significant stenosis always results in LV hypertrophy, with a decreased diastolic compliance. Clinically, this is manifest as a presystolic apical pulsation on palpation and as an S_4 on auscultation (see Fig. 10-76). In patients older than age 12, the S_4 is generally associated with a LV diastolic pressure above 11 mmHg and a left atrial *a*-wave peak of about 13 mmHg. The relationship between the severity of obstruction and the presence of S_4 gallops is indirect, reflecting hypertrophy and decreased compliance of the left ventricle rather than obstruction per se.

Because of the frequent coexistence of hypertensive or arteriosclerotic heart disease in elderly patients with calcific aortic stenosis, the presence of an S_4 is nonspecific and correlates poorly with the severity of obstruction. The S_3 gallops also may be heard in LV outflow tract obstruction, particularly when decompensation occurs (see Fig. 10-76).

The diagnosis of hemodynamically significant aortic stenosis in the elderly presents a particularly difficult problem. The murmur is often of low intensity due to the decreased cardiac output and poor LV function. An ejection sound or click is rarely present, due to calcific fixation of the valve leaflets, and S_2 is of low amplitude. The murmur is often loudest at the apex, has a high-frequency content, and may be difficult to define as ejection in nature because S_1 and A_2 may be poorly heard and therefore lost as landmarks defining the onset and end of mechanical systole.[283] In most patients with severe aortic stenosis, no A_2 is heard, and the systolic murmur obliterates P_2. In the elderly, the rate of rise of the carotid pulse may be nearly normal due to the hard, sclerotic vessels even with severe obstruction. As shown in Fig. 10-80, the response of the murmur following a premature ventricular contraction (PVC) may be very helpful in confirming the ejection nature of the murmur. Differentiation from the benign murmur of mild aortic sclerosis may be difficult and often necessitates confirmation of obstruction and its quantitation by echo-Doppler examination[284] (see also Chaps. 15 and 56).

RV Outflow Tract Obstruction

Obstructions to RV outflow are congenital anomalies and may be at the level of the valve, infundibulum, and proximal or distal branches of the pulmonary artery. Isolated infundibular pulmonic stenosis with an intact septum is rare and is usually associated with a large VSD (tetralogy of Fallot). When the ventricular septum is intact, there is an excellent correlation between both the intensity and duration of the murmur and the severity of obstruction.[285] Figure 10-81 contrasts the auscultatory findings of progressively more severe valvular pulmonic stenosis with an intact ventricular septum with those in tetralogy of Fallot with progressively more severe RV outflow obstruction.[286] As with valvular aortic stenosis, an early systolic ejection sound defines the level of obstruction at the valve. In mild to moderate valvular obstruction, the intensity of this sound is markedly attenuated or may disappear with inspiration. In more severe valvular obstruction, this sound may fuse with S_1 or actually may present as a presystolic click when the pressure generated by a forceful right atrial contraction exceeds RV end-diastolic pressure, causing doming of the stenotic valve in late diastole. Although obstruction to RV outflow in tetralogy of Fallot is usually at the infundibular level, valvular stenosis also may be present. In this setting, a pulmonary valvular ejection sound introduces a systolic murmur, and little variation in the intensity of the ejection sound is found with respiration.

The classic late peaking of the systolic ejection murmur of severe pulmonic stenosis with an intact ventricular septum is demonstrated in Fig. 10-82. Note that the late vibrations of the murmur completely envelop A_2, whereas P_2 is markedly delayed and decreases in intensity secondary to the low pulmonary artery closing pressure. In moderate to severe valvular pulmonic stenosis, an excellent correlation has been found between the A_2-P_2 interval and the RV peak pressure. When the ventricular septum is intact in severe RV outflow obstruction, prominent *a* waves are present in the JVP in association with a right-sided S_4 that may increase with inspiration. Neither of these is present in uncomplicated tetralogy of Fallot. Occasionally, in very severe pulmonic stenosis, a low-pitched presystolic murmur may be present due to forward flow across the stenotic valve that has been opened prematurely by forceful right atrial contraction in late diastole. Such patients are often cyanotic due to right-to-left shunting through a patent foramen ovale.

In isolated infundibular obstruction, a pulmonic ejection sound is usually not encountered, and the pulmonic closure (P_2) is usually not audible except in the mildest cases. Both valvular pulmonic stenosis and isolated infundibular pulmonic stenosis with an intact septum can be differentiated from tetralogy of Fallot by noting the marked intensification of the ejection murmur after the inhalation of amyl nitrite. In contrast, the murmur of tetralogy of Fallot shortens and decreases in intensity.

In branch stenosis of the pulmonary artery, there is a systolic murmur of varying intensity at the upper left sternal border that is widely transmitted to the right side of the chest, back, and both axillae. The murmur is usually less harsh and of higher pitch than the murmur of valvular stenosis. With more peripheral branch stenosis, systolic ejection murmurs or even continuous murmurs may be heard over the lung fields. The wide radiation of this murmur is particularly helpful in alerting the clinician to this type of right-sided obstruction.

Systolic Regurgitant Murmurs

Systolic regurgitant murmurs are produced by retrograde flow from a chamber of high pressure to a chamber of lower pressure. The classic examples of such murmurs are the holosystolic (pansystolic) murmur of mitral regurgitation, tricuspid regurgitation, and VSD. Since there is usually a high-pressure differential between the two chambers throughout systole, the murmurs are holosystolic in duration, high-pitched and blowing in quality, and plateaulike in configuration.

HOLOSYSTOLIC REGURGITANT MURMURS

The murmur of chronic mitral regurgitation is the prototype of the holosystolic regurgitant murmur, as shown in Fig. 10-77. It begins with or replaces S_1 and continues throughout systole in a plateaulike fashion beyond A_2, finally terminating when the LV pressure drops to the level of the left atrial pressure during isovolumic relaxation.[287] In contrast to the systolic ejection murmur, there is little variation in its intensity

with varying cycle lengths.[288] It is heard best at the apex and radiates well into the axilla; only the loudest murmurs are associated with a thrill at the apex. There is little variation in its intensity with respiration, and it is frequently accompanied by a loud diastolic filling sound followed by a short rumble. In this situation, the loud S_3 is not a manifestation of congestive failure but a reflection of hemodynamically significant mitral regurgitation. Likewise, the short rumble does not mean concomitant obstruction at the mitral valve but rather is secondary to extremely rapid early diastolic filling. The intensity of the murmur is directly related to the pressure gradient between the left ventricle and the left atrium.

The diagnosis of hemodynamically significant mitral regurgitation is established by the presence of the holosystolic regurgitant murmur and loud S_3 associated with a short flow rumble. The etiology, however, is determined by the clinical presentation and associated physical findings and is best confirmed by echocardiography (see Chap. 13).

The classic holosystolic (pansystolic) murmur of tricuspid regurgitation in the setting of RV pressure overload is best heard at the lower left sternal border. At times it may be heard laterally to the midclavicular line, indicating that the right ventricle occupies the region of the cardiac apex. Furthermore, it generally can be differentiated from mitral regurgitation because its intensity is usually strongly influenced by respiration.[289] During continuous and accentuated respiration, the murmur increases in intensity with inspiration due to the increased venous return and RV filling associated with inspiration. The inspiratory increase in loudness of right-sided auscultatory events is known as *Carvallo's sign*. Careful inspection of the JVP while auscultating the murmur will be of further help in defining its tricuspid origin, showing a prominent *v* wave with a rapid *y* descent that augments during inspiration. In severe RV failure, this respiratory variation may be absent, but it may reappear as the state of compensation improves. With severe tricuspid regurgitation, a short flow rumble introduced by an S_3 can be present, just as with mitral regurgitation, and both will increase with inspiration.[290]

The holosystolic murmur of VSD is heard best just off the sternal border in the fourth, fifth, and sixth intercostal spaces and is usually accompanied by a forceful thrill.[291] The murmur does not radiate to the axilla as with mitral regurgitation and does not have the respiratory variation characteristic of tricuspid regurgitation. Wide physiologic splitting with an easily heard P_2 is usually present when the left-to-right shunt is hemodynamically significant. When the shunt is large, there is a left ventricular S_4 followed by a short flow rumble. The regurgitant murmur is due to high-velocity flow from the high-pressure left ventricle to the lower-pressure right ventricle, and its intensity correlates poorly with the degree of left-to-right shunting. For example, a grade 5 murmur may be associated with a very high velocity flow through a small hemodynamically insignificant muscular VSD (Roger). On the other hand, an equally loud murmur associated with a thrill may be present with a larger defect having massive left-to-right shunting. When the defect is very large and the RV and LV pressures are equal, however, no murmur may be produced across the defect; instead, the short pulmonary ejection murmur of severe pulmonary hypertension is present (Eisenmenger's VSD). The murmur of VSD is very sensitive to vasoactive agents that alter vascular impedance, and a marked decrease in both the LV-RV pressure gradient and the intensity of the murmur is seen following the administration of amyl nitrite.

EARLY SYSTOLIC REGURGITANT MURMURS

Rarely, a regurgitant murmur confined to early systole is seen in the presence of a small VSD. This murmur begins in the usual manner at the onset of ventricular systole and stops suddenly in early or middle systole.[292] The sudden cessation of the murmur is due to the fact that as ejection continues and ventricular size decreases, the small defect is sealed shut as the ventricular septum thickens during systole and the flow ceases. This murmur is important because it is characteristic of the type of VSD that may disappear with age.

In contrast to the holosystolic murmur of chronic mitral regurgitation, acute severe mitral regurgitation may present as an early systolic spindle-shaped murmur.[293] Common conditions producing acute mitral regurgitation include spontaneous rupture of the chordae tendineae of a myxomatous valve, acute or subacute bacterial endocarditis of the mitral valve, papillary muscle rupture or dysfunction secondary to acute MI, and disruption of the mitral apparatus due to chest trauma.[294] In each of these conditions, large-

volume flow regurgitates into a relatively normal left atrium that has not had the time to make the adaptive changes in compliance seen in chronic long-standing mitral regurgitation. As a result, an extremely high *v* wave is generated in the left atrium.

This high *v* wave abolishes the left ventricular-left atrial gradient during the latter part of systole, resulting in termination of retrograde flow and abbreviation of the systolic murmur. As shown in a patient with acute mitral regurgitation secondary to spontaneous rupture of the chordae tendineae of a myxomatous valve, the murmur ends before A_2. Audible expiratory splitting with an accentuated P_2 is present at the base, and a loud S_4 is recorded at the apex. The presence of the S_4 associated with a prominent presystolic impulse on palpation is an important clue that indicates the acute nature of the mitral regurgitation and is rarely present in mitral regurgitation of a chronic nature. The systolic murmur of acute mitral regurgitation, which can mimic ejection murmurs, may have classic radiation to the axilla and back, especially if it is due to prolapse of the anterior leaflet of the valve with flow directed over the posterior leaflet. When the murmur is loud, it may be conducted to the top of the head and to the sacrum along the spinal column. Occasionally, the murmur is conducted to the base of the heart and great vessels, simulating aortic stenosis. The quick-rising carotid pulse with rapid falloff, as well as the wide physiologic splitting of the second heart sound, helps differentiation from aortic stenosis.[295]

The systolic murmur of organic tricuspid regurgitation is often unimpressive and presents as an early systolic murmur ending well before A_2, even in the presence of severe regurgitation.[296] In this condition, the RV pressure is nearly normal, and massive regurgitation may be present with only a small pressure differential between the right ventricle and the right atrium. The small pressure head results in a low-velocity flow, minimal turbulence, and a soft, abbreviated murmur. Occasionally, only minimal early systolic vibrations are heard. In most patients, large *v* waves are readily apparent in the JVP. The murmur retains the characteristic inspiratory augmentation seen in right-sided regurgitant murmurs and is frequently associated with an S_4 that increases in intensity with inspiration. A right-sided S_4 and a prominent diastolic tricuspid flow rumble are the rule when the tricuspid regurgitation is acute, as in endocarditis of the tricuspid valve. After total excision of the tricuspid valve for infective endocarditis related to intravenous drug abuse, the systolic murmur is often very unimpressive or may be completely absent. Giant *v* waves in the neck are easily visible, however, and palpable venous thrills and a murmur at the base of the neck may be present secondary to rapid retrograde flow in the jugular system.[297] Other causes of organic tricuspid regurgitation include carcinoid heart disease, RV infarction, chest trauma, and damage of the tricuspid valve during open heart surgery.

MID- AND LATE-SYSTOLIC REGURGITANT MURMURS

Midsystolic murmurs can occur with mitral regurgitation due to papillary muscle dysfunction.[298] The timing of the murmur of papillary muscle dysfunction also may be late systolic, and the murmur may be either intermittent or constant. It occurs with ischemia or infarction of either the posteromedial or anterolateral papillary muscle. Often these murmurs are transient, being provoked by episodes of ischemia.

Varying degrees of mitral valve prolapse are the most frequent cause of a late-systolic murmur, and this entity is one of the most common causes of systolic murmurs seen in clinical practice[299] (see Chap. 58). The murmur is best heard at the apex and often has a tendency to a late systolic crescendo. It is frequently introduced or accompanied by nonejection clicks. These clicks may be single or multiple, and they can occur independently without an accompanying systolic murmur. As shown in Fig. 10-67, the click occurs near the time of maximal prolapse in midsystole, and the late-systolic murmur continues up to and through A_2 due to prolapse of the posterior leaflet during the remainder of systole.

The timing and intensity of these murmurs vary with physiologic and pharmacologic maneuvers that alter the end-diastolic volume of the heart (see Fig. 10-68). These murmurs are also sensitive to conditions that alter the peripheral vascular impedance as well as the inotropic state of the heart. These variations in the timing and duration of the murmur can be understood most easily by considering mitral valve prolapse as a condition in which the valve is too big for the ventricle (see Chap. 58). This valvuloventricular disproportion manifests itself at a given geometric size and configuration during LV contraction. These dynamic changes can best be appreciated at the bedside by examining the patient in the supine, left lateral,

sitting, and standing positions as well as during prompt squatting. Late-systolic murmurs also may originate from prolapse of the tricuspid valve (see Chap. 59).

Levine and Harvey[215] described a musical, apical systolic murmur that they called a "whoop" because it simulated the "whoop" of whooping cough. These murmurs are loud, high-pitched, musical, sonorous, and vibratory, are best heard at the apex in late systole, and are frequently intermittent. They may vary strikingly with respiration, from beat to beat, and from examination to examination. They are often preceded by clicks and originate in the mitral valve. They are associated with ballooning of the mitral valve or mitral regurgitation (or both), and their unusual quality is secondary to the high-frequency vibrations of the mitral apparatus. The systolic "whoop" or "honk," together with late systolic murmurs, with or without associated clicks, is part of a continuum representing abnormalities of the mitral valve apparatus of varying etiologies. Similar honking noises, with or without clicks, may arise from the tricuspid valve and also have been produced by transvenous pacemaker catheters situated across the valve. These murmurs are best auscultated at the fourth left intercostal space and have the typical inspiratory augmentation of tricuspid murmurs (see Chap. 59).

MURMUR OF HYPERTROPHIC "OBSTRUCTIVE" CARDIOMYOPATHY

The classic cardiac findings of hypertrophic cardiomyopathy (HCM) with a LV outflow gradient are demonstrated in Fig. 10-83, and the echocardiogram on the right gives insight into the mechanism of production of the systolic murmur. Systolic anterior motion of the mitral apparatus impinges on the massively thickened septum, producing high-velocity flow in middle and late systole, resulting in a midsystolic ejection murmur usually with its maximal intensity at the left sternal edge.[300] Varying degrees of mitral regurgitation also may be present during systole due to the distorted mitral apparatus. Frequently, on auscultation, the skilled clinician has difficulty deciding whether the systolic murmur found in HCM is ejection or regurgitant in nature.[301] Usually, the murmur recorded by the precordial phonocardiogram is actually the summation of the murmurs of LV outflow obstruction and mitral regurgitation as transmitted to the chest wall.[302]

In patients with dynamic LV outflow gradients, the intensity of both the systolic ejection murmur and the mitral regurgitant murmur varies directly with the magnitude of the pressure gradient. Thus physiologic maneuvers and pharmacologic interventions that increase the pressure gradient will increase the intensity of the precordial murmur, and vice versa. Decreases in LV preload and afterload or increases in LV contractility are associated with increases in the pressure gradient and the intensity of the murmur, whereas increases in LV preload and afterload or decreases in LV contractility will decrease the pressure gradient and the intensity of the murmur.[303,304] For example, the upright posture and the strain phase of the Valsalva maneuver decrease venous return and LV preload, and the murmur increases in intensity. On reclining or with prompt squatting, augmented venous return increases LV preload, and the murmur decreases in intensity. Vasoactive drugs such as amyl nitrite decrease blood pressure, and a marked increase in the intensity of the murmur occurs, whereas vasoconstrictive drugs such as phenylephrine increase the afterload, and the murmur is decreased or abolished (see Chap. 67).

These responses to vasoactive drugs should be compared with the diametrically opposite responses shown in a patient with a holosystolic murmur of chronic mitral regurgitation.

In the absence of a LV outflow gradient at rest or with provocation, the murmur of HCM is less impressive. Although a short ejection murmur is usually recorded due to rapid early LV ejection, it is often softer and extends through less of systole than when a gradient is present. There is also little variation in the intensity with changes in preload, afterload, or contractility.

In HCM with and without a gradient across the LV outflow tract, massive LV hypertrophy is present, and a prominent presystolic impulse associated with a LV S_4 is the rule when normal sinus rhythm is present. An S_3 is also a common finding in patients with HCM, and occasionally there is an early diastolic rumble that may mimic the diastolic murmur of mitral stenosis. Such rumbles are felt to be due to the increased impedance to LV filling secondary to the decreased diastolic compliance of the left ventricle.

Diastolic Murmurs

Diastolic murmurs have two basic mechanisms of production. Diastolic filling murmurs or rumbles are due to forward flow across an AV valve, whereas diastolic regurgitant murmurs are due to retrograde flow across an incompetent semilunar valve[305] (Fig. 10-84).

DIASTOLIC FILLING MURMURS (RUMBLES)

Diastolic rumbles are caused by forward flow across the AV valves and are delayed from their respective semilunar closure sound by the isovolumic relaxation period. Only following this period, when the atrial pressure exceeds the declining ventricular pressure, do the AV valves open and filling begins. Since there are two phases of rapid ventricular filling-early diastole and presystole-these murmurs have a tendency to be most prominent during these two filling periods. Because the velocity of flow is relatively low, these murmurs have a low-frequency content and are rumbling in character.

Diastolic Rumbles due to Obstruction of the AV Valve

The murmur of mitral stenosis is heard best at the apex in the left lateral position, and its duration correlates well with the duration of the mitral diastolic gradient. Its intensity is related to the severity of the obstruction and to the flow across the valve.[306] As a result, there is poor correlation between the intensity of the murmur and the severity of the obstruction; e.g., high flow across a mild obstruction may produce a loud rumble, whereas low flow across a severely stenotic valve may produce a very soft murmur or may be silent. When the stenotic mitral valve is mobile, the murmur is introduced by a prominent opening snap (see Fig. 10-64, *left*). The duration of the interval between A_2 and the opening snap correlates well with the level of left atrial pressure; the shorter the A_2-opening snap interval, the higher is the left atrial pressure, and vice versa. The S_1 is also loud when the stenotic valve is mobile and is usually preceded by a crescendo murmur. Although originally attributed to increased flow secondary to left atrial systole, phonoechocardiographic studies have suggested that this short "presystolic" murmur is actually due to high-velocity antegrade flow through a progressively narrowing mitral orifice during very early (isovolumic) ventricular systole (see Fig. 10-64, *left*). This mechanism also may be responsible for the brief crescendo presystolic murmur observed in patients with mitral stenosis in atrial fibrillation following a short cycle length. The exact physical principles causing the production of this crescendo murmur are still in question.

Although the intensity of the diastolic rumble in mitral stenosis correlates poorly with the severity of obstruction, there is an excellent correlation of severity with the duration of the murmur. When sinus tachycardia or rapid atrial fibrillation is present, a rumble starting with an opening snap and continuing to S_1 may not be meaningful because of the short diastolic time. Carotid sinus pressure may be very helpful in temporarily slowing the heart rate, thereby allowing the clinician to uncover the potential length of the rumble.

Obstruction of the mitral orifice also can be produced by a left atrial tumor. The diastolic murmur may be very similar to that produced by mitral stenosis (as shown in Fig. 10-64, *center*). A loud tumor "plop" is present instead of the opening snap, and the presystolic crescendo murmur occurs as the protruding tumor mass returns rapidly through the mitral orifice into the left atrium during early ventricular systole. A systolic murmur of mitral regurgitation also may be present, and both murmurs may vary from examination to examination and with changes in body position.

The murmur of tricuspid stenosis is usually heard in the xiphoid area just off the sternal border. Since right atrial systole occurs earlier than left, the diastolic murmur of tricuspid stenosis may have a crescendo-decrescendo configuration. Even when the PR interval is normal, the presystolic accentuation of the diastolic rumble may terminate before S_1. Since tricuspid stenosis almost always occurs in the presence of mitral stenosis, this diastolic diamond-shaped murmur, which augments during inspiration, and the presence of large *a* waves in the JVP are clues to this additional diagnosis. When atrial fibrillation is present, the murmur is in middiastole and has the typical inspiratory augmentation. A tricuspid opening snap, which usually follows the mitral opening snap, also may be present and may initiate the murmur.

Diastolic Rumbles due to High Flow Across the AV Valves

High-velocity flow across the normal or insufficient AV valve may result in short middiastolic rumbles often accompanied by an S_3 and should not be confused with murmurs produced by true obstruction of the AV valves. Such rumbles are common in both VSD and patent ductus arteriosus due to the large flow across the mitral valve secondary to the left-to-right shunt.[307] Likewise, the left-to-right shunt in a large ASD often produces a tricuspid rumble. Similar low-pitched rumbling murmurs also may be present in hyperkinetic states and occasionally are heard in patients with complete heart block and increased diastolic blood flow in each cardiac cycle. Common to all these conditions is high-volume flow during the latter phase of the rapid filling period. Phonoechocardiography has shown that these murmurs occur during the rapid closing motion of the mitral valve, suggesting a functional "obstruction" during the period of rapid early diastolic filling.[308] Identical phonoechocardiographic correlates also have been shown with mitral and tricuspid regurgitation, where early diastolic filling is also extremely rapid. With tricuspid regurgitation, the early rumble will increase with inspiration, typical of right-sided murmurs across the tricuspid valve. During rapid atrial fibrillation, ventriculogenic closure of the normal mitral valve during the rapid filling phase of a short cardiac cycle may cause a "presystolic" murmur by a similar mechanism.

Mitral valvulitis during an episode of acute rheumatic fever may cause a short diastolic rumble, the *Carey Coombs murmur*.[309] This rumble, especially in children or in the presence of fever and anemia, may be introduced by an S_3 rather than by an opening snap. This combination of an S_3 with a short rumble indicates that there is not enough obstruction to the valve to alter the characteristics of rapid early ventricular filling.

The Austin Flint murmur, as originally described in 1862,[310] consisted of an apical presystolic murmur observed in two patients with considerable aortic regurgitation and no evidence of mitral stenosis at autopsy. Since its original description, the timing of this murmur has been extended to include a middiastolic component. It is heard best at the apex and has many of the qualities of the murmur of mitral stenosis. It is introduced by an S_3 rather than by an opening snap, however, and S_1 is of normal or decreased amplitude. Maneuvers or pharmacologic agents that increase the degree of aortic regurgitation, such as hand grip or vasoconstricting drugs, will increase the intensity of the rumble, whereas vasodilating agents such as amyl nitrite will decrease its intensity. In most cases of severe aortic regurgitation, particularly when the regurgitation is acute, the presystolic component of the Austin Flint murmur is lost. In this situation, there is marked elevation of the LV end-diastolic pressure, and the reverse pressure gradient between the left ventricle and the left atrium causes premature closure of the mitral valve.

Elegant phonoechocardiographic studies have shown that the murmur is associated with the rapid closing motion of the mitral valve leaflets during middiastole and presystole, presumably due to antegrade flow across a closing orifice in a manner similar to the flow rumble of AV valvular regurgitation and high-output states.[311] Austin Flint murmurs have been observed in the absence of rapid closing of the mitral valve, however, and Reddy et al.[312] have suggested that incomplete valve opening rather than excessively rapid closure rates may be the essential requirement for producing the increased mitral flow velocity. One echo-Doppler study has suggested that patients with an Austin Flint murmur usually have an aortic regurgitant jet aimed directly at the mitral valve, causing deformity and shuddering of the valve, in contrast to patients with equally severe regurgitation, in whom the murmur is absent.[313] Right-sided Austin Flint murmurs of similar quality have been reported in association with severe pulmonic regurgitation associated with pulmonary hypertension.[314]

DIASTOLIC REGURGITANT MURMURS

Holodiastolic Aortic Regurgitant Murmurs

The early diastolic murmur of aortic regurgitation is blowing and high-pitched in character and is often more difficult to record than to hear because of its high-frequency content. Since isovolumic relaxation of the left ventricle is very rapid, a large gradient quickly develops between the aortic and LV diastolic pressures, and the murmur builds up to maximum intensity almost immediately after A_2. As diastole progresses, the gradient between the two chambers falls slowly, and the murmur envelope closely parallels

the pressure drop in a decrescendo fashion up to S_1. When the aortic regurgitation is valvular in origin, the murmur is usually best heard at the third and fourth left parasternal areas. The finding that the murmur is heard best to the right of the sternum should alert the clinician to an aortic root etiology of the regurgitation.[315] It should be pointed out that this finding is helpful only if present, since most patients with aortic regurgitation secondary to dilatation of the aortic root have the usual radiation with peak intensity to the left of the sternum. Although the frequency content of the murmur is in a range advantageous to the human ear, the amplitude of the vibrations may be quite small and the murmur quite faint. Therefore, the murmur may be overlooked if the examiner does not listen with the patient sitting up and leaning forward and does not listen with the diaphragm of the stethoscope pressed firmly against the chest wall. In addition, one should listen while the patient holds his or her breath after deep expiration.

The degree of aortic regurgitation is directly proportional to the pressure head driving the flow in a retrograde fashion. Maneuvers or pharmacologic agents that increase or decrease the diastolic aortic-left ventricular pressure gradient will increase or decrease the intensity of the regurgitant murmur. Prompt squatting often will bring out a very faint aortic regurgitant blowing murmur at the bedside, and inhalation of amyl nitrite will markedly decrease its intensity. It should be remembered that the murmur of mild aortic regurgitation often disappears during the latter stages of pregnancy due to the low peripheral vascular resistance. Pure aortic regurgitation without associated valvular stenosis may present with a prominent systolic ejection murmur as well as an Austin Flint rumble at the apex. The carotid pulse is rapid-rising and has a large volume. The A_2 is often diminished or even absent when the regurgitation is valvular in origin due to inadequate coaptation and checking of the retrograde blood column by the deformed leaflets.

The etiology of the aortic regurgitation usually cannot be determined by the quality of the murmur. An exception to this rule is the presence of a "cooing dove" or musical diastolic murmur, which usually denotes a rupture or retroversion of an aortic cusp. Such ruptures occur secondary to trauma, bacterial endocarditis, and occasionally in the presence of arteriosclerotic involvement of the aortic valve. Retroversion and subsequent rupture of the aortic valve with a musical murmur are also a complication of syphilitic aortic regurgitation (see Chap. 56).

Abbreviated Aortic Diastolic Regurgitant Murmur

The murmur of very mild aortic regurgitation may be abbreviated and may end by middiastole. This is particularly true of the functional aortic regurgitant murmur of systemic arterial hypertension. As the volume of blood in the aorta decreases during diastole, the aortic annulus becomes smaller, and coupled with the decreasing aortic-left ventricular diastolic gradient, retrograde flow ceases, and the murmur disappears.

The murmur of aortic regurgitation also may be abbreviated if the aortic regurgitation is acute. Acute regurgitation of blood into a ventricle that has not had time to adapt to a large-volume load results in marked elevation of the LV end-diastolic pressure and equilibration of the aortic and LV diastolic pressures. With this, retrograde flow ceases, and the murmur disappears in the latter part of diastole. In the syndrome of acute aortic regurgitation, there may be preclosure of the mitral valve, resulting in a soft or absent S_1 as well as absence of the presystolic component of the Austin Flint murmur. The auscultatory findings of acute versus chronic aortic regurgitation are contrasted in Fig. 10-85. Common causes of acute aortic regurgitation include aortic valve endocarditis, trauma, acute aortic dissection, and dehiscence of an aortic valve prosthesis (see Chap. 56).

Holodiastolic Pulmonic Regurgitant Murmur

Pulmonic regurgitation is found most commonly in the setting of severe pulmonary hypertension and dilatation of the pulmonary artery with inadequate coaptation of the leaflets of the pulmonic valve. The functional murmur of pulmonic regurgitation (Graham Steell murmur)[316] is similar in both frequency and contour to that of aortic regurgitation because the hemodynamics responsible for their production are identical. The differential diagnosis is made by the "company the murmur keeps," and when it is associated with the peripheral signs of hemodynamically significant aortic regurgitation or with the findings of severe pulmonary hypertension, there is rarely a problem. However, when rheumatic mitral stenosis is the primary lesion, the semilunar regurgitant murmur may be secondary either to associated rheumatic aortic

regurgitation or to the Graham Steell murmur if the pulmonary hypertension is severe. Careful investigation of the semilunar blowing murmur in the setting of mitral stenosis has shown that it is almost always due to aortic regurgitation, even when significant pulmonary hypertension is present.[317] More common causes of the Graham Steell murmur of functional pulmonary regurgitation are primary pulmonary hypertension and Eisenmenger's syndrome.

Early diastolic murmurs occasionally are heard in end-stage renal failure, particularly when there is concurrent anemia, hypertension, and fluid overload. Doppler echocardiography demonstrated that these murmurs are usually pulmonic in origin.[318] They are often transient in nature and are related to fluid overload. Such murmurs are diminished by extracellular fluid removal and reflect correctable pulmonary hypertension.[318]

Delayed Pulmonic Regurgitant Murmur

The murmur of organic (non-pulmonary hypertensive) pulmonary regurgitation is quite different in quality and duration as compared with either aortic regurgitation or the Graham Steell murmur of pulmonary hypertension.[319] The murmur is delayed from P_2 by a short interval and then builds up quickly to a crescendo followed by a decrescendo that ends well before S_1. In organic pulmonic regurgitation, the pulmonary artery pressure may be normal, and the diastolic gradient between the pulmonary artery and right ventricle may be very small, resulting in low-velocity retrograde flow and a lower-pitched murmur. The murmur is heard only during the period of maximal gradient in early and middle diastole, as the pulmonary artery pressure begins to equilibrate with the RV end-diastolic pressure in the latter part of diastole. This type of murmur may be congenital or acquired, as with pulmonary valve endocarditis, carcinoid syndrome, or surgical procedures on the pulmonic valve. It is often associated with a prominent systolic ejection murmur secondary to the large RV stroke volume.

CONTINUOUS MURMURS

A *continuous murmur* is defined as one that begins in systole and extends through S_2 into part or all of diastole. It need not occupy the entire cardiac cycle; therefore, a systolic murmur that extends into diastole without stopping at S_2 is considered to be continuous even if it fades completely before the subsequent S_1. A physiologic classification of continuous murmurs as described by Myers[320] is detailed in Table 10-13.

Table 10-13: Physiologic Classification of Continuous Murmurs

Continuous murmurs due to rapid blood flow
Venous hum
Mammary souffle
Hemangioma
Hyperthyroidism
Acute alcoholic hepatitis
Hyperemia of neoplasm (hepatoma rental cell carcinoma, Paget's disease)
Continuous murmurs due to high-to-low pressure shunts
Systemic artery to pulmonary artery (parent ductus arteriosus, aortopulmonary window, truncus arteriosus, pulmonary atresia, anomalous left coronary, bronchiectasis, sequestration of the lung)
Systemic artery to right heart (ruptured sinus of Val-salva, coronary artery fistula)
Left-to-right atrial shunting (Lutembacher's syndrome, mitral atresia plus atrial septal defect)

Venovenous shunts (anomalous pulmonary veins, portosystemic shunts)
Arteriovenous fistula (systemic or pulmonic)
Continuous murmurs secondary to localized arterial ob- struction
Coarctation of the aorta
Branch pulmonary stenosis
Carotid occlusion
Celiac mesenteric occlusion
Renal occlusion
Femoral occlusion
Coronary occlusion

SOURCE: From Myers JD. The mechanisms and significances of continuous murmurs. In: Leon DF, Shaver JA, eds. *Physiologic Principles of Heart Sounds and Murmurs*. Monograph 46. New York: American Heart Association; 1975:202. Reproduced with permission from the American Heart Association, Inc., and author.

Continuous Murmurs due to Rapid Blood Flow

High-velocity blood flow through veins and arteries may cause a continuous murmur. The cervical venous hum is a continuous murmur with diastolic accentuation and is easily heard in almost all children. This murmur also can be heard in healthy adults and is present in nearly all women in the later stages of pregnancy. High cardiac output states such as thyrotoxicosis and anemia are also associated with easily heard venous hums. This murmur is usually poorly heard in the supine position, and its presence in this position in an adult strongly suggests a hyperdynamic circulatory state. Peak intensity is in the supraclavicular fossa just lateral to the sternocleidomastoid muscle, and it is usually more prominent on the right side. When the murmur is loud, it may radiate below the clavicles and occasionally can be confused with the continuous murmur of patent ductus arteriosus. This error should never be made, however, because the cervical venous hum can be terminated easily by digital compression of the JVP.

The mammary souffle is another example of a continuous murmur occurring in 10 to 15 percent of pregnant women during the second and third trimesters and in the early postpartum period, particularly in lactating women, and is heard between the second and sixth anterior intercostal spaces. This murmur may be obliterated by firm pressure on the stethoscope or by digital pressure applied just lateral to the site of auscultation and therefore should not be confused with the continuous murmur of patent ductus arteriosus or with arteriovenous fistula. The mammary souffle disappears after termination of lactation. Other causes of continuous murmurs due to rapid blood flow through arterial or venous channels are outlined in Table 10-13.

Continuous Murmurs due to High-to-Low-Pressure Shunts

A group of congenital cardiovascular anomalies has shunting from the high-pressure systemic (aortic) circulation to the low-pressure pulmonary arterial circulation, resulting in a large gradient between the two systems throughout the cardiac cycle. The murmur of patent ductus arteriosus is the classic example of this type of anomaly. It is heard best in the left infraclavicular area and the second left intercostal space. The peak intensity of the murmur is at the time of S_2, after which it gradually wanes until it terminates before S_1.[221] The length of the murmur is determined by the difference in the vascular resistance between the greater and lesser circulation. As the pulmonary vascular resistance increases, the diastolic pressure in the

pulmonary artery approaches and finally reaches systemic levels, diminishing and finally abolishing diastolic flow and the diastolic portion of the murmur. With equilibration of aortic and pulmonary artery pressure, systolic flow across the shunt diminishes and finally disappears, leaving the ductus silent (Eisenmenger's patent ductus arteriosus). Surgically produced aortopulmonary connections (Blalock, Waterston, and Pott's shunts), as well as the murmur of aortic pulmonary window, have identical qualities, and the effect of pulmonary hypertension on their length is analogous. It is important to distinguish these types of continuous murmurs from to-and-fro murmurs. The latter is a combination of the systolic ejection murmur and a semilunar diastolic murmur. The classic example of a to-and-fro murmur is the murmur of aortic stenosis and regurgitation. The continuous murmur builds to a crescendo around S_2, whereas the to-and-fro murmur has two components. The midsystolic ejection component decrescendos and may disappear as it approaches S_2, leaving a silent period before the onset of the regurgitant murmur. Truncus arteriosus is a rare congenital anomaly and probably produces a continuous murmur only if there is coexisting pulmonary artery stenosis (see Chap. 63). In the presence of severe RV outflow obstruction, bronchial collateral arteries can enlarge their normal precapillary anastomoses with pulmonary arteries, and the resulting aortic pulmonary fistula can produce a continuous murmur. This murmur can be heard in the same location as the patent ductus but radiates widely, especially over the posterior thorax. Large bronchial collateral arteries producing such continuous murmurs are more common with pulmonary atresia but also occur with tetralogy of Fallot. Bronchial artery-pulmonary artery collaterals sufficient to produce continuous murmurs are also found in far-advanced bronchiectasis and sequestration of the lung (see Chap. 63).

An anomalous left coronary artery arising from the pulmonary artery may cause a continuous murmur when the left-to-right shunt flow is large; it is usually best heard at the left sternal border. In this condition, the origin of the right coronary artery is from the aorta, and the left-to-right shunt is from the high-pressure right coronary arterial bed through large arterial collaterals to the left coronary system, which empties into the low-pressure pulmonary artery.

Sinus of Valsalva aneurysms may cause continuous murmurs when they rupture into the right side of the heart. In almost all cases, rupture occurs from the right and noncoronary sinuses into the right atrium or the right ventricle.[321] The murmur is heard maximally at the lower sternal border or xiphoid over the area corresponding to the fistulous tract. Diastolic accentuation of this murmur is an important sign to differentiate ruptured sinus from patent ductus arteriosus or arteriovenous fistula. Systolic suppression of the murmur is due to both mechanical narrowing of the fistulous tract during systole as well as the probable Venturi effect created by the rapid ejection of blood past the aortic origin of the fistula.

Coronary artery fistulas usually empty into the right atrium or ventricle and cause a continuous murmur that is best heard to either the left or the right of the lower sternal area. Since the majority of coronary flow occurs during diastole, the diastolic component of the murmur is louder. When the coronary artery fistula empties into a high-pressure right ventricle, only a diastolic murmur may be heard because the pressure gradient across the shunt is reduced during systole. Left-to-right shunting through an uncomplicated ASD produces no murmur audible on the chest wall because of the minimal pressure gradient and absence of turbulence. When mitral valve obstruction is present, as with Lutembacher's syndrome or mitral atresia, however, there can be a high-pressure gradient between the left and right atria across a small defect, and a continuous murmur may be present.[322] This murmur increases in intensity with inspiration and decreases with the Valsalva maneuver. Occasionally, a small ASD is produced following transseptal catheterization or balloon valvuloplasty for mitral stenosis, and a continuous murmur is produced due to high-velocity flow resulting from the large pressure gradient from the left to the right atrium.

Total anomalous pulmonary venous drainage into a systemic vein may produce a continuous venous hum usually heard in the pulmonary area or the left infraclavicular area. Frequently, a constriction at the junction of the anomalous venous conduit and the innominate vein or superior vena cava may cause augmentation of the murmur (see Chap. 63).

Arteriovenous fistulas between peripheral vessels produce a classic continuous murmur with systolic accentuation caused by shunting of a large volume of blood at rapid flow rates from a high-pressure artery into a low-pressure vein. These murmurs are best heard at the site of the fistula. Local compression of the veins may decrease the intensity of the murmur by raising venous pressure and reducing the arteriovenous

pressure gradient. Complete obliteration of the fistula will terminate the murmur, and if the shunt is of considerable magnitude, a baroreceptor-mediated reflex bradycardia may occur (Branham's sign). Likewise, a reflex tachycardia will occur on release of the obstruction. Pulmonary arteriovenous fistulas usually produce only a systolic murmur because the peripheral vascular resistance of the normal lung is very low, and the normally small diastolic pressure gradient from pulmonary artery to pulmonary vein is not significantly increased by the presence of the fistula.

Continuous Murmur Secondary to Localized Arterial Obstruction

Localized stenosis of systemic or pulmonary arteries may produce a continuous murmur or bruit if the obstruction is critical and adequate collateral flow is not available.[323] Most partially obstructed arteries have only systolic murmurs that are delayed relative to cardiac systole, depending on the transit time of pulsatile flow from the heart to the site of obstruction. This lack of diastolic gradient is explained by the fact that the collateral arteries around the obstruction deliver adequate flow such that the diastolic pressure on either side of the localized obstruction is essentially equal. Thus a localized, partial arterial obstruction characteristically produces only a systolic murmur or bruit. If adequate collateral flow is not present, however, a diastolic and a systolic pressure gradient can be produced, together with a continuous murmur with systolic accentuation. Depending on the degree of inadequacy of collaterals, the murmur is truly continuous when collateral circulation is essentially nonexistent, or it extends only partially through diastole when collateral flow is somewhat compromised. Such is the case in severe coarctation of the aorta, where, in addition to the systolic and/or continuous murmurs heard over the thorax and produced by rapid blood flow through the tortuous intercostal collaterals, a continuous murmur may be produced at the site of the coarctation. This latter murmur is best heard over the back midline between the scapulae.

Continuous murmurs also may arise from branch pulmonary stenosis or partial obstruction of a major pulmonary artery occluded by a massive pulmonary embolus. Other common locations of continuous murmurs secondary to localized arterial obstructions are listed in Table 10-13. Common to all these murmurs is critical narrowing of the vessel with inadequate collateral flow such that a continuous pressure gradient is produced throughout the cardiac cycle. Murmurs produced by obstruction of major coronary arteries are rarely loud enough to be transmitted to the chest wall. When audible, they produce only diastolic murmurs, even with inadequate collateral circulation.

* This text is modified from Chap. 11 by N. Banks Anderson, Jr., in the ninth edition of *The Heart.*

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

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Figure 10-61: Graphic representation of apical movements in health and disease. Heavy line indicates palpable features. P_2, pulmonary component of second heart sound; A, atrial wave, corresponding to a fourth heart sound (S_4) or atrial gallop; F, filling wave, corresponding to third heart sound (S_3) or ventricular gallop. (From Willis P IV. Inspection and palpation of the precordium. In: Hurst JW, ed. *The Heart*, 7th ed. New York: McGraw-Hill; 1990:164. Reproduced with permission from the publisher and author.)

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Figure 10-63: Base and apex phonocardiograms are recorded simultaneously with the mitral valve echocardiogram in a 62-year-old man who developed acute mitral regurgitation secondary to rupture of the chordae tendinae of a myxomatous valve. During diastole, multiple echoes arise from the flail posterior mitral leaflet (PML), and during early ventricular systole, effective mitral valve closure does not occur, resulting in an inaudible low-frequency vibration on the apex phonocardiogram. During systole, there is separation of the anterior (AML) and posterior mitral leaflets, resulting in severe mitral regurgitation. The murmur has a crescendo-decrescendo contour simulating the murmur of aortic stenosis ending prior to A_1. Wide physiologic splitting of S_1 is present. The prominent S_4 present on the apex phonocardiogram was associated with an apical presystolic impulse. (From Shaver JA. The physical examination in cardiac diagnosis. *Cardiol Consult* 1985; 6:3. Reproduced with permission from the publisher and author.)

Figure 10-64: Simultaneous phonocardiograms are recorded with the mitral valve echocardiograms in three patients: mitral stenosis (*left*), left atrial myxoma (*center*), and prolapse of the mitral valve (*right*). In each condition, a loud M_1 is present and coincident with the closing point of the mitral valve echocardiogram. Common to each condition is wide separation of the mitral leaflets at the onset of LV systole, with high-velocity closure occurring over a large excursion. In the left panel, a mobile stenotic valve is demonstrated, and a loud opening snap is coincident with the E point. In the center panel, an early diastolic tumor plop (TP) is coincident with the maximal excursion of the tumor during its rapid descent into the ventricle. Note the presystolic crescendo murmur (PSM) occurring during the rapid closure of the mitral valve in both mitral stenosis and left atrial myxoma. In the right panel, a pansystolic murmur (PSM) with late systolic accentuation is secondary to the prolapse of the mitral valve with late systolic hammocking. (From Shaver JA. Current uses of phonocardiography in clinical practice. In: Rapaport E, ed. *Cardiology Update: Reviews for Physicians. New York*: Elsevier; 1981:370. Reproduced in part (center panel) with permission from the publisher and author. Copyright 1981 by Elsevier Science Publishing Co, Inc.)

Figure 10-65: External sound, equisensitive LV and left atrial pressures (catheter-tipped micromanometer), LV *dP/dt*, and left atrial sound are recorded simultaneously with the mitral valve echocardiogram in a patient with hemodynamically significant mitral stenosis. A significant presystolic gradient is present due to atrial contraction, and the onset of the rapid closure of the mitral valve (*B*) is delayed until the LV pressure exceeds left atrial pressure. This occurs 40 ms after the beginning of the LV pressure rise at a time when LV *dP/dt* is much higher than normal. Following left atrial-left ventricular pressure crossover, there is rapid ventriculogenic closure of the mitral valve (*BC*), resulting in a very loud M_1 coincident with the *C* point of the mitral valve echocardiogram. Its separation from A_2 is determined by both the level of the left atrial pressure and the rate of LV pressure decline. (From Shaver JA, et al. Normal and abnormal heart sounds in cardiac diagnosis: I. Systolic sounds. *Curr Probl Cardiol* 1985; 10:10-53. Reproduced with permission from the publisher and the authors.)

Figure 10-66: Base and apex phonocardiograms are recorded simultaneously with the aortic valve echocardiogram in a young man with valvular aortic stenosis. A prominent aortic valvular ejection sound (AVES) is recorded at the apex and is coincident with the maximal excursion of the aortic valve in early systole. It is followed by a crescendo-decrescendo systolic ejection murmur (SEM) that ends well before a loud A_2.

Figure 10-67: Simultaneously recorded base and apex phonocardiograms and mitral valve echocardiogram (MVE) demonstrating the frequent association of a late systolic murmur with a prominent late systolic click. Although the murmur is well transmitted to the base, the click transmits poorly. In the first two complexes, an additional softer click precedes the click murmur complex. The last complex shows only a single click, demonstrating the variability of the auscultatory findings even at rest. The large click occurs at maximal prolapse, and the smaller click occurs near the onset of echocardiographic prolapse.

Figure 10-68: A midsystolic nonejection sound (*C*) occurs in mitral valve prolapse and is followed by a late systolic murmur that crescendos to S_1. With assumption of the upright posture, venous return decreases, the heart becomes smaller, the *C* moves closer to S_1, and the mitral regurgitant murmur has an earlier onset. With prompt squatting, both venous return and afterload increase, the heart becomes larger, the *C* moves toward S_2, and the duration of the murmur shortens. (From Shaver JA. *Examination of the Heart*, Part IV: Auscultation. Dallas: American Heart Association; 1990:13. Reproduced with permission from the publisher and the authors.)

Figure 10-69: The cardiac cycle recorded by high-fidelity catheter-tipped micromanometers. The aortic (A_2) and pulmonic (P_2) closure sounds are coincident with the incisurae of their respective arterial traces. Although the LV and RV mechanical systoles are nearly equal in duration, the RV systolic ejection period terminates after LV ejection because of an increased right-sided "hangout" interval. (From Shaver JA. The second heart sound: Newer concepts: I. Normal and wide physiological splitting. *Mod Concepts Cardiovasc Dis* 1997; 46:7. Reproduced with permission from the American Heart Association and the authors.)

Figure 10-70: (*Left*) The base and apex phonocardiograms are recorded simultaneously with the aortic valve echocardiogram. The first high-frequency component of A_2 is coincident with the completion of closure of the aortic valve. (*Right*) Base and apex phonocardiograms are recorded with the pulmonary valve echocardiogram. The first high-frequency component of P_1 is coincident with the completion of closure of the pulmonic valve. (From Shaver JA, et al. Normal and abnormal heart sounds in cardiac diagnosis: I. Systolic sounds. *Curr Probl Cardiol* 1985: 10:43. Reproduced with permission from the publisher and the authors.)

Figure 10-71: (*Top*) Normal physiologic splitting. During expiration, A_2 and P_2 are separated by less than 30 ms and are appreciated as a single sound. During inspiration, the splitting interval widens, and A_2 and P_2 are clearly separated into two distinctly audible sounds. (*Bottom*) Audible expiratory splitting. In contrast to normal physiologic splitting, two distinct sounds are easily heard during expiration. Wide physiologic splitting is due to delay in P_2. Reversed splitting is due to delay in A_2, resulting in paradoxical movement; i.e., with inspiration, P_2 moves toward A_2, and the splitting interval narrows. Narrow physiologic splitting is seen in pulmonary hypertension, and both A_2 and P_2 are heard during expiration at a narrow splitting interval due to an increased intensity and high-frequency composition of P_2. (From Shaver JA. *Examination of the Heart*, Part IV: Auscultation. Dallas: American Heart Association; 1990:17. Reproduced with permission from the publisher and the authors.)

Figure 10-72: (*Left*) Wide physiologic splitting of S_2 is seen in a patient with complete right bundle branch block. Audible expiratory splitting that widens normally with inspiration is present. Note also the wide splitting of the first heart sound into its mitral (M_1) and tricuspid (T_1) components, as recorded at the apex. (*Right*) The base phonocardiogram is recorded simultaneously with high-fidelity catheters in the right ventricle and pulmonary artery during cardiac catheterization. There is marked prolongation of the Q to the onset of the RV pressure rise of 96 ms, resulting in wide physiologic splitting of S_2. The delayed P_2 is secondary to delayed activation of the right ventricle. (From Shaver JA. Current uses of phonocardiography in clinical practice. In: Rapaport E, ed. *Cardiology Update: Reviews for Physicians*. New York: Elsevier; 1981:337. Reproduced originally in part (left panel) with permission from the publisher and author, and from Shaver JA, et al. Normal and abnormal heart sounds in cardiac diagnosis: I. Systolic sounds. *Curr Probl Cardiol* 1985; 10:48. Reproduced in total with permission from the publisher and authors.)

Figure 10-73: (*Upper left*) Sound and pressure correlates of S_2 in a 45-year-old woman with a normotensive atrial septal defect (shunt 2:1). Wide, fixed splitting of S_2 is demonstrated; P_2 and A_2 are coincident with their respective incisurae, and the duration of the "hangout" interval is nearly equal to the A_2-P_2 interval. (*Upper right*) Simultaneous RV and LV pressures clearly show that the duration of RV and LV systole is equal. (*Lower left*) Sound and pressure correlates of a patient with idiopathic dilatation of the pulmonary artery. P_2 is coincident with the incisura of the pulmonary artery and separated from the RV pressure tracing by a "hangout" interval of 90 ms (almost identical to the splitting interval). (*Lower right*) Similar sound and pressure correlates in a patient with mild valvular pulmonic stenosis and aneurysmal dilatation of the pulmonary artery. Most of the delay in P_2 is due to a wide "hangout" interval of 56 ms. In each patient all pressures are recorded by catheter-tipped micromanometers. (From Shaver JA, et al. Second heart sound: The role of altered greater and lesser circulation. In: Leon DF, Shaver JA, eds. *Physiologic Principles of Heart Sounds and Murmurs*. Monograph 46. New York: American Heart Association;1975:63. Reproduced originally in part (top panel) with permission from the publisher and the authors, and from Shaver JA. The second heart sound: Hemodynamic determinants. *Acta Cardiol* 1985; 40:12. Reproduced in total with permission from the publisher and authors.)

Figure 10-74: *A.* The S_4 occurs in presystole and is frequently called an atrial, or presystolic, gallop. *B.* The S_3 occurs during the rapid phase of ventricular filling. It is a normal finding and is commonly heard in children and young adults, disappearing with increasing age. When it is heard in a patient with cardiac disease, it is called a pathologic S_3, or ventricular gallop, and usually indicates ventricular dysfunction or AV valvular incompetence. *C.* In constrictive pericarditis, a sound in early diastole, the pericardial knock (K), is heard earlier and is louder and higher-pitched than the usual pathologic S_3. *D.* A quadruple rhythm results if both S_4 and S_3 are present. *E.* At faster heart rates, the S_3 and S_4 occur in rapid succession and may give the illusion of a middiastolic rumble. *F.* When the heart rate is sufficiently fast, the two rapid phases of ventricular filling reinforce each other, and a loud summation gallop (SG) may appear; this sound may be louder than either the S_3 or S_4 alone. (From Shaver JA. *Examination of the Heart*, Part IV: Auscultation. Dallas: American Heart Association; 1990:27. Reproduced with permission from the publisher and the authors.)

Figure 10-75: (*Top*) A physiologic S_3 (normal variant) recorded in a 24-year-old woman without evidence of cardiovascular disease. The onset of the S_3 occurs during the rapid filling wave (RFW) of the ACG between the *O* and *F* points. The remainder of the cardiovascular examination was entirely within normal limits. (*Bottom*) A very prominent S_3 gallop is recorded in a patient with severe congestive cardiomyopathy (COCM). On physical examination, there was a small-volume carotid pulse and marked engorgement of the neck veins with elevated venous pressure. The ACG shows a very prominent presystolic pulsation (a), and an extremely rapid filling wave is present. The onset of the S_3 occurs during the RFW of the ACG. The first heart sound is soft. (From Shaver JA. Early diastolic events associated with the physiologic and pathologic S_3. *J Cardiogr*. 1984; 14(suppl 5):30. Reproduced with permission from the publisher and the authors.)

Figure 10-76: Atrial diastolic (ADG) and ventricular diastolic gallops (VDG) are recorded in an adult with severe calcific aortic stenosis. The ADG is associated with a prominent presystolic apical impulse (a), and the VDG occurs during the rapid filling wave of the ACG. The carotid pulse has a very slow rate of rise and a markedly prolonged LV ejection time. The classic diamond-shaped systolic ejection murmur (SM) is present at the base and apex. Note the higher-frequency composition of the SM at the apex but preservation of the crescendo-decrescendo pattern. (From Shaver JA. Current uses of phonocardiography in clinical practice. In: Rapaport E, ed. *Cardiology Update: Reviews for Physicians*. New York: Elsevier; 1981:356. Reproduced with permission from the publisher and author. Copyright 1981 by Elsevier Publishing Co., Inc.)

Figure 10-77: Midsystolic ejection murmurs are caused by forward flow across the LV or RV outflow tract, whereas pansystolic regurgitant murmurs are caused by retrograde flow from a high-pressure cardiac chamber to a low-pressure one. (*Left*) Diagrammatic representation of the midsystolic ejection murmur and the pansystolic regurgitant murmur, as related to LV, aortic, and left atrial (LA) pressures. The systolic ejection murmur occurs during the period of LV ejection; the onset of the murmur is separated from S_1 by the period of isovolumic contraction and the crescendo-decrescendo murmur terminates before A_2. The pansystolic regurgitant murmur begins with, or may replace, S_1, and the murmur continues up to and through A_2 as LV pressure exceeds left atrial pressure during the period of isovolumic relaxation. The murmur has a plateau configuration and varies little with respiration. (*Right*) Flow diagram. (Left panel reproduced from Reddy PS, Shaver JA, Leonard JJ. Cardiac systolic murmurs: Pathophysiology and differential diagnosis. *Prog Cardiovasc Dis* 1971; 14:19. Entire figure reproduced with permission from Shaver JA. Systolic murmurs. *Heart Dis Stroke* 1993; 2:10.)

Figure 10-78: The simultaneous time-intensity course of the murmur "envelope," aortic flow velocity, and LV and central aortic pressure. During normal LV ejection (*left*), peak flow velocity is early, with two-thirds of the ventricular volume ejected during the first half of systole. The murmur threshold may be exceeded during the early peak flow and the corresponding murmur envelope inscribed. (*Center*) Exaggeration of the normal pattern of LV ejection with a high stroke volume, as in high-output states. With critical aortic stenosis (*right*), rapid early ejection is no longer possible; the flow velocity is increased, and the contour becomes rounded and prolonged, producing the typical diamond-shaped murmur of aortic stenosis. (Modified from Reddy PS, et al. Cardiac systolic murmurs: Pathophysiology and differential diagnosis. *Prog Cardiovasc Dis* 1971; 14:4. Reproduced with permission from the publisher and the authors.)

Figure 10-79: The differential diagnosis of the innocent murmur versus the pathologic systolic murmur is made by the "company the murmur keeps." The innocent murmur must be found in the setting of an otherwise normal cardiovascular examination. C, midsystolic nonejection sound; AVES, aortic valvular ejection sound; PVES, pulmonic valvular ejection sound; AR, aortic regurgitation. (From Shaver JA, et al. *Examination of the Heart*, Part IV. Auscultation. Dallas: American Heart Association; 1990:40. Reproduced with permission from the publisher and the authors.)

Figure 10-80: Effect of the long diastolic filling period following a premature ventricular contraction (PVC) on the intensity of a systolic ejection murmur (SEM). There is a marked increase in the intensity of the aortic stenosis murmur recorded at the base and at the apex. Despite the higher-frequency content of the apical murmur, this response clearly identifies this murmur as ejection in nature. (From Paley H. Left ventricular outflow tract obstruction: Heart sounds and murmurs. In: Leon DF, Shaver JA, eds. *Physiologic Principles of Heart Sounds and Murmurs*. Monograph 46. Dallas: American Heart Association; 1975:112. Reproduced with permission from the publisher and the author.)

Figure 10-81: In valvular pulmonic stenosis with intact ventricular septum, RV systolic ejection becomes progressively longer with increasing obstruction to flow. As a result, the murmur becomes louder and longer, enveloping the aortic closure sound. At the same time, pulmonic closure occurs later; splitting becomes wider but is more difficult to appreciate because the aortic closure sound is lost in the murmur; and the pulmonic closure sound becomes progressively softer due to the low pulmonary artery pressure. With increasing severity of pulmonic stenosis, the pulmonary ejection sound may fuse with S_1. In severe obstruction with concentric hypertrophy and decreased RV compliance, an S_4 appears. In tetralogy of Fallot, with increasing obstruction at the infundibular area, more and more RV blood is shunted across a silent VSD with less flow across the obstructed RV outflow tract. With increasing obstruction, the murmur becomes shorter, earlier, and fainter. The pulmonic closure sound is absent in severe tetralogy of Fallot. The dilated aorta receives almost all the cardiac output from both ventricular chambers, and there is an aortic ejection sound (Aej). (From Leonard J, et al: *Examination of the Heart*, Part 4: Auscultation. Dallas: American Heart Association; 1974:45. Reproduced with permission from the publisher and authors.)

Figure 10-82: (*Left*) The phonocardiogram of a patient with severe valvular pulmonic stenosis as recorded at the second left intercostal space (2LICS) and the apex. The long ejection murmur (ESM) has late systolic peaking and spills through A_2. There is a marked delay in P_2, which is very small in amplitude. (*Right*) At cardiac catheterization, the markedly delayed P_2 is shown to be secondary to a very large systolic pressure gradient, and its decreased intensity is due to the low pulmonary artery pressure at the time of valve closure. The late peaking of the ejection murmur correlates with the maximal pressure gradient between the right ventricle and the pulmonary artery. (From Curtiss EI, et al. First and second heart sound. In: Horwitz LD, ed. *Signs and Symptoms in Cardiology*. Philadelphia: Lippincott; 1985:200. Reproduced with permission from the publisher and authors.)

Figure 10-83: Simultaneous base and apex phonocardiograms are recorded with the carotid pulse and ACG in the left and center panels, respectively, in a 54-year-old man with hypertrophic cardiomyopathy. The carotid pulse rises rapidly and has a late systolic plateau and a prolonged ejection period. Prominent S_4 and S_1 are demonstrated and are associated with the *a* wave and the rapid filling wave (RFW), respectively, of the ACG. Note the late systolic bulge (LSB) on the ACG. S_2 is single. A loud, grade 5 systolic ejection murmur is present and is of greatest intensity at the apex. In the right panel, the apical systolic murmur is recorded together with the M-mode echocardiogram. Simultaneous high-fidelity LV and central aortic pressures are recorded by catheter-tipped micromanometers. Marked thickening of the interventricular septum and SAM of the mitral valve are present on the echocardiogram. A large systolic pressure gradient is demonstrated beginning shortly after the onset of the SAM. (From Shaver JA, et al. Phonoechocardiography and intracardiac phonocardiography in hypertrophic cardiomyopathy. *Postgrad Med J*. 1986; 62:538. Reproduced with permission from the publisher and the authors.)

Figure 10-84: Diastolic filling murmurs or rumbles are caused by forward flow across the AV valves, whereas diastolic regurgitant murmurs are caused by retrograde flow across incompetent semilunar valves. (*Left*) Diagrammatic representation of the diastolic filling murmur and the diastolic regurgitant murmur as related to LV, aortic, and left atrial (LA) pressures. The diastolic filling murmur occurs during the diastolic filling period and is separated from S_2 by the isovolumic relaxation period. The rumbling murmur is most prominent during rapid, early ventricular filling and presystole, terminating with S_1. The diastolic regurgitant murmur begins immediately after S_2 and continues in a decrescendo fashion up to S_1, closely paralleling the aortic LV diastolic pressure gradient. (*Right*) Flow diagram. (From Shaver JA. Diastolic murmurs. *Heart Dis Stroke* 1993; 1:98-103. Reproduced with permission from the American Heart Association.)

Figure 10-85: Diagram contrasting the auscultatory findings in chronic and acute aortic regurgitation. In chronic aortic regurgitation, a prominent systolic ejection murmur (SEM), resulting from the large forward stroke volume, is heard at the base and apex and ends well before S_2. The aortic diastolic regurgitant murmur begins with S_2 and continues in a decrescendo fashion, terminating before S_1. At the apex, the early diastolic component of the Austin Flint (AF) murmur is introduced by a prominent S_3. A presystolic component of the AF is also heard. In acute aortic regurgitation, there is a significant decrease in the intensity of the SEM compared with chronic aortic regurgitation because of the decreased forward stroke volume. S_1 is markedly decreased in intensity because of preclosure of the mitral valve, and at the apex the presystolic component of the AF murmur is absent. The early diastolic murmur at the base ends well before S_1 because of the equilibration of the LV and aortic end-diastolic pressure. Significant tachycardia is usually present. (From Shaver JA. Diastolic murmurs. *Heart Dis Stroke* 1993; 1:98-103. Reproduced with permission from the American Heart Association.)

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Chapter 10: THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 11:

THE RESTING ELECTROCARDIOGRAM

Authors: Agustin Castellanos, Alberto Interian, Jr., Robert J. Myerburg

What is commonly called an *electrocardiogram* (ECG) is the graph obtained when the electrical potentials of an electrical field originating in the heart are recorded at the body surface.[1-4] Although the ECG gives very useful clinical information, it only provides an approximation of the voltage produced by the source. The ECG has not been able to achieve interesting new insights into its own *basic* theoretic limitations, which some have considered as the solutions of the "forward" problem and the "inverse" problem of electrocardiography.[1,2] Whereas the former seeks the description of a specific electrocardiographic pattern in response to a specific local or regional intracardiac change in electrical activity, the latter seeks to predict the behavior of the cardiac generator from potentials recorded at the body surface.[1,2] Nevertheless, recent experimental studies have provided new information capable of expanding the clinical usefulness of the ECG, as will be discussed throughout this chapter. The ECG has many uses: It may serve as an independent marker of myocardial disease; it may reflect anatomic, hemodynamic, molecular, ionic, and drug-induced abnormalities of the heart; and it may provide information that is essential for the proper diagnosis and therapy of many cardiac[1] problems[4] (see also Chap. 24). In fact, it is the most commonly used laboratory procedure for the diagnosis of heart disease. Underreading or misreading due to insufficient knowledge of pathologic conditions, overreading due to an inability to recognize technical errors, and most important, failure to correlate ECG findings with the clinical findings may result in iatrogenic heart disease. Every physician interpreting ECGs as well as those learning electrocardiographic interpretation should read the *Guidelines for Electrocardiography of the American College of Cardiology, American Heart Association Task Force*.[4]

VENTRICULAR DEPOLARIZATION AND REPOLARIZATION

Fluxes of ions across the cell membranes cause the differences in voltage between resting and activated myocardial cells. To understand the electrical forces produced by the heart as a whole at the body surface, it has been conventional to first discuss the electrical properties of a hypothetical muscle strip from the free wall of the left ventricle extending from endocardium to epicardium.[5-7] In the resting or polarized state, the charges are at rest. A unipolar electrode facing the epicardial side of the strip, such as V_6, registers an isoelectric line.[5-13] If activation of this relatively large muscle strip starts in the endocardial side, it initiates the process called *depolarization*.[5-13] The *sequence* of this process is thus from endocardium to epicardium. Depolarization has been described as a moving wave *with the positive charges in front of the negative charges*. The previously mentioned lead V_6 overlying the epicardium of the left ventricle will record a positivity because it consistently faces positive charges throughout the entire depolarization sequence.[5-13] On the other hand, the *sequence* of ventricular repolarization is from epicardium to endocardium.[5-13] The *negative charges*, however, travel *in front* because repolarization tends to reestablish the resting, polarized state of the previously depolarized cells. As a consequence of the latter, V_6 will record a positive deflection (T wave) because it constantly faces positive charges throughout the entire repolarization sequence. The earlier epicardial end of repolarization has been attributed to the shorter duration of repolarization that epicardial cells have in comparison with

endocardial cells. Thus repolarization finishes at the epicardium while it still has not been completed at the endocardium. Hence the *sequence* of repolarization is, as noted previously, from epicardium to endocardium. This simplistic view is of didactic value only because it fails to take into consideration the role played by the M cells described by Antzelevitch et al.[14] since the beginning of this decade. According to these authors, M cells play a determining role in the inscription of the T wave **because** currents flowing down voltage gradients on either side of the usual (but not necessarily) mid-myocardial cells determine both the height and width of the T wave, as well as the degree to which the ascending or descending limbs of the T wave are interrupted.

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Chapter 11: THE RESTING ELECTROCARDIOGRAM

ELECTROCARDIOGRAPHIC LEADS

To record an ECG, an electric circuit between the heart and the electrocardiograph must be completed.[11] For this purpose, electrodes are placed on different parts of the body surface and are connected to the instrument by means of cables.[11] Thus the whole system consists of an instrument, electrodes, cables, and leads.

Bipolar Standard Leads

An ECG lead can be defined as a pair of terminals with designated polarity, each of which is connected either directly or via a passive-active network to recording electrodes. In 1913, Einthoven et al.[3] developed a method of studying the electrical activity of the heart by representing it graphically in a *two-dimensional* geometric figure, namely, an equilateral triangle. There are several simplifying assumptions on which Einthoven's hypothesis is founded[3-13]: (1) The body is a homogeneous volume conductor. Although the conductivity of the various tissues is not the same, the differences are not great enough to invalidate that the body can be considered as a homogeneous volume conductor. (2) The sum of all the electric forces, or the mean of all the forces generated during the cardiac cycle, can be considered as originating in a dipole located in the electrical center of the heart. (3) Electrodes placed on the right arm (RA), left arm (LA), and left leg (LL) are used to pick up the potential variations on these extremities. Standard (bipolar) leads (I, II, and III) are obtained by recording, respectively, the potential differences between LA and RA, LL and RA, and LL and LA. These leads record potential variations in a single frontal plane only. (4) Attachment between these limb electrodes, on the forearms and limbs, corresponds to a position in the root of the corresponding limb. For example, an electrode in the right forearm records the electrical activity that reaches the right shoulder. It should be pointed out that when the electrodes are placed proximally to the roots of the extremities, they lose their relatively "far" distance from the heart. Hence Einthoven's equilateral theory does not hold. The latter is of importance to understand why leads placed proximally to the roots of the extremities, such as those used for exercise testing and coronary care unit and Holter monitoring, by being only "equivalent" to the corresponding bipolar leads, are in some cases markedly different from the "true" standard bipolar leads.

Wilson Central Terminal

The sum of the potentials from the right arm (RA), left arm (LA), and left leg (LL) is equal to zero throughout the cardiac cycle with respect to any point at the body surface.[3,5,6,13] Lead wires attached to electrodes on each limb are connected together, through 5000-Ω resistors, at a point. When this common point-*Wilson's central terminal*-is attached to the negative pole of the ECG machine and an "exploring" electrode is connected to the positive pole, the potential variations recorded will be those of the latter only. A lead taken by this method is called a *unipolar lead.* Actually, the central terminal is not zero because the RA, LA, and LL are not equidistant from each other and from the heart, the body tissues vary in resistance, and the heart and extremities do not lie in exactly the same plane in the body. The potential of the central terminal has been said to average around 0.3 mV.[9]

Unipolar Extremity Leads

At present, unipolar extremity leads are obtained by disconnecting the input to the central terminal of Wilson from the extremity being explored. This results in a one-and-a-half increase in their voltage. These *augmented* (a) extremity leads are the ones usually used for clinical electrocardiography and are labeled aV_R, aV_L, and aV_F.[5,9,13]

Unipolar Precordial Leads

The unipolar precordial ECG is obtained by placing the exploring electrode (connected to the positive pole of the ECG machine) on the classic six locations of the anterior and left portions of the chest.[5,6,13] The central terminal is used as the indifferent electrode. Precordial (V) leads yield a positive deflection when facing positive charges and negative deflections when facing negative charges.[5,6,12,13,15-17] They do this according to what Wilson called the *solid-angle concept*.[5,13] A solid angle is merely an imaginary cone extending from the site in the chest throughout the heart. The precordial electrode is at its apex, and its base is at the opposite epicardial surface.[13] This concept is most important to understand precordial lead morphologies. According to Wilson's scalar concept of electrocardiography, this occurs because the solid angle subtended by the corresponding lead records the electrical activity from the regions of the heart over which the lead is placed as well as from distant regions.[5,13] Thus, if V_2 is placed over (thereby facing) the right ventricle, part of the initial positive ventricular deflection reflects right ventricular activation, with the corresponding electrical forces moving toward the electrode.[13] Most portions of the terminal S wave represent activation of muscle other than the right ventricle (septum and free left ventricular wall), reflecting electrical forces moving away from the electrode.[13] Acceptance that the amount of muscle activity recorded by various unipolar leads is not the same implies different "real" duration of depolarization and repolarization, irrespective of that supposedly resulting from the projections of a vector on an idealized horizontal lead axis (see sections on QT dispersion and vectorcardiography). For practical purposes, the peak of the r (or R) wave in precordial leads gives a rough estimate of the moment of arrival of excitation (*intrinsicoid* deflection) at the muscle underneath the electrode.[13] This encompasses a considerable number of muscle fibers (given by the solid-angle concept), however-in fact, a greater number than if the electrode is placed directly on the epicardial surface.[13] In the latter case, the moment of arrival of excitation at the electrode affects a lesser number of fibers and is thus given by the *intrinsic* deflection.[13]

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Chapter 11: THE RESTING ELECTROCARDIOGRAM

NORMAL ACTIVATION OF THE HEART: VENTRICULAR DEPOLARIZATION

After emerging from the sinus node, the cardiac impulse propagates throughout the atria in its journey toward the atrioventricular (AV) node. The *normal* P wave (resulting from activation of the myocardium of both atria) is a consequence of, but does not directly represent, sinus node activity. During sinus rhythm, the right atrium is activated before the left atrium.[6] This explains why high-fidelity recordings of the P waves of some normal persons show a small notch at the top. The latter simply reflects the normal asynchrony existing between the atria.[6] Because of the anatomic position of the sinus node, the sequence of atrial depolarization occurs in an inferior, leftward, and somewhat posterior direction. The normal P waves are always positive in leads I, II, aV_F, and V_3 to V_6 and negative in lead aV_R. According to the anatomic position of the heart, the P wave may be diphasic in V_1 and aV_L or negative in the latter lead. Atrial repolarization, also called T_a, is directly opposite in polarity to the P wave.[6,11] It is usually not seen because it coincides with the PR segment (not to be confused with the PR interval) and QRS complex. The PR interval (used to estimate AV conduction time) includes conduction through the "true" AV structures (AV node, His bundle, bundle branches, and main divisions of the left bundle branch), as well as through those parts of the atria located between sinus and AV nodes.[8] The onset of ventricular depolarization (given by the beginning of the normal q wave) reflects activation of the left side of the interventricular septum. This has been attributed to the fact that the left bundle system is shorter than the right bundle branch.[8,15] In addition, the large fanlike distribution of the ramifications of the fascicles of the left bundle branch on the left septal surface produces activation of a greater number of ordinary muscle cells per unit of time.[6,8,15] For this reason, the normal initial depolarization is oriented from left to right, therefore explaining the small q wave in lead V_6 and the small r wave in lead V_1. After the cardiac impulse descending through the right bundle branch reaches the right septal surface, the interventricular septum is activated in both directions. Septal activation is thereafter encompassed within or neutralized by free-wall activation. The most distal ramifications of both bundle branches (Purkinje fibers) form networks within the subendocardial regions of both ventricular walls. The latter are activated as soon as the multiple ramifications emerge from the Purkinje fibers.[6,15] The greater mass of the left ventricular (LV) free wall explains why LV free-wall events overpower those of the interventricular septum and right ventricular free wall.

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Chapter 11: THE RESTING ELECTROCARDIOGRAM

ELECTRICAL AXIS

The *electrical axis* (EA) may be defined as a vector originating in the center of Einthoven's equilateral triangle.[3,13] A *vector* is a mathematical value expressed as an arrow that has magnitude, sense, and direction. On the other hand, *scalar* values only have magnitude. When applied to the EA of the QRS complexes, the vector that represents it also gives the direction of the activation process as projected in the plane of the limb leads. Its length represents the manifest potential of the dipole in the center of the triangle. These general considerations apply either to the instantaneous EA (the vector indicating the direction of the impulse at the instant at which it is determined) or to the mean EA (which is the resultant of all instantaneous electrical axes). Although the term *EA* can be used in reference to any of the major components of the ECG (P, T, or QRS), it is generally applied to the QRS. There are many methods for determining the mean EA. The one recommended by electrocardiographers of the classical school consists of calculating the net areas enclosed by the QRS complex in leads I, II, and III.[3,6,7,12,13] The net area is the absolute sum of the positive and negative areas of the QRS complex in the corresponding lead. One of the drawbacks of this method is that the absolute values of the net area cannot be determined *accurately* by inspection. Since the absolute magnitude of the EA is not of fundamental clinical importance, it has been recommended that arbitrary units be used. When this is done, the results can be counterchecked by using Einthoven's law. For example, if in a given case lead I is +4 units, lead II is +2 units, and lead III is -2 units, the calculation is accurate because the sum of leads I and III (+4 plus -2) must always equal lead II (+2). After having determined the net area, the results are plotted on the sides of the triangle, and perpendiculars are dropped from two or all three leads. The perpendiculars will meet at a point away from the center of the triangle. A line drawn from the latter to the former defines the mean EA. A simpler, though less precise, method of calculating the quadrant (or parts of a quadrant) in which the EA is located consists of using the maximal QRS deflection in leads I and aV_F and, when necessary, lead II. This method is inexact from the mathematical viewpoint but has the value of simplicity.[15,16]

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VENTRICULAR GRADIENT

The relationship between the EA of the QRS complex and the T wave was referred to by Wilson as the *ventricular gradient*.[17] In contrast to what occurs in an epicardial-to-endocardial muscle strip (as mentioned previously), in the isolated muscle strip, the *sequence* of ventricular depolarization occurs in the same direction as that of repolarization.[12] Although the QRS and T deflections have opposite polarity, the algebraic sum of QRS and T *areas* is zero. In the human heart, however, not only is the sequence different, but the pathways of ventricular depolarization and repolarization are not exactly the same.[12] Thus the algebraic sum of QRS and T *areas* is no longer zero. Therefore, a *gradient* is said to exist. The ventricular gradient can be calculated by determining the electrical axis of the QRS and T (using *areas*) and then obtaining the resultant by the parallelogram method. Wilson considered that the ventricular gradient could be of help in differentiating between T-wave inversion of various causes (primary changes) and the obligatory secondary T-wave changes resulting from abnormalities in depolarization, such as bundle branch block, ventricular hypertrophy, ventricular pacing, and preexcitation syndromes.[12,13,17] In practice, calculation of the ventricular gradient is difficult and time consuming because it has to be determined by areas and not maximal amplitude.

Apparent Challenges to the Concept of the Ventricular Gradient

Rosenbaum et al.[18] studied the prolonged depolarization occurring during long periods of ventricular stimulation and found two types of altered ventricular repolarization. One, corresponding to Wilson's classic theory, was transient and proportional in magnitude to the QRS complex but of opposite polarity. The other, concealed by (and during) the former, required a longer time (even days) to reach maximal effect as well as to disappear, becoming apparent *only when* normal activation recurred (Fig. 11-1). The latter type was attributed to modulated electrotonic interactions occurring during cardiac activation in such a way that repolarization was accelerated at ventricular sites where depolarization begins and delayed in areas where depolarization terminates. T-wave changes appearing after prolonged depolarization was no longer present showed accumulation and (fading) *long-term* memory for variable time (see "Secondary ST-T-Wave Changes," below).[18] Recently, Goyal et al.[19] reported the occurrence of *short-term* memory after periods of altered ventricular repolarization as short as 1 min in duration. In addition, according to Surawicz,[20] the term *memory* also has been applied to gradual adjustments of action potential duration (corresponding to QT intervals) after abrupt changes in cycle lengths (events influenced by past history) without necessarily requiring abnormal ventricular repolarization (Fig. 11-2). The cellular mechanism responsible for any form of cardiac memory is beyond the scope of this chapter.

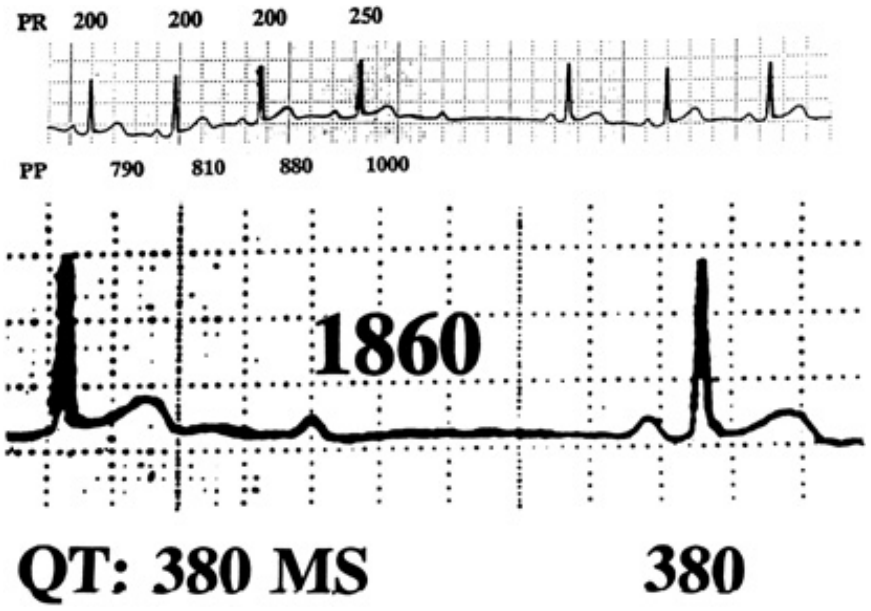

Figure 11-2: Vagal-induced AV nodal block in a young person without structural heart disease. All values are expressed in milliseconds. The uncorrected QT interval does not increase at the end of an 1860-ms (RR) pause. This can be due to the form of short-term cardiac memory whereby the QT interval "remembers" its prepause values because of the slow adjustment to abrupt changes in cycle length in otherwise *normal* subjects.

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Chapter 11: THE RESTING ELECTROCARDIOGRAM

ABNORMAL ST-SEGMENT CHANGES

In orthodox ECG language, *injury* implies *abnormal* ST-segment changes, *necrosis* implies *abnormal* Q waves, and *ischemia* implies *symmetric* T-wave inversion (or elevation).[5-7,9-13,16] Following conventional ECG theory, several authors consider that ECG "injury" occurs because the affected cells are unable to maintain their normal polarization during diastole.[5-7,12,16,21] Various hypotheses have been postulated to explain how this diastolic hypopolarization or generalized diastolic depolarization is manifested as abnormal ST-segment shifts in the surface ECG[21-24] (Fig. 11-3). One hypothesis is based on the existence of a diastolic current of "injury." During the control (diastolic) period, both membrane resting potential and surface ECG baseline are at their normal level. At the onset of injury, the resting intracellular potential decreases (e.g., from 90 to 70 mV), and the ECG baseline shifts below its preinjury level. Because the injured cells leak negative ions, their *exterior* becomes relatively negative (or less positive) than that of the normal cells. Thus a "current of injury" flows between the negative ("injured") zone and the positive ("normal") region.[10] This produces a negative displacement of the surface ECG *baseline* in the leads facing the injured region. In the surface ECG, depolarization (by virtue of the electrical negativization of the nonaffected area) practically reduces the potential difference between noninjured and injured regions. Therefore, the ST segment remains at the preinjury level, which is relatively *elevated* in reference to the injury baseline.[21-24] Consequently, the ST segment appears to be abnormally displaced above the latter. Note that the apparent presence of a systolic current of injury actually reflects disappearance of the diastolic current of injury. Finally, after the end of repolarization, the current of injury between injured and noninjured regions is reestablished, and the ECG baseline is again depressed (as it was immediately before depolarization). Since the precise moment at which injury starts is not recorded in the usual alternating-current (ac) electrocardiographic recordings, the baseline that is almost invariably recorded is the postinjury baseline.[10] It also has been shown that the abnormal ST-segment elevation in leads facing the affected zone does not merely represent the (passive) return of the baseline to its preinjury level but reflects a true, active, positive displacement.[10,21-24] Thus, when depolarization of both normal and injured regions has occurred, the surface of the normal cells will (on account of their greater initial polarization) be able to accumulate more negative ions. Hence the normal regions become more negative than the injured regions, which are relatively more positive. In consequence, the ST segment becomes actively elevated above and beyond the preinjury baseline because of the relative potential difference existing at the end of depolarization. Most likely, injury reflects both disappearance of diastolic baseline shifts and active ST-segment elevation.[10,24]

According to the current-of-injury theory, this process results in ST-segment elevation when the injured muscle is located between normal muscle and the corresponding unipolar electrode. On the other hand, ST-segment depression occurs when normal muscle is located between the injured tissue and the corresponding electrode[10,12] (see Fig. 11-3). The mechanism of abnormal ST-segment elevation in anatomically defined ventricular aneurysms has not been fully established. Some authors consider that it results from the earlier repolarization of a ring of persistently viable (but nevertheless affected) tissue surrounding the aneurysm.[8,10] For other investigators, chronic ST-segment elevation reflects functional (echocardiographic) dyskinesia, thus not necessarily being due to a pathologic ventricular aneurysm.[8,25-27] Coronary artery disease is the most frequent cause of abnormal ST-segment elevation. The latter, when generalized, also can be due to

epicardial injury due to pericarditis. Both should be differentiated from the benign "early repolarization" pattern, a normal variant.[28,29] In its classic form, there is J-point elevation (of no more than 3 mm) with an upwardly concave ST segment. R waves may be tall and at times have a distinct notch and slur on the downstroke (Fig. 11-4). ST-segment elevation is more frequent in chest leads but can occur in leads I and II. These dynamic ECG changes may be affected by exercise and hyperventilation. Isoproterenol reduces and propranolol increases ST-segment elevation.[30,31] Although the mechanism of early repolarization has not been fully elucidated, it has been related to enhanced activity of the right sympathetic nerves.[30]

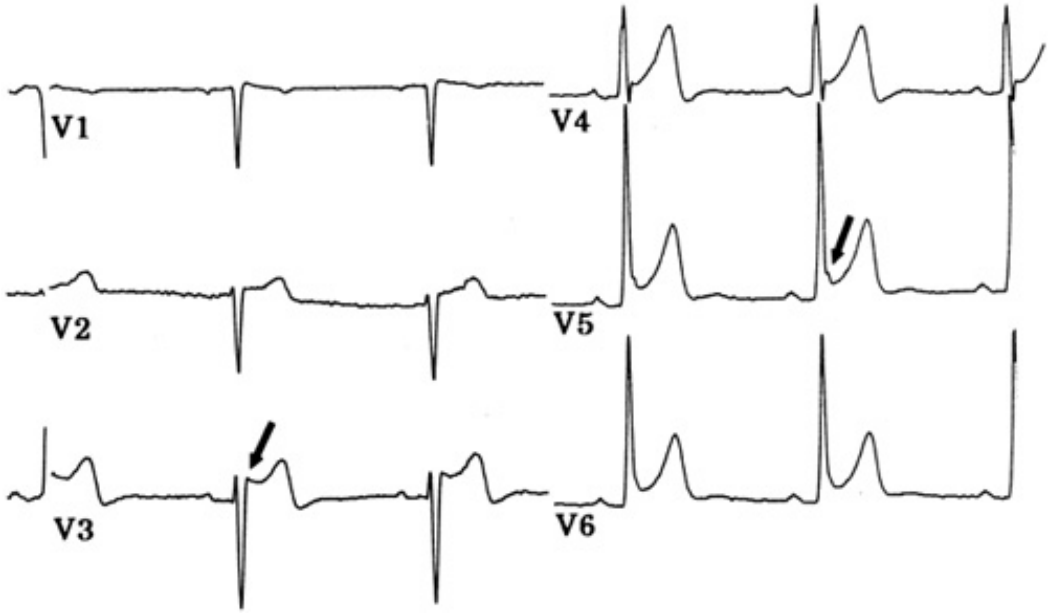

Figure 11-4: Early repolarization. This normal variant is characterized by narrow QRS complexes with J-point and ST-segment elevation in the chest leads. Left chest leads often show tall R waves with a distinct notch or slur in their downstroke (*arrow* in V_5), while the right chest leads may display ST segments having a "saddleback" or "humpback" shape (*arrow* in V_3).

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SELECTIVE NONISCHEMIC ST-SEGMENT ELEVATION IN THE RIGHT PRECORDIAL LEADS

High-takeoff ST segments of either the caved or saddleback type localized to the right chest leads associated with different degrees of right bundle block with or without T-wave inversion and sudden death due to ventricular fibrillation are seen in the *Brugada syndrome*[32] (Fig. 11-5, *left*). This is a familial entity ascribed to a "primary" electrophysiologic abnormality. Similar findings were reported in the familial cardiomyopathy and sudden cardiac death syndrome described by Corrado et al.[33] Strong Na channel blocking drugs can produce ST-segment elevations even in patients without any evidence of syncope or ventricular fibrillation.[34] The changes produced by potassium are discussed in the section of hyperkalemia (below). Slight ST-segment elevation with an incomplete right bundle branch block pattern showing an epsilon wave has been described in arrhythmogenic right ventricular dysplasia[35] (see Fig. 11-5, *right*).

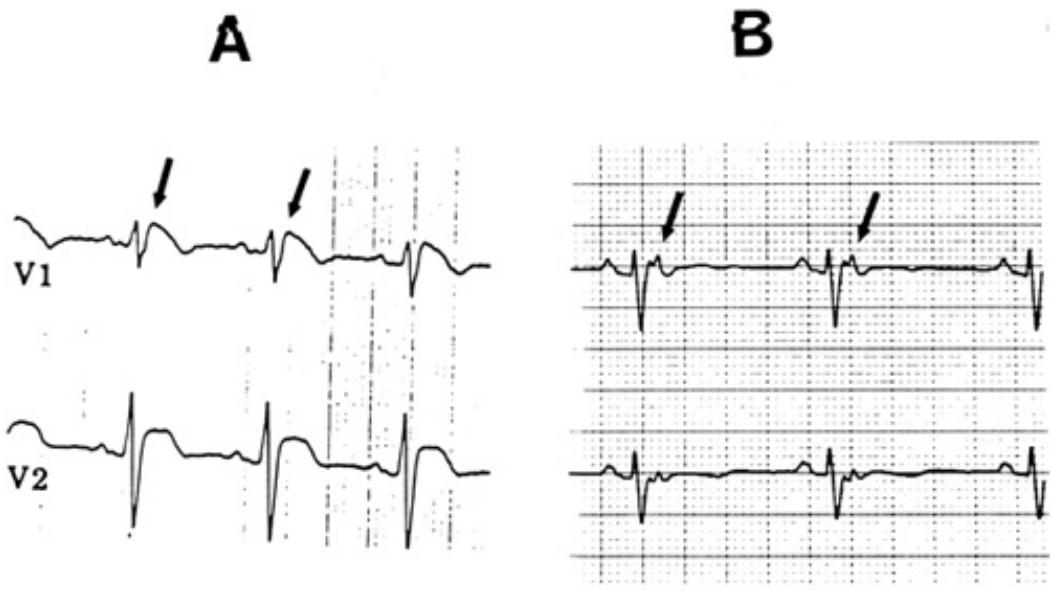

Figure 11-5: *A.* Nonischemic ST-segment elevation in the right precordial leads in a young patient with the Brugrada syndrome. *B.* Epsilon wave of a patient with arrhythmogenic right ventricular dysplasia.

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ABNORMAL Q WAVES

Abnormal Q waves appearing several hours after total occlusion of a coronary artery result from necrosis secondary to the decreased blood supply. The number of affected cells has to be large enough so as to produce changes reflected at the body surface. In general, the depth of the Q wave is proportional to wall-thickness involvement.[7] Thus, in lead aV_F a QS complex was said to reflect transmural necrosis. On the other hand, clinical myocardial infarction (MI) without abnormal Q waves was categorized as subendocardial infarction. Presently, MIs are no longer classified as transmural or subendocardial (but as Q or non-Q MIs).[36] The duration of the Q wave is proportioned to the extent of the area of necrosis parallel to the epicardial surface. If the latter is large enough, starts in the subendocardium, and extends toward (but not quitereaching) the epicardium, the corresponding unipolar leads will record QR or Qr complexes depending on the amount of living tissue located between dead tissue and the recording electrode. Therefore, abnormal Q waves may occur in MIs that are not completely transmural.[7,36] The following changes have been said to be equivalent to Q waves in non-Q-wave MI: R/S ratio changes, acute frontal plane right-axis deviation, new left-axis deviation or left bundle branch block, initial and terminal QRS notching, and some types of "poor r-wave progression."[36] Although the concept of non-Q-wave MI as a discrete clinicopathologic entity, different from Q-wave MI, has gained almost universal acceptance, it was challenged recently by a group of respectable electrocardiographers.[36]

In the course of the clinical entity known as *acute myocardial infarction* (MI), persisting Q waves are usually (but not invariably, as will be discussed subsequently) due to anatomic (lack of blood flow-related) necrosis. Abnormal Q waves also can occur transiently in unstable angina, Prinzmetal's angina, coronary artery spasm (without chest pain), and exercise-induced ischemia. This has been attributed to an intensity of cellular affectation ("injury") severe enough to produce a significant degree of hypopolarization (to, let us say, around 60 mV). Because the cells become electrically unexcitable (even though they are not anatomically, irreversibly necrotic),[7,8,15,16] abnormal Q waves occur. Spontaneous recanalization of an occluded vessel, spontaneous reversion of the ischemia, or spasm and interventions (pharmacologic or mechanical) that improve cellular metabolism and oxygenation can restore the normal polarization. If these cells become again excitable, the abnormal Q waves may disappear or vanish.[16,37] Ischemic necrosis usually takes longer to appear than the accelerated abnormal Q waves seen in the majority of patients with Q-wave MI after successful thrombolysis or effective coronary artery angioplasty performed early in the course of the process.[5] The genesis of these Q waves is not well understood.[37] Some authors consider them an expression of the acceleration of necrosis secondary to explosive cell swelling in already irreversibly injured tissue.[31] Because some of these Q waves also tend to disappear quickly, other authors consider that they reflect factors other than myocardial necrosis, such as reversal of regional dysmetabolism or the occurrence of transient interstitial ischemia or hemorrhage.[38] Profound and prolonged ischemia can cause myocardial stunning with reversible functional, metabolic, ultrastructural, and electrophysiologic abnormalities.[39] Thus transient Q waves may be the ECG counterpart (electrical stunning) of the corresponding mechanical stunning.[37-40] It is possible for myocardial stunning to lag behind electrical recovery.[37] *Myocardial stunning* should be differentiated from *myocardial hibernation*. The latter is a term used in reference to mechanical dysfunction of an ischemic area that is not transient but chronic.[41,42] Although the ECG counterpart of this type of mechanical dysfunction requires

further study, it is conceivable that (in some cases) the disappearance of chronic Q waves after coronary artery bypass surgery with improvement of wall motion abnormalities indicates that these Q waves were due not to cellular death but to cellular hibernation[41,42] (see also Chaps. 37 and 40). Finally, abnormal Q waves need not be the end result of coronary artery disease because they may be seen after primary (due to infections or drugs) cellular necrosis and in other pathologic processes such as myocardial infiltration and certain types of interventricular septal (and LV) hypertrophy, Wolff-Parkinson-White syndrome, and muscular dystrophies.[43]

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ISCHEMIC T-WAVE CHANGES

Symmetric T waves, inverted or upright (as in "hyperacute" T waves), characteristic of ECG "ischemia," have been considered to reflect a type, or degree, of cellular affection resulting only in action potentials of increased duration.[7,10,16] Because the QT interval recorded at the body surface can be considered as the sum of all action potentials (i.e., of the QT intervals of individual cells), any process (such as ECG ischemia) that increases action potential duration will cause prolongation of ventricular depolarization and QT interval. T-wave inversions[7,10] do not always reflect "physiologic" ischemia (due to decreased blood supply) because they also can be seen in evolving pericarditis, myocardial contusion, and increased intracranial pressure, as well as in the right chest leads of young patients (persistent juvenile pattern).[43]

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SECONDARY ST-T-WAVE CHANGES

Alterations in the sequence of (and sometimes delay in) ventricular depolarization (such as those produced by bundle branch blocks, ventricular pacing, ectopic ventricular impulse formation, preexcitation syndromes, and ventricular hypertrophy) result in a change in the sequence of ventricular repolarization. The latter causes nonischemic T-wave inversions (secondary T-wave changes) in leads showing a predominantly positive QRS deflection.[6,10,12,17] As mentioned earlier in the discussion of ventricular gradient and cardiac memory, disappearance of these alterations in ventricular depolarization may be followed by narrow QRS complexes with negative T waves[18] (see Fig. 11-1). After disappearance of "complete" left bundle branch block (LBBB) and in right ventricular pacing, inverted T waves appear in leads (such as V_1 and V_2) where the S wave predominates (see Fig. 11-1). Finally, marked ST-segment changes may occur *during* rapid supraventricular tachycardias, even in young patients without metabolic evidence of (physiologic) ischemia.[44]

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NONSPECIFIC ST-SEGMENT-T-WAVE CHANGES

While it seems more appropriate to discuss ST-segment and T-wave changes separately, they will be dealt with together because of their often coexistence. While nonspecific (or rather, nondiagnostic) ST-segment-T-wave changes are the most commonly diagnosed ECG abnormalities, they have not been categorized adequately and represent different findings for various interpreters.[45] In the classic paper, Friedberg and Zager[46] considered depth of ST-segment depression and T-wave inversion as well as their contour (Fig. 11-6).[46] When analyzed without clinical information, this diagnosis was made in 40 percent of 410 abnormal ECGs. The number was reduced to 10 percent, however, when clinical data became available. In the absence of structural heart disease, these changes can be due to a variety of physiologic (i.e., hyperventilation, anxiety, body position, food, neurogenic influences, and temperature), pharmacologic (i.e., antiarrhythmic and psychotropic drugs, digoxin), and extracardiac (i.e., electrolyte abnormalities, upper gastrointestinal processes, allergic reactions, etc.) factors.[45]

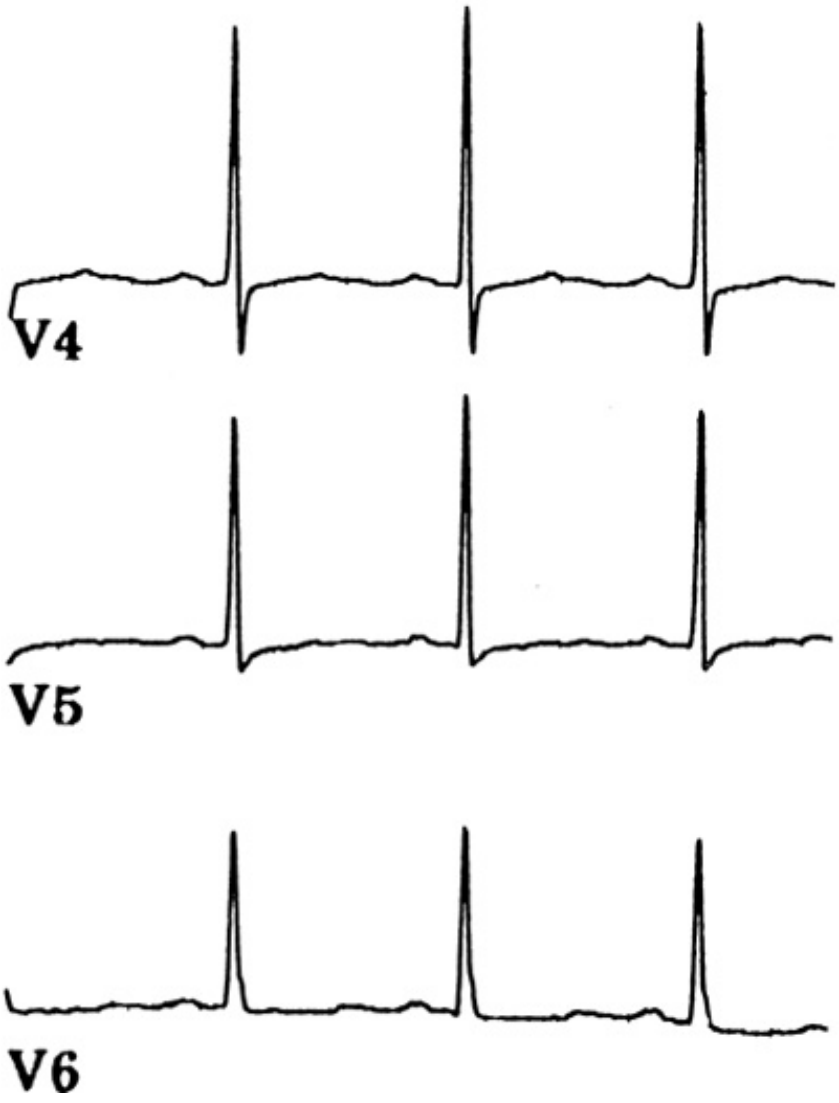

Figure 11-6: Nonspecific (nondiagnostic) ST-segment-T-wave changes, the most common abnormalities in ECG interpretation.

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U WAVE

A number of hypotheses have been advanced to explain the genesis of the U wave. Foremost among them is the relationship to late repolarization of the Purkinje system. A criticism of this hypothesis is that the conducting system does not have sufficient mass to generate a large deflection at the body surface. The recent identification of another population of (M) cells between epicardium and endocardium may provide the necessary mass to produce not only U waves but also the J (or Osborn) wave characteristic of hypothermia.[14] What sometimes appears to be a U wave merging with a T wave simple may be a notched T wave whose ascending or descending limbs are interrupted by differences in the end of the composite action potential of epicardial and M cells.[14] The normal U wave, most prominent in leads V_2 and V_3, has the same polarity as the T wave and is approximately 10 percent of its amplitude. A large positive U wave may be due to hypokalemia and multiple antiarrhythmic drugs. In orthodox ECG interpretation, merging of T and U is still considered a stage in hypokalemia but can result from such drugs as quinidine and sotalol.[14] According to Antzelevitch, repolarization of the His-Purkinje system was first suggested by Watanabe as the most likely cause of the "real" U wave.[14] Causes of negative U waves are ischemia, hypertension, and occasionally, right ventricular enlargement.[45]

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ACUTE MI

Although a recent article challenged this distinction,[36] MIs are no longer classified as transmural and subendocardial but as Q-wave and non-Q-wave.[36,47-50] In the thrombolytic era, the prevalence of the latter seems to be greater than that of the former (see Chap. 42), presumably due to a reduction in infarct size.[42-44] The prethrombolytic "classic" evolution of acute MI has been transformed by pharmacologic therapy and interventional techniques.[49,50] The succession of events in the course of a Q-wave MI is from hyperacute positive T waves (on occasion) to ST-segment elevation to abnormal Q waves to T-wave inversion[49,50] (Figs. 11-7 and 11-8). Commonly, two or more of these findings appear together, depending on the timing of the first recorded static ECG. Acceleration of these phases can occur with effective reperfusion. The time course of ST-segment elevation is a good predictor of reperfusion. Because prethrombolytic 12-lead ECG studies on ST-segment evolutions were based on static recordings obtained at fixed time intervals, it became clear that continuous monitoring in the coronary care unit (which falls outside the realm of this chapter) was essential to adequately record the dynamics of ST-segment trends (Figs. 11-9 and 11-10). Sensitivity increases as frequency of monitoring increases.[51-53] Continuous monitoring is thus essential to evaluate occurrence of reperfusion. Resolution of ST-segment elevation has been defined as a progressive decrease within 40 to 60 min to less than 50 percent of its maximally elevated value.[51,52] It has been suggested that in patients treated with thrombolytics, the dichotomization for Q-wave and non-Q-wave MI should be made by the predischarge, rather than the 24-h, ECG due to possible crossover from one group to another.[54]

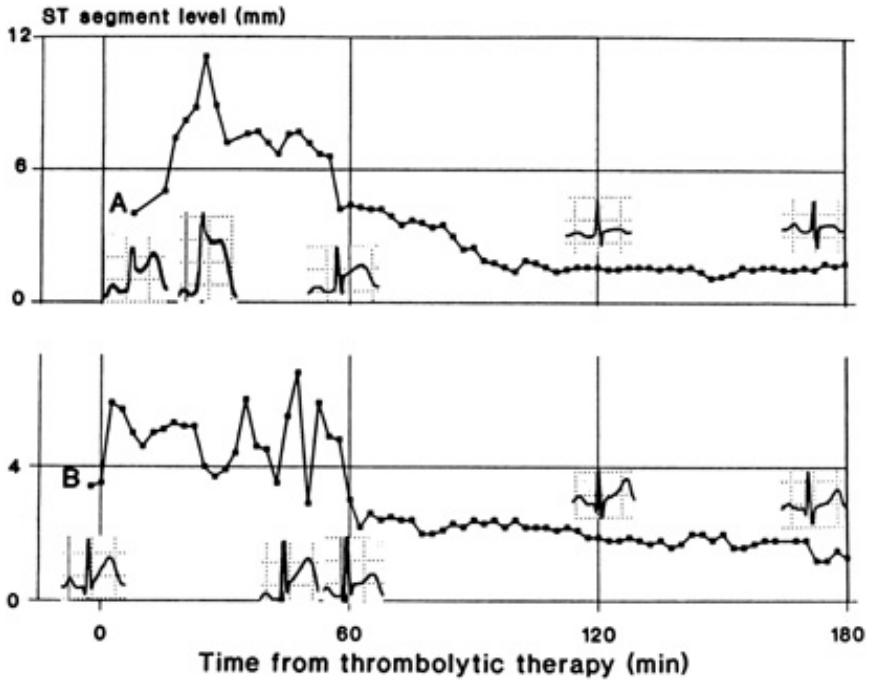

Figure 11-9: Plots of ST-segment levels versus time from therapy in two selected patients with patency of the infarct-related vessel at 60 min. Note that a 50 percent decrease in ST-segment

levels within 60 min occurred only when measurements were made from the peak ST-segment level (highest ST-segment level measurement within the first 60 min).

Aspects of the ECG other than ST-segment changes may be altered particularly during acute, anterior-wall MI. In fact, the same degree of ST-segment elevation in V_2 and V_3 with disappearance of the S waves indicates a greater degree of affectation than with preservation of this negative wave[55] (see Fig. 11-8, *top*).

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LOCATION OF THE SITE OF Q-WAVE MI

Table 11-1 shows an acceptable classification for the ECG location of MI according to leads showing abnormal Q waves. In addition, it depicts other processes that may result in false patterns of Q-wave MI. During the acute phase, ST-segment changes give a clue to the area at risk, but because of the normal variability in coronary anatomy and the presence of previous occlusions, there is sometimes more than one possible explanation for a specific ECG pattern.[55]

Table 11-1: Electrocardiographic Location of Infarction Sites Based on the Presence of Abnormal Q Waves

Site	Leads	False Patterns
Inferior (diaphragmatic)	II, III, aV_F	WPW (PSAP), HCM
Inferolateral	II, III, aV_F, V_4-V_6	
'True' posterior (postero-basal)	V_1*	RVH, 'atypical' incomplete RBBB, Left AP
Inferoposterior	II, III, aV_F, V_1*	WPW (left PSAP), HCM
Inferior-right ventricular	II, III, aV_F plus V_{4R}-V_{6R} or V_1-V_3	ASMI as defined from axis
Anteroseptal	V_1, V_2, V_3	LVH, chronic lung disease, LBBB, chest electrode misplacement
Anterolateral	I, II, V_4-V_6	HCM, ventricular septal defect
Extensive anterior	I, aV_L, V_1-V_6	
High lateral	I, aV_L	
Anterior (apical)	V_3-V_4	
Posterolateral	V_4-V_6, V_1*	WPW (LFWAP)
Right ventricular	V_{4R} with V_{4R}-V_{6R} or V_1-V_3	ASMI

*Tall R wave, 'reciprocal' to changes in 'indicative' back lead.

NOTE: ASMI = anteroseptal myocardial infarction; HCM = hypertrophic cardiomyopathy; LBBB = left bundle branch block; LFWAP = left free-wall accessory pathway; PSAP = posteroseptal accessory pathway; WPW = Wolff-Parkinson-White syndrome; RVH = right ventricular hypertrophy.

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RECIPROCAL ST-SEGMENT CHANGES

In an inferior MI with abnormal ST-segment elevation limited to this wall, the reciprocal ST-segment changes will occur in diametrically opposed leads located in the *same* plane. For example, "indicative" ST-segment elevation in leads III and aV_F,which record the electrical activity of the inferior (posteroinferior or diaphragmatic) wall, yields "reciprocal" ST-segment depression in leads I and aV_L because they face the superior (anterolateral) wall[11,56,57] (see Fig. 11-3). ST-segment depression in lead V_2 may reflect injury in the anterior subendocardial wall as well as injury in the posterobasal (or true) posterior wall.[10] The ECG by itself cannot distinguish with absolute certainty between these two possibilities.[10] The differential diagnosis perhaps can best be made by performing cardiac catheterization or radionuclear studies in the acute phase of the MI, when the ST-segment changes are still present. Another way is by analyzing ST-segment changes occurring during percutaneous transluminal coronary angioplasty in patients with proven single-vessel disease.[58,59] This has shown that reciprocal ST-segment depression in leads V_2 and V_3 can occur during balloon occlusions of dominant right, as well as of dominant left, coronary arteries.[59]

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RIGHT VENTRICULAR MI

According to Braat et al.,[60] an ST-segment elevation of at least 1 mm in lead V_{4R} in patients with *acute inferior MI* had a sensitivity of 100 percent, a specificity of 87 percent, and a predictive accuracy of 92 percent for the diagnosis of right ventricular infarction in patients with ST-segment elevation in leads II, III, and aV_F (see Fig. 11-3). These changes disappeared within 10 to 18 h after the onset of chest pain in 50 percent of their patients and after 72 h in the remaining patients.[60] In addition to V_{4R}, ST-segment elevation can be seen in leads V_5 and V_{6R} and in some cases (with decreasing amplitude) in V_1, V_2, and even V_3. It is possible for ST-segment depression in V_5 and V_6 to be reciprocal to right ventricular involvement (see Fig. 11-3).

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PERICARDITIS

The ECG pattern of acute (generalized) pericarditis not due to MI is produced by the associated epimyocarditis, which in turn results in diffuse epicardial "injury."[6] The ST segments can be elevated in all leads except aV_R and, rarely, in V_1 (Fig. 11-11). Symmetric T-wave inversion (due to epicardial "ischemia") usually develops after the ST segments have returned to the baseline (but can appear during the injury stage).[6] Neither reciprocal ST-segment changes nor abnormal Q waves are seen. In most cases of acute pericarditis, the PR segment is depressed (see Fig. 11-11). Average ECG resolution occurs in close to 2 weeks.[11] The ECG pattern of acute pericarditis has to be differentiated from the normal variant referred to as *early repolarization* (see Fig. 11-4).

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FASCICULAR BLOCKS

Generalities

There are several ways of proving that a given QRS pattern is due to a specific type of conduction abnormality.[15,57,61] First is extrapolation from animal experiments.[15,61] Second is ECG-pathologic correlation.[15,61] Third is an analysis of **QRS** changes produced by the inadvertent section of the conduction fascicles during open heart surgery or catheter-induced trauma.[62] Fourth is a comparison of tracings obtained before, during, and after the appearance or disappearance of conduction disturbances that are either persistent or (spontaneously or iatrogenically) intermittent. Under such circumstances, the QRS changes produced by fascicular block occur side by side with the control morphologies.[8,15,6162-63] The various criteria proposed for diagnosis of fascicular blocks, though empirical, have been accepted for a very pragmatic reason: the need to interpret clinical ECGs. In reality, the sensitivity and specificity of these criteria require independent confirmation.[61,64] One can speculate that the latter may be provided by newer methods of intraoperative and body surface mapping and refinements in the technique of phase imaging or even perhaps Carto mapping, since few centers in the United States are currently performing histopathologic studies of the distal intraventricular conduction system.

Left Anterior Fascicular Block

In left anterior fascicular block (LAFB), the posteroinferior regions of the LV endocardium are activated abnormally before the anterosuperior LV area.[8,15] After emerging from the posteroinferior division of the left bundle branch, the impulse first propagates in an inferior, rightward, and usually anterior direction for a short period of time, producing q waves in leads I and aV_L and r waves in leads II, III, and aV_F (see Fig. 11-12). Thereafter, the general direction of the activation process (which determines the direction of the EA) occurs in a superior and leftward direction. Consequently, from the ECG viewpoint, the fascicles of the left branch behave more as if they were "superior" and "inferior" rather than "anterior" and "posterior" (Figs. 11-12 and 11-13). For this reason, the most significant abnormalities produced by LAFB, in the absence of complete right bundle branch block (RBBB), occur in the standard and unipolar extremity leads rather than in the precordial leads[8,15] (see Figs. 11-12 and 11-13). S waves frequently are recorded V_5 and V_6 because the depolarization wave first moves towards them and later, because of their relatively low position, away, in a more superior direction. The degree of left-axis deviation required for the diagnosis of complete LAFB has been a subject of debate and speculation.[8] It should be remembered that LAFB is but one of the causes of left-axis (superior and leftward) deviation (Table 11-2). Criteria for the diagnosis of pure LAFB are presented in Table 11-3,[864-68] and illustrative examples are shown in Figs. 11-12 and 11-13. When LAFB coexists with certain congenital types of right ventricular enlargement and extensive anterolateral MI, the EA can be shifted to the "undeterminate" (right superior) quadrant. Thus the constant feature of the axis deviation produced by LAFB is its *superior* orientation, not its superior and leftward orientation (abnormal left-axis deviation).[61] Because of the multiple interconnections between the fascicles of the left bundle branch system, the appearance of LAFB does not increase QRS duration by more than 0.025 s.[8] Therefore, a LAFB pattern with a wider QRS complex generally indicates the presence of additional conduction disturbances such as RBBB (Fig. 11-14, *top*), MI, or intraventricular conduction delays due to free wall fibrosis. Masquerading RBBB is said to be present when (with the classic findings in lead V_1) lead I shows what seems to be a left bundle branch block (LBBB) due to the absence of q and S waves (see Fig. 11-14, *bottom*). This pattern has been attributed to a terminal delay perpendicular to lead I associated with diffuse intramyocardial fibrosis.[15]

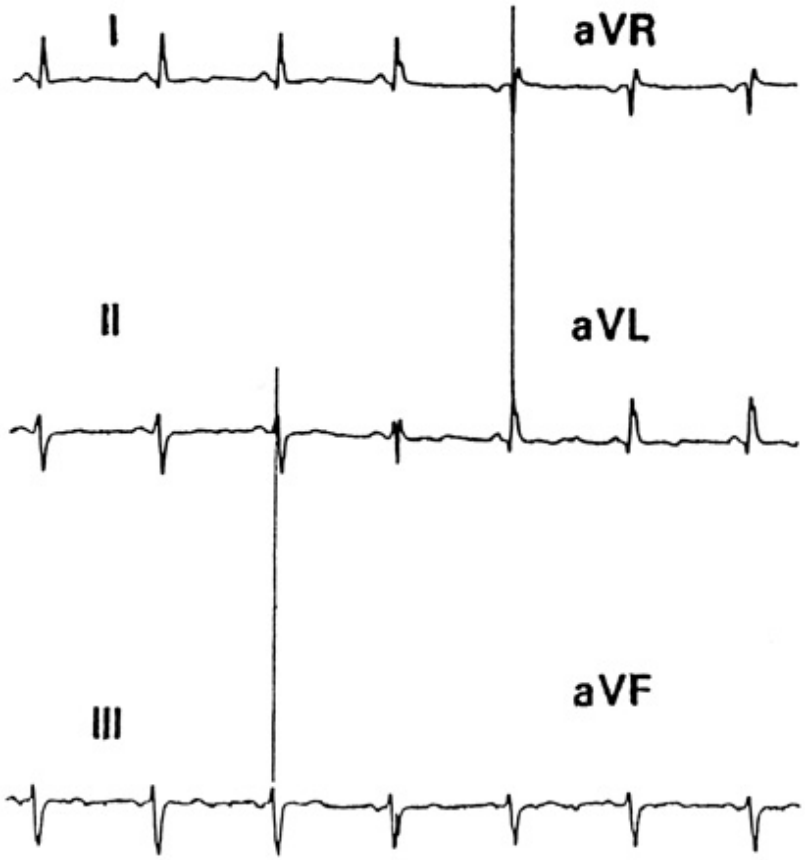

Figure 11-12: LAFB in a patient with primary conduction system disease. QRS duration: 0.10 s. At normal paper speeds (25 mm/s), the relationship between the peaks of the R waves (*vertical lines*) in simultaneously recorded leads II and III and aV_L and aV_R cannot be determined with the desired accuracy (see Fig. 11-13).

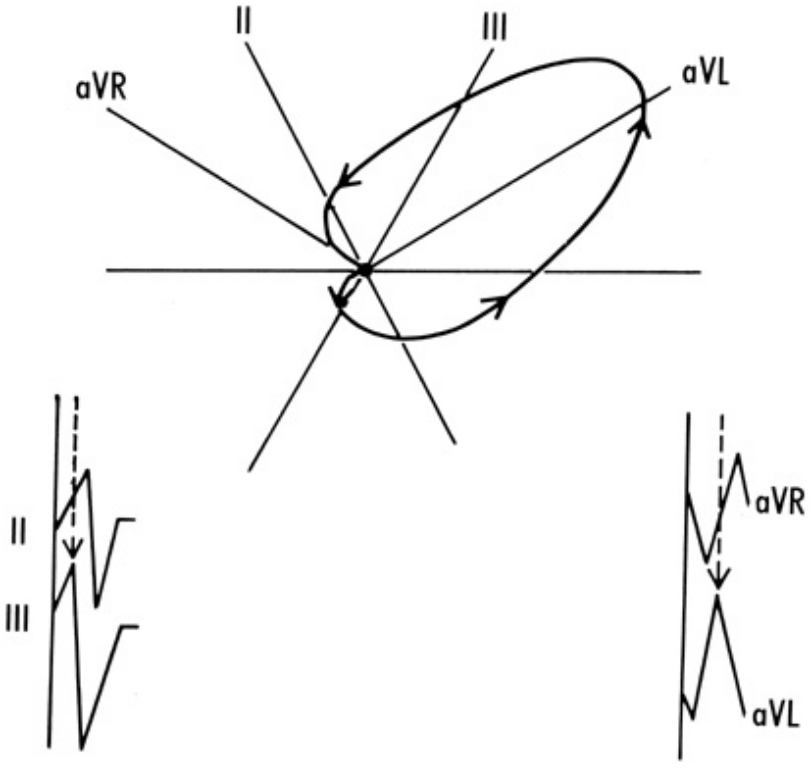

Figure 11-13: Derivation of electrocardiographic leads from a frontal plane QRS loop showing LAFB. Due to the counterclockwise rotation of the left superior loop, the peak of the R in aV_L preceded the peak of this deflection in aV_R (lower right). Furthermore, because the initial portion of the loop was inscribed on the positive half of the axis of lead III before it was inscribed on the positive half of the axis of lead II, the peak of the R in the former lead occurred before that in the latter lead. (From Castellanos A, Pina L, Zaman L, et al. Recent advances in the diagnosis of fascicular blocks. *Cardiol Clin* 1987; 5:469-488. Reproduced with permission from the publisher and authors.)

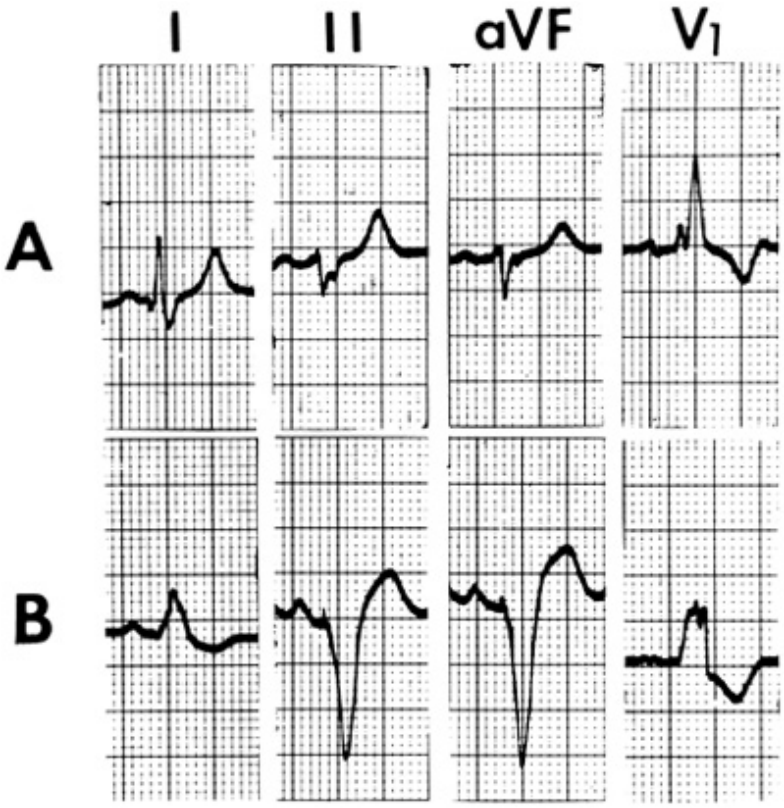

Figure 11-14: LAFB with wide QRS complexes. Whereas panel *A* shows LAFB with RBBB, these conduction disturbances coexist with diffuse septal and inferoposterior fibrosis in panel *B*. Consequently, the expected small q wave and the wide S wave in lead I are not present. This pattern has been called "masquerading" bundle branch block because the standard leads suggest LBBB, while the chest leads are diagnostic of RBBB.

Table 11-2: Causes of Abnormal (-30° to -90°) Left-Axis Deviation

Cause	Characteristic Features
1. Left anterior fascicular block	1. rS complexes in lead II with positive T waves
2. Extensive inferior wall (AC5)MI	2. Qr complexes in lead II with ST-segment elevation and/or T-wave inversion
3. Extensive inferior wall MI with possible (AC7)LAFB	3. QS pattern in leads II, III, and aV_F with ST-segment elevation and/or T-wave inversion
4. Wolff-Parkinson-White syndrome (posteroseptal accessory pathway)	4. Short PR interval; delta wave
5. Hyperkalemia	5. Wide QRS complexes; peaked T waves

6. Pulmonary emphysema	6. Low voltage; peaked P waves, S waves in standard and precordial leads
7. Right ventricular apical pacing	7. Pacemaker spikes; predominantly negative ventricular deflections in V_1
8. Middle cardiac vein pacing	8. Pacemaker spikes; predominantly positive QRS deflections in V_1
9. Left coronary arteriography	9. Knowledge that dye was injected in left coronary artery

SOURCE: Used with permission from Castellanos and Myerburg.[15]

Table 11-3: Criteria for Diagnosis of Pure Left Anterior Fascicular Block

1. Abnormal left-axis deviation (usually between -45 and -60°)
2. rS complexes in leads II, III, and aV_F and qR complexes in leads I and aV_L
3. Delayed intrinsicoid deflection in leads I and aV_L
4. Peak of r wave in lead III occurring earlier than peak of r wave in lead II
5. Peak of R wave in lead aV_L occurring earlier than peak of R wave in aV_R

SOURCE: From Castellanos et al.[61] and Milliken,[64] with permission.

Left Anterior Fascicular Block Coexisting with MI

The ECG changes imposed by MIs of different locations on the LAFB are shown in Fig. 11-15. An inferior wall MI can be masked by a LAFB if the infarction does not involve the areas first depolarized by the impulse emergency from the unaffected fascicle.[8] In these cases, an r (slurred or not) can be seen in leads III and aV_F. It also has been stated that the change in left septal activation produced by the fascicular block may produce small r waves in V_1, V_2, and V_3 capable of modifying the characteristics QS complexes produced by anteroseptal MI in these leads.[8]

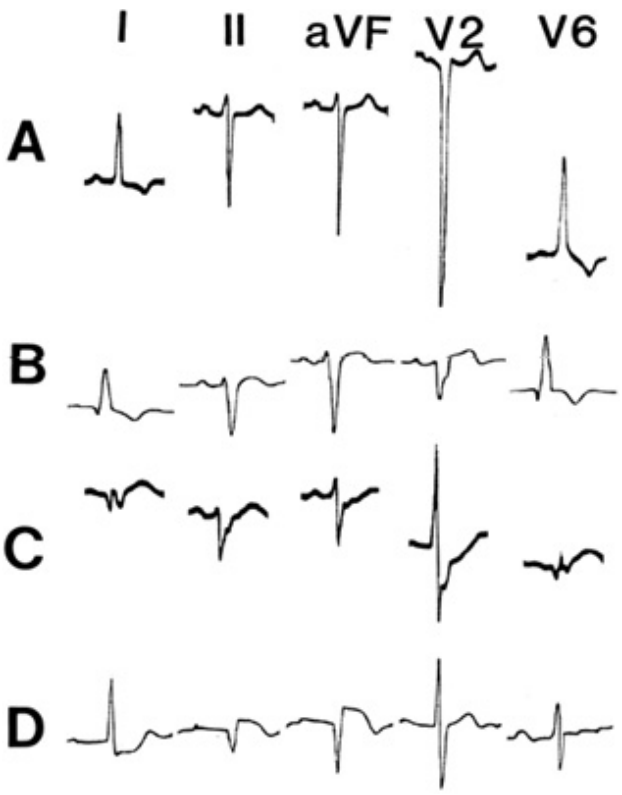

Figure 11-15: Diagnosis of LAFB associated with MI. Diagnostic feature given in parentheses. *A*. LAFB and anteroseptal MI (QR or QS complex in right chest leads). *B*. LAFB and anterolateral MI (abnormal Q wave in leads I and V_6). *C*. LAFB and anterolateral MI with electrical axis in the right superior quadrant (Q wave in leads I and V_6). *D*. LAFB and inferior wall MI (QR or QS complexes and elevation of J point and ST segments in leads II and III).

Nonspecific Intraventricular Conduction Delays

Several names have been applied to the conduction disturbances occurring in the left-sided Purkinje-myocardial junctions, left septal surface, or free wall of the left ventricle: *arborization block*, *diffuse (nonspecific) intraventricular block*, *peri-infarction block*, *parietal block*, *focal block*, etc.[8,66-75] These conduction disturbances have different electrogenetic mechanisms. Thus the cellular "affectation" due to acute injury resulting from coronary artery disease, hyperkalemia, drugs, and intracoronary injections of contrast material occurs within (inside) the affected regions.[5,15,75] Blocks occurring in subacute or chronic MI after the appearance of abnormal Q waves (peri-infarction block) (Fig. 11-16), as well as those occurring in the presence of diffuse myocardial fibrosis (Fig. 11-17), are due to the circuitous and irregular activation of living cells surrounding areas of fibrotic tissue.[68-75]

Left Posterior Fascicular Block

In pure left posterior fascicular block (LPFB), the impulse emerges from the unblocked anterosuperior division, thus producing small q waves in leads II, III, and aV_F.[8,15] Thereafter, the impulse moves through the electrically predominant left ventricle in an inferior and rightward direction, thus explaining the S waves in leads I and aV_L as well as the R waves in leads II, III, and aV_F.[8,15] Radiologic studies of the human heart in situ have shown that the paraseptal regions of the posteroinferior (diaphragmatic) surface of the anatomic *left* ventricle are spatially located more to the *right* than certain (anterior) portions of the anatomic right ventricle.[15] Since the portions of the left ventricle that are spatially located to the right are less than those located superiorly, the degree of right-axis deviation produced by pure LPFB is of lesser magnitude than that of left-axis deviation produced by LAFB.[15] The hallmark of LPFB, therefore, is an "inferior" axis shift as much as "right" axis deviation (Figs. 11-18 to 11-20). Because a similar sequence of ventricular activation also can occur in right ventricular hypertrophy, pleuropulmonary disease (acute or chronic), and extremely vertical anatomic heart positions due to a slender body build or chest wall

deformities, it is evident that the diagnosis of "pure" LPFB cannot be made from the ECG alone. Additional clinical, radiologic, or pathologic information is required for this purpose.[8,15,61,66] The changes imposed in LPFB by MIs of different locations are depicted in Figs. 11-18 to 11-20.

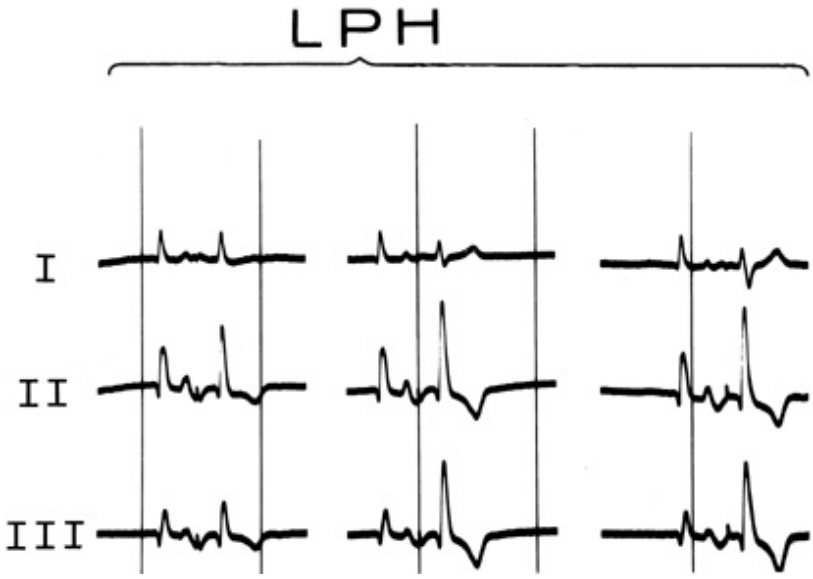

Figure 11-18: Premature atrial beats showing increasing degrees of (incomplete and complete) LPFB aberration. The first beats in all panels are escape beats with the same morphology as that of sinus beats. The second, aberrantly induced ventricular complexes show different degrees of right-axis shift with an increase in size of the R waves in leads II and III. Note that the fundamental characteristic of LPFB was not right-axis deviation (beyond +90°) but an inferior-axis shift. (From Castellanos A, Myerburg RJ. *The Hemiblocks in Myocardial Infarction*. New York: Appleton-Century-Crofts; 1976. Reproduced with permission from the publisher and authors.)

Left Fascicular Blocks Produced by Intra-His Bundle Lesions

Rosenbaum et al.[8] attributed surgically induced LAFB (coexisting with RBBB) to a lesion of the "pseudobifurcating" part of the His bundle. The production of LBBB and LPFB by catheters located in the right-sided cavities, however, cannot be explained by assuming direct affectation of these left-sided structures.[76,77] Nevertheless, they have been reported and attributed to the His bundle trauma produced by Swan-Ganz catheters.[76,77] In fact, certain clinical and experimental studies have shown that some bundle branch block patterns could be normalized by distal His bundle pacing.[78] Longitudinal dissociation of conduction within a usually diseased His bundle should be present for this to occur. There is, however, disagreement as to the mechanism involved, especially in regard to the predestination of fibers (within the His bundle) to specific right- or left-sided structures and to the role played by the transverse fibers connecting the various longitudinal strands.[77-80]

Left-Middle (Septal) Fascicular Blocks

This disorder has been demonstrated anatomically and is associated with ischemic heart disease and fibrosis of the middle (septal) fascicle of the left branch.[81,82] While some authors consider that the right precordial leads show prominent R waves (similar to those found in true posterior, basal, myocardial infarction), others have described Q waves in leads V_1, V_2, and V_3.[81,82] It also has been considered that left-middle (septal) fascicular blocks are manifested by the absence of the expected q waves in leads V_5 and V_6 in ECG intermediate or horizontal hearts. Such a diversity of diagnostic criteria shows that there are marked discrepancies regarding the ECG characteristics of this conduction disturbance. Recently, Dhala et al.[83] described what they considered as the unmasking of the trifascicular conduction system by catheter ablation of the right bundle branch with a diseased left intraventricular conduction system. In these cases, ablation-

induced damage to "predestined" fibers in a diseased His bundle cannot be totally excluded.

Complete RBBB

A "complete" RBBB pattern (with QRS duration of ≥0.12 s) does not necessarily reflect the existence of a total conduction block in the right branch. This pattern only indicates that the entire or major parts of both ventricles are activated by the impulse emerging from the left branch.[15,84,85] Thus a significant degree of conduction delay ("high grade" or "incomplete" RBBB) can produce a similar pattern. In pure complete RBBB, the EA should not be deviated *abnormally* either to the left or to the right. These axis deviations reflect coexisting fascicular block (see Figs. 11-14 and 11-19) or right ventricular hypertrophy.

Incomplete RBBB Pattern

For many years what has been proven with endocardial (catheter) and epicardial mapping has been recognized-namely, that incomplete RBBB "patterns" can be produced by various mechanisms[84-90]: (1) different degrees of conduction delays through the main trunk of the right bundle branch, (2) an increased conduction time through an elongated right bundle branch that is stretched because of a concomitant enlargement of the right septal surface, (3) a diffused Purkinje-myocardial delay due to right ventricular (RV) stretch or dilatation, (4) surgical trauma or disease-related interruption of the major ramifications of the right branch ("distal" RBBB), or (5) congenital variations of the distribution of the major distal ramifications resulting in a slight delay in activation of the crista supraventricularis.[6] In arrhythmogenic RV dysplasia, the S wave in V_1 is followed by a sharp, wide, positive deflection (epsilon wave; Fig. 11-5*B*) attributed to delayed ventricular activation (postexcitation) in some RV myocardial fibers.[39] Wide QRS complexes in this lead (wider than in other precordial leads) were attributed to a "parietal" block superimposed on a RBBB.[35]

Concealed RBBB

A minor conduction delay in the main trunk of the right bundle branch or in its major ramifications may be "concealed" (not manifested in the surface ECG) when there are coexisting (and of greater degree) conduction disturbances in the main left bundle branch, the anterosuperior division of the left bundle branch, and/or the free LV wall.[8,15] An RBBB also can be concealed in some patients with Wolff-Parkinson-White syndrome if the ventricular insertion of the accessory pathway causes preexcitation of the RV regions that would be activated late because of the RBBB.[91]

Complete LBBB

This conduction disturbance is characterized by wide (>0.11 s) QRS complexes. The diagnostic criteria consist of prolongation of the QRS complexes (>0.11 s) with neither a q nor an S wave in leads I, aV_L, and a *properly placed* V_6. A wide R wave with a notch on its top ("plateau") is seen in these leads. Apparently, the EAs of most *uncomplicated* complete LBBBs usually are not located beyond 30°.[8,15,16] Complete LBBB with abnormal left-axis deviation indicates a great degree of left Purkinje and myocardial disease.

Complete LBBB with Acute MI

The classic pattern of LBBB may not be modified by a small area of myocardial necrosis. This explains why thrombolytics may be given if clinical findings characteristic of MI occur in patients with a LBBB pattern. Recent studies, however, have shown that occlusions of a coronary artery by either an angioplasty balloon or (a presumably large) MI can produce ST-segment changes as in the absence of a conduction disturbance.[112] Recently, Sgarbossa[92] has suggested that ST-segment elevation of 1 mm or more concordant with QRS polarity has a high specificity and sensitivity. ST-segment elevation of 5 mm or more discordant with QRS polarity, ST-segment depression of 1 mm or more in V_1, V_2, and V_3, and (sudden) positive T waves in V_4 and V_5 have a high specificity but a low sensitivity. The latter can occur transiently during acute ischemia (pseudonormalization) without myocardial necrosis or be persistently present in

cases where its significance is unclear. Examples of LBBB complicated by acute anterior and inferior MI are shown in Figs. 11-21 and 11-22. The above-mentioned criteria also can be applied to diagnose acute MI in patients with pacemakers.[92,93]

Complete LBBB with Old MI

Normally, in complete LBBB, the impulse emerges from the right bundle branch and propagates inferiorly, to the left, and slightly anteriorly. This orientation of the initial forces tends to abolish previously present inferiorly and laterally located abnormal Q waves characteristic of inferior and lateral wall MIs.[15,93,94] If the infarction is anteroseptal, however, the impulse cannot propagate toward the left. Instead, the initial vectors point toward the free wall of the right ventricle because now the RV free-wall forces are not neutralized by the normally preponderant septal and/or initial LV free-wall forces.[15] Thus a small q wave will be recorded in leads I, V_5, and V_6, where it is not normally present in complete LBBB (Fig. 11-23*A*). For a recent review of this subject, see Ref. 92. Similar findings can be seen in paced beats when in lead I the spike is followed by a well-defined q wave (see Fig. 11-23*B*). Several studies reported that Q waves in lead I or in two or more lateral leads (I, aV_L or V_5 and V_6) have high specificity but moderate sensitivity.[92] The sign of Cabrera and Friedland (late notching of S waves in V_3 through V_5) has been found to have higher to moderate specificity and moderate to low sensitivity.[94] Notching of the upstroke of the R wave in leads I, aV_L, V_5, and V_6 (sign of Chapman) has a sensitivity of 21 percent and a specificity of 82 percent.[94]

Complete LBBB with LV Hypertrophy

This is discussed under "LV Hypertrophy," below.

Incomplete LBBB Pattern

An incomplete LBBB pattern can be diagnosed if leads I and an *appropriately placed* V_6 show an R wave not preceded by a q wave.[6] Lead V_1 shows rS or QS complexes, and lead V_2 shows rS complexes. Although QRS duration usualy ranges between 0.08 and 0.11 s, this *pattern* can be observed with QRS durations of 0.12 and 0.13 s.

Wide QRS Complexes in Patients with Manifest Preexcitation Syndromes

The characteristic pattern of manifest Wolff-Parkinson-White syndrome during sinus rhythm is well known.[95-103] The ventricular complex is a fusion beat resulting from ventricular activation by two wave fronts.[116-126] The degree of preexcitation (amount of muscle activated through the accessory pathway) is variable and depends on many factors. Foremost among these are the distance between the sinus node and atrial insertion of the accessory pathway and, more important, the differences in refractory period duration and in conduction time through the normal pathway and the accessory pathway. Other things being equal, a patient with rapid (enhanced) AV nodal conduction will have a smaller delta wave than a patient with slow conduction through the AV node. Moreover, if there is total block at the AV node or His-Purkinje system, the impulse will be conducted exclusively via the accessory pathway bundle.[96,99-101] Consequently, the QRS complexes are different from fusion beats, although the direction of the delta wave remains the same. Moreover, the QRS complexes are as wide as (and really simulating) those produced by artificial or spontaneous beats arising in the vicinity of the ventricular end of the accessory pathway.[96,99-101] The original ECG classification of manifest Wolff-Parkinson-White syndrome proposed by Rosenbaum et al.[97] is now of historical interest only. Nevertheless, initial noninvasive determination of the anatomic position of the accessory pathway is of great clinical importance because of the introduction of surgical and catheter ablative techniques for symptomatic cases of preexcitation.

Toward the end of the millennium, Basiouny et al.[104] reported that there were 41 publications dealing with methods for localizing the accessory pathways of patients with preexcitation syndrome. Of these, they analyzed what they considered the most important algorithms available for this purpose. The interested

reader can consult this article.[104] For the purposes of this chapter and due to space limitations, we will refer to the pioneer study of Milstein et al.,[102] who analyzed the direction of the delta wave and divided the mitral and tricuspid ring areas where the pathways are located into various segments. These investigators considered that only four segments were necessary. This appeared logical, for at the time that this method was proposed, most ablations were performed surgically.[102,103] Left free-wall accessory pathways are characterized by isoelectric and even positive delta waves in leads I, aV_L, V_5, or V_6. Lead V_1 shows R or Rs complexes (Fig. 11-24). During sinus rhythm, the electrical axis may be normal, but when atrial fibrillation develops and exclusive accessory pathway conduction occurs, the EA is deviated to the right and inferiorly (see Fig. 11-24). Posteroseptal accessory pathways show negative delta waves in leads III and aV_F and R waves in V_2. An Rs (or RS) wave in V_1 suggests a left posteroseptal pathway; a QS complex in the same lead may correspond to a right posteroseptal pathway (Fig. 11-25). Right free-wall accessory pathways display an LBBB pattern defined, for purposes of accessory pathway localization, by an R wave greater than 0.09 s in lead I and rS complexes in leads V_1 and V_2 with an electrical axis ranging between +30 and -60° (Fig. 11-26).

Right anteroseptal accessory pathways show an LBBB pattern (as defined) with an electrical axis ranging between +30 and +120° (Fig. 11-27). A q wave may be present in lead aV_L but *not* in leads I and V_6. Mixed patterns resulted from the existence of two separate accessory pathways.

Since accessory pathways can traverse almost any part of the atrioventricular annulus, this classification is obviously insufficient when catheter ablation is contemplated. As mentioned earlier, multiple algorithms have been proposed. Since the most useful are complex, electrocardiographers find them difficult to memorize. They are also not completely satisfactory, since smaller degrees of preexcitation seem to limit diagnostic accuracy, and the polarity of delta waves [positive, biphasic (+ or -), negative, and isoelectric] has to be properly categorized. Figure 11-28 illustrates a useful algorithm to predict accessory pathway location from the 12-lead ECG.[105]

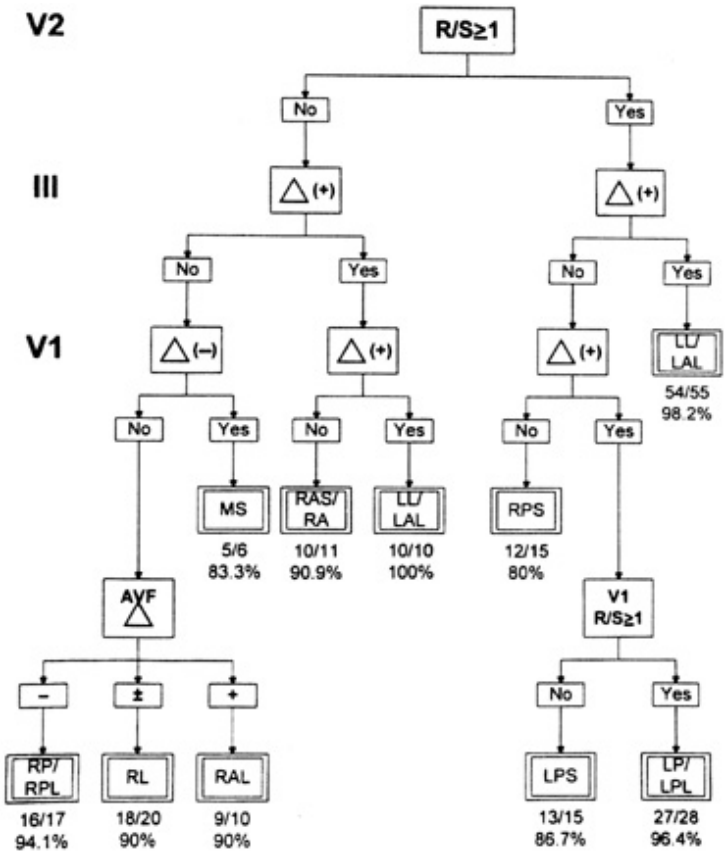

Figure 11-28: Useful algorithm to predict accessory pathway location from the 12-lead ECG. Step 1:

Analysis of R/S ratio in V_2. Step 2: Existence of positive (+) delta wave in lead III (initial 40 ms). Step 3: Existence of positive or negative (-) delta wave in V_1 (initial 60 ms). Step 4: Delta-wave polarity in aV_F (initial 40 ms) or analysis of R/S ratio in V_1 (± = biphasic or isoelectric). The accuracy of the algorithm for each location in 187 prospective patients is also shown at the bottom. LAL, left anterolateral; LL, left lateral; LP, left posterior; LPL, left posterolateral; LPS, left posteroseptal; MS, midseptal; RA, right anterior; RAL, right anterolateral; RAS, right anteroseptal; RL, right lateral; RP, right posterior; RPL, right posterolateral; RPS, right posteroseptal. (From Chiang et al.[105] Reproduced with permission from the publisher and authors.)

Wide QRS Complexes Produced by Ventricular Pacing from Different Sites

In determining the location of the stimulating electrodes, one should take special care not to consider that the distortion produced by large unipolar spikes constitutes parts of the pacing-induced QRS complexes. It is best *not* to describe the electrically produced ventricular beats as having an RBBB or LBBB morphology, since what is relevant is the polarity of the *properly positioned* V_1 and V_2 electrodes and the direction of the EA[106,107] (Fig. 11-29). For example, endocardial or epicardial stimulation of the *anteriorly* located right ventricle at any site [apical (inferior), or mid/outflow tract (superior)] yields predominantly negative deflections in the right chest leads due to the *posterior* spread of activation (first and second vertical rows in Fig. 11-29). The reverse (positive deflections in V_1 and V_2) occurs when the epicardial stimulation of the superior and lateral portions of the posterior left ventricle by catheter electrodes in the distal coronary sinus or great and middle cardiac veins (or by implanted electrodes in the nearby muscle) results in *anteriorly* oriented forces (third and fourth vertical rows in Fig. 11-29). Right ventricular apical pacing may produce positive deflections in V_1 if this lead is (mis)placed above its usual level. On the other hand, *superior* deviation of the electrical axis only indicates that a spatial *inferior* ventricular site has been stimulated, regardless of whether this site is the apical portion of the right ventricle or the inferior part of the left ventricle, the latter being paced through the middle cardiac vein (first and fourth vertical rows in Fig. 11-29). Conversely, an *inferior* vertical axis is simply a consequence of pacing from a *superior* site, which can be the endocardium of the RV outflow tract or the epicardium of the posterosuperior and lateral portions of the left ventricle (second and third vertical rows in Fig. 11-29). The changes produced on the basic ECG patterns of paced beats produced by MI were briefly discussed in the section of LBBB and MI. The method discussed above to locate the site of impulse initiation during pacing is simpler than the more complicated ones used to determine the ventricular sites of exit from accessory pathways (crossing the AV junction), which require the use of right anterior oblique and, specially, left anterior oblique projections. The currently used nomenclature for accessory pathway location was discussed recently and challenged by a group of notable experts in the field of preexcitation.[108]

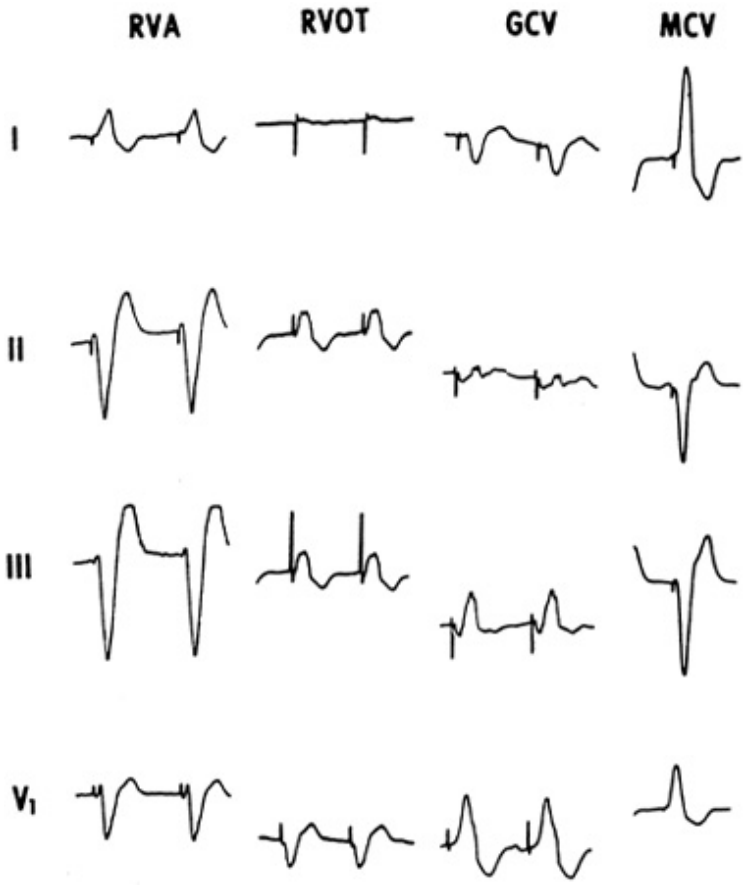

Figure 11-29: QRS changes (location of the electrical axis and polarity of lead V_1) produced by pacing from right ventricular apex (RVA), right ventricular outflow tract (RVOT), great cardiac vein (GCV), and middle cardiac vein (MCV).

Left Atrial Hypertrophy

Munuswamy et al.,[109] using M-mode echocardiography as the "gold standard," evaluated the specificity and sensitivity of the most important clues for determining left atrial hypertrophy. These included (1) P wave duration greater than 0.11 s and notched P wave with an interpeak interval in excess of 0.04 s and (2) negative phase of P in V_1 longer than 0.04 s and greater than 1 mm in lead V_1. There are, however, problems when applying these criteria in a given ECG. For example, according to Josephson,[110] prolonged duration of the P wave and of (posteriorly directed) terminal forces reflected delayed left atrial activation, not left atrial enlargement. In fact, most criteria mentioned above also apply for intraatrial block. Moreover, a negative P wave in lead V_1[110] may reflect improper (high) placement of this lead, a common error made by ECG technicians. Generally, if the previously mentioned findings are found in patients with LV enlargement or mitral stenosis, left atrial hypertrophy is most likely present, but in their absence, such findings usually indicate an intraatrial conduction defect. In any case, the ECG pattern of left atrial hypertrophy results from a hypertrophy-induced (stretching) intraatrial conduction delay.

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LV HYPERTROPHY

As emphasized by Surawicz,[111] since the advent of other noninvasive techniques, there has been a changing role for the ECG in the diagnosis of ventricular hypertrophy. Necropsy studies have exposed the superiority of echocardiography (see Chap. 13) with respect to electrocardiography to detect LV hypertrophy.[111] Echocardiography is also a better method for the serial follow-up of changes during progression or regression of LV hypertrophy. Multiple criteria have been proposed to diagnose LV hypertrophy using necropsy or echocardiographic information[49,112-115] (Tables 11-4 and 11-5). Of these, the Sokolow-Lyon criterion (SV_1 + RV_{5-6} ≥35 mm) is the most specific (>95 percent) but is not very sensitive (≈45 percent) (see Table 11-4). The Romhilt-Estes score has a specificity of 90 percent and a sensitivity of 60 percent in studies correlated with echocardiography. The following are some of the other criteria[49]: The Casale (modified Cornell) criterion (Ra_{VL} + SV_3 >28 mm in men and >20 in women) is somewhat more sensitive but less specific than the Sokolow-Lyon criterion.[116] The Talbot criterion[117] (R ≥16 mm in a_{VL}) is very specific (>90 percent), even in the presence of MI and ventricular block, but not very sensitive. The Koito and Spodick criterion[118] (RV_6 > RV_5) claims a specificity of 100 percent and a sensitivity of more than 50 percent. According to Hernandez Padial,[119] a total 12-lead QRS voltage of greater than 120 mm is a good ECG criterion of LV hypertrophy in systemic hypertension and is better than those most frequently used. With echocardiography as the "gold standard," several authors postulated ECG criteria for diagnosis of LV hypertrophy in the presence of complete LBBB and LAFB[120,121] (Tables 11-6 and 11-7). The high sensitivity and specificity reported by Gertsch et al.[121] for diagnosis of LV hypertrophy with LAFB have not been corroborated in preliminary studies performed in our department (unpublished observations; nevertheless indicated in Table 11-7).

Table 11-4: Electrocardiographic Criteria for Left Ventricular Enlargement

	SENSITIVITY		
Specificity Accuracy Voltage Criteria	(%)	(%)	(%)
RI + S_{III} > 25 mm	10.6	100	55
RVL > 7.5 mm	22.5	96.5	59.5
RVL > 11 mm	10.6	100	55
RVF > 20 mm	1.3	99.5	50
SV_1 + RV_{5-6} > 35 mm (Sokolow-Lyon)	55.6	89.5	73
In V_1-V_6, the tallest S + the tallest R > 45 mm	45	93	69
RV_{5-6} > 26 mm	25	98	62

Romhilt-Estes score	See Table 11-5

SOURCE: Used with permission from Bayes de Luna.[49]

Table 11-5: Point Score System of Romhilt and Estes for Diagnosis of Left Ventricular Hypertrophy

1. Amplitude, 3 points
Any of the following:
a. Largest R or S wave in the limb leads ≥ 20 mm
b. S wave in V_1 or V_2 ≥ 30 mm
c. R wave in V_5 or V_6 ≥ 30 mm
2. ST-T-segment changes (typical pattern of left ventricular strain with the ST-T-segment vector shifted in direction opposite to the mean QRS vector)
Without digitalis, 3 points
With digitalis, 1 point
3. Left atrial involvement, 3 points
Terminal negativity of the P wave in V_1 is 1 mm or more in depth with a duration of 0.04 s or more
4. Left-axis deviation: -30° or more, 2 points
5. QRS duration ≥ 0.09 s, 1 point
6. Intrinsicoid deflection in V_5, V_6 = 0.05 s, 1 point

Note: sensitivity, 54%; specificity, 97%.
SOURCES: From Bayes de Luna[49] and Romhilt and Estes,[115] with permission.

Table 11-6: Criteria for Diagnosis of Left Ventricular Hypertrophy in Presence of Complete Left Bundle Branch Block

1. RaV_L ≥ 11 mm
2. Electrical axis ≥ 40° (or $S_2 \geq R_1$)
3. SV_1 + RV_5 or RV_6 ≥ 40 mm
4. SV_2 ≥ 30 and SV_3 ≥ 25 mm

Sensitivity (%)	Specificity (%)
24	100
39	100
58	97

	75		90

Note: Left ventricular hypertrophy diagnosed by echocardiography when left ventricular mass is 115 g/m^2 or more.
SOURCE: Used with permission from Kafka et al.[120]

Table 11-7: Criteria for Diagnosis of Left Ventricular Hypertrophy in Presence of Left Anterior Fascicular Block[*]

Study	ECG Criteria	Sensitivity(%)	Specificity(%)	PositivePredictiveValue (%)	NegativePredictiveValue (%)
Bozzi and Figini	SV_1 + (RV_5 + SV_5) ≥ 25 mm	69	92	90	73
Milliken	RaV_L ≥ 13 mm	35	92	82	56
Milliken	SIII ≥ 15 mm	38	87	77	57
Gerstch et al.[143]	SIII + maximal sum of R+S in any single precordial lead	96	87	89	95
Reevaluated Gerstchcriteria[†]		80	55	78	58

*Left ventricular hypertrophy diagnosed by echocardiography when left ventricular mass is ≥ 124 g/m^2.†Unpublished observations performed in our department.
SOURCE: Used with permission from Gerstch et al.[121]
SOURCE: See text.

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PROCESSES PRODUCING OR LEADING TO RV HYPERTROPHY AND ENLARGEMENT

RV hypertrophy is manifest in the ECG only when the RV forces predominate over those of the left ventricle. Since the latter has, roughly, three times more mass than the former, the right ventricle may double in size (when the left ventricle is normal) or triple its weight (when there is significant LV hypertrophy) and still not result in the necessary requirements to pull the electrical forces anteriorly and to the right. For these reasons, RV hypertrophy cannot be recognized easily in adult patients. Despite these limitations, the ECG manifestations of RV hypertrophy or enlargement can be subdivided into the following main types[1] (see Figs. 11-11, 11-12, and 11-16): (1) the posterior and rightward displacement of the QRS forces associated with low voltage, as seen in patients with pulmonary emphysema (Fig. 11-30), (2) the incomplete RBBB pattern *with right-axis deviation* occurring in patients with chronic lung disease and some congenital cardiac malformations resulting in volume overloading of the right ventricle (Fig. 11-31), (3) the true posterior wall MI pattern with normal to low voltage of the R wave in V_1 of mitral stenosis (Fig. 11-32), and (4) and the classic RV hypertrophy and strain pattern seen in young patients with congenital heart disease (producing pressure overload) or in adult patients with high-pressure ("primary" pulmonary) hypertension (Fig. 11-33). False patterns of RV hypertrophy may occur in patients with true posterior (basal) MI, complete RBBB with LPFB, and Wolff-Parkinson-White syndrome resulting from AV conduction through left free wall or posteroseptal accessory pathways.

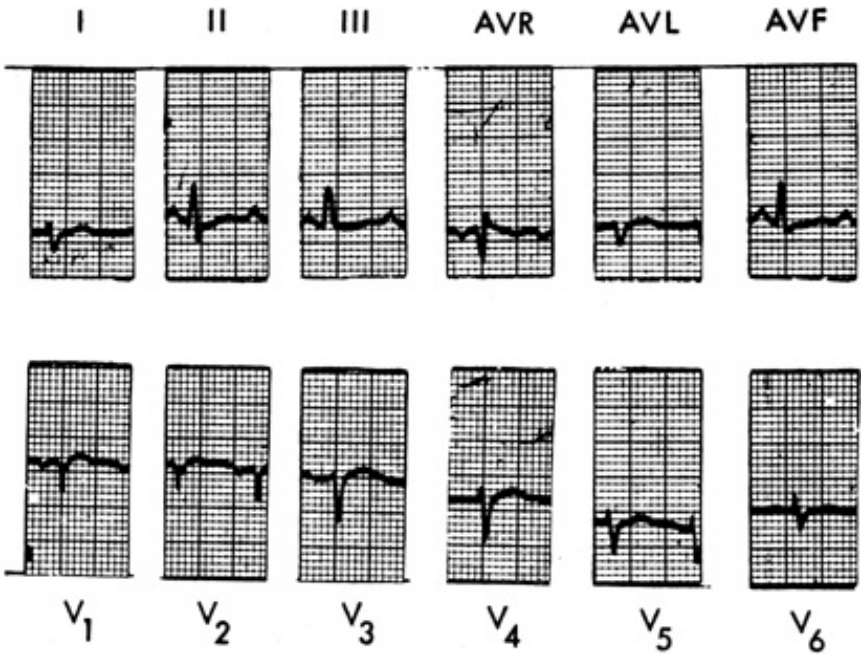

Figure 11-30: ECG taken on a patient with pulmonary emphysema showing slight right-axis deviation with small rS complexes in lead I, an electrically vertical heart position, overall tendency to low voltage, and rS complexes in all chest leads. (From Lemberg and Castellanos.[151] Reproduced with permission from the publisher and authors.)

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ELECTROLYTE IMBALANCES

Because multiple factors can affect ventricular repolarization in diseased hearts, the finding characteristic of a specific electrolyte abnormality may be modified, and even mimicked, by various pathologic processes and the effects of certain drugs. In practice, the major problem with the ECG diagnosis of electrolyte imbalance is not the negative ECG with abnormal serum values but the production of similar changes by other conditions in patients with normal serum values.[122]

Hyperkalemia

The initial effect of acute hyperkalemia is the appearance of peaked T waves with a narrow base (Fig. 11-34, *left*). The diagnosis of hyperkalemia is almost certain when the duration of the base is 0.20 s or less (with rates between 60 and 110 beats per minute).[122] As the degree of hyperkalemia increases, the QRS complex widens (Fig. 11-35), with the electrical axis usually being deviated abnormally to the left and only rarely to the right. In addition, the PR interval prolongs, and the P wave flattens until it disappears.[45,122] If untreated, death ensues either due to ventricular standstill or coarse, slow ventricular fibrillation. Death also can result if wide QRS complexes occurring at fast rates are diagnosed as ventricular tachycardia and the patient is treated with antiarrhythmic drugs. On the other hand, class IA, IC, and III drugs as well as large doses of tricyclic antidepressants (especially when ingested for suicidal purposes) also can produce marked QRS widening. These processes, however, do not coexist with narrow-based, peaked T waves. Rarely, hyperkalemia produces (in the absence of coronary artery disease) a degree of ST-segment elevation in the right chest leads capable of suggesting anteroseptal myocardial injury (see Fig. 11-35). These constitute the "dialyzable currents of injury in potassium intoxication" reported by Levine et al.[123]

Hypokalemia

The abnormal and delayed repolarization that occurs in hypokalemia is best expressed as QU, rather than QT, prolongation, since at times it can be difficult to differentiate between notchingof the T wave and T- and U-wave fusion.[122] On the basis of the previously mentioned M cells, these U waves are part of notched T waves, suggesting that that term be used in place of U. As the serum potassium level falls, the ST segment becomes progressively more depressed, and there is a gradual blending of the T wave into what appears to be a tall U wave (Fig. 11-36, *top*). An ECG pattern similar to that of hypokalemia can be produced by some antiarrhythmic drugs, especially quinidine and, experimentally, DL-sotalol. In any case, when repolarization is greatly prolonged, ventricular arrhythmias, including the so-called torsades de pointes, can occur.

Hypomagnesemia

Hypomagnesemia does not produce QU prolongation unless the coexisting hypokalemia (with which it is almost invariably associated) is severe.[122] Long-standing and very marked magnesium deficiency lowers the amplitude of the T wave and depresses the ST segment.[122] It may be difficult to differentiate the changes produced by magnesium from those produced by potassium. For this reason, it has been stated that hypomagnesemia does not cause any changes in the ECG.[45]

Hypermagnesemia

Similarly, in clinical tracings, the effects of hypermagnesemia on the ECG are difficult to identify because the changes are dominated by calcium.[124] According to some authors, administration of intravenous magnesium to patients with normal ECGs may shorten the QT interval.[45] Other authors found no effects on ventricular refractoriness that are reflected by changes in the QT interval.[125] Intravenous magnesium given to patients with torsades de pointes controls the arrhythmia in a high percentage of patients without changing the prolonged QT interval significantly.[126] The calcium-blocking activity of magnesium was suggested to be one of the mechanisms responsible for this antiarrhythmic activity.[146]

Hypercalcemia

During sinus rhythm with normal rates, the QT interval is short (see Fig. 11-36, *bottom*). In some cases, the Q-to-apex of T intervals is also short. If factors known to modify the QT interval are not present, it has been said that a reasonably accepted correlation exists between the duration of the interval and serum calcium levels.[122] Occasionally, the ST segment disappears, and the T waves may become inverted in left and right chest leads. Digitalis also shortens the QT interval but produces its characteristic "effects" in leads where the R waves predominate. The classic upward concavity of the ST segment is seen in the left chest leads in patients with LV hypertrophy and in leads V_1 and V_2 when there is RV hypertrophy (with predominantly positive deflections in these leads).

Hypocalcemia

The typical ECG pattern of hypocalcemia consists of QT prolongation at the expense of the ST segment.[45,122] The T wave is usually of normal width but can be narrow if there is coexisting (moderate) hyperkalemia (see Fig. 11-34*B*). A very marked injury (with the so-called hyperacute ST-T changes) can produce a similar pattern, but in such cases the T wave, though peaked, is not as narrow based. It has been said that hypocalcemia per se does not produce T-wave inversion. When present, the latter is usually a reflection of coexisting processes such as LV hypertrophy and incomplete LBBB. An ECG pattern similar to that of hypocalcemia can be produced by some organic abnormalities of the central nervous system and by congenitally prolonged QT intervals (see below).

QT Interval: Normal and Prolonged

The QT interval is measured from the beginning of the q wave to the end of the T wave.[1,11] The latter may be difficult to define. The point at which the maximal downslope of the T wave crosses the baseline helps to identify the end of this wave.[45] The QT interval is affected by autonomic tone and cathecolamines and has day-night differences. It varies with heart rate and sex. Several formulas have been proposed to take these variables into account and provide a corrected measurement (QTc interval).[127]

In general, the unadjusted (noncorrected), usually resting QT interval decreases from ±0.42 s at rates of 50/min to ±0.32 s at 100/min to ±0.26 s at 150/min.[9,11] During exercise, the rate becomes faster; the QTc first increases until reaching, approximately, a rate of 120/min, thereafter again decreasing.[128] Although the value of the normal QTc is open to question, it is still used in routine computer interpretations. Because the 12-lead ECG shows a normal degree of QT and QTc dispersion, indexes have been used to quantify the extent of heterogeneity in ventricular repolarization. The difference between the longest and shortest QT interval is referred to as *QT dispersion*.[129-134] Since 1990 it has been used as a prognostic marker not only in patients with

prolonged QT intervals but also in those with acute MI.[130-132] The upper limits of normal vary with different investigators; a value of 65 may be an acceptable compromise according to Antzelevitch.[14] Others may disagree. Coumel et al.[133] emphasized that QT dispersion could be an illusion or a reality.[133] Inferred from the oncoming section on spatial vectorcardiography, the fact is that a truly *spatial* QRS-T loop cannot yield *abnormal* QT dispersion, for in planar projections of this spatial loop (as well as in the standard and unipolar extremity leads of the ECG) the shortest interval occurs because the terminal forces are perpendicular to the plane or derived lead. On the other hand, if precordial leads are considered scalar leads capable of recording (as stated in a previous section) local potentials with different durations, then QT dispersion is a reality.

The M-cell studies of Antzelevitch allow for the differentiation of this global "dispersion" (derived from *multiple* leads) from "local" transmural dispersion in *single* leads reflecting the time elapsing between the peak of the T wave (given by the end of the composite epicardial action potentials) and the end of the T wave (given by the end of the composite M-cell action potentials).[14]

The QT intervals are shortened with hypercalcemia, pure hyperkalemia, digoxin, and acidosis.[45] Prolongation of the QT interval may be congenital or acquired and is an important marker for malignant ventricular arrhythmias (see Chap. 24). A partial list of conditions causing a prolonged QT or, in some instances, prolonged QU intervals (delayed repolarization) is given in Table 11-8.[45]

Table 11-8: Acquired QT Prolongation Usually Bradycardia-and(or) Pause-Dependent

1. Electrolyte disturbances
a. Hypokalemia
b. Hypocalcemia
c. Hypomagnesemia
2. Drugs
a. Class IA antiarrhythmic agents (quinidine, disopyramide, procainamide)
b. Class III antiarrhythmic agents (amiodarone, sotalol)
c. Psychotropic drugs
3. Central nervous system diseases
a. Subarachnoid hemorrhage
b. Ruptured berry aneurysm
c. Cryptococcal meningitis
4. Congenital syndromes
5. Electrocardiographic ischemia
6. Arrhythmias
a. Posttachycardia syndrome

b. Cardiac arrest of any etiology
c. Chronic idioventricular rhythms
7. Hypothermia

Hypothermia

Characteristic ECG changes develop when the body temperature drops to approximately 30°C.[11] The QT interval becomes prolonged. In addition, a deflection, called an *Osborn wave*, appears in a place said to be located between the end of the QRS complex and the beginning of the ST segment[135] (Fig. 11-37). This deflection has been attributed to delayed depolarization, to a current of injury, or to "early" repolarization.[153] In leads facing the left ventricle, the deflection is positive, and its size is inversely related to body temperature. The role played by the intramyocardial M cells in its genesis has been discussed previously.[14]

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ARTIFACTS

During the last few years, the number and types of instruments used for noninvasive and invasive (electrical and nonelectrical) study of cardiac functions have multiplied. Naturally, physicians and hospital administrators have concentrated their attention on them. Technicians have been more interested in working in these more lucrative services. Such factors, and others, have downgraded the importance of recording 12-lead ECGs, relegating them to less qualified personnel. Not surprisingly, the quality of technicians and of the ECG that they record has deteriorated in many centers. Optimal quality can only be achieved if the parties involved understand what is happening. The following are some of the artifacts commonly seen in current routine 12-lead ECGs. They are important because they can confound the interpreter and, worse, the computer program.

Muscle Tremor and Alternating-Current Interference

These are the most frequently encountered artifacts because some patients will continue to have disease processes producing tremor and because the amount of electronic equipment causing interference in a hospital environment has increased.

Improper Limb-Lead Positioning

This has become more frequent after relaxation of quality control, especially in hospitals with inadequate standards for hiring technicians and with poor on-site training. Mixing up the cables from the ECG machine has gone beyond switching the right arm and left arm cables.[11] Various types of misplacements of only one cable are illustrated in Fig. 11-38. The method depicted in this illustration, based on the use of unipolar extremity leads only, is simpler than those incorporating the analysis of bipolar standard leads.[11] Not frequently recognized in ECG textbooks is the incontrovertible fact that in some centers even the "sanctity" of the attachment of the right leg (ground) cable to the right leg has been violated[136] (Fig. 11-39). In our experience, this error is usually identified as improper lead placement, but determination of the cables involved is usually not made correctly.[136]

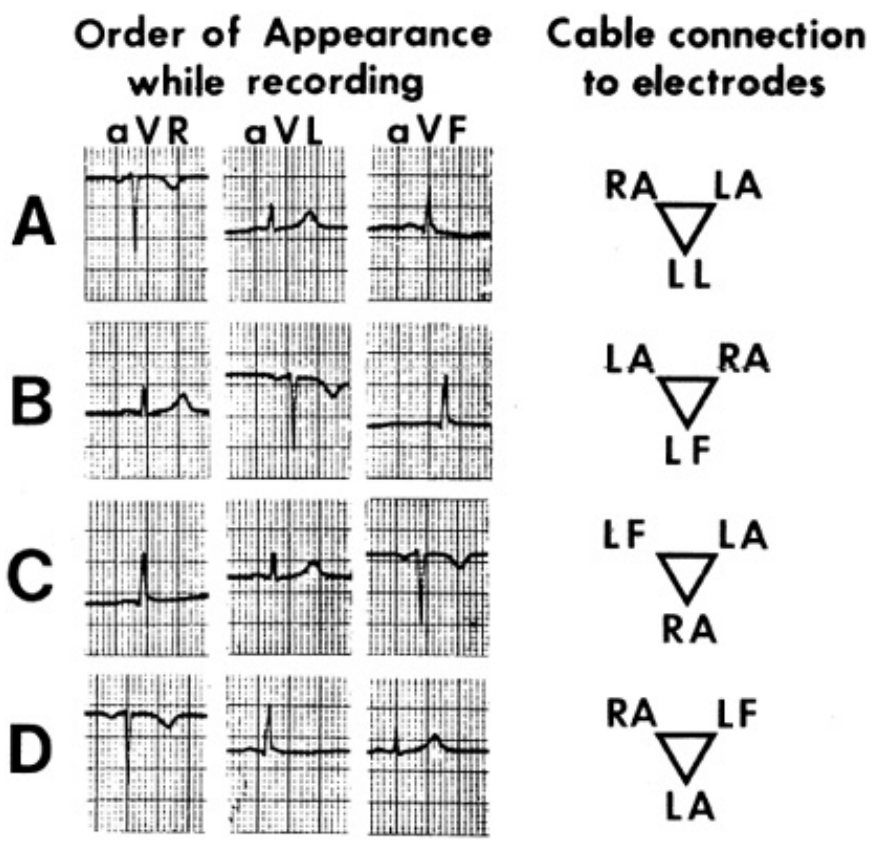

Figure 11-38: Identification of improper connections of a single cable from the electrocardiographic machine to the corresponding electrodes placed on the patient's limbs. Note that aV_R, aV_L, and aV_F invariably refer to whatever morphology is recorded when, while the ECG is being obtained, the corresponding knobs are turned in this order (regardless of whether the cables were attached properly or improperly). On the other hand, RA (right arm), LA (left arm), and LL (left leg) or LF (left foot) correspond to the normal morphology recorded by the cables so labeled. This method, based solely on the analysis of the unipolar extremity leads, is simpler than the method based on the study of the bipolar standard leads but is useful only when a single cable is misconnected. *A.* Normal. *B.* Since LA appears in aV_R and RA appears in aV_R (with LF being in its normal position), the right arm and left arm cables must have been switched. *C.* Since LF appears in aV_R and RA appears in aV_F (with LA in its normal position), the right arm and left leg cables must have been switched. *D.* Since LA appears in aV_F and LF appears in aV_L (with RA in its normal position), the left arm and left leg cables must have been switched.

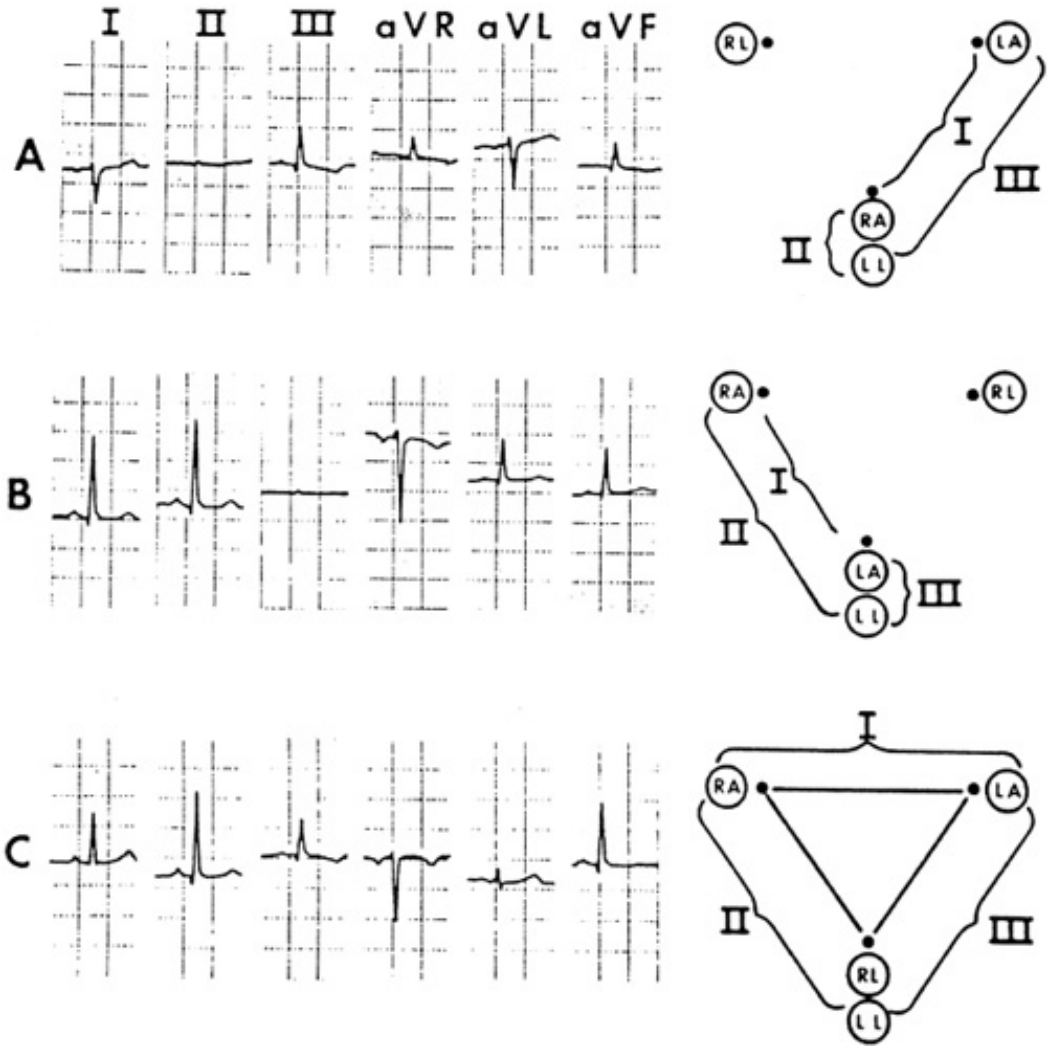

Figure 11-39: Identification of improper connections of the right leg (RL) (ground) cable. *C* can be regarded as almost equal to the control tracing because the RL (ground) and left leg (LL) cables were switched. The corresponding morphologies are not identical to the control morphologies because a very small difference in potential between both legs does exist. The latter is seen in *A*. Because the RL and RA cables were switched, lead II (RA-LL) records the difference in potential between both legs, which seems to be approximately 0.15 mV. The latter results in an almost straight line interrupted by a small blip. In addition, lead I represents the mirror image of normal lead III, and lead III is the normal lead III. In *B*, where the LA and RL cables have been switched, lead III (LA-LL) records almost a straight line. In addition, lead I is the normal lead II, and lead II is the normal lead II. [From Castellanos A, Saoudi NC, Schwartz A, et al. Electrocardiographic patterns resulting from improper connection of the right leg (ground) cable. *PACE* 1985; 8:364-368. Reproduced with permission from the publisher and authors.]

Variations in Precordial-Lead Placement

This is a problem more common now than when, in 1961, Simonson noted the considerable variation in chest lead placement in the same patient by different technicians and even by the same technician in several ECGs in the same patient.[137] Simonson also found that in a controlled study, placement of the V_2 electrode varied 10 cm vertically and 8 cm horizontally in 103 healthy subjects.[137] Moreover, Kerwin et al.[138] found a rather large error in placement of chest electrodes (2 to 3 cm in both the horizontal and vertical directions) in repeated trials in the same patients by the same technicians.[138] Perhaps the frequency of precordial-lead misplacement is greater than that of somatic tremor. In our institution, the most frequent cause of "poor" r-wave progression in the anteroseptal leads (often misinterpreted by the computer as indicative of anteroseptal MI) is

misplacements of leads V_2 and V_3.

False Variations in Voltage

Garson[139] noticed how, in several patients, ECGs taken weeks apart showed markedly different QRS voltages. The latter were sometimes of enough magnitude to cause a pseudonormalization of a ventricular hypertrophy pattern. There had been no changes in hemodynamics, but different types of ECGs were used. A study of this problem demonstrated that electrocardiographic data had a different voltage depending on whether they were recorded and displayed on an analog electrocardiograph or on a digital electrocardiograph. Thus, if there is a statistically significant difference among ECGs, the serial comparisons must be done with the same machine. Moreover, criteria for voltage are only applicable to the type of instrument with which the data were gathered.

In addition, overshooting, overdamping, and running down of the standardization battery can cause significant changes in QRS voltage and ST segments.

How Should an ECG Be Performed?

This question is appropriate in view of the many artifacts and technical (machine and human) problems occurring when ECGs are recorded. The Task Force of the American College of Cardiology (ACC)-American Heart Association (AHA) in their *Guidelines for Electrocardiography*[4] have stated that the ECG should be performed and interpreted in accordance with the guidelines for optimal electrocardiography described in the ACC *Tenth Bethesda Conference Report*,[140] the guidelines for training described in the ACC *Seventeenth Bethesda Conference Report on Cardiology Training*,[141] the recommendations for standardization of leads and specifications for instruments in electrocardiography and vectorcardiography of the AHA,[142] and the recommendations for standardization and specifications for automated electrocardiography of the AHA.[143]

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COMPUTER APPLICATIONS

It has been almost 40 years since the first attempts were made to apply computer technology to the interpretation of ECGs.[144] Today its use is universal.[1,144-147] In general, computer systems for true analysis of ECGs have, as their main component, a program usually having the following four basic functions: (1) the measuring of ECG parameters, which includes an automatic wave-front-recognition section and a measurement section that extracts the wave fronts, a set of values, and control, (2) theinterpretation of previously acquired information, responsible for the final statements generated by the program, (3) the identification of various rhythms, both normal and abnormal, and (4) the comparison with previous ECGs to recognize significant changes. There is a lack of standardized, universally agreed-on diagnostic terms and criteria. This problem, however, is not solely that of computers but is related to all ECG interpretations, whether performed by individuals or by machines. It has to be remembered that the program used depends on criteria imposed on it by human programmers. Physicians should insist that the program selected has to be "tuned in" with the operational environment (e.g., community hospital or teaching institution, urban center or rural areas, etc.) in which it has to perform. Once a program has been selected and is in use, it requires initial and periodic evaluation. The most practical method consists of accepting as standard constrained human observers, the constrained observers being given a set of measurements or criteria agreed on before the evaluation. Proper computerization has the following definite advantages: (1) speed in providing reports with the resulting improved turnaround time, (2) optimal utilization of emergency ECG services, (3) reproducibility of measurements, (4) improvements in quality control, (5) possible decrease in physician's reading time and more consistency in interpretations, (6) enhancement of the capacity to handle large volumes of ECGs, and (7) substantial improvement in record storage and retrieval with better comparison with previous tracings.

Administrators are usually the ones selecting equipment, and frequently they know nothing about its medical performance. They usually use standard cost-effective, not medically-effective methods. That is, the economics involved-initial investment, operational costs, payroll, overhead, and professional fees-become priorities. This is important because it was estimated that even 10 years ago more than 40 percent of all ECGs recorded in the United States were obtained by some type of automatic system.[144] Presently, however, this figure is reaching 100 percent. Finally, emphasis should be placed on the obvious: All computer ECG interpretations, particularly those of rhythm disturbances, must be checked by a physician qualified to interpret ECGs and with an in-depth knowledge of the program used. Decisions based on a computerized interpretation may, on occasion, lead to improper patient care. This also can have medicological implications. Of clinical importance was the report finding that computer interpretations of ECGs obtained 1 min apart were grossly different in 36 of 92 (39 percent) unselected pairs of tracings.[148] The latter refers to only one program but nevertheless should be an impetus to designers and manufacturers to improve their product and a warning to those who rely, exclusively, on computer interpretations.[148] The ACC/AHA Task Force on Guidelines for Electrocardiography states: "There is no computer program that can replace the skilled physician."[4] Finally, cardiology fellows in training should interpret ECGs without a printed computer interpretation rather than by having to evaluate the latter.

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SPATIAL VECTORCARDIOGRAPHY

Generalities

The following statements, which need reemphasis, should not be considered redundant: (1) Since the ECG deals with electrical forces, it follows that very strictly speaking, electrocardiography can be considered vectorial.[149,150] (2) Orthodoxically, a scalar quantity only has magnitude, whereas a vector quantity has magnitude, direction, and sense. When analyzing the vectorcardiogram (VCG), one should consider the activation of each muscle cell as producing an electrical force that can be represented by a vector depicting the spatial orientation and magnitude of this force.[149]

During the spread of the activation process, innumerable electrical forces are generated. These multiple forces vary in magnitude and differ in direction. At any given moment, the resultant of these electrical forces can be represented by a spatial vector possessing magnitude, direction, and sense. This vector is referred to as an *instantaneous vector* and represents the resultant of *all* the forces of the heart acting at that particular moment. Immediately afterward, the wave of accession spreads to different areas of the myocardium, and the new instantaneous vector representing all the forces of the heart now occupies a different spatial position and has a different magnitude. This continues throughout the cardiac cycle, with the succeeding instantaneous vector occupying different spatial positions. If all manifest spatial vectors are diagrammatically represented as having a common point of origin, and if the distal points of the vectors are joined, a single spatial loop is formed for ventricular depolarization (QRS), ventricular repolarization (ST-T), and the atrial complex (P). The VCG consists of four different loops. The electrical activity of the atria is recorded as a small loop designated the *P loop*, the depolarization of the ventricles is recorded as a large loop designated the *QRS loop*, while the repolarization of the ventricles is recorded as a smaller loop designated the *ST-T loop*. Finally, at high magnifications, even a small *U loop* also can be recorded.[149-153]

Space: The Final Frontier

The theory of the truly spatial VCG is theoretically attractive. Because the heart is a tridimensional structure (located in space), its electrical activity should best be recorded by a spatial method. Indeed, space, as conceived by physicists through objects and their motion, has three dimensions, and positions are characterized by three numbers. The instant of an event is the fourth number. Four definite numbers correspond to every event; a definite event corresponds to any four numbers. Therefore, the world of events really forms a four-dimensional continuum. Unfortunately, judging by what is being published in the literature, the quest for finding an optimal method of visualizing the spatial loop apparently has been abandoned. Nevertheless, the spatial VCG is still of importance in children with congenital and acquired heart disease because in this population the criteria for pressure and volume overloading have proven value.[151] In our opinion, it is also of great value in categorizing the various types of intraventricular conduction defects.[151-153] While this may be attributed to the spatial technique per se, it also can be due to the use of instruments having a higher fidelity than routinely employed electrocardiographs. The VCG also has been found useful in detecting MI and certain types of RV enlargement.[151-153] In practice, it has not been proven that the VCG gives more information than the routine 12-lead ECG,[151] although some computer programs may still use the Frank orthogonal leads *X*, *Y*, and *Z*.

These programs thus constitute a 15-lead system. In addition, the time required to obtain a VCG is longer than the time required to record a 12-lead ECG. These are the main reasons for the decrease in the use of spatial vectorcardiography during recent decades. Other reasons are nonreimbursement and the continuously increasing interest in other noninvasive methods of recording electrical activity (such as signal averaging, body surface mapping, and heart rate variability) or nonelectrical activity (such as echocardiography or magnetic resonance imaging, which looks at planes from *different* views). To obtain the spatial VCG, electrodes are placed on the body surface in a way to record three leads whose planes are at right angles to each other. The true spatial VCG requires three corrected orthogonal leads with the following features[151-154]: (1) Mutual perpendicularity, with each lead being parallel to one of the rectilinear coordinate axes of the human body. Such axes are the horizontal, *X* (left-to-right and right-to-left) axis; the vertical, *Y* (inferosuperior or superoinferior) axis; and sagittal, *Z* (anteroposterior or posteroanterior) axis. (2) Equal amplitude from the vectorial viewpoint. (3) Retention of the same magnitude and direction for all points where cardiac electromotive forces are generated. For example, even if the leads forming Einthoven's frontal plane were to be spatially correct, Einthoven's theory itself would make any electrodes placed for the purpose of obtaining the horizontal and sagittal planes (such as the tetrahedral system) spatially incorrect. The most widely used, corrected spatial VCG method probably is the one introduced by Frank.[154] Since the spatial loop cannot be analyzed tridimensionally, it is customary to study its planar projections (Fig. 11-40). By proper attachment to the oscilloscope, the *X* and *Y* leads are used for the frontal plane, the *X* and *Z* leads for the horizontal plane, and the *Z* and *Y* leads for the sagittal plane (of which the right side has been the most popular).

Differences between Electrovectorcardiography and Spatial Vectorcardiography

Spatial vectorcardiography is distinctly different from the various vectorial methods of ECG interpretation, such as those of Sodi-Pallares et al.[7] and Grant.[56,57] In clinical practice and in teaching, both seem to be considered equal, but this is so only for pragmatic and didactic reasons. Although the spatial VCG and the ECG should each be studied as distinct methods, most electrocardiographers either memorize loop patterns or attempt to derive the leads with which they are familiar from the corresponding QRS loops. Thus bipolar standard and unipolar extremity leads are derived from the frontal plane more or less as when, in clinical ECG, they are derived from the electrical axis. To do this in spatial vector loops, the electrical axis is equated with the maximal QRS vector that extends from the point of origin of the loop to its farthest point. The unipolar precordial leads are derived from the horizontal plane loops. Leads thus derived are different from the usual precordial ECG leads. The latter, as mentioned previously, record electrical forces moving toward or away from them, including local potentials that can be of different duration in different precordial leads.[13,35,133] In the 12-lead ECG (especially when the precordial electrodes are misplaced), however, these forces can move spatially not only in a left-to-right and anteroposterior direction but also in an inferosuperior direction as in leads V_5 and V_6 in patients with a very superior and leftward deviation of the EA. On the other hand, the theory of spatial vectorcardiography states that the horizontal plane and unipolar leads derived from them just record left-to-right and anteroposterior forces and that they do not record local potentials so that any difference in the duration of intervals is merely an illusion[133,151] (Fig. 11-41). In spatial vectorcardiography, electrical forces oriented superiorly or inferiorly cannot be reflected in the horizontal plane but only in the frontal and sagittal planes. Most of the information contained in the sagittal plane is present in the frontal and horizontal planes. In practice, the sagittal plane is useful to act as a "judge" in cases of apparent discrepancy between the other two planes. For example, it serves to determine if a localized delay present in one of the two planes is "real" or is due to perpendicularity of vectors. It also serves for a better evaluation of the upward or downward direction of the initial 0.01- and 0.02-s vectors than the frontal plane. Projections of normal spatial QRS and ST-T loops in the corresponding planes are depicted in Fig. 11-42.

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Figure 11-22: Morphologic features of complete LBBB complicated by acute inferior MI. There is abnormal ST-segment elevation in leads II, III, and aV_F (QRS duration: 0.14 s). AV block is also present.

Figure 11-23: *A.* Complete LBBB with old anterior MI. Abnormal Q waves are present in lead I (QRS duration: 0.18 s). *B.* Pacing-induced complete LBBB pattern in a patient with old anterior MI. There are abnormal Q waves in lead I after spikes (QRS duration: 0.20 s). Note resemblance between natural and artificial (electrically induced) QRS patterns.

Figure 11-24: Wolff-Parkinson-White syndrome in a patient with a left free-wall accessory pathway. *A.* Sinus rhythm with fusion beats showing different degrees of preexcitation. *B.* Maximal preexcitation during atrial fibrillation. Note marked change in QRS duration and electrical axis.

Figure 11-25: Wolff-Parkinson-White syndrome in a patient having a posteroseptal accessory pathway. Note short PR intervals with negative delta waves in leads III and aV_F (false pattern of inferior MI). Lead V_2 shows all-positive QRS complexes.

Figure 11-26: Wolff-Parkinson-White syndrome in a patient with a right free-wall accessory pathway. Note LBBB "pattern" characterized for diagnostic (of accessory pathway location) purposes by a QRS duration greater than 0.09 s in lead I with rS complexes in leads V_1 and V_2. The electrical axis is approximately +15°.

Figure 11-27: Wolff-Parkinson-White syndrome in a patient with a right anteroseptal accessory pathway. Note LBBB pattern (as defined in Fig. 11-26). The most important difference with the latter is that the electrical axis points more vertically, toward +60°, thereby being located within the range of the axis (+30 to +120°) reported for right anteroseptal accessory pathways.

Figure 11-28: Useful algorithm to predict accessory pathway location from the 12-lead ECG. Step 1: Analysis of R/S ratio in V_2. Step 2: Existence of positive (+) delta wave in lead III (initial 40 ms). Step 3: Existence of positive or negative (-) delta wave in V_1 (initial 60 ms). Step 4: Delta-wave polarity in aV_F (initial 40 ms) or analysis of R/S ratio in V_1 (± = biphasic or isoelectric). The accuracy of the algorithm for each location in 187 prospective patients is also shown at the bottom. LAL, left anterolateral; LL, left lateral; LP, left posterior; LPL, left posterolateral; LPS, left posteroseptal; MS, midseptal; RA, right anterior; RAL, right anterolateral; RAS, right anteroseptal; RL, right lateral; RP, right posterior; RPL, right posterolateral; RPS, right posteroseptal. (From Chiang et al.[105] Reproduced with permission from the publisher and authors.)

Figure 11-29: QRS changes (location of the electrical axis and polarity of lead V_1) produced by pacing from right ventricular apex (RVA), right ventricular outflow tract (RVOT), great cardiac vein (GCV), and middle cardiac vein (MCV).

Figure 11-30: ECG taken on a patient with pulmonary emphysema showing slight right-axis deviation with small rS complexes in lead I, an electrically vertical heart position, overall tendency to low voltage, and rS complexes in all chest leads. (From Lemberg and Castellanos.[151] Reproduced with permission from the publisher and authors.)

Figure 11-31: ECG from a patient with RV enlargement (volume overload in type) due to a small atrial septal defect (ostium secundum). Right-axis deviation was associated with an incomplete RBBB pattern (rsR' complexes in lead V_1). (From Lemberg and Castellanos.[151] Reproduced with permission from the publisher and authors.)

Figure 11-32: ECG from a patient with RV hypertrophy due to pure mitral stenosis showing P "mitrale," right-axis deviation, an all-positive deflection (R wave of only approximately 5 mm) in V_1, and rS complexes from V_2 to V_6. (From Lemberg and Castellanos.[151] Reproduced with permission from the publisher and authors.)

Figure 11-33: ECG from a 17-year-old patient who had RV enlargement (pressure overloading in type) due to severe pulmonic stenosis. Note extreme right-axis deviation, overall high voltage, and qR complexes in lead V_1 without an incomplete RBBB pattern. (From Lemberg and Castellanos.[151] Reproduced with permission from the publisher and authors.)

Figure 11-34: Electrocardiographic manifestations of early hyperkalemia. The nonprolonged QRS complex is followed by a peaked T wave having a very narrow base. Uncorrected and corrected QT intervals of 0.32 and 0.44 s, respectively (*A*). Hyperkalemia with hypocalcemia characterized by prolongation of the QT interval at the expense of the ST segment preceding the narrow-based T wave. Uncorrected and corrected QT intervals of 0.52 and 0.53 s, respectively (*B*).

Figure 11-35: Advanced hyperkalemia. The wide (0.14-s) QRS complexes are followed by peaked T waves (best seen in lead V_3). The hyperkalemia-induced ST-segment elevation in lead V_1 (*arrows*), known as the *dialyzable currents of injury*, disappeared after appropriate treatment.

Figure 11-36: Electrocardiographic manifestations of hypokalemia (*upper strip*) and hypercalcemia (*lower strip*).

Figure 11-37: ECG obtained from a patient with hypothermia. The characteristic Osborn wave (*arrows*) is the terminal deflection inscribed between the slender part of the QRS complexes and the beginning of the ST segment. Note that it is not easy to determine where the ST segment starts. In addition, there is marked prolongation of the QT interval.

Figure 11-38: Identification of improper connections of a single cable from the electrocardiographic machine to the corresponding electrodes placed on the patient's limbs. Note that aV_R, aV_L, and aV_F invariably refer to whatever morphology is recorded when, while the ECG is being obtained, the corresponding knobs are turned in this order (regardless of whether the cables were attached properly or improperly). On the other hand, RA (right arm), LA (left arm), and LL (left leg) or LF (left foot) correspond to the normal morphology recorded by the cables so labeled. This method, based solely on the analysis of the unipolar extremity leads, is simpler than the method based on the study of the bipolar standard leads but is useful only when a single cable is misconnected. *A*. Normal. *B*. Since LA appears in aV_R and RA appears in aV_R (with LF being in its normal position), the right arm and left arm cables must have been switched. *C*. Since LF appears in aV_R and RA appears in aV_F (with LA in its normal position), the right arm and left leg cables must have been switched. *D*. Since LA appears in aV_F and LF appears in aV_L (with RA in its normal position), the left arm and left leg cables must have been switched.

Figure 11-39: Identification of improper connections of the right leg (RL) (ground) cable. *C* can be regarded as almost equal to the control tracing because the RL (ground) and left leg (LL) cables were switched. The corresponding morphologies are not identical to the control morphologies because a very small difference in potential between both legs does exist. The latter is seen in *A*. Because the RL and RA cables were switched, lead II (RA-LL) records the difference in potential between both legs, which seems to be approximately 0.15 mV. The latter results in an almost straight line interrupted by a small blip. In addition, lead I represents the mirror image of normal lead III, and lead III is the normal lead III. In *B*, where the LA and RL cables have been switched, lead III (LA-LL) records almost a straight line. In addition, lead I is the normal lead II, and lead II is the normal lead II. [From Castellanos A, Saoudi NC, Schwartz A, et al. Electrocardiographic patterns resulting from improper connection of the right leg (ground) cable. *PACE* 1985; 8:364-368. Reproduced with permission from the publisher and authors.]

Figure 11-40: The spatial vectorcardiographic loops cannot be analyzed routinely in space with presently available techniques. Therefore, it is customary to study their projections in three planes seen as depicted in this figure. Note that (1) the frontal plane conforms to Einthoven's view of his equilateral triangle, (2) the horizontal plane is seen in such a way that the anterior surfaces of the heart and sternum are displayed in the inferior portions of the paper (in contrast to other noninvasive, nonelectrical methods), and (3) the sagittal plane is viewed from the right side of the patient. (From Lemberg and Castellanos.[151] Reproduced with permission from the publisher and authors.)

Figure 11-41: Method used to derive the morphology of a unipolar precordial lead (in this example lead V_6) from the planar projection of the spatial QRS and ST-T loops on the horizontal plane. First (*left panel*), a line is drawn from the estimated location of the corresponding electrode to the point of origin of the loops. Thereafter, a perpendicular to this line passing from the point of origin is drawn. This divides the thorax into a negative area (for V_6) that is located beyond the perpendicular line and a positive area that is located between the perpendicular line and the electrode. Thus, in the top right schematic, the small part of the loop located beyond the perpendicular line produces the small q wave in V_6. The other schematics show how progression of depolarization and repolarization produces parts of the QRS loop (and the entire ST-T loop), which are positive in lead V_6. The S wave occurs because the terminal part of the QRS loop is located beyond the perpendicular line. When using this type of lead derivation, any precordial lead will only record forces moving in an anteroposterior (or posteroanterior) and in a left-to-right or right-to-left direction. Forces moving up or down will not be recorded. This contrasts with scalar concept of precordial leads which can, especially when misplaced, record forces moving in any direction. (From Lemberg and Castellanos.[151] Reproduced with permission from the publisher and authors.)

Figure 11-42: Planar projections of normal spatial VCG obtained with the Frank method. The ST-T loops are enlarged in the bottom view. In the horizontal plane, the QRS loop shows the expected, normal, counterclockwise (CCW) rotation (indicated by arrows). Although the narrow frontal plane QRS loop has clockwise (CW) rotation, in this plane either CCW, CW, or figure-eight rotations can be normal. In the right sagittal plane, the QRS loop displays its normal (CW) rotation. Enlargement of the ST-T loop clearly shows that its first half is inscribed more slowly. Therefore, the dashes (each representing 0.0025 s, or 25 ms) are closer together. Note that the rotation of the ST-T loop is similar to the rotation of the QRS loop in all planes. (From Lemberg and Castellanos.[151] Reproduced with permission from the publisher and authors.)

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Chapter 11: THE RESTING ELECTROCARDIOGRAM

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 12:

THE CHEST ROENTGENOGRAM AND CARDIAC FLUOROSCOPY

Author: James T. T. Chen

On November 8, 1895, Wilhelm Conrad Roentgen discovered x-rays[1] and ushered in a new era of diagnostic roentgenology. With wavelengths only 1/10,000 those of visible light, x-rays can penetrate the human body to produce roentgenograms, which revolutionized the field of medical diagnosis. Chest roentgenography in particular has since become a routine part of medical workup because of the invaluable information it can provide.

Familiarity with the altered anatomy and understanding of the underlying pathophysiology of a diseased heart are the cornerstones to appropriate interpretation of its roentgen manifestations. The conventional four-view cardiac series is tabulated in Table 12-1 and the views are illustrated in Fig. 12-1*C* *D* *E* to *F*.

Table 12-1: Conventional Four-View Cardiac Series

Posteroanterior (PA) view	With barium
Left lateral (lateral) view	With barium
45° Right anterior oblique (RAO) view	With barium
60° Left anterior oblique (LAO) view	Without barium

The approach to the chest roentgenogram should be thorough and objective so that no clue is overlooked and no bias is incorporated in the process of radiographic analysis.[2-5] Rib notching (see Fig. 12-1*A*, *B*), for example, offers important clues to the diagnosis of coarctation of the aorta.[4,6] To prevent occasional erroneous clinical information from misleading the radiographic interpretation, films should at first be read without any knowledge about the patient. A patient may be referred, for instance, because of "bronchial asthma" refractory to therapy, only to be found later to suffer from cardiac asthma due to critical mitral stenosis. In this case, the classic radiographic manifestations of severe mitral stenosis should help clarify the confusion and prompt a change in patient management.

On other occasions, a secundum atrial septal defect may be misinterpreted as mitral stenosis because of similar physical signs. The split second sound may be misinterpreted as the opening snap. The diastolic rumble due to increased flow through a normal tricuspid valve may mimic the diastolic murmur of mitral stenosis. The x-ray signs of the two entities, however, are quite different (Fig. 12-2*B* versus Fig. 12-3*A*).

The final radiologic conclusion, however, should be drawn only after correlating the x-ray findings with clinical information and other laboratory parameters.

The radiologic examination for heart disease consists of six major steps. They are (1) roentgenographic examination for anatomy; (2) fluoroscopic examination for dynamics, (3) comparison, (4) statistical guidance, (5) clinical correlation, and (6) conclusion (Table 12-2).

Table 12-2: Major Steps of Roentgenologic Examination

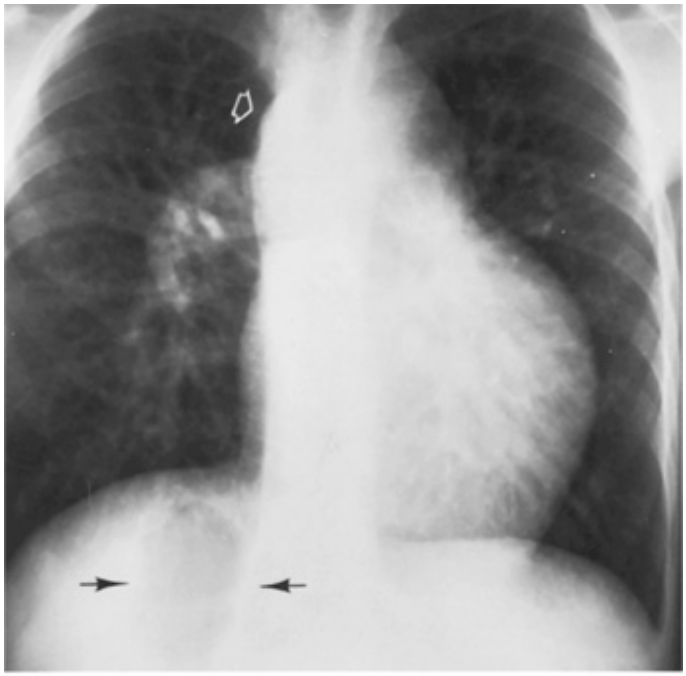
Roentgenographic examination for anatomy
Overview, e.g., rib notching
Pulmonary vascularity, e.g., shunt vascularity in ASD
Lung parenchyma, e.g., ossification in critical MS
Cardiac size, e.g., huge right heart in Ebstein's anomaly
Cardiac contour, e.g., boot-shaped heart in TOF
Abnormal densities, e.g., calcification of LV aneurysm
Abnormal lucency, e.g., conspicuous fat stripes in PE
Cardiac malpositions, e.g., dextrocardia with SS
Other abnormalities, e.g., Holt-Oram syndrome
Fluroscopic observation for dynamics
Comparison
Statistical guidance
Clincal correlation
Conclusion

ABBREVIATIONS: ASD = atrial septal defect; MS = mitral stenosis; TOF = tetralogy of Fallot; LV = left ventricle; PE = pericardial effusion; SS = situs solitus.

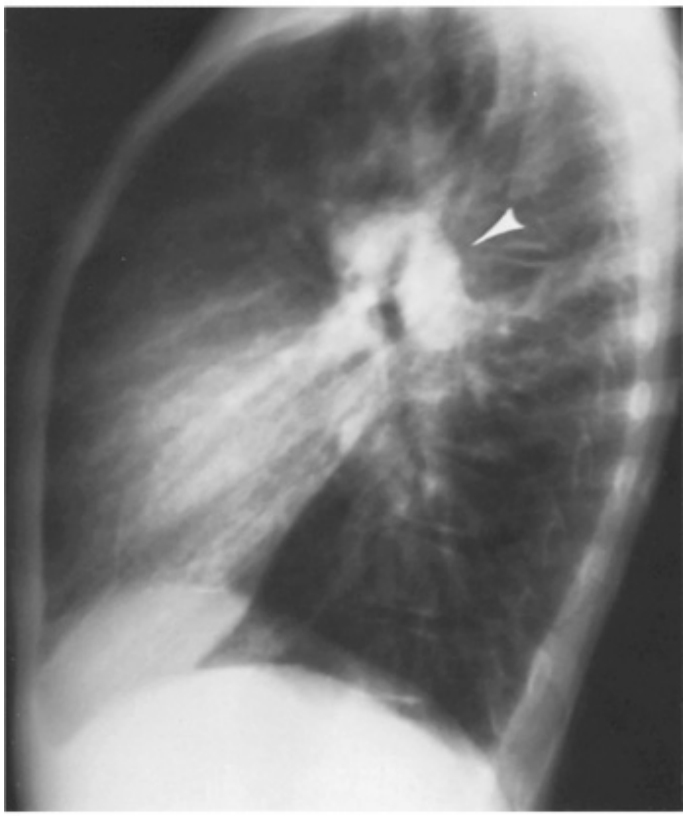
ROENTGENOGRAPHIC EXAMINATION FOR ANATOMY

An Overview

The first step is to survey the roentgenogram and assess the entire situation, searching particularly for noncardiac conditions that may reflect heart disease. For instance, a right-sided stomach with an absent image of the inferior vena cava may suggest the possibility of congenital interruption of the inferior vena cava with azygos continuation[7,8] (Fig. 12-4). A narrowed anteroposterior diameter of the thorax may be the cause of an innocent murmur[9] (Fig. 12-5).



A



B

Figure 12-4: Patient with situs ambiguous, interruption of the inferior vena cava, ventricular septal defect, and polysplenia. *A.* Posteroanterior view shows that the aortic arch and the heart are left-sided and the stomach (*lower arrows*) is right-sided. The azygos vein (*upper arrow*) is markedly enlarged. The heart is mildly enlarged, and there is a moderate increase in pulmonary vascularity. *B.* Lateral view shows an absent image of the inferior vena cava. The azygos arch (*arrow*) is markedly dilated.

Pulmonary Vasculature

The lung may often reflect the underlying pathophysiology of the heart. By careful evaluation of the pulmonary vasculature, one may narrow down the diagnostic possibilities to a manageable level. For

example, if uniform dilatation of all pulmonary vessels is present, the diagnosis of a left-to-right shunt (see Fig. 12-2*B*) is more likely than a left-sided obstructive lesion. The latter typically shows a cephalic pulmonary blood flow pattern (see Fig. 12-3*A*). More detailed analysis of the pulmonary vascularity will be discussed separately below.

Lung Parenchyma

With right-sided heart failure, the lungs become unusually radiolucent because of decreased pulmonary blood flow (PBF). On the other hand, significant failure on the left side of the heart is characterized by the presence of pulmonary edema and/or a cephalic blood flow pattern (Fig. 12-6). Long-standing, severe pulmonary venous hypertension may lead to hemosiderosis and/or ossification of the lung.[10,11] When right-sided heart failure results from severe left-sided heart failure, the preexisting pulmonary congestion may improve because of the decreased pulmonary blood flow (see Fig. 12-6*B*).

Cardiac Size

A significantly enlarged heart is always abnormal; however, mild cardiomegaly may reflect a higher than average cardiac output from a normal heart, as seen in athletes in active training. The cardiothoracic ratio remains the simplest and most practical yardstick for assessment of cardiac size.[2] The mean value for adults in an upright position in the posteroanterior (PA) view is 44 percent. More accurate roentgen measurements of cardiac size have been well documented[12,13] but are beyond the scope of the present discussion.

The nature of cardiomegaly usually can be determined by the specific roentgen appearance. As a rule, when the PBF pattern remains normal, cardiac lesions with volume overload tend to present a greater degree of cardiomegaly than lesions with pressure overload alone. For example, patients with aortic stenosis typically show features of left ventricular hypertrophy without dilatation. On the other hand, the left ventricle both dilates and hypertrophies in the case of aortic regurgitation, producing a much larger heart even before the development of congestive heart failure.

Both right- and left-sided heart failure can cause gross cardiac enlargement. The associated vascular abnormality in each case, however, is drastically different (see "Pulmonary Vascularity," below).

A smaller than average heart is encountered in patients with chronic obstructive pulmonary disease (Fig. 12-7*A*), Addison's disease, anorexia nervosa, and starvation. An abnormally small heart, however, is difficult to define except in a retrospective fashion, when the heart has returned to its normal capacity following successful therapy. For example, in patients with Addison's disease, the heart may become significantly larger following appropriate steroid therapy.

Cardiac Contour

Any significant deviation from the normal cardiovascular contour may serve as a clue to the correct diagnosis. For instance, *coeur en sabot*, a "boot-shaped heart" (see Fig. 12-2*C*), is characteristic of tetralogy of Fallot. A bulge along the left cardiac border with a retrosternal double density is virtually diagnostic of left ventricular aneurysm (Fig. 12-8). A markedly widened right cardiac contour in association with a straightened left cardiac border is seen frequently in patients with severe mitral stenosis leading to tricuspid regurgitation (see Fig. 12-7*D*).

Abnormal Densities

Besides the familiar double density cast by an enlarged left atrium, other increased densities may be found within the confines of the heart, indicating a variety of dilated vascular structures, e.g., tortuous descending aorta, aortic aneurysm, coronary artery aneurysm, pulmonary varix, etc.[3] Furthermore, large cardiac calcifications are seen easily, particularly in lateral and oblique views. If smaller calcific deposits are suspected, they should be verified promptly or ruled out by cardiac fluoroscopy or computed tomographic (CT) scanning (see Chap. 17). Any radiologically detectable calcification in the heart is of clinical importance. The heavier the calcification, the more significant it becomes (see Fig. 12-1*F*). The

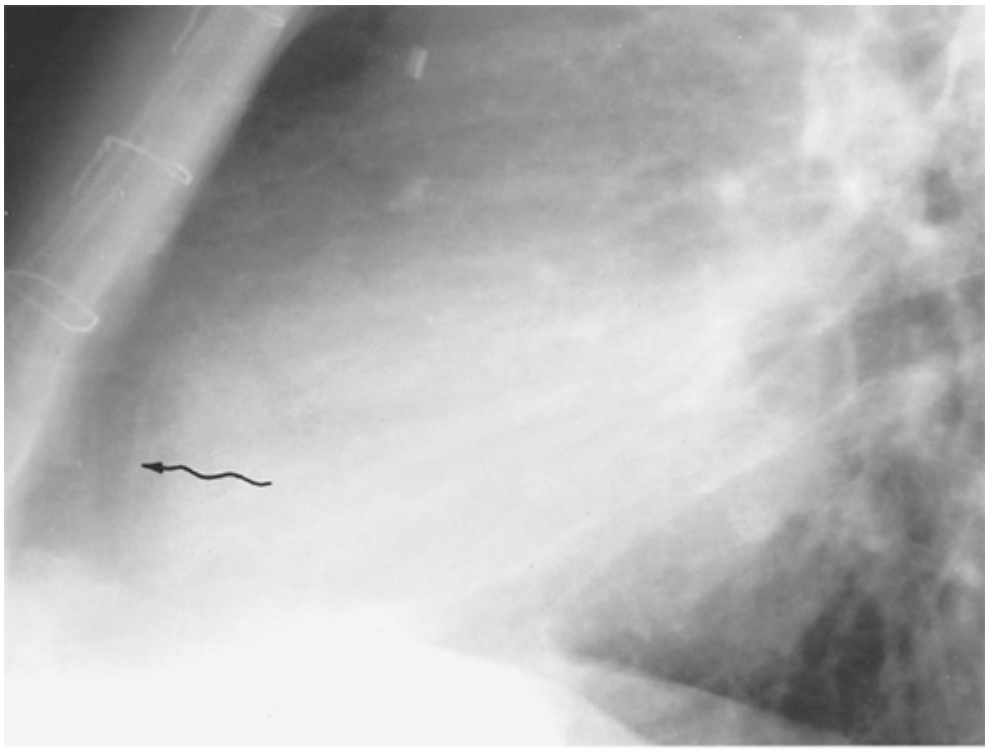
extent of valvular calcification tends to be proportionate to the severity of the valve stenosis regardless of the other roentgen signs of the disease.[2,3,14,15] Calcification of the coronary artery is almost always atherosclerotic in nature. Mönckeberg's medial calcification of the coronary system is extremely rare. A fluoroscopically detectable coronary calcification is correlated with major vessel occlusion in 94 percent of patients with chest pain;[16] however, the sensitivity of the test is only 40 percent (see "Cardiac Fluoroscopy," below).

Recently, electron-beam CT scanning has proved to be a sensitive tool for the detection and quantification of coronary calcifications (see Chap. 17). A negative result may indicate no need for further testing in asymptomatic individuals. A positive result, however, does not necessarily denote obstructive coronary artery disease. The sensitivity for detecting any coronary calcifications is greater than 95 percent with a *specificity of less than 65 percent* for significant coronary artery disease. Another use of this method is to identify high-risk patients with calcific nonobstructive atherosclerotic lesions. By vigorous therapeutic intervention, one may be able to halt progression or even cause regression of their disease. In fact, the results of such interventions can be correlated with the increase or decrease in coronary calcific plaques[15] (see Chap. 17).

A calcified ascending aortic aneurysm with aortic regurgitation is highly suggestive of syphilitic aortitis[14] (Fig. 12-9).

Abnormal Lucency

The abnormal lucent areas in and about the heart include (1) displaced subepicardial fat stripes caused by effusion or thickening of the pericardium (Fig. 12-10), (2) pneumopericardium (Fig. 12-11), and (3) pneumomediastinum. Pneumomediastinum is differentiated from pneumopericardium by the fact that the former shows a superior extension of the air strip beyond the confines of the pericardium.



A

B

Figure 12-10: Developing pericardial effusion in 2 weeks. *A.* A magnified view of the retrosternal area showing the hairlike normal pericardium (*arrow*) sandwiched between the subepicardial fat stripe interiorly and the mediastinal fat stripe exteriorly. The maximal width of normal pericardium is 2 mm. *B.* The same patient 2 weeks later, with moderate pericardial effusion. The pericardial cavity now measured more than 1 cm in width (*arrow*).

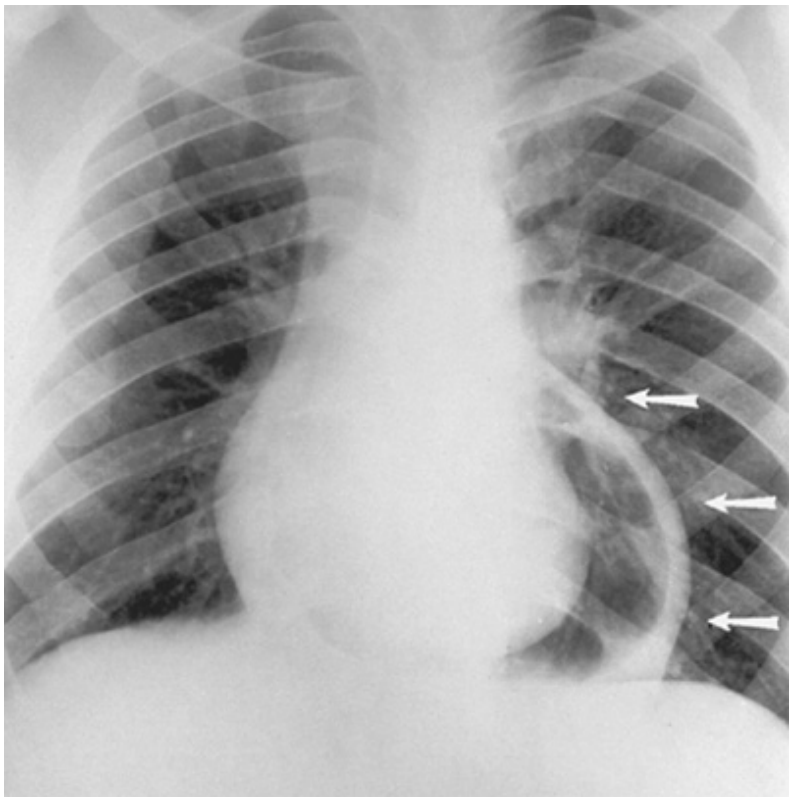


Figure 12-11: Traumatic constrictive-effusive pericarditis in a young man. Following emergent pericardiocentesis and injection of air, a radiograph was taken in the supine position. Air is confined to the left side of the pericardium. Note markedly thickened parietal layer (*arrows*).

Cardiac Malposition

According to Elliott and Schiebler, "cardiac malpositions" are diagnosed only when either the heart or the stomach is out of the normal left-sided position. This definition is crucial in distinguishing an isolated right-sided aortic arch from a cardiac malposition.[7,8]

DEXTROCARDIA WITH SITUS INVERSUS

Recently, the term *dextrocardia* has been used to indicate any congenital right-sided heart regardless of the position of abdominal viscera. To specify the kind of dextrocardia under test, one must affix the status of the abdominal viscera. *Dextrocardia with situs inversus* means the mirror image of normal. In this situation, the incidence of congenital heart disease is only 5 percent, which is a ninefold increase over the general population. The combination of dextrocardia, sinusitis, and bronchiectasis is known as *Kartagener's triad*.

DEXTROCARDIA WITH SITUS SOLITUS

This represents an anomaly with normal situs but a right-sided heart. Radiographically, normal situs (situs solitus) is a certainty when both the aortic knob and the gastric air bubble are on the left side. *Situs solitus* also means that both the abdominal viscera and the atria are in the normal position. Under these circumstances, if the ventricles fail to swing from the primitive right-sided position to the normal left-sided position, abnormal relationships between the ventricles and the rest of the cardiovascular structures are bound to develop. This entity was formerly termed *dextroversion*.

In patients with dextroversion, the incidence of congenital heart disease has been estimated at 98 percent. More than 80 percent have congenitally corrected (or L-loop) transposition of great arteries. The next most commonly associated lesions are a combination of ventricular septal defect and pulmonary stenosis, a tetralogy-like pathophysiology (Fig. 12-12). Therefore, from a statistical point of view, it is important to be able to differentiate this entity from dextrocardia with situs inversus, which is associated with a much lower incidence of congenital heart disease (see above and also Chap. 63).

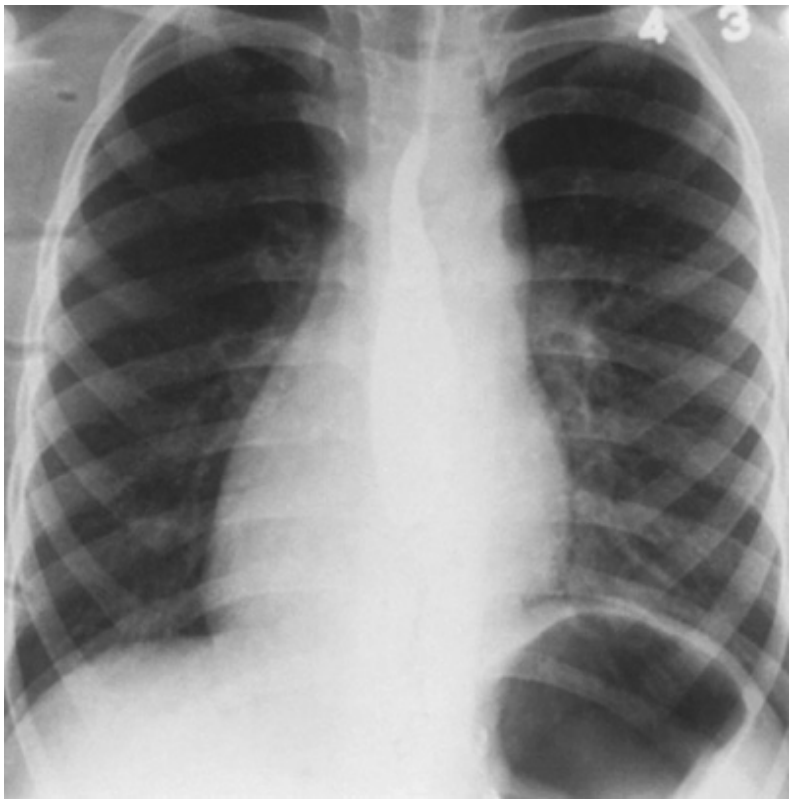


Figure 12-12: Posteroanterior view of a patient with dextrocardia and situs solitus. Note that the aortic arch and the stomach air bubble are both on the left (*situs solitus*) and the apex of the ventricles is pointing to the right inferiorly. According to statistics and proved by cardiac catheterization, this patient had the typical

combination of congenitally corrected transposition of the great arteries, ventricular septal defect, and pulmonary stenosis. He was cyanotic. The pulmonary vascularity appears decreased.

LEVOCARDIA WITH SITUS INVERSUS

This is a mirror image of dextroversion, and it is associated with an extremely high incidence (nearly 100 percent) of cyanotic congenital cardiac lesions similar to those seen in dextroversion. This entity was formerly termed *levoversion*.

LEVOCARDIA WITH SITUS SOLITUS

This is entirely normal.

CARDIAC MALPOSITIONS WITH SITUS AMBIGUUS

In this group, the patient's heart may be either left- or right-sided. The situs is ambiguous because the aortic arch and the stomach are not on the same side. Under these circumstances, we are dealing with either asplenia or polysplenia syndrome. Patients with polysplenia syndrome tend to be acyanotic, running a milder clinical course, and frequently survive into adulthood. The associated lesions are bilateral left-sidedness, interruption of the inferior vena cava with azygos continuation (see Fig. 12-4), polysplenia, and a left-to-right shunt, most frequently an atrioventricular septal defect.[17] Patients with asplenia syndrome, on the other hand, tend to be cyanotic and critically ill and die in infancy. The associated lesions are bilateral right-sidedness, asplenia, midline liver, and pulmonary stenosis or atresia with oligemic lungs. It is noteworthy that interruption of inferior vena cava has never been reported in patients with asplenia.

Other Abnormalities

GREAT VESSELS

The roentgen appearance of the great vessels often provides valuable information for the diagnosis of heart disease.[2,3,18,19] For example, selective dilatation of the ascending aorta is the hallmark of valvular aortic stenosis (Fig. 12-13); generalized dilatation of the entire thoracic aorta (Fig. 12-14), on the other hand, favors the diagnosis of aortic regurgitation, systemic hypertension, or both, depending on the size of the left ventricle. A larger left ventricle is associated with aortic regurgitation because of volume overload. In atrial septal defect and mitral stenosis, the pulmonary trunk is quite large, and the aortic knob is usually small (see Figs. 12-2*B* and 12-3*A*). This is explained on the basis of a leftward cardiac rotation that occurs when an enlarged right ventricle coexists with a normal-sized left ventricle. When the heart rotates to the left, the aorta folds on itself in the midline and becomes inconspicuous. Meanwhile, the pulmonary trunk is brought laterally and looks larger than it actually is. Aortic aneurysm (Fig. 12-15) and dissection frequently are associated with hypertensive and atherosclerotic disorders.

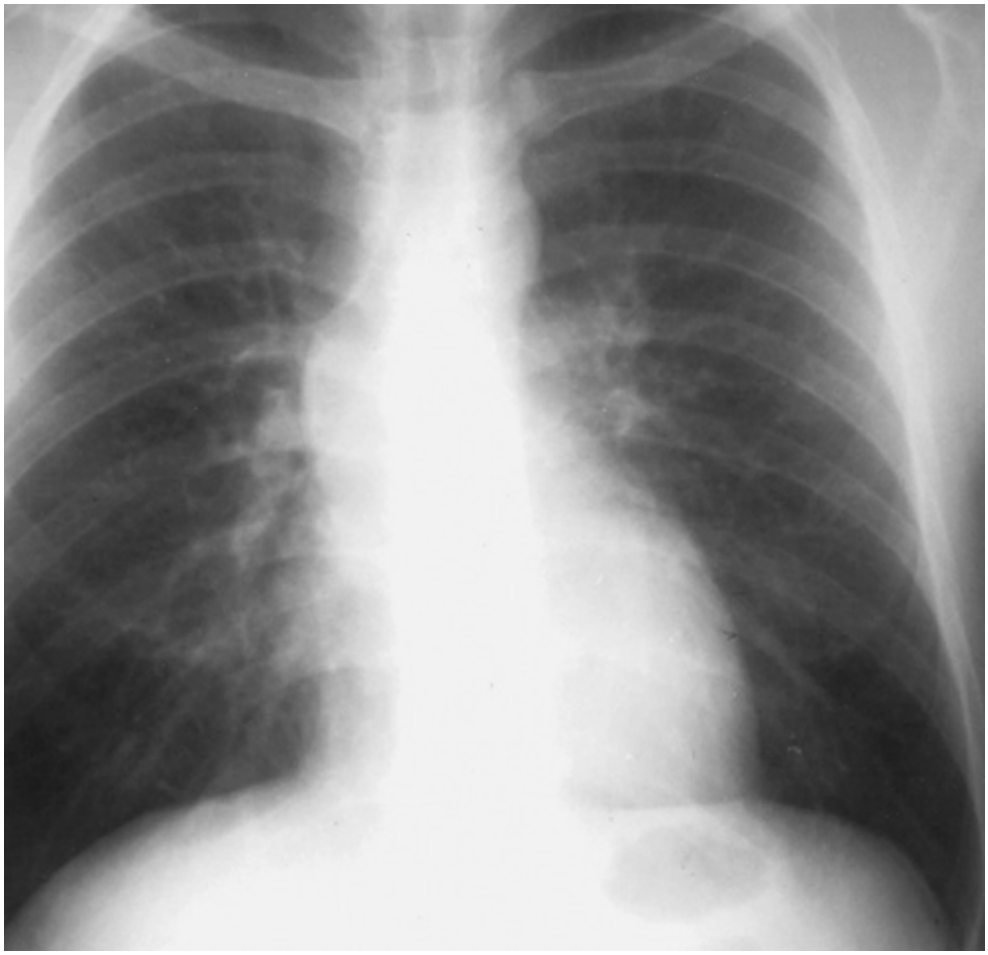
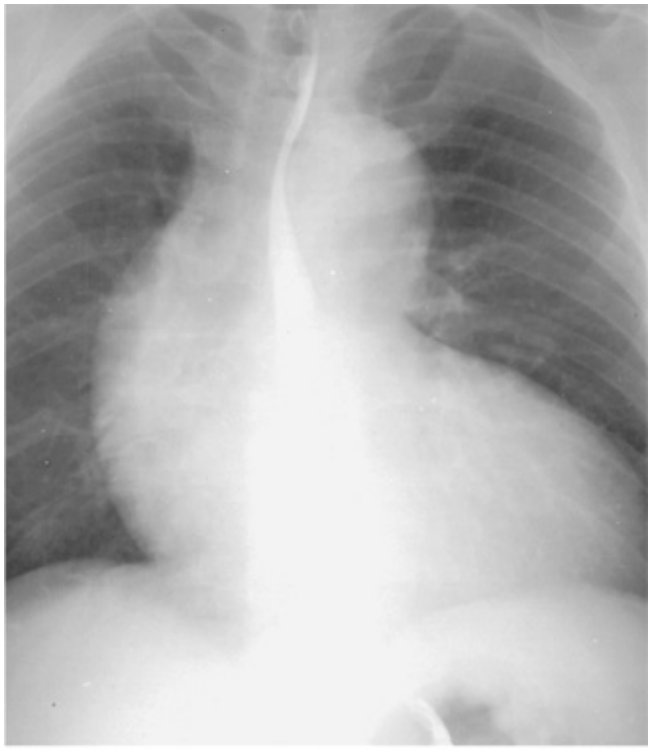


Figure 12-13: A 17-year-old boy with congenital aortic valve stenosis. Note dilatation of the ascending aorta, increased convexity of the left ventricle, and normal pulmonary vascularity. The systolic aortic pressure gradient was 100 mmHg.



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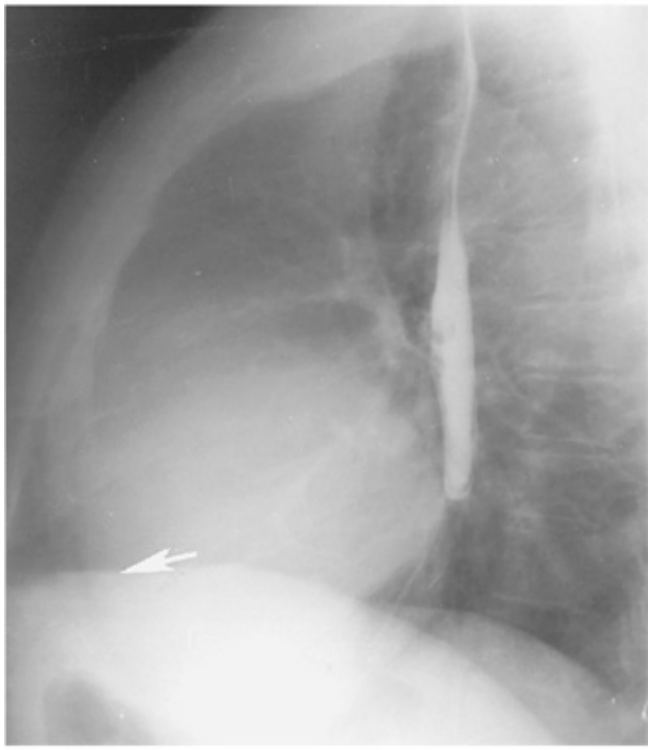

B

Figure 12-14: A 45-year-old man with Marfan's syndrome, severe aortic regurgitation, and proximal aortic dissection into the pericardial cavity. *A*. Posteroanterior view shows a huge left ventricular and aneurysmal dilatation of the ascending aorta. There is no sign of heart failure. *B*. Lateral view shows a small pericardial effusion (*arrow*).

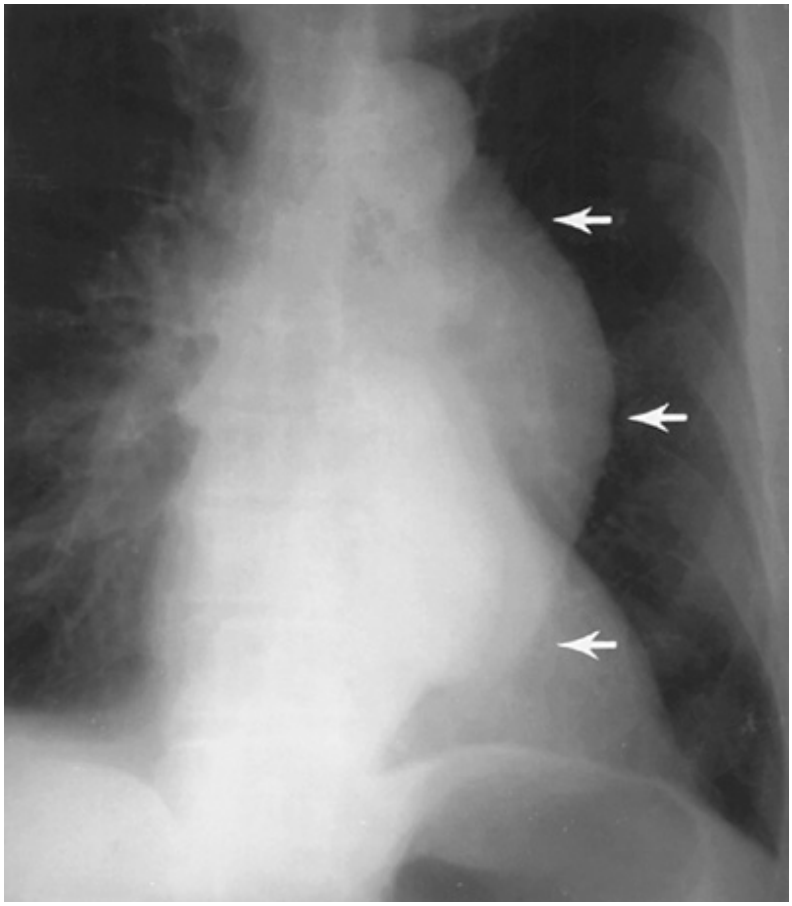

Figure 12-15: Posteroanterior view of a 77-year-old man shows a huge descending aortic aneurysm (*arrows*).

As already mentioned, prominence of the pulmonary trunk is a reliable secondary sign of right ventricular enlargement (Fig. 12-16; also see Fig. 12-2*B*), with the following exceptions: (1) tetralogy of Fallot with right ventricular hypertrophy but pulmonary trunk hypoplasia, (2) idiopathic dilatation of the pulmonary artery, (3) patent ductus arteriosus with dilated pulmonary trunk but normal right ventricle, and (4) straight-back syndrome, pectus excavatum, and scoliosis with narrowed anteroposterior diameter of the chest. Under the latter conditions, the heart is compressed, displaced, and rotated to the left, giving rise to a falsely enlarged pulmonary artery.

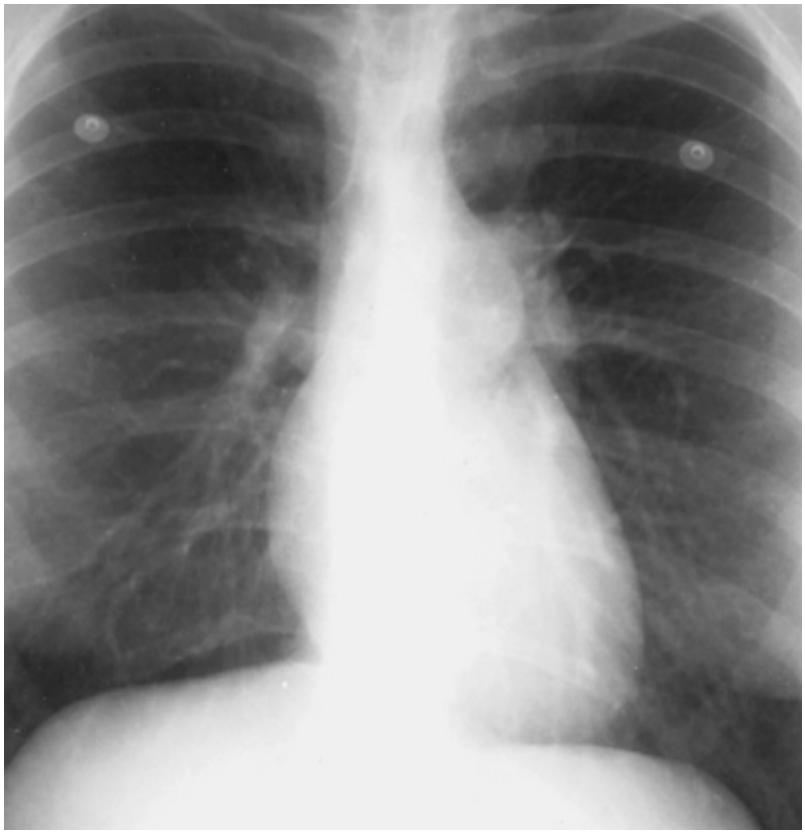

Figure 12-16: A 37-year-old woman with congenital valvular pulmonary stenosis. Note enlarged pulmonary trunk and left pulmonary artery versus diminished right pulmonary artery. Also note increased pulmonary blood flow on the left side and decreased pulmonary blood flow on the right side.

In coarctation of the aorta, the engorged aortic knob and the poststenotic dilatation of the descending aorta may cause a "3 sign" on the aorta and an "E sign" on the barium-filled esophagus, both depicting the site of coarctation[6] (see Fig. 12-1*C*).

The abnormal size and distribution of both the pulmonary and systemic veins are important clues to the presence of certain conditions, e.g., anomalous pulmonary venous connections, pulmonary arteriovenous fistulas, pulmonary varix, persistent left superior vena cava, and interruption of inferior vena cava with azygos continuation (see Fig. 12-4).

The significance of aortic arch anomalies is discussed under "Statistical Guidance," below.

MEDIASTINAL STRUCTURES

The mediastinal organs frequently are affected by the cardiovascular structures because of their close spatial interrelationships. An enlarged left atrium not only displaces the esophagus (see Fig. 12-1*C*, *D*, *E*) and the descending aorta but also elevates and compresses the left mainstem bronchus. A double aortic arch may compress both the trachea and the esophagus. On the other hand, malignant processes may invade the heart and great vessels, causing cardiac tamponade or the superior vena cava syndrome, for example. Usually, these mediastinal changes are evident on the chest roentgenogram and should be recognized promptly.[18-22]

PLEURA

A right-sided pleural effusion often is present with left-sided heart failure. A bilateral hydrothorax, on the other hand, suggests bilateral heart failure or a noncardiac etiology of the effusion. Congestive heart failure is also known to be associated with a pseudotumor or "vanishing" tumor, representing an interlobar collection of pleural fluid (Fig. 12-17). As congestive heart failure improves, the "tumor" disappears.

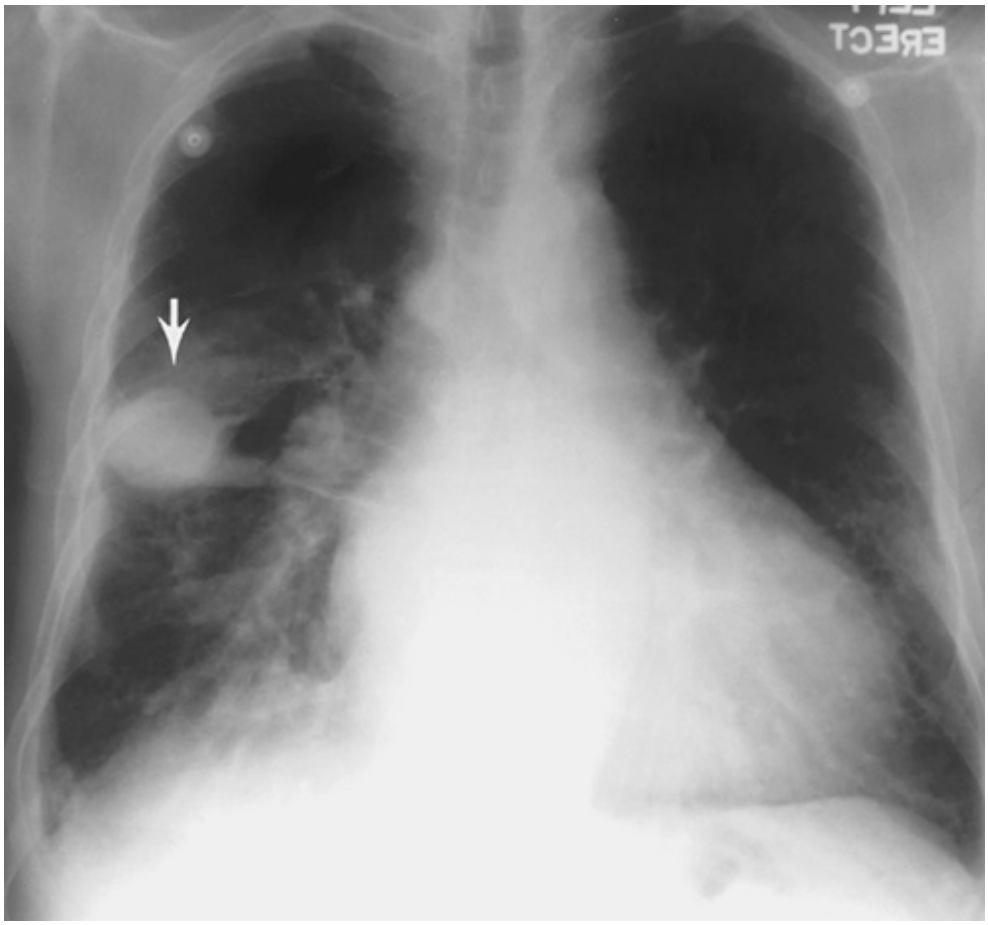

Figure 12-17: Patient with congestive heart failure. Note gross cardiomegaly, cephalization, interstitial pulmonary edema, and right-sided pleural effusion. Some of the fluid was loculated in the minor interlobar fissure (*arrow*), which disappeared with improved cardiac function.

BONES AND JOINTS

Notching of the ribs has many origins. Basically, any of the three major intercostal structures can enlarge, compress, and erode the lower borders of the ribs, producing areas of notching. They are intercostal arteries, veins, and nerves. Coarctation of the aorta[6] (see Fig. 12-1*A*) represents the most common cause of rib notching due to dynamic dilatation and tortuosity of the arteries. Superior vena cava syndrome may cause a similar phenomenon of venous origin. Neurofibromatosis also can produce rib notching by numerous intercostal neurofibromas.

SOFT TISSUES OVER THE CHEST

Patients with renal failure may show severe edema in the soft tissues over the chest as part of the picture of general anasarca (Fig. 12-18).

EXTRATHORACIC STRUCTURES

In Holt-Oram syndrome (Fig. 12-19), the upper extremity abnormalities may be evident in a chest roentgenogram or on other films in the patient's x-ray folder (see also Chap. 63). A large arteriovenous malformation with curvilinear calcifications may be seen in the neck, thereby providing a clue as to the etiology of the patient's congestive heart failure. Radiographic evaluation of the patient's abdominal viscera is an integral part of the workup for cardiac malpositions.[7,8]

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Chapter 12: THE CHEST ROENTGENOGRAM AND CARDIAC FLUOROSCOPY

FLUOROSCOPIC OBSERVATION FOR DYNAMICS

Cardiac fluoroscopy is a valuable adjunct to the chest roentgenogram.[2] Its advantages and limitations are detailed at the end of this chapter.

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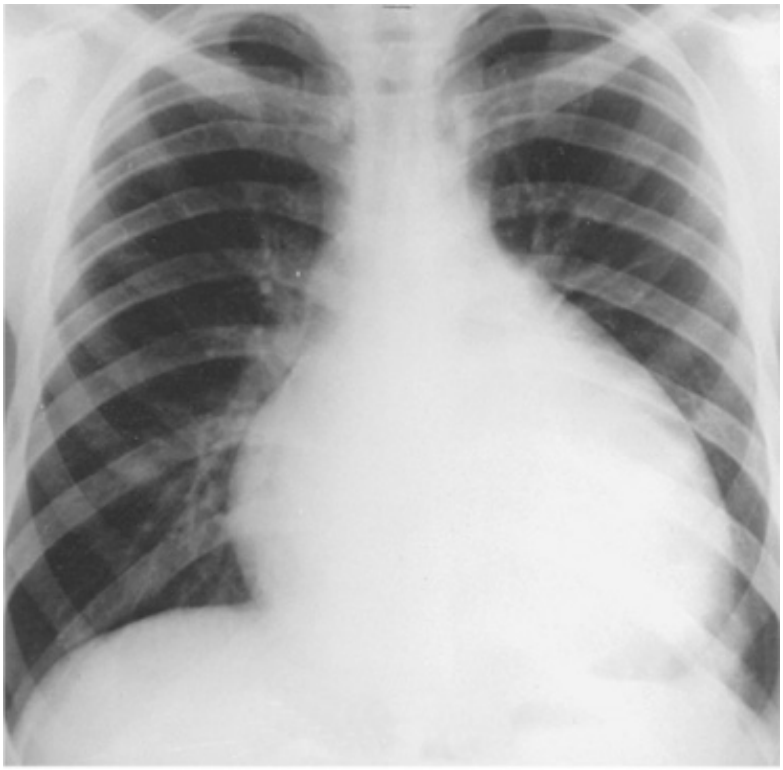
Chapter 12: THE CHEST ROENTGENOGRAM AND CARDIAC FLUOROSCOPY

COMPARISON

To appreciate the acuteness or chronicity of the disease or its response to therapy, one must carefully compare serial roentgenograms. As demonstrated in Fig. 12-7*B*, the heart may be considered neither enlarged nor failing if the baseline study made 3 years earlier in Fig. 12-7*A* were not available for comparison (see "Heart Failure," below). Similarly, an enlarging heart with normal pulmonary vascularity is highly suggestive of pericardial effusion. Conversely, a shrinking heart in the presence of normal vascularity is compatible with resolution of a pericardial effusion (Fig. 12-20).



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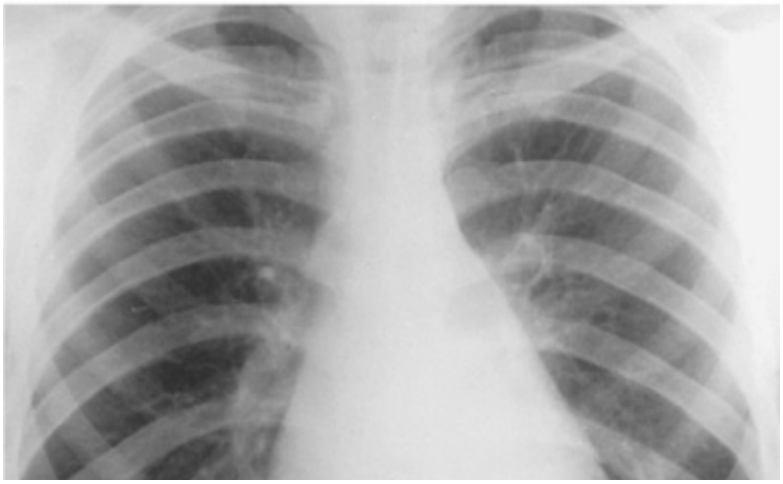

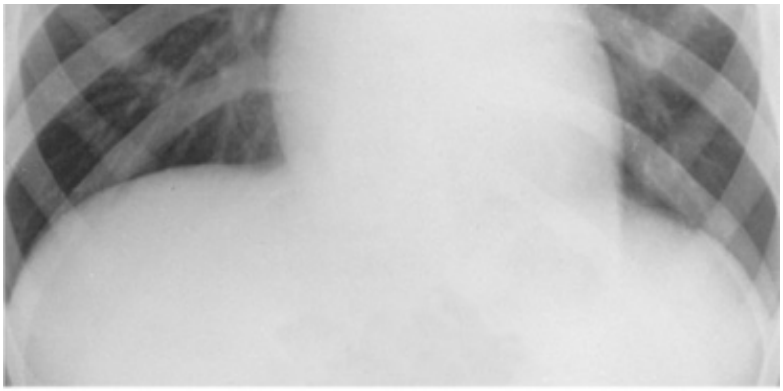

B

Figure 12-20: Young man with acute pericarditis with effusion. *A.* Posteroanterior view shows a water bottle-shaped cardiomegaly, clear lungs, and normal pulmonary vascularity. *B.* Repeat film taken 5 days later shows excellent response to therapy.

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Chapter 12: THE CHEST ROENTGENOGRAM AND CARDIAC FLUOROSCOPY

STATISTICAL GUIDANCE

Certain roentgenologic findings are by themselves diagnostic of a disease; other signs are suggestive of a diagnosis on the basis of statistics only. Nevertheless, the latter can be quite useful by virtue of their high predictive value of a particular disease or a group of similar diseases. Therefore, one should always keep the statistical information in mind.

The incidence of congenital heart disease in patients with right-sided aortic arch increases 10- to 100-fold depending on the anatomic details of the anomaly.[21,22] Of practical importance, there are only two types of right-sided aortic arch. The first has been called the *avian type*, implying a normal status for birds but a detrimental one for humans. The overwhelming majority of patients with this type are born with cyanotic congenital heart disease. The second may be called the *common type* because of its higher incidence in the general population. Most patients with the common type are physiologically normal and have their anomaly incidentally diagnosed on chest radiographs or a barium meal study. The x-ray findings of the two types are similar in the PA view but are quite different in the lateral view (Fig. 12-21). The incidence and list of congenital heart diseases with each type[20] are shown in Table 12-3. Only 2 percent of patients with the avian type are physiologically normal. Tetralogy of Fallot should be the diagnosis in these patients until proved otherwise.[21,22]

Table 12-3: Cardiac Defects Associated with Each Type of Right-Sided Aortic Arch

	Type of Anomaly	
	Avian	Common
Anatomic details	With mirror-image branching; the arch is anterior to the trachea	With aberrant left subclavian artery arising from a large aortic diverticulum that is posterior to the esophagus
Patients with cardiac defects, %	98	12
Type of defects, %		
Tetralogy of Fallot	90	71
Truncus arteiosus	2.5	
Transposition of great arteries	1.5	
Atrial septal defect and/or ventricular septal defect	0.5	21
Coarctation of aorta		7

Others	5.5	1

Patients with a double aortic arch, on the other hand, rarely have congenital heart disease, although they tend to be symptomatic in infancy because of a compressing vascular ring.[21]

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Chapter 12: THE CHEST ROENTGENOGRAM AND CARDIAC FLUOROSCOPY

CLINICAL CORRELATION

The next step in the examination is to correlate the roentgenologic findings with the clinical information and other laboratory parameters for a final conclusion. It may become necessary at this point to reexamine the radiograph or review the fluoroscopic observation or both. After detailed analysis of some finer points, a wrong impression may be corrected or a correct diagnosis reinforced[2] (see Table 12-2).

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Chapter 12: THE CHEST ROENTGENOGRAM AND CARDIAC FLUOROSCOPY

PULMONARY VASCULARITY

Normal

The normal roentgen appearance of the pulmonary vasculature of an upright human being is typified by a caudal flow pattern because of gravity. The pressure differential between the apex and the base of the lung is approximately 22 mmHg in adults in the upright position.[2,23] Therefore, more flow under higher distending pressure is expected in the lower-lobe vessels than in the upper. Normally, one sees very little vascularity above the hilum, whereas more and larger vessels are found below the hilum. Since the pulmonary resistance is normal, all vessels taper gradually in a treelike manner from the hilum toward the periphery of the lung. The right descending pulmonary artery measures 10 to 15 mm in diameter in males and 9 to 14 mm in females[2,24] (see Fig. 12-2).

Abnormal

Abnormal pulmonary vascularity can be classified into two categories, either in terms of volume or in terms of distribution[2,10,25] (Table 12-4).

Abnormalities in Volume

In the evaluation of pulmonary vasculature, the caliber of the vessels is more important than the length or the number. As long as the PBF pattern remains normal, with a greater amount of flow to the bases than to the apices, the volume of the flow is proportional to the caliber of the pulmonary arteries (see Fig. 12-2). In addition to measuring the right descending pulmonary artery, one also may assess the pulmonary blood volume by comparing the size of the pulmonary artery with that of the accompanying bronchus where they are viewed on end. Normally, the two structures have approximately equal diameters.[2,26] When the artery-bronchus ratio is greater than unity, increased blood flow is suggested. Conversely, when the ratio is smaller than unity (see Fig. 12-2), decreased flow is likely.

INCREASED PBF

In the case of mild to moderate left-to-right shunts, for example, the vessels dilate in proportion to the increased flow with no significant change in pressure, resistance, or flow pattern. This phenomenon is also called *shunt vascularity* or *equalization*. Equalization of PBF between the upper and lower lung zones is only apparent rather than real, however; the lower lobes still receive a great deal more blood than the upper lobes, although the ratio of PBF between the two zones has changed-e.g., from 5:1 to 4:1 or 3:1. A mild increase in pulmonary vascularity with slight cardiomegaly is commonly found in pregnant women and trained athletes with increased cardiac output and supernormal performance of the heart (see Chaps. 82 and 85).

DECREASED PBF

Patients with tetralogy of Fallot frequently show decreased pulmonary vascularity with smaller and shorter pulmonary arteries and veins and more radiolucent lungs (see Fig. 12-2*C*).

Marked reduction in PBF is also encountered in patients with isolated right-sided heart failure without a right-to-left shunt (see Fig. 12-7). This is attributed to the significant decrease in cardiac output from both ventricles.

Abnormalities in Distribution

An abnormal distribution of PBF (or an abnormal PBF pattern) always reflects a changed pulmonary vascular resistance, either locally or diffusely.

CEPHALIZATION

In the presence of postcapillary pulmonary hypertension, physiologic disturbances may begin when the total intravascular pressure exceeds the oncotic pressure of the blood. As a result, fluid leaks out of the vessels and collects in the interstitium before pouring into the alveoli.

Pulmonary edema interferes with gas exchange, resulting in a state of hypoxemia. Alveolar hypoxia has a profound influence on the pulmonary vessels, causing them to constrict. Since there is greater alveolar hypoxia in the lung bases than in the apices, the basilar vessels constrict significantly, forcing the blood to flow upward. This phenomenon actually represents a reversal of the normal PBF pattern: redistribution or cephalization of the pulmonary vascularity.

Cephalization occurs in any of three conditions: (1) left-sided obstructive lesions, e.g., mitral stenosis[24] (see Fig. 12-3*A*) or aortic stenosis, (2) left ventricular failure, e.g., coronary heart disease or cardiomyopathies, and (3) severe mitral regurgitation even before pump failure of the left ventricle occurs. It should be emphasized that unless there is obvious constriction of the lower-lobe vessels, the diagnosis of cephalization should not be made. Dilatation of the upper-lobe vessels is of secondary importance and can be found without narrowing of the basilar vessels in a number of entities, most noticeably left-to-right shunts.

CENTRALIZATION

In the presence of precapillary pulmonary hypertension, the pulmonary trunk and central pulmonary arteries dilate, whereas the distal pulmonary arteries constrict in a concentric fashion from the periphery of the lung toward the hilum. This phenomenon is called *centralization of the pulmonary vascularity*. It occurs in patients with primary pulmonary hypertension (see Fig. 12-3*B*), Eisenmenger's syndrome, recurrent pulmonary thromboembolic disease, or severe obstructive emphysema (see Fig. 12-7*A*, *B*).

LATERALIZATION

Massive unilateral pulmonary embolism may cause a lateralized PBF pattern. Since one major pulmonary artery is obstructed, the blood is forced to flow through the healthy lung only. The paucity of pulmonary vascularity in the diseased lung with the obstructed pulmonary artery is termed the *Westermark sign* (see Fig. 12-3*C*). In the case of congenital valvular pulmonary stenosis, a jet effect from the stenotic valve can cause a lateralized PBF pattern in favor of the left side (see Fig. 12-16).

LOCALIZATION

A localized abnormal flow pattern is exemplified by a congenital pulmonary arteriovenous fistula in a cyanotic child (see Fig. 12-3*D*).

COLLATERALIZATION

Patients with markedly decreased PBF (e.g., severe tetralogy of Fallot) tend to show numerous small and tortuous bronchial arterial collaterals in the upper medial lung zones near their origin from the descending aorta. The native pulmonary arteries are extremely small, although smooth and gracefully branching (see Fig. 12-3*E*).

Combined Abnormalities

In reality, an abnormal pulmonary vascularity is often a mixed type. There is a great variety of possible combinations-e.g., cephalization plus decreased flow in severe mitral stenosis (see Fig. 12-3*A*) or centralization with increased PBF in Eisenmenger's atrial septal defect (Fig. 12-22).

Summary

Roentgen analysis of the pulmonary vasculature is accomplished in two steps. First, the volume of the pulmonary flow can be estimated by the degree of pulmonary arterial enlargement as long as the PBF pattern remains normal. Second, the distribution of the pulmonary flow is assessed by the presence of an abnormal flow pattern. The volume and the distribution of pulmonary blood flow may change singly or in combination de pending on the nature and severity of the underlying heart disease.

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Chapter 12: THE CHEST ROENTGENOGRAM AND CARDIAC FLUOROSCOPY

HEART FAILURE

In addition to specific chamber enlargement, the pulmonary vasculature uniquely portrays the underlying pathophysiology of heart failure. In the chronic setting, decreased flow with increased pulmonary lucency is the hallmark of right-sided heart failure (see Fig. 12-7); striking cephalization of the pulmonary vasculature is typical for left-sided decompensation (see Figs. 12-3*A* and 12-6*B*).

Left-Sided

ACUTE LEFT-SIDED HEART FAILURE

The pulmonary vascular changes associated with acute left ventricular failure are usually not discernible for two reasons: (1) the resulting severe pulmonary edema obscures the pulmonary vasculature, and (2) the redistribution of PBF secondary to acute left-sided heart failure is usually relatively mild. The combination of alveolar pulmonary edema and a normal-sized heart is the hallmark of acute left-sided heart failure[10] (see Fig. 12-6*A*), most commonly seen in acute myocardial infarction. The edema fluid under this circumstance tends to distribute in a butterfly pattern.[27] The reason for this is poorly understood.

CHRONIC LEFT-SIDED HEART FAILURE

Chronic left-sided heart failure is characterized by gross cardiomegaly, striking cephalization of the pulmonary vasculature and interstitial pulmonary edema or fibrosis with multiple distinct Kerley B lines. Pulmonary hemosiderosis, ossification, or both may result from long-standing severe postcapillary pulmonary hypertension (see Figs. 12-6*B*, *C*, *D* to *E*).

Right-Sided

ACUTE RIGHT-SIDED HEART FAILURE

Acute right-sided heart failure most commonly results from massive pulmonary embolism. The typical radiographic signs are rapidly developing centralization of the pulmonary vasculature and dilatation of the right-sided cardiac chambers and venae cavae. In addition, the lungs may show localized or lateralized oligemia (see Fig. 12-3*C*). Eventually, opacities in either or both lungs may develop as a result of pulmonary infarction.

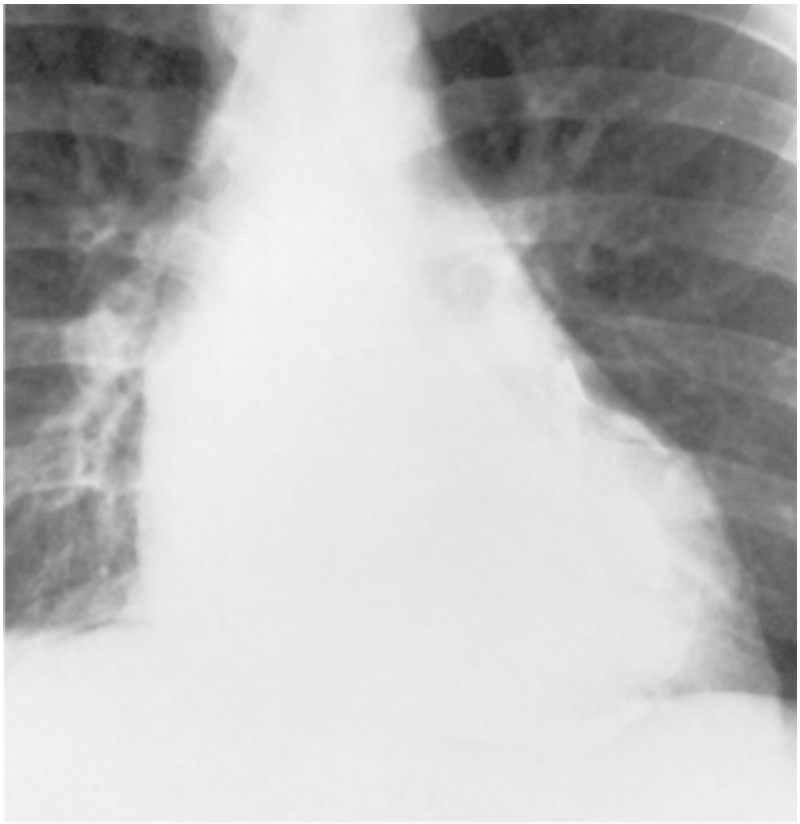
CHRONIC RIGHT-SIDED HEART FAILURE

Chronic right-sided heart failure has a number of causes. The common ones include congenital pulmonary stenosis, Ebstein's anomaly, severe chronic obstructive pulmonary disease, and recurrent pulmonary thromboembolic disease. Diffusely decreased pulmonary vascularity with unusually lucent lungs is seen in patients with right-sided heart failure without pulmonary hypertension (see Fig. 12-7*C*). Centralized PBF pattern is encountered when the right-sided heart failure is secondary to precapillary pulmonary hypertension (see Fig. 12-7*A*, *B*). A cephalized flow pattern with unusually lucent lungs is found in patients with right-sided

heart failure secondary to long-standing severe left-sided heart failure (see Fig. 12-7*D*). The degree of right-sided chamber enlargement is proportional to the severity of tricuspid regurgitation.

Combined

It is generally believed that right-sided heart failure is caused most often by severe left-sided heart failure. This is exemplified by patients with severe mitral stenosis leading to severe tricuspid regurgitation (see Fig. 12-7*D*). Other examples of bilateral heart failure are cardiac tamponade and constrictive pericarditis, when both sides of the heart are affected (Fig. 12-23).



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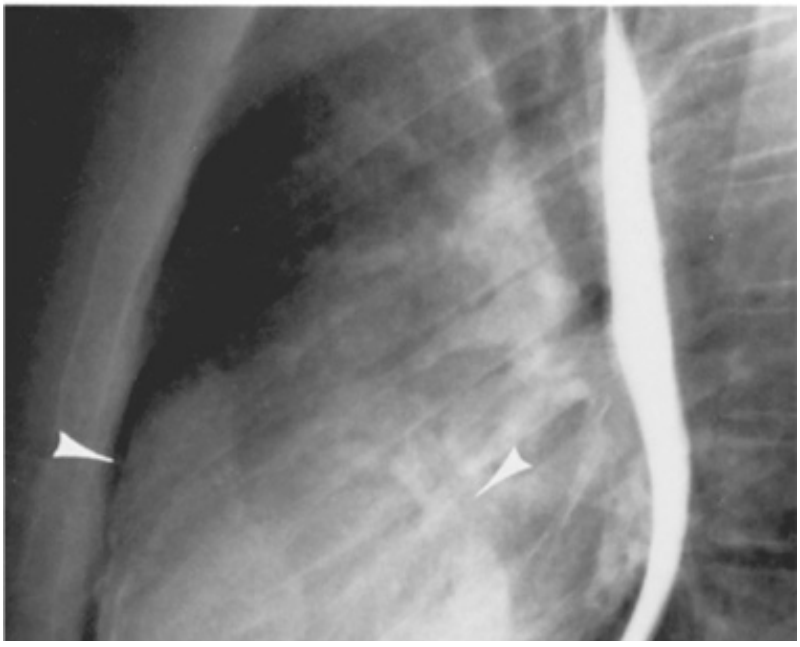

B

Figure 12-23: Patient with calcific constrictive pericarditis. Typically there is only mild postcapillary pulmonary hypertension due to left-sided constriction. Severe pulmonary venous congestion is prevented by the concurrent right-sided constriction. *A*. Posteroanterior view shows moderate cardiomegaly and mildly cephalic pulmonary blood flow pattern. *B*. Lateral view shows heavy calcification of the pericardium (*arrows*) and left atrial enlargement deviating the barium-filled esophagus posteriorly.

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CARDIAC FLUOROSCOPY

Cardiac radiography deals primarily with anatomic details by filming at short exposure times that stop the motion. Cardiac fluoroscopy, on the other hand, explores the dynamic features of the organ that are discernible only in motion.[28] The two techniques are mutually complementary.

Description

A good-quality image intensifier is a prerequisite for the proper performance of cardiac fluoroscopy.[2,19] The modern intensifier with cesium iodide phosphors has increased the brightness of the fluoroscopic image at least 10,000 times. Television viewing permits cone vision under dim light with better perception of detail. The attached videotape or videodisk recorder providesa means for instant playback as well as future analysis of the fluoroscopic observations.

The milliamperage and kilovoltage of the fluoroscope should be adjusted according to the patient's size in different projections. The milliamperage ranges from 1.5 to 3.5 mA, and the kilovoltage varies between 90 and 120 kV. Too high a kilovoltage tends to reduce the contrast, and excessive milliamperage blurs the margin of the image. The shortest fluoroscopic time and the smallest shutter opening are employed to keep the dose of radiation to the patient to the minimum. The average examining time for this author is 3 min.

The patient is routinely examined in the erect position with four views. The patient should be asked to stop breathing during the brief moment of fluoroscopy. A barium meal is given only after a thorough search for cardiac calcifications is completed. Occasionally, a recumbent position is used for better visualization of small calcifications, as well as for a critical evaluation of cardiac asynergy. The cardiac output increases and the heart rate decreases on assuming recumbency, thereby giving a truer and more representative picture of the left ventricular contractility. In obese patients, the thick layer of soft tissue over the thorax is compressed and pushed aside, thereby improving the fluoroscopic image significantly.

Results

When performed properly, cardiac fluoroscopy is useful in the following areas of investigation: (1) assessment of cardiovascular dynamics, (2) detection of small cardiovascular calcifications, (3) visualization of important anatomic landmarks, e.g., subepicardial fat stripes, (4) differentiation of cardiac from noncardiac disease, and (5) evaluation of cardiac valve prostheses, pacemakers, and radiopaque foreign bodies.

Precautions

Although no complication from modern fluoroscopy has been reported, both the patient and the examiner should be protected from excessive radiation. Even with an image intensifier, a routine cardiac fluoroscopy still involves more radiation than does two-view chest roentgenography. Therefore, the fluoroscopist should accomplish the task within the shortest possible period of time. Although all aspects of the heart are surveyed briefly, one should emphasize special areas of interest for each patient, as suggested by the baseline radiographs. If coarctation of the aorta is suspected in a patient older than 40 years of age, for instance, particular attention should be paid

to finding calcium in a stenotic bicuspid aortic valve.

Applications

ASSESSMENT OF CARDIOVASCULAR DYNAMICS

The chest roentgenogram that is taken at random largely records the diastolic image of the heart. Fluoroscopy, on the other hand, provides a continuous vision of the pulsating organ through the entire cardiac cycle. On becoming familiar with the normal cardiovascular movements, the fluoroscopist will find that any deviation from the norm will be obvious.[2,29-32]

The telltale x-ray signs of many cardiac lesions manifest themselves only in ventricular systole. Therefore, what may be missed on the film is often readily seen and diagnosed under the fluoroscope. For instance, left ventricular enlargement may be the only radiographic abnormality of severe aortic regurgitation in children or young adults. On fluoroscopy, however, the aorta is vigorously expanding in systole and rapidly collapsing in diastole. This dynamic alternation is characteristic of aortic regurgitation (Fig. 12-24). Other examples include mild mitral regurgitation, mitral valve prolapse, left ventricular dyskinesia, and broad-based left ventricular aneurysm.

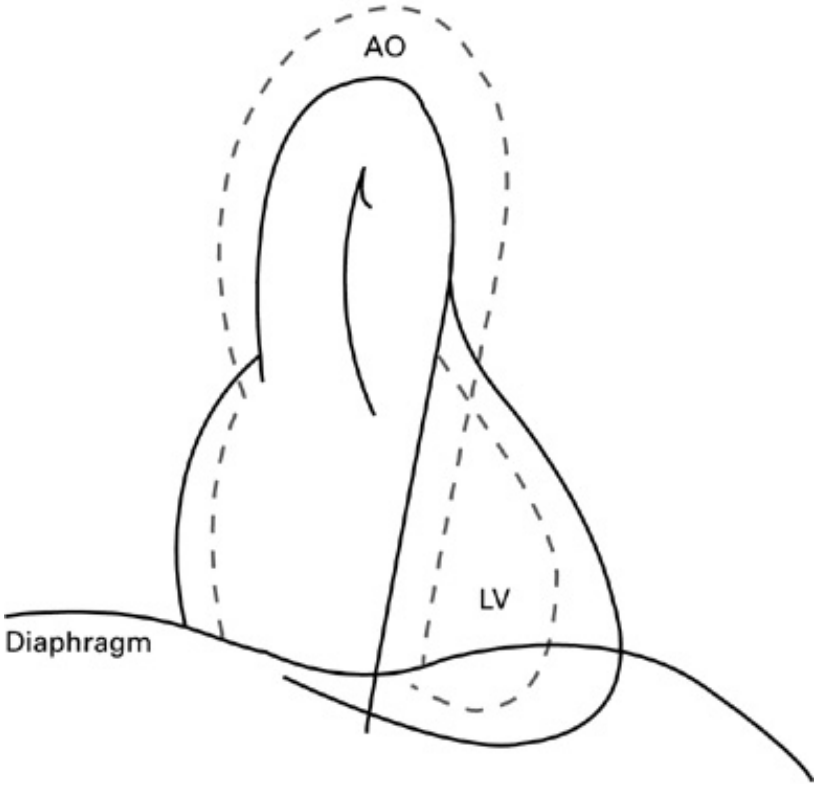

Figure 12-24: Schematic representation of dynamic changes of aortic regurgitation. Blue interrupted lines represent images in systole; solid lines, those in diastole.

In valvular pulmonary stenosis, vigorous pulsation of the pulmonary trunk and its left branch is in bold contrast to the diminished pulsation of the right pulmonary artery.[31] Increased pulsation of diffusely enlarged pulmonary arteries is characteristic of left-to-right shunts. When marked discrepancy in size and pulsation is noted between the central and peripheral vessels, Eisenmenger's syndrome should be considered. Exaggerated left atrial expansion in ventricular systole is a reliable sign of mitral regurgitation.[32]

DETECTION OF CARDIOVASCULAR CALCIFICATIONS

Heavy calcifications of the heart and vessels are easily detected by chest roentgenography, particularly in the lateral and oblique views (Fig. 12-25). Small calcifications, on the other hand, can be registered only by fluoroscopy by virtue of their rhythmic movements from the pulsating heart.[3,8] Detection of even tiny coronary artery calcifications is of vital practical importance. The combination of chest pain and coronary calcification results from major vascular obstruction 94 percent of the time.[16] Since the major coronary arteries are embedded in the subepicardial fat stripes in the grooves between cardiac chambers (Fig. 12-26), such fat stripes can be used effectively to locate the calcified arteries. Under the fluoroscope, the fat stripes present as pulsating radiolucent (bright) lines, in contrast to the accompanying pulsating radiopaque (dark) lines of calcified coronary arteries. If the artery coincides with the fat line within the left atrioventricular groove (aL), it portrays the circumflex coronary artery. The right coronary artery is moving synchronously with the right atrioventricular groove (aR). The anterior descending artery coincides with the anterior interventricular groove (vA), as does the posterior descending artery with the posterior interventricular groove (vP).

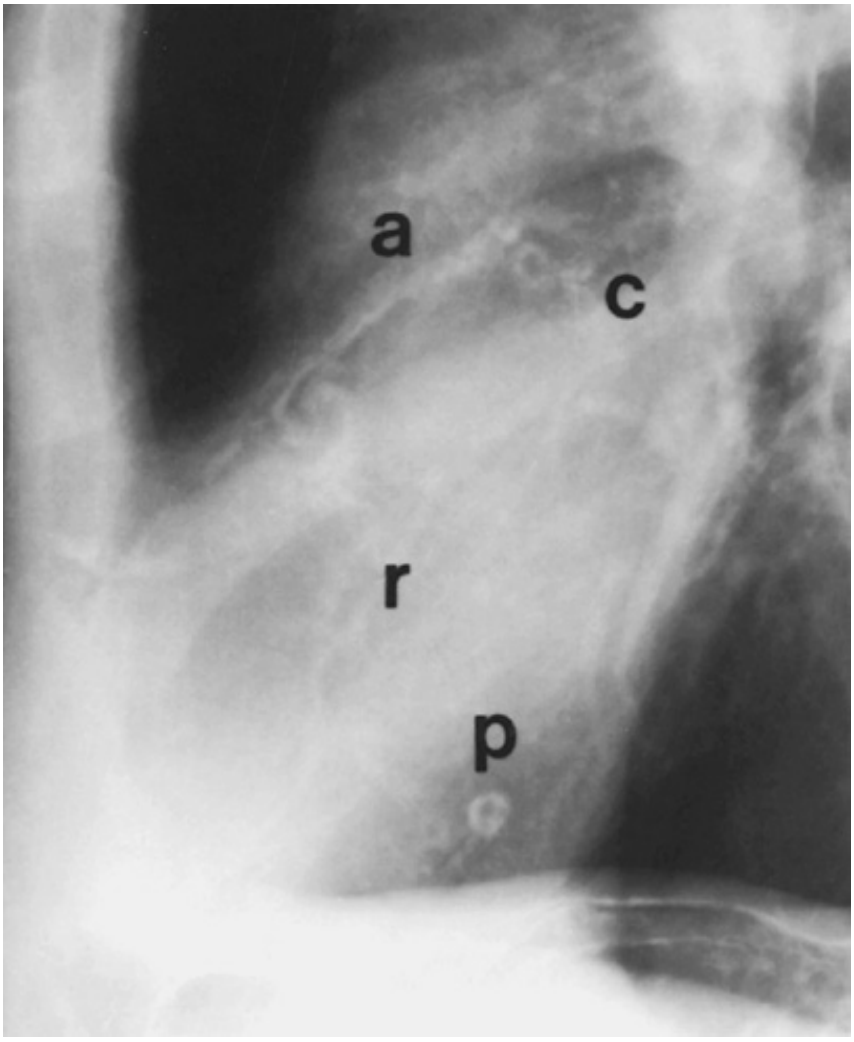

Figure 12-25: Lateral view shows heavy railroad track-like calcification of all three major coronary arteries. r, right coronary artery; a, anterior descending; c, circumflex; p, posterior descending. Note the ringlike densities representing vessels viewed on end.

The lateral view is the best or the only view for detection of a calcified right coronary artery. The left anterior oblique view at 20 to 30° is the most suitable for localizing the bifurcation of the left coronary artery. In this view, the left coronary artery is brought into relief between the hilar shadow anteriorly and the spinal column posteriorly. A ringlike density is seen frequently in this view, representing the end-on image of the calcified anterior descending artery. The right anterior oblique angle is used to view a calcified left main coronary artery. If both the anterior descending and the circumflex branches are also calcified, a Y-shaped density may be seen. The calcified cardiac valves, the myocardium, and the pericardium are easily confirmed by fluoroscopy.[2,29]

VISUALIZATION OF SUBEPICARDIAL FAT STRIPES

The subepicardial fat lines are important landmarks in the diagnosis of heart disease. The fat stripe is a cushion-like structure separating the myocardium from the pericardium. Normally, it is difficult to see the fat line because of the adjacent similar radiolucency of the air-filled lung. The in-between hairline density of the normal pericardium is delicate and also difficult to see except in the left lateral view (Fig. 12-10*A*). In the presence of pericardial effusion or thickening, the subepicardial fat line is displaced interiorly and becomes more visible because of the added background of water density (**see** Fig. 12-10*B*). The subepicardial fat pulsates with the contracting myocardium within the immobile band of pericardial fluid. This is diagnostic of pericardial effusion.[33] In contrast, when pericardial thickening alone is present, the exterior border of the heart pulsates with the fat line. This, in turn, suggests the diagnosis of pericardial constriction.

Although the displaced subepicardial fat stripe is visualized only in the lateral radiograph (**see** Fig. 12-10*B*), fluoroscopically, the pulsating fat line is clearly visible in all four views throughout the entire cardiac cycle (Fig. 12-27).

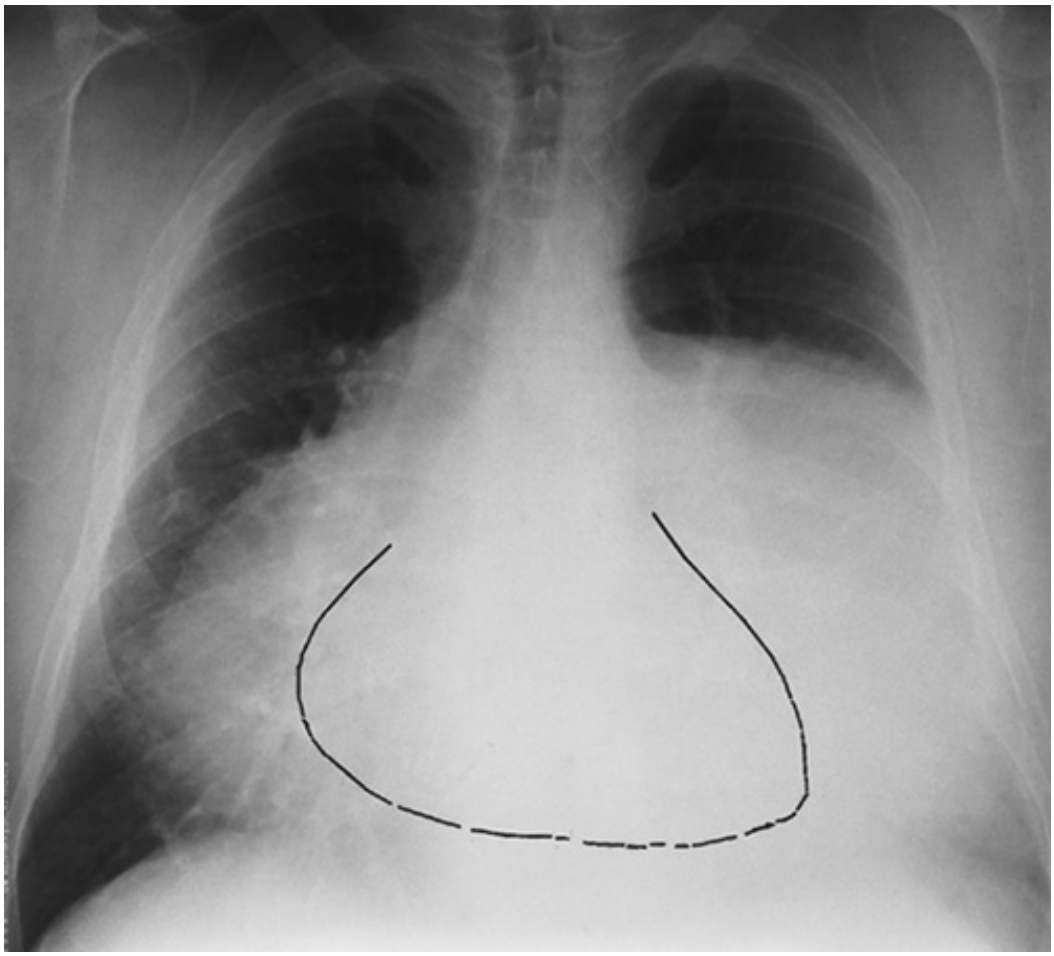

Figure 12-27: A young man with a slowly developed pericardial effusion without cardiac tamponade. His posteroanterior view shows a huge water bottle-like cardiac silhouette. Note the lungs are clear and the PBF pattern is normal. The subepicardial fat stripe (black curvilinear line) within the immobile pericardial effusion was clearly visible and bouncing vigorously under the fluoroscope. The amplitude of excursion of the fat stripe reflected the normally functioning myocardium.

DIFFERENTIATION OF CARDIAC FROM NONCARDIAC DISEASE

When respiration is suspended, any structures that are moving are likely to be cardiovascular in nature. Conversely, noncardiac structures are immobile. This is exemplified by a bullet in the heart versus another in the chest wall. A pulmonary varix or an azygos vein collapses on Valsalva maneuver, with exaggerated pulsation following release of the breath. Enlarged lymph nodes in these areas, on the other hand, will not change with such a maneuver.

EVALUATION OF VALVE PROSTHESES AND PACEMAKERS

The normal movements of cardiac valve prostheses are parallel between the two phases of the cardiac cycle. If a significant angle of tilt (more than 12°) is formed between the two phases, instability of the valve with associated regurgitation is nearly always present.[2,29,32,34]

The bileaflet St. Jude valve[35] is used in both mitral and aortic positions. The valve is difficult to see radiographically (Fig. 12-28) but is readily detected under the fluoroscope.[1,2,35] When the leaflets move sluggishly, thrombotic stenosis of the valve should be suspected. Rarely, one leaflet may dislodge and embolize distally, causing acute valvular regurgitation.[35]

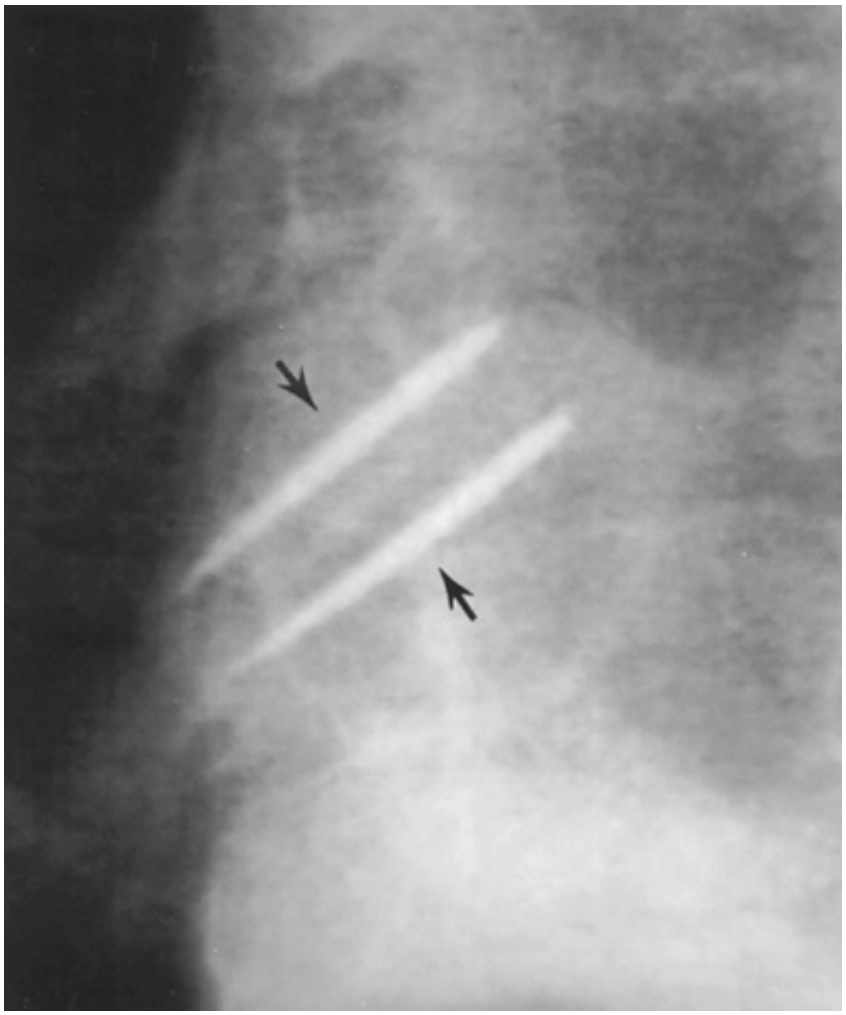

Figure 12-28: Patient with congenitally corrected transposition of the great arteries. The left-sided atrioventricular valve was replaced with a St. Jude prosthesis. The valve was caught in the opened position (in diastole), when both leaflets were seen as a pair of parallel lines (*arrows*). The same valve was invisible in the closed position (*not shown*).

The position of the pacemaker can be determined promptly under the fluoroscope and recorded on film.[2,36] The subepicardial fat line overlies the myocardium and underlies the pericardium. If the pacing catheter is found within the fat stripe, it may have passed through the coronary sinus and entered one of the major cardiac veins. If the tip of the catheter is seen outside the fat stripe, however, it may have perforated the myocardium and thus be lying in the pericardium or beyond.[2] Although the wires and electrodes of a transmediastinal pacemaker may look normal on the films, minor breakage can be appreciated only in ventricular systole with the aid of fluoroscopy.[36]

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Figure 12-4: Patient with situs ambiguous, interruption of the inferior vena cava, ventricular septal defect, and polysplenia. *A.* Posteroanterior view shows that the aortic arch and the heart are left-sided and the stomach (*lower arrows*) is right-sided. The azygos vein (*upper arrow*) is markedly enlarged. The heart is mildly enlarged, and there is a moderate increase in pulmonary vascularity. *B.* Lateral view shows an absent image of the inferior vena cava. The azygos arch (*arrow*) is markedly dilated.

Figure 12-5: A 16-year-old girl with straight-back syndrome. *A.* Posteroanterior radiograph shows normal pulmonary vascularity and normal heart size. Note leftward displacement and rotation of the heart, making its left border unusually prominent. *B.* Lateral view shows that the anteroposterior diameter of the chest is extremely narrow. The heart is squeezed, creating an innocent murmur.

Figure 12-6: Roentgen appearance of left-sided heart failure. *A.* Acute. Patient with acute mitral regurgitation due to rupture of chordae tendineae showing "bat wings" appearance of severe alveolar type of pulmonary edema and a normal-sized heart. *B.* Chronic. Patient with severe mitral and tricuspid regurgitation and mild aortic regurgitation. This is a predominantly left-sided failure pattern. Note gross cardiomegaly with striking cephalization and interstitial pulmonary edema. The giant left atrium forms the right cardiac border (*open arrow*), makes its appendage bulge outward on the left side (*upper large arrow*), and splays the mainstem bronchi wide apart (*solid lines*). The huge right atrium forms a double density within the right cardiac border (*three small arrows*). The upper small arrow marks the peribronchial cuffing of edema fluid. The lower large arrow points to multiple Kerley B lines. *C.* Magnified view of right costophrenic sulcus showing multiple Kerley B lines (*arrow*). *D.* A 44-year-old woman with severe mitral stenosis. Her radiograph shows a diffuse stippling with fine nodules representing hemosiderosis. Hemosiderin-laden macrophages were found in her sputa. *E.* Posteroanterior radiograph of a 63-year-old man with severe mitral stenosis, status post mitral valve replacement, shows multiple scattered bony nodules (*arrows*) 2 to 10 mm in diameter throughout the lower two-thirds of both lungs, compatible with pulmonary ossification.

Figure 12-7: Roentgen appearance of right-sided heart failure. *A.* Patient with severe obstructive emphysema showing overaeration of the lungs, centralized flow pattern, and a small heart size. *B.* Three years later, the patient was in frank right-sided heart failure. Note that the heart got bigger as his emphysema got worse. The centralized flow pattern became more severe. *C.* Patient with Ebstein's anomaly showing gross cardiomegaly with severe decrease in pulmonary vascularity. The right cardiac border represents the huge right atrium, and the left cardiac border represents the giant right ventricle. *D.* Patient with mitral stenosis showing a giant right atrium (*arrow*) representing severe functional tricuspid regurgitation due to unrelenting left-sided failure. The pulmonary venous congestion had improved following the onset of right-sided heart failure.

Figure 12-8: Left ventricular aneurysms. *A.* Posteroanterior view of patient 1 shows a localized bulge (*arrows*) along the left cardiac border representing a left ventricular aneurysm from the anterolateral wall. *B.* Lateral view shows a double density with sharp borders anteriorly and superiorly (*arrows*). This is the left ventricular aneurysm that casts a shadow on the normal right ventricle. Fluoroscopically, it is easy to confirm its origin and to separate it from the right ventricle by rotating the patient under direct vision. *C.* Posteroanterior view of patient 2, a 69-year-old man, shows total calcification of an anterolateral apical left ventricular aneurysm (*arrows*). *D.* Lateral view shows the same (*arrows*).

Figure 12-9: A 71-year-old woman with syphilitic aortitis. Her posteroanterior radiograph (*A*) shows a huge, calcified ascending aortic aneurysm (*arrows*). In addition, the entire aorta and the left ventricle are markedly dilated, compatible with severe aortic regurgitation (From Chen,[14] with permission.) A magnified view of the ascending aorta (*B*) shows the calcified aneurysm to better advantage.

Figure 12-10: Developing pericardial effusion in 2 weeks. *A.* A magnified view of the retrosternal area showing the hairlike normal pericardium (*arrow*) sandwiched between the subepicardial fat stripe interiorly and the mediastinal fat stripe exteriorly. The maximal width of normal pericardium is 2 mm. *B.* The same patient 2 weeks later, with moderate pericardial effusion. The pericardial cavity now measured more than 1 cm in width (*arrow*).

Figure 12-11: Traumatic constrictive-effusive pericarditis in a young man. Following emergent pericardiocentesis and injection of air, a radiograph was taken in the supine position. Air is confined to the left side of the pericardium. Note markedly thickened parietal layer (*arrows*).

Figure 12-12: Posteroanterior view of a patient with dextrocardia and situs solitus. Note that the aortic arch and the stomach air bubble are both on the left (*situs solitus*) and the apex of the ventricles is pointing to the right inferiorly. According to statistics and proved by cardiac catheterization, this patient had the typical combination of congenitally corrected transposition of the great arteries, ventricular septal defect, and pulmonary stenosis. He was cyanotic. The pulmonary vascularity appears decreased.

Figure 12-13: A 17-year-old boy with congenital aortic valve stenosis. Note dilatation of the ascending aorta, increased convexity of the left ventricle, and normal pulmonary vascularity. The systolic aortic pressure gradient was 100 mmHg.

Figure 12-14: A 45-year-old man with Marfan's syndrome, severe aortic regurgitation, and proximal aortic dissection into the pericardial cavity. *A.* Posteroanterior view shows a huge left ventricular and aneurysmal dilatation of the ascending aorta. There is no sign of heart failure. *B.* Lateral view shows a small pericardial effusion (*arrow*).

Figure 12-15: Posteroanterior view of a 77-year-old man shows a huge descending aortic aneurysm (*arrows*).

Figure 12-16: A 37-year-old woman with congenital valvular pulmonary stenosis. Note enlarged pulmonary trunk and left pulmonary artery versus diminished right pulmonary artery. Also note increased pulmonary blood flow on the left side and decreased pulmonary blood flow on the right side.

Figure 12-17: Patient with congestive heart failure. Note gross cardiomegaly, cephalization, interstitial pulmonary edema, and right-sided pleural effusion. Some of the fluid was loculated in the minor interlobar fissure (*arrow*), which disappeared with improved cardiac function.

Figure 12-18: A child suffering from nephrotic syndrome, which was treated successfully. *A.* Posteroanterior view during the worst period of his disease shows general anasarca, pulmonary edema, and pleural effusion. Note considerable soft tissue edema in the chest wall. *B.* With proper treatment, everything returned to normal in 2 weeks.

Figure 12-19: Patients with Holt-Oram syndrome. *A.* Posteroanterior view of patient 1, a 7-year-old girl, shows a globular cardiac contour with increased pulmonary blood flow. The aortic arch is on the right side. Catheterization diagnosis: secundum atrial septal defect. *B.* Her left arm shows absent radius and thumb with radial clubhand. Her right arm is a mirror image of the left (not shown). *C.* Forearms of patient 2, a 33-year-old woman with secundum atrial septal defect, show bilateral absence of thumb.

Figure 12-20: Young man with acute pericarditis with effusion. *A.* Posteroanterior view shows a water bottle-shaped cardiomegaly, clear lungs, and normal pulmonary vascularity. *B.* Repeat film taken 5 days later shows excellent response to therapy.

Figure 12-21: Statistical guidance focusing on the best diagnostic possibilities. *A.* Posteroanterior view of a patient with tetralogy of Fallot showing a right aortic arch, avian type. Note that the esophagus and trachea are deviated to the left. The cardiovascular structures are otherwise within normal limits. *B.* Lateral view of the same patient showing the aortic arch normally situated, in front of the trachea and esophagus. *C.* Posteroanterior radiograph of a healthy woman shows a right aortic arch (*large arrow*) with a large aortic diverticulum (*small arrow*) that protrudes to the left of the midline. The distal segment of the trachea is deviated to the left side by the right arch. Unlike double aortic arch, the left lateral margin of the trachea is not indented because the diverticulum is posterior and not lateral in position. *D.* Lateral view of similar patient, a healthy man. Note that both the esophagus and the trachea are markedly displaced anteriorly by a huge diverticulum, which invariably gives rise to the aberrant left subclavian artery.

Figure 12-22: A 42-year-old man with Eisenmenger's atrial septal defect. Note increased pulmonary blood flow with a centralized pattern.

Figure 12-23: Patient with calcific constrictive pericarditis. Typically there is only mild postcapillary pulmonary hypertension due to left-sided constriction. Severe pulmonary venous congestion is prevented by the concurrent right-sided constriction. *A.* Posteroanterior view shows moderate cardiomegaly and mildly cephalic pulmonary blood flow pattern. *B.* Lateral view shows heavy calcification of the pericardium (*arrows*) and left atrial enlargement deviating the barium-filled esophagus posteriorly.

Figure 12-24: Schematic representation of dynamic changes of aortic regurgitation. Blue interrupted lines represent images in systole; solid lines, those in diastole.

Figure 12-25: Lateral view shows heavy railroad track-like calcification of all three major coronary arteries. r, right coronary artery; a, anterior descending; c, circumflex; p, posterior descending. Note the ringlike densities representing vessels viewed on end.

Figure 12-26: Schematic representation of the subepicardial fat stripes in relation to major coronary arteries. *A.* Posteroanterior view. *B.* Lateral view. *C.* Right anterior oblique view. *D.* Left anterior oblique view. AL, left atrioventricular groove (circumflex); aR, right atrioventricular groove (right); vA, anterior interventricular groove (anterior descending); vP, posterior interventricular groove (posterior descending); F, apical fat pad; AO, aorta; LV, left ventricle.

Figure 12-27: A young man with a slowly developed pericardial effusion without cardiac tamponade. His posteroanterior view shows a huge water bottle-like cardiac silhouette. Note the lungs are clear and the PBF pattern is normal. The subepicardial fat stripe (black curvilinear line) within the immobile pericardial effusion was clearly visible and bouncing vigorously under the fluoroscope. The amplitude of excursion of the fat stripe reflected the normally functioning myocardium.

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 13:

THE ECHOCARDIOGRAM

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INTRODUCTION

The term *echocardiography* refers to the evaluation of cardiac structure and function with images and recordings produced by ultrasound. In the past three decades it has rapidly become a fundamental component of the cardiac evaluation. Currently, echocardiography provides essential (and sometimes unexpected) clinical information and has become the second most frequently performed diagnostic procedure after electrocardiography.[1] What began as a one-dimensional method performed from the precordial area to assess cardiac anatomy has evolved into a two-dimensional (2D) modality performed from either the thorax or from within the esophagus, capable of also delineating flow and deriving hemodynamic data.[2] Newly evolving technical developments likely will extend the capacity of ultrasound to routine 3D visualization[3] as well as to the assessment, in conjunction with contrast agents,[4] of myocardial perfusion.

The development of echocardiography is usually credited to Elder and Hertz in 1954.[5] Primitive cross-sectional images of the excised human heart were produced in 1957[6]; however, for nearly two additional decades, clinical echocardiography consisted primarily of 1D time-motion (M-mode) recordings, as popularized by Feigenbaum.[7] In the mid-1970s, Bom and associates developed a multielement linear-array scanner that could produce spatially correct images of the beating heart.[8] 2D images of superior quality were soon achieved by mechanical sector scanners[9,10] and ultimately by phased-array instruments as developed by Thurston and Von Ramm, which are the present-day standard.[11] In the past several years, 3D instruments capable of real-time volumetric imaging have been developed.

Although efforts to use the Doppler principle to measure flow velocity by ultrasound were begun in the early 1970s by Baker et al.,[12] clinical application of this technique did not thrive until the work of Hatle in the early 1980s.[13,14] Pulsed and continuous-wave Doppler recordings soon were expanded to full 2D color-flow imaging.[15] Most recently, miniaturization of ultrasound transducers has led to their incorporation into gastroscopes and cardiac catheters to achieve transesophageal and intravascular images.[16,17]

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Chapter 13: THE ECHOCARDIOGRAM

PRINCIPLES OF ECHOCARDIOGRAPHY

Physics and Instrumentation

Sound is an energy form that travels through a medium as a series of alternating compressions and rarefactions of the molecules (Fig. 13-1). Sound is typically characterized by its wavelength, which is the distance between any two consecutive phases of the cycle (e.g., peak compression to peak compression), and by its frequency, which is the number of wavelengths per unit time [customarily expressed as cycles per second, or hertz (Hz)]. The velocity of sound is the product of wavelength and frequency; thus there is an inverse relationship between these two characteristics: the greater the frequency, the shorter the wavelength. Ultrasound is sonic energy with a frequency above the audible range of the human ear (greater than 20,000 Hz) and is useful for diagnostic imaging, since, like light, it can be directed as a beam that will obey the laws of reflection and refraction.[14-18] Thus, an ultrasound beam will travel in a straight line through a homogeneous medium. If the beam meets an interface of different acoustic impedance, however, part of the energy will be reflected, and the remaining attenuated signal will be transmitted. The reflected energy, or echo, is used to construct an image-in the case of echocardiography, an image of the heart (Fig. 13-2).

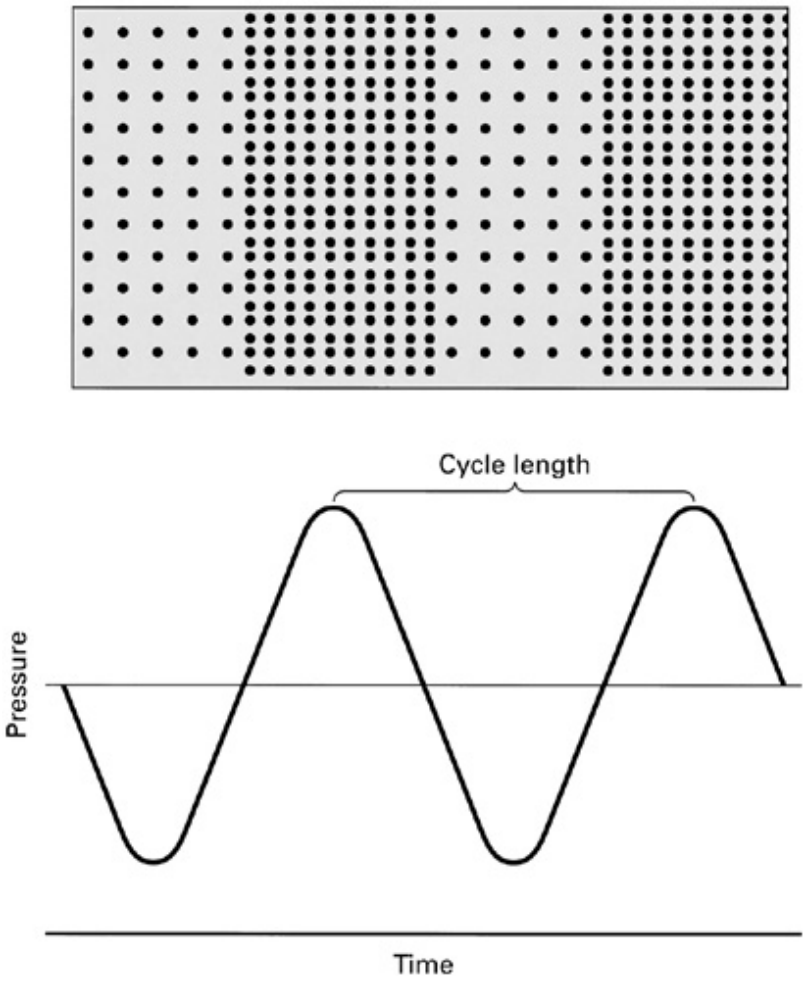

Figure 13-1: Sound energy results in alternating compression and rarefaction of particles in a conducting

medium. This alternation, which can be plotted against time (or distance), conforms to a sine-wave pattern (*bottom panel*). (Modified from Hagan AD, DeMaria AN. *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler.* Boston: Little, Brown; 1989, with permission.)

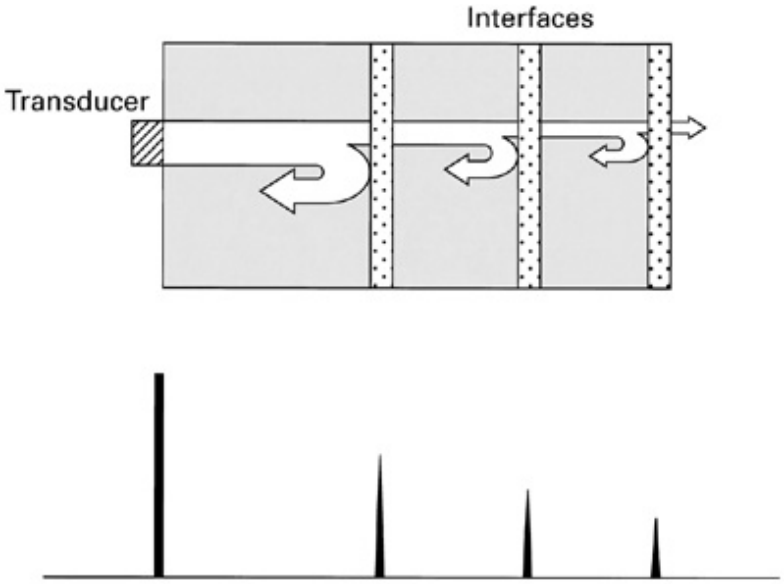

Figure 13-2: *Upper panel:* Attenuation of an ultrasound beam emitted from a transducer. There is reflection and progressive loss of energy at each interface encountered. *Lower panel:* the reflected wavefronts are recorded as signals of varying amplitudes (A mode) via the piezoelectric crystal. (Upper panel modified from Hagan AD, DeMaria AN. *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler.* Boston: Little, Brown; 1989, with permission.)

The most fundamental component of any echocardiographic instrument is the transducer, which is responsible for both transmitting and receiving the ultrasound signal. The transducer consists of electrodes and a piezoelectric crystal whose ionic structure results in deformation of shape when exposed to an electric current.[18] Thus, piezoelectric crystals are composed of synthetic materials, such as barium titanate, that, when exposed to electric current from the electrodes, alternately expand and contract to create sound waves. When subjected to the mechanical energy of sound returning from a reflecting surface, the same piezoelectric element changes shape, thereby generating an electrical signal detected by the electrodes (Fig. 13-3). Thus the transducer both produces and receives ultrasonic signals.

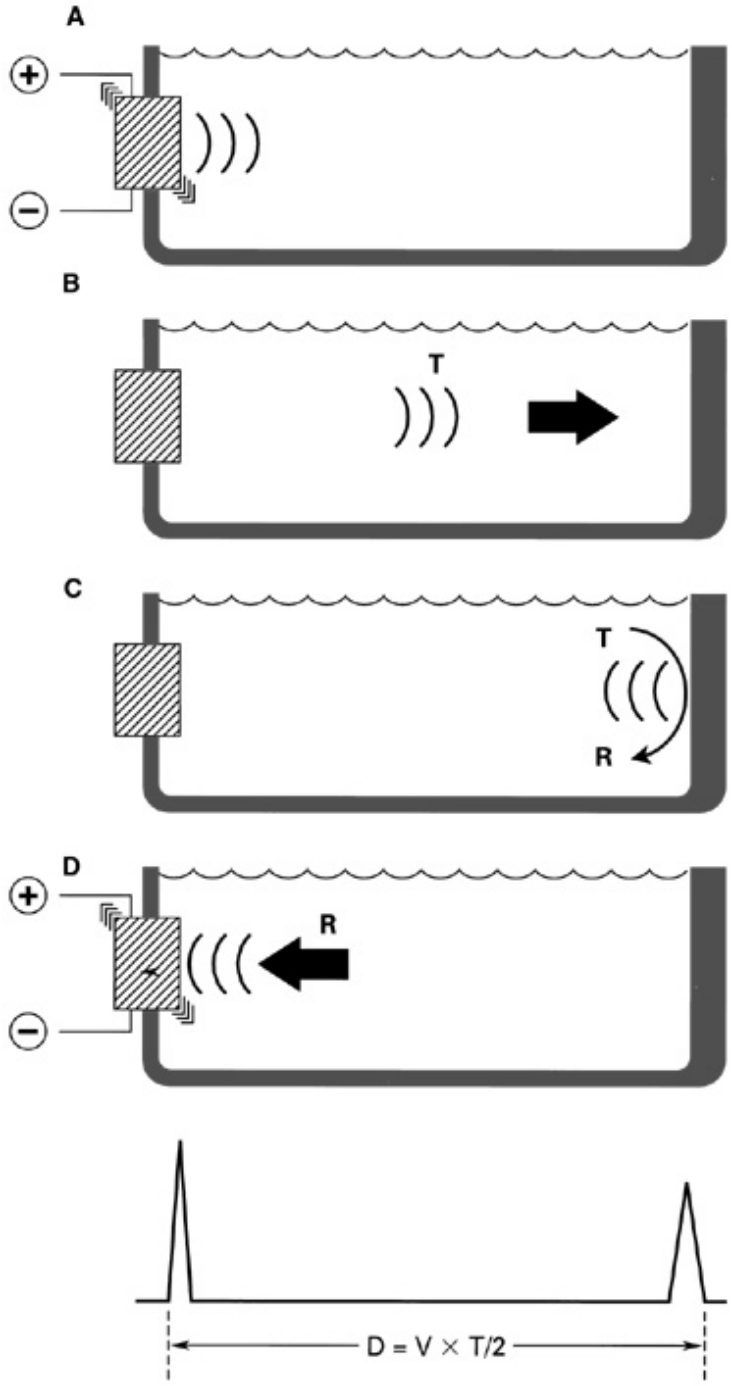

Figure 13-3: *A* through *D:* the basic principle of ultrasonic imaging. The piezoelectric crystal is activated, producing a transmitted pulse (T), which reflects off the interface. The reflected pulse (R) excites the crystal, producing an electric current. As the velocity of the pulse is constant, distance can be calculated based on the transit time. (Because the pulse must travel back and forth from the interface, the time is divided by 2.) (Modified from Weyman AE. *Principles and Practice of Echocardiography,* 2d ed. Philadelphia: Lea & Febiger; 1994, with permission.)

In the past, echographs have both transmitted and received signals of the same frequency. Recently, *harmonic imaging* has been implemented, in which ultrasound energy is transmitted at one frequency (fundamental) and received at a higher harmonic of that frequency (usually the first). Tissue harmonic signals are created by alteration of the frequency of the wave as it propagates through the structure.[18a] Contrast microbubbles produce harmonics by virtue of resonating (expanding/constricting) in the ultrasound field.[18b] The net effect of harmonic imaging is to reduce the signal intensity of background noise and enhance that from true tissue (or microbubble) structure, although some blooming of the signals from valves may be observed.[18a]

As an imaging modality, ultrasound carries with it several unique technical difficulties. Sound energy is poorly transmitted through air and bone, and the ability to record adequate images is dependent upon a thoracic window that gives the interrogating beam adequate access to cardiac structures. The degree to which ultrasonic energy will be reflected when striking an interface of differential impedance is dependent upon how perpendicular the interrogating beam is to the interface. When the ultrasound beam is directed parallel or near parallel to the interface, little or no sound energy will be reflected to the transducer. Therefore poor signal transmission, a nonorthogonal orientation of the ultrasound beam to the surface, and energy attenuation can result in failure to record signals from cardiac structures-a phenomenon referred to as *echo dropout*.[19] Conversely, some structures may be such strong ultrasonic reflectors-being perpendicular to the beam or extremely dense-that sufficient energy returns to the transducer to be reflected and again transmitted into the field. This phenomenon can lead to reverberations, or the reproduction of the echoes of anatomic structures at multiple locations within the image.[20] In addition, background noise artifacts, or signals generated from the system rather than tissue, can also be encountered. Finally, since the ultrasound beam diverges with distance from the transducer and always has a finite width, targets lying on the periphery of the beam may be recorded and displayed as if they were located along the central scan line (Fig. 13-4). This problem may be accentuated in the setting of very strong reflectors that result in the formation of *side lobes*.[21] In either case, beam-width problems associated with ultrasound may result in the depiction of targets in erroneous locations and create problems in interpreting the images.[22]

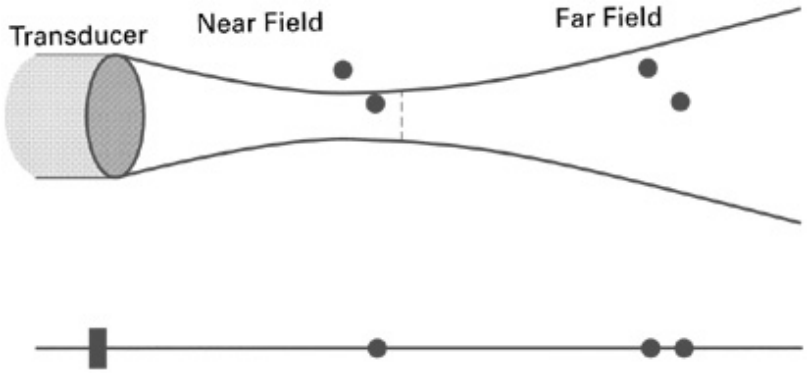

Figure 13-4: *Upper panel:* The transducer emits an ultrasonic beam that has a near field (where the beam is relatively focused) and a far field (where the beam width increases). *Lower panel:* B-mode diagram showing the effect of beam width. In the near field, the beam reflects off only one of two objects in close proximity to each other. In the far field, however, two similarly positioned objects are both within the beam width. Therefore, lateral resolution is compromised and the objects' positions are misrepresented.

The construction of a cardiac image from ultrasound signals is based upon computation of the distance between an anatomic structure and the transducer (Fig. 13-3). Thus, an ultrasound beam is produced by a hand-held transducer positioned on the thorax and directed into the heart. This beam will travel in a straight line until it reaches an interface between structures of different acoustic impedance, such as blood and myocardium. At this point, some ultrasonic energy will be reflected (depending on the density of interface), some will be scattered, and some will continue forward. The amplitude of the propagating signal will be attenuated because of the reduction in energy at the interface (Fig. 13-2). The reflected sound waves return to the transducer and form the basis of the echogram. Electronic circuitry within the echograph measures the time interval required for the transit of the ultrasound beam from the transducer to the interface and back again. Since the velocity of sound in soft tissue is constant (approximately 1540 m/s), the instrument can calculate the total distance traveled to and from the reflecting surface as the product of transit time and velocity of sound. Interface location is derived as one-half of the total transit distance, and a signal is depicted on an oscilloscope or video monitor at that point (Fig. 13-3). The amplitude of ultrasonic energy reflected from each target interface is represented by the brightness of the signal that is displayed.

The one-dimensional ultrasonic B- (or brightness) mode scan line resulting from a single transmitted beam is the cornerstone of echocardiographic imaging. In the most basic form of echocardiography, a single scan line produced by a piezoelectric crystal is passed through the heart (Fig. 13-5). At each structural

interface, ultrasonic energy is reflected back and displayed at the appropriate distance as a signal, whose amplitude represents the acoustic impedance or density of the material encountered. These signals are subsequently displayed as dots, whose brightness is proportional to the amplitude of reflected ultrasonic energy. The distance from the transducer of these B-mode dots changes as the cardiac structures move during the cardiac cycle. Accordingly, if repetitive B-mode scan lines are produced and swept across the screen over time, the movement of the heart can be obtained as a time-motion (or M-mode) recording,[23] providing dynamic rather than merely static cardiac images (Fig. 13-5). In clinical use, the piezoelectric crystal within the transducer is activated by alternating electric current to transient at a rate of approximately 1000 pulses per second. This same crystal also receives the returning echo reflections and actually spends the great majority of the time (>90 percent) in the "receive" rather than "transmit" mode. Because the beam is confined to a single location and transmits ultrasound signals at the pulse rate of the transducer, M-mode echocardiography provides very high temporal resolution. Importantly, M mode is an excellent modality for timing cardiac events or recording high-velocity motion.

As ultrasound technology advanced and it became possible to determine accurately the spatial orientation of the interrogating beam, multiple B-mode scan lines from different imaging angles were collected and displayed in proper alignment to create a 2D image. As opposed to B- or M-mode recordings, which are unidimensional (on an anterior-posterior axis), 2D echocardiography provides additional information in either superior-inferior or medial-lateral directions. At the current time, M-mode recordings are derived from the 2D images rather than as a stand-alone signal.

Several characteristics of sound energy are of fundamental importance in determining the quality of the images obtained. High-quality images require optimal resolution-that is, the ability to distinguish two individual objects separated in space. Short wavelengths yield excellent resolution in echo imaging, since the shorter the cycle length, the smaller the object that will reflect the signal and be detected by the echo scanner. Since wavelength is inversely related to frequency, transducers that emit a high-frequency signal (3.5 to 7.0 MHz or greater) yield high-resolution images. High-frequency signals also overcome an important limitation of ultrasonic imaging associated with lateral resolution. Since ultrasonic beams diverge as they propagate away from the transducer, the width of the beam can become sufficiently great to encompass multiple targets and diminish resolution (Fig. 13-4). The degree of beam divergence is less with high-frequency sonic energy than with low-frequency signals. The smaller wavelengths associated with high-frequency signals, however, are subject to greater reflection and scattering (therefore substantially higher attenuation) as the beam propagates through tissue. The resultant attenuation is greater than that with low-frequency signals and leads to decreased sensitivity. Therefore, in clinical practice, echocardiographic examinations are performed utilizing the highest-frequency transducer capable of obtaining signals from all potential targets within the ultrasound field.[23]

M-Mode Echocardiography

THE STANDARD M-MODE EXAMINATION

Although largely supplanted by 2D imaging, M-mode echocardiography remains a useful part of a complete ultrasound examination. Figure 13-6*A* through *D* shows the typical views obtained when the transducer is placed at the left parasternal area and rocked through the heart from apex to base. Tissue typically reflects ultrasound at its surface (specular reflectors) and from internal inhomogenicity (backscatter), while blood is homogenous and does not produce reflections. Thus, blood is free of ultrasonic signals on the echocardiogram. At the mitral valve level (Fig. 13-6*C*), the cardiac structure seen closest to the transducer is the right ventricular (RV) free wall; it is followed by the RV cavity, the interventricular septum, the mitral valve apparatus, and the left ventricular (LV) posterior wall as the beam travels backward. At this level, mitral valve excursion is well seen and is more easily recorded for the longer anterior leaflet. For the anterior leaflet, diastolic mitral opening is bipeaked (M-shaped), with maximal opening during early diastolic filling at the E point, a subsequent reclosure downslope to the F point, and a reopening with atrial contraction at the A point prior to valve closure at the C point[24] (Fig. 13-7). The posterior leaflet manifests a mirror-image W-shaped pattern. When LV end-diastolic pressure is elevated, a shoulder (B notch) is often present between the A and C points[25] (Fig. 13-8). If the transducer beam is directed inferolaterally from the mitral valve level, the papillary muscles and LV apex will be imaged (Fig. 13-6*A*). With superior and medial angulation, the left atrium, aortic valve, and aortic root are seen. The tricuspid valve can be imaged by angulating the transducer inferomedially and

the pulmonic valve by angulating slightly superiorly and laterally.

ASSESSMENT OF SYSTOLIC FUNCTION BY M-MODE ECHOCARDIOGRAPHY

Measurements of the LV cavity dimension and wall thickness can be readily derived from M-mode recordings (Fig. 13-9) and are usually made according to the recommendations of the American Society of Echocardiography at end diastole (the onset of the QRS complex) and end systole (the point of maximum upward motion of the LV posterior wall endocardium).[26] These measurements should be made from leading edge to leading edge to avoid incorporating artifacts and reverberations; they are accurate if the beam is orthogonal to the long axis of the ventricle. By convention, left atrial (LA) dimension is measured at end systole and aortic root diameter is recorded at end diastole at the level of the base of the heart (Fig. 13-9). During systole, opening of the aortic leaflets appears as a parallelogram produced by motion of the right coronary and (usually) the noncoronary aortic valve cusps.[27]

The M-mode LV cavity dimensions can be used to estimate ventricular volumes and ejection fraction (EF) if desired, most simply by merely cubing the value (D^3); but these calculations involve several assumptions regarding LV geometry that are not uniformly valid.[28,29] In addition, the M-mode dimension may not be representative of the entire ventricle. The fractional shortening can also be determined.[30] This value is often helpful in assessing systolic function, but it reflects the function of the LV in one chord and in one plane and can be misleading with asynchronous contraction [for example, left bundle branch block (LBBB)] or segmental dyssynergy.[31] An additional M-mode marker of systolic function is *E point-septal separation* (EPSS), or the distance between the anterior mitral valve leaflet at its most anterior opening excursion (the E point) and the interventricular septum. A value of 8 mm or greater is abnormal.[32] The normal M-mode measurements are seen in Table 13-1.

Table 13-1: Normal Values

	Mean ± Standard Deviation	Range	Mean ± Standard Deviation	Range
No. of patients	25	-	50	-
Age, years	10 ± 3	4-18	24 ± 6	1.10-2.53
BSA, m^2	1.33 ± 0.38	0.72-2.04	1.81 ± .34	1.10-2.53
$LVID_d$, mm	44 ± 6	32-50	50 ± 3	42-60
$LVID_s$, mm	28 ± 7	32-50	50 ± 3	22-43
FSLV	34 ± 4	25-42	33 ± 3	28-37
IVS thickness, mm	8 ± 2	5-10	9 ± 1	7-12
IVS excursion, mm	7 ± 1	5-9	9 ± 1	7-12
PW_d thickness, mm	7 ± 2	4-9	9 ± 1	7-12
PW_s thickness, mm	12 ± 3	8-17	16 ± 2	13-20
Δ thickening PW	0.70 ± 0.25	0.41-0.95	0.50 ± 0.19	0.32-0.69
PW excursion, mm	9 ± 2	7-14	11 ± 2	9-17
RVD_d supine, mm	-	-	15 ± 6	7-22
RVD_d left lateral, mm	-	-	20 ± 8	10-37
$Aorta_d$ mm	23 ± 4	15-27	28 ± 5	26-36

LAD_s mm	25 ± 5	20-31	27 ± 6	12-35

ABBREVIATIONS: BSA = Body surface area; $LVID_d$ = left ventricular internal diameter, end diastole; $LVID_s$ = left ventricular internal diameter, end systole; FSLV = fractional shortening of left ventricle; PWV = posterior wall velocity; IVS = interventricular septum; PW = posterior wall; RVD = right ventricular dimension; LAD = left atrial dimension.
SOURCE: Felner JM, Schlant RC. *Echocardiography: A Teaching Atlas.* New York: Grune & Stratton; 1976. Reproduced with permission from the publisher and authors.

Two-Dimensional Echocardiography

A number of technical approaches exist by which multiple individual B-mode scan lines can be rapidly transmitted, received, and displayed in appropriate spatial orientation to construct a 2D image of the heart. The initial approach simply utilized a linear array of 20 piezoelectric crystals placed side by side, each of which transmitted and received signals independently[8] (Fig. 13-10*A*). The resulting scan lines were displayed simultaneously to yield rectangular images. Unfortunately, transducer size and interaction between the elements resulted in images of unsatisfactory quality.

Current 2D scanners utilize B-mode scan lines that are independently transmitted and received and are directed through a wedge-shaped sector of cardiac anatomy by means of mechanical or electrical beam steering (Fig. 13-10*B* to *D*). A variety of motorized devices are available that, by rapidly oscillating or rotating one or more ultrasonic crystals through space, can mechanically direct multiple scan lines through a sector arc of the cardiovascular system.[9,10] The position of the beam in space is derived by determining the orientation of the piezoelectric crystal. A majority of current 2D scanners utilize a phased-array approach, where multiple ultrasonic crystals are employed in concert to create individual B-mode scan lines.[11] The piezoelectric crystals are activated in a closely coordinated temporal sequence such that the individual wavelets produced by each element merge to form a single beam whose direction is determined by the sequence of crystal firing (Fig. 13-11). Since the direction of the resultant beam is determined by the sequence of activation of the individual elements, the beam can be electrically swept throughout a 90-degree sector arc. In addition to electronic beam steering, a firing sequence can be employed that results in dynamic focusing of the beam along its length to achieve minimal beam width and increased resolution. Phased-array 2D scanners employ small transducers without moving parts that could require repair. The increased complexity of these scanners, however, makes the systems more costly.

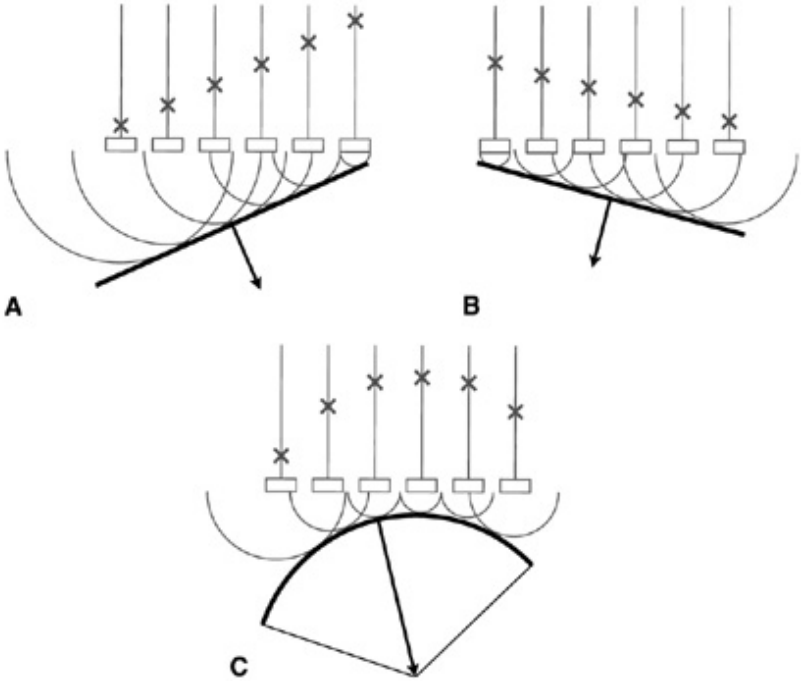

Figure 13-11: Electronic "steering" of a phased-array ultrasound beam. *A.* Elements are fired in sequence from left to right, resulting in a beam directed to the left. *B.* Elements are fired in sequence opposite to those in (*A*), producing a beam directed to the right. *C.* Elements are fired from the periphery toward the center, producing a beam that converges on a given focal point. (From Hagan AD, DeMaria AN. *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler.* Boston: Little Brown; 1989, with permission.)

Originally, echocardiographic data were displayed in analog form on a standard oscilloscope, transferred to a video monitor by a television camera, and hard-copied onto videotape or paper. Currently, computerized analog-to-digital scan conversion is standard, so that the polar signals of individual scan lines are converted to a series of numerical gray-level values for individual box-like picture elements (pixels) aligned along *X-Y* coordinates.[33] The ability of a digital step-gradation technique to reproduce the continuous gradation of analog methods is a function of the density of pixels in the matrix and the shades of gray levels available. No loss of data can be detected in current digitally converted images, and the digital format provides the opportunity for image processing, enhancement, and quantitation. More importantly, storage in digital format can avoid the image degradation inherent in videotape, provide random access and easy comparison of studies, enable rapid image transmission, and prevent deterioration with image copying and prolonged storage. Technology for fully digital echocardiography is now becoming available, and fully digital acquisition and storage of echocardiograms will be commonplace in the near future, replacing analog videotape recordings.

THE STANDARD TWO-DIMENSIONAL EXAMINATION

The heart can be imaged through a multitude of planes with 2D echocardiography. To help standardize the 2D examination, the American Society of Echocardiography has recommended that cardiac imaging be performed in three orthogonal planes: long-axis (from aortic root to the apex), short-axis (perpendicular to long axis), and four-chamber (traversing both ventricles and atria through the mitral and tricuspid valves)[34] (Fig. 13-12). It is important to recognize that the long and short axes are those of the heart, not the body. These three planes can be visualized using four basic transducer positions: parasternal, apical, subcostal, and suprasternal[35,36] (Figs. 13-13*A*, *B*, and *C*). In general, the long-axis plane is best imaged from parasternal, apical, and occasionally the suprasternal positions, while the short-axis plane is best imaged in the parasternal and subcostal positions. The four-chamber views are obtained from the apical and subcostal positions. The American Society of Echocardiography recognizes that these basic positions and planes may be modified somewhat and recommends that an image obtained within 45 degrees of a basic orthogonal plane be identified with that orthogonal plane. Table 13-2 lists the standard transducer positions and transthoracic echocardiographic views. Anatomic drawings of the various imaging planes are

seen in Figs. 13-13, 13-14, 13-15, 13-16, 13-17, 13-18, 13-19 and 13-20.

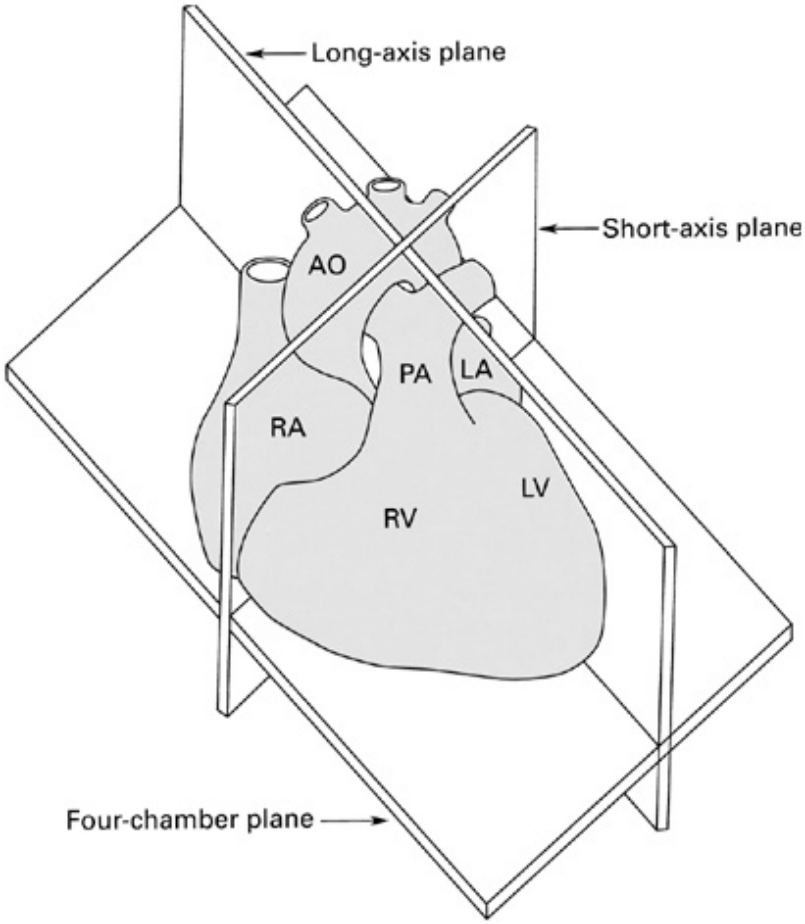

Figure 13-12: The three basic tomographic imaging planes used in echocardiography: long-axis, short-axis, and four-chamber. LV = left ventricle; LA = left atrium; RV = right ventricle; RA = right atrium; PA = pulmonary artery; AO = aorta. (From Hagan AD, DeMaria AN. *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*. Boston: Little, Brown; 1989, with permission.)

Table 13-2: Standard Two-Dimensional Echocardiographic Transducer Positions

PARASTERNAL POSITION
Long axis
Left ventricular long axis
Right ventricular long
Right ventricular outflow
Short axis
Short axis through the plane of
The cardiac base
The mitral valve

The chordae tendineae
The papillary muscles
The apex
APICAL POSITION
Four-chamber plane
Five-chamber plane
(Four-chamber plane angled superiorly to include the aorta)
Two-chamber plane
Three-chamber plane
SUBCOSTAL POSITION
Four-chamber plane
Short-axis through the plane of
The mitral valve
The papillary muscles
The cardiac base
Posteriorly directed planes through the venae cavae and atria
SUPRASTERNAL POSITION
Long axis (through the ascending and descending aorta)
Short axis

As opposed to other types of cardiac imaging, such as chest radiography, which are well standardized, the echocardiographic examination is iterative and largely determined by the anatomic characteristics of the patient and manual manipulation of the transducer by the operator. Of paramount importance is the identification of a thoracic site (window) that enables transmission of the ultrasound signal to the heart. In actual practice, the echocardiographic examination is performed with the operator either to the patient's left or right. The patient is in the left lateral decubitus position for most of the examination, with the head of the bed elevated 20 to 30 degrees. Alternate positioning may be employed for individual patients and views. Use of a thick foam rubber mattress (made expressly for echocardiography) that has a removable section under the area of the cardiac apex may facilitate the examination.

The examination customarily begins with the transducer in the left parasternal position in the long-axis view (Fig. 13-14). This provides excellent images of the left ventricle, aorta, left atrium, and the mitral and aortic valves. By angling the beam slightly rightward and inferiorly (right ventricular inflow view), the right atrium, right ventricle, and tricuspid valve are visualized (Fig. 13-15). If the beam is turned slightly leftward and rotated clockwise from the standard parasternal long-axis view, the right ventricular outflow tract, pulmonic valve, and main pulmonary artery appear (right ventricular outflow view).

A 90-degree clockwise turn of the transducer produces the parasternal short-axis view. Slight axial angulation of the transducer enables visualization of the LV at various levels of the short axis, including the papillary muscle, mitral leaflets, and aortic valve (Fig. 13-16). With angulation toward the base, the LA right heart structures, main pulmonary artery, and occasionally the left atrial appendage are also

recorded.

The apical views are best acquired with the patient in a steep left lateral decubitus position and the transducer at the point of the apical impulse. The four-chamber view is obtained by turning the transducer so that both ventricles, atrioventricular valves, and atria are visualized (Fig. 13-17). In this view, the septal, apical, and lateral walls of the LV are visualized. Slight superior angulation of the transducer will add the aortic valve and proximal ascending aorta to the echocardiographic image (apical five-chamber view). From the four-chamber view, 90 degrees of counterclockwise transducer rotation will produce the apical two-chamber view (Fig. 13-18). This imaging plane demonstrates the LA and the inferior, apical, and anterior wall segments of the LV (the right heart structures are absent). If the transducer is rotated slightly back toward the four-chamber plane, a three-chamber view similar to the parasternal long-axis view is produced (Fig. 13-18) and provides images of the posterior, apical, and anteroseptal LV wall segments as well as the LA, aorta, and mitral and aortic valves.

To facilitate subcostal imaging, the patient is moved into a supine position. The subcostal four-chamber view is much like the apical four-chamber view (Fig. 13-19), but because the ultrasound beam is now more perpendicular to the interventricular and interatrial septa, subcostal imaging is often helpful in the examination of these structures. A 90-degree rotation of the transducer will record a subcostal short-axis view. The transducer can also be angled to image the RV outflow and pulmonary artery as well as the inferior vena cava (Fig. 13-19).

The long-axis suprasternal imaging plane is shown in Fig. 13-20. In adult echocardiography, the LV is usually not visualized satisfactorily from the suprasternal position, but these imaging planes are well suited for examination of the thoracic aorta, pulmonary artery, and great vessels. Normal values for 2D echocardiographic measurements are shown in Table 13-3.

Three-Dimensional Echocardiography

Several approaches exist to obtaining 3D echocardiographic images. The simplest approach is to merely move the transducer through a defined space and align the tomographic slices appropriately. A variety of spatial locator devices can be attached to the transducer to provide spatial orientation. This enables the acquisition of data from many transducer positions. Recently, two orthogonally positioned crystal arrays have been applied in conjunction with rapid parallel signal processing to achieve real-time 3D volumetric imaging. A pyramid-shaped ultrasound beam is produced that can often encompass the entire heart from one transducer location and acquire an entire data set in a single cardiac cycle (Fig. 13-20*C*). The resultant 3D data sets from any approach can be displayed as 2D tomographic cuts with 3D spatial orientation, as wire runs, or with surface rendering. 3D images have been particularly of value in providing accurate quantitation, in assessing congenital heart disease, and in evaluating structures of complex geometry such as the right ventricle.[36a,36b]

ASSESSMENT OF SYSTOLIC FUNCTION BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Because 2D echocardiography enables visualization of the entire LV perimeter in multiple planes, it is significantly superior to M-mode approaches for the measurement of cardiac chamber volumes and EF.[37-40] Numerous algorithms have been applied to calculate LV volumes by echocardiography (Fig. 13-21). Most such algorithms have assumed that the LV conforms to the shape of a prolate ellipsoid and calculated volume by diameter-length or area-length formulas.[38,41] Multiple studies comparing LV volume calculated by area-length methods to those obtained by other techniques have yielded good correlations, with the best results obtained utilizing biplane apical views.[41,42] Other algorithms have assumed an LV cavity configuration that is a combination of geometric shapes, such as a cylinder-cone or a cylinder-hemiellipse.[41,43] Currently, the most commonly used algorithm to calculate LV volumes is based upon the Simpson rule, which derives measurements by dividing the LV by parallel planes into a number of small segments and then summating the area of the individual disks. This approach has the advantage of making no assumptions about the geometry of the ventricle. A number of modifications of the basic Simpson rule method have been applied to calculate LV volumes. Although all have yielded good results, the optimal correlations have been achieved with a modification that separately quantifies the volume of the apex as an ellipsoid.[40-45]

Regardless of the methodologic approach used, accurate calculations of LV volumes by echocardiography require attention to detail and are critically dependent upon high-quality images to delineate the endocardium and image the entire LV perimeter. As a rule, echocardiographic estimates of LV volumes underestimate those calculated by other techniques and are most accurate in the absence of significant alterations of LV size and contraction. End-systolic measurements are more accurate than those made at end-diastole, probably owing to superior endocardial definition. Nevertheless, echocardiographic calculations of LV volumes have generally yielded correlation coefficients in excess of 0.75 as compared with radionuclide angiography, cineangiography, and autopsy studies regardless of the algorithm employed.[37-45] Of importance, calculation of LV volumes generally yields values with a standard error of estimate that renders these measurements suitable for clinical decision making in the care of most patients.

In an attempt to refine and facilitate the derivation of LV volume measurements from echocardiography, a number of technical developments have been evaluated. Images of the power spectrum of the Doppler signal produced by contraction/relaxation and colorization of the B-mode tissue image have been utilized to visualize the endocardial surface.[46] These techniques have been reported to be useful in identifying endocardial signals, particularly in patients with suboptimal tissue images. Greater enhancement of endocardial border delineation and improvement of the reliability of measures of LV size and contraction has been achieved through utilization of tissue harmonic imaging and by the injection of ultrasonic contrast agents to produce LV cavity opacification.[18a,46a] A software package that provides instantaneous and automated endocardial border delineation throughout the cardiac cycle has been developed based upon the display of tissue signals as backscatter rather than specular reflection.[47] This technique of automated quantitation can yield continuous measurements of LV volume throughout the cardiac cycle and can derive values for ejection fraction, ejection rate, and rate of filling during diastole (Fig. 13-22). This same technology has been utilized to display endocardial excursion throughout systolic contraction or diastolic expansion in a color format superimposed upon the tissue image (Fig. 13-23, Plate 53). This technique has proved to be of value in the recognition of abnormalities of LV contraction and regional disturbances of LV diastolic function.[4849-49a] Finally, studies employing 3D echocardiography have reported improved reproducibility of measures over 2D methods. Although these technical developments are relatively untested, they promise to facilitate the quantitative assessment of LV size and function from routine echocardiograms.

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Chapter 13: THE ECHOCARDIOGRAM

DOPPLER ECHOCARDIOGRAPHY: PRINCIPLES AND APPLICATIONS

The Doppler Principle

Although 2D and M-mode echocardiography provide abundant information about cardiac structure and movement, they supply no direct data concerning blood flow. This is a significant limitation, as the presence and severity of conditions such as valvular regurgitation and intracardiac shunting can be suspected or inferred only indirectly by 2D imaging. Using the principle first delineated by the physicist Johann Christian Doppler,[50] one can use ultrasound to determine the velocity and direction of blood flow by measuring the change in frequency produced when sound waves are reflected from red blood cells.[51-53] In this way, information regarding the presence, direction, velocity, and turbulence of blood flow can be acquired by cardiac ultrasound.[54]

The Doppler principle states that when a sound (or light) signal strikes a moving object, the frequency of that signal will be altered, and the increase or decrease in frequency will be proportional to the velocity and direction at which the object is moving. This is illustrated in Fig. 13-24. If a stationary transducer at the apex emits a sound wave with a transmitted frequency of *fo* and the wave is reflected by nonmoving red blood cells (RBCs) in an isovolumic phase of the cardiac cycle, then the received frequency *fr* will be identical to *fo*. If the signal is reflected by RBCs that are moving toward the transducer, as through the mitral valve in diastole, the returning waves will be compressed so that *fr* will be greater than *fo*. Conversely, if the target RBCs are moving away from the transducer, as in the outflow tract in systole, the returning sound waves will be elongated and the received frequency will be decreased. Of importance, the magnitude of change in the received frequency is directly related to the velocity at which blood is flowing toward or away from the transducer.[53] If the velocity of sound and the angle θ between the direction of RBC flow and the beam path are known, then the velocity of the RBCs is described by the Doppler equation:

$$V = fd(c)/2fo(\cos\theta)$$

where *fd* is the frequency shift recorded, *fo* the transmitted frequency, and *c* the velocity of sound. Note that the denominator is doubled because the sound wave does not originate with the RBC but must travel back and forth from the transducer. By measuring Doppler shift frequencies, the velocity and direction of blood flow can be calculated, displayed, and recorded.

The angle between the direction of blood flow and the course of the sound beam is a most important factor in Doppler ultrasound (Fig. 13-25). Velocity is a vectorial entity, having magnitude and direction, and Doppler will detect only those velocities parallel or near parallel to the interrogating signal. Since the relationship between velocity and the angle is a cosine function and the cosine of angles up to 20 degrees is 0.9, little error is introduced within this range.[53] Because the processor that calculates blood velocity assumes that the angle is 0 degrees, however, considerable errors occur when it is greater than 20 degrees. Moreover, the angle of incidence in 3D space usually cannot be determined with certainty from 2D echocardiographic images. Therefore, in order to obtain accurate velocity determination by Doppler, it is crucial to position and direct the transducer so that the beam is as parallel to flow as possible.

In clinical use, the frequency of transmitted ultrasound is in the range of 2 to 7 MHz, the velocity of sound in tissue is approximately 1540 m/s, and the Doppler shift frequency is relatively small (approximately 1 to 4 kHz) as compared with the transmitted frequency. As the Doppler shift frequencies are in the audible range, a speaker integrated into the Doppler echocardiography system can present them as an audible signal. Normal signals are tonal or musical. The Doppler shift also can be presented graphically to provide a hard copy printout and enable measurement.

Figure 13-26 shows the typical graphic pulsed Doppler pattern of normal systolic blood flow through the RV outflow tract into the pulmonary artery, with flow velocity on the *y* axis and time on the *x* axis. The location and size of the area from which Doppler recordings are derived is determined by the operator by positioning a sample volume on the echo image. The absence of flow is represented by the zero or no-flow line, termed the *baseline.* By convention, flow toward the transducer is displayed above the baseline and flow away from the transducer is displayed below the baseline. The velocities above and below baseline represent flow toward or away from the transducer and not forward or backward in the circulation. Because of the effects of viscous friction, the sample volume almost invariably includes RBCs flowing at slightly different velocities. Even normal laminar blood flow in the great vessels varies in velocity across the lumen, as RBCs in the center of the vessel move at higher velocity than those exposed to viscous friction at the wall, and this creates a parabolic rather than a flat flow profile. Therefore, any returning Doppler shifted signal contains a spectrum of velocities, each of which can be displayed by means of fast Fourier transform analysis. The graphic output of the Doppler signal displays the range of velocities within the sample volume site at any time in gray scale and the number of RBCs moving at any velocity as relative intensity. Normal laminar flow is characterized by a uniformity of velocity and direction of individual RBCs, and therefore a narrowly dispersed signal, while disturbed or turbulent flow is manifest by marked variability in velocity and direction and therefore a broad signal, which is multitoned, dissonant, and harsh.

Recently, echographs have been modified to enable recording of the low-velocity, high-amplitude Doppler signals produced by moving tissue as well as those of RBCs. The ability to asses tissue velocity provides an evaluation of transmural rate of contraction and relaxation.[53a] Also, Doppler tissue recordings permit assessment of regional function, and appear to be less susceptible to the influence of LV loading conditions than are Doppler blood flow recordings.[53b,53c]

Continuous- and Pulsed-Wave Doppler

Time-velocity spectral recordings of blood flow are generally obtained with two types of Doppler interrogation: continuous wave and pulsed wave (Fig. 13-27).[54,55] In the *continuous-wave* (CW) mode, sound waves are both transmitted and received continuously. This requires two piezoelectric crystals in each transducer, one for transmitting and one for receiving. Because all flow velocities along the beam are recorded, CW Doppler cannot define individual signals at specific distances from the transducer-a problem referred to as *range ambiguity.* Continuous-wave Doppler, however, has no upper limit of velocity that can be accurately recorded. Thus, a CW Doppler beam can accurately measure the direction and velocity of overall flow but cannot discern the precise site of origin of individual components within the signal (Fig. 13-28*B*).

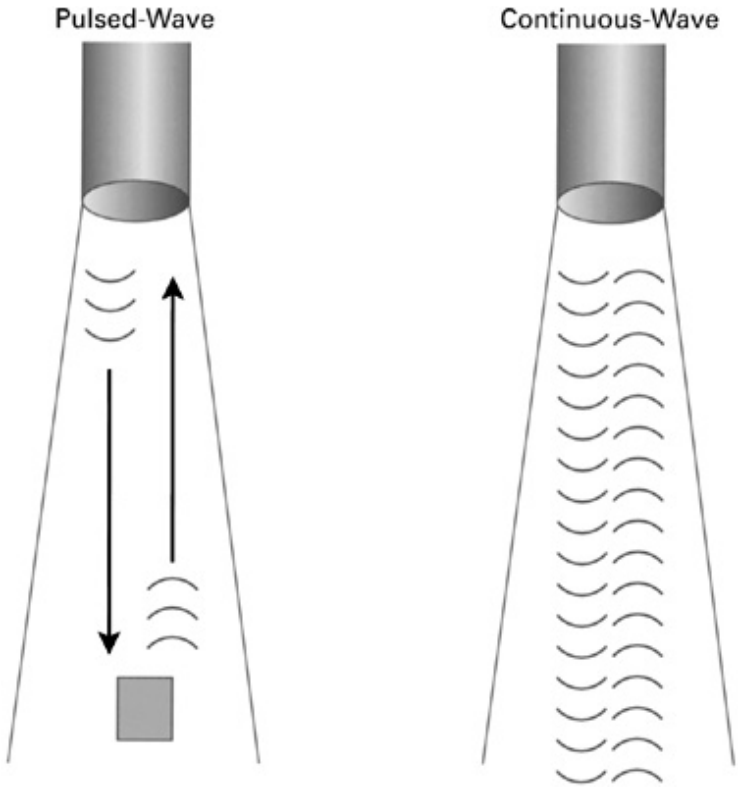
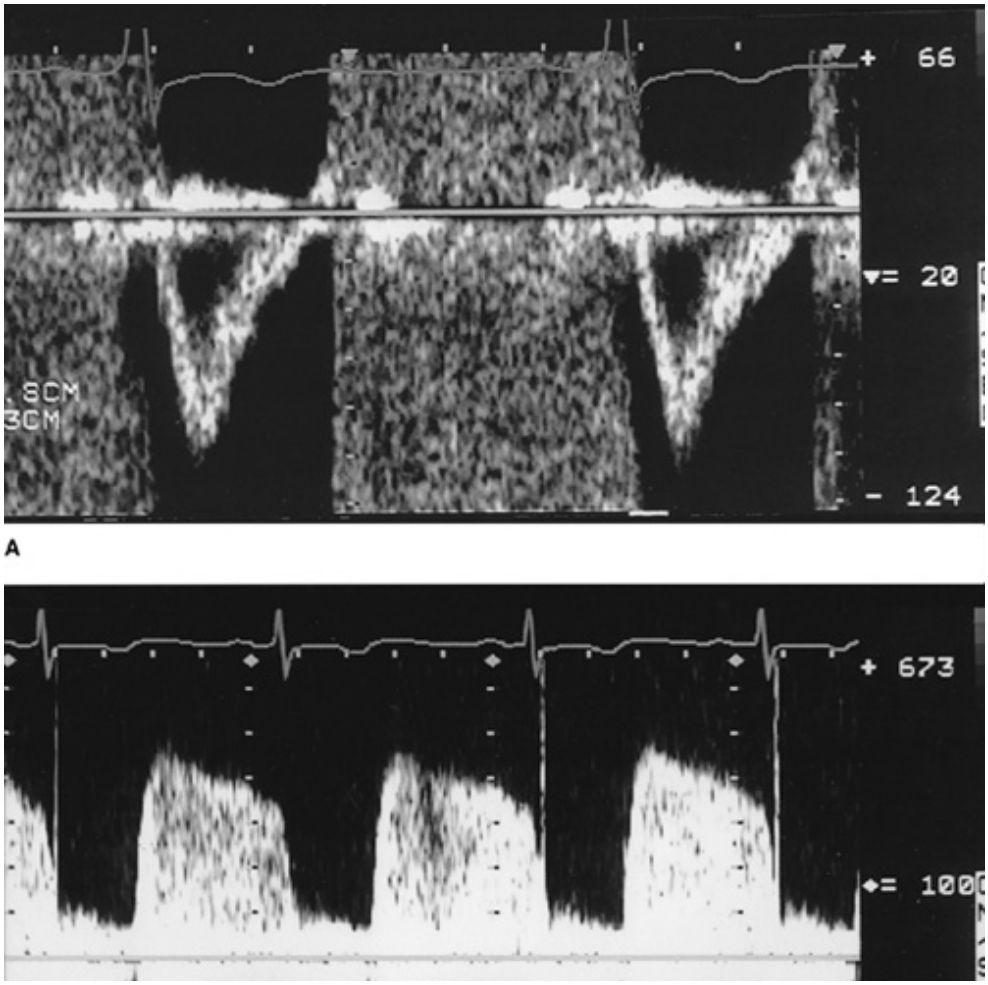
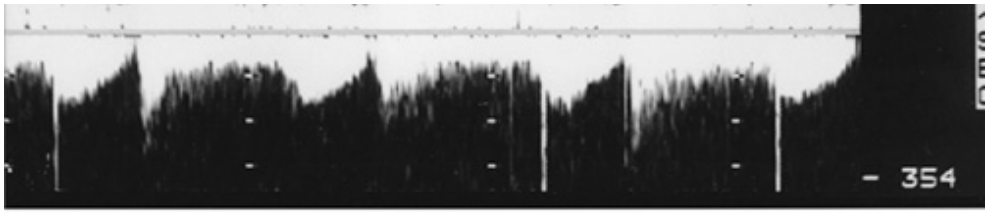


Figure 13-27: Pulsed-wave (PW) and continuous-wave (CW) Doppler. With PW, a single pulse of ultrasound energy is emitted and its reflection from a sample volume is received before the following pulse is transmitted. With CW, there is continuous transmission and reception of ultrasound energy.





B

Figure 13-28: *A.* Pulsed-wave Doppler tracing from a patient with aortic regurgitation. The transducer is in the apical position and the sample volume is in the left ventricular outflow tract. A laminar envelope is seen during systole, while aliased flow is present during diastole because of high-velocity flow. *B.* Continuous-wave Doppler tracing through the left ventricular outflow tract (with transducer in the apical position). The maximal velocity of the aortic regurgitation is now measurable, but all other velocities along the Doppler beam are recorded as well.

The problem of range ambiguity can be overcome by *pulsed-wave* Doppler. In this mode, short bursts of signal are transmitted from the transducer at a given *pulse-repetition frequency* (PRF). The instrument then receives the signal for only a brief period-an interval that corresponds to the time required for sound energy to travel and return from a specific site along the beam path. In practice, the operator selects the location at which flow is to be examined by positioning a sample volume, and the instrument determines the period during which to receive the incoming reflected frequencies. With pulsed-wave Doppler, only a single piezoelectric crystal is needed and flow can be recorded in one small area within the heart or vasculature.[54,55] Unfortunately, pulsed Doppler techniques employ intermittent sampling and are therefore susceptible to a problem of range ambiguity referred to as *aliasing*.[56] By definition, aliasing is the erroneous representation of flow in the direction opposite to that in which it is actually occurring. To correctly record the velocity of blood flow by pulsed Doppler, the PRF must be at least double the Doppler shift frequency, a value known as the *Nyquist limit.* If the blood flow examined is of very high velocity or far from the transducer (requiring a long transit time), it may necessitate an unobtainably high PRF. In such cases, aliasing will occur as Doppler signals that depict flow at high velocity in ambiguous or opposite directions compared to actual flow (Fig. 13-28). An intermediate mode between pulsed and CW methods, high-PRF Doppler, is also available.[57,58] This mode enables higher-velocity recordings to be obtained at a compromise of depicting two to four sample sites simultaneously.

Color-Flow Doppler

The major limitation of pulsed and CW Doppler (sometimes referred to as *spectral Doppler*) is that no spatial information regarding the size, shape, and 2D direction of flow is provided. An extension of pulsed-wave Doppler techniques, *color-flowDoppler* (CFD), provides real-time M-mode or 2D imaging of blood flow by presenting the velocity and direction of RBC movement as shades of color superimposed upon gray-level 2D tissue structure. Standard pulsed Doppler yields flow signals from a single site along a single scan line. In CFD, rapid pulsed-wave interrogations are performed at multiple sites for multiple scan lines to create a spatially correct and dynamic display of moving blood within the heart and vasculature[59-61] (Fig. 13-29). Doppler signals are presented as colors assigned to individual sites (Fig. 13-30, Plate 54). Blood flow moving toward the transducer is displayed in red, flow away from the transducer is displayed in blue, and increasing velocity is depicted in brighter shades of each color. The variance within each signal is calculated as a statistical marker of turbulence and is presented by adding green to the image (Fig. 13-31, Plate 55). Therefore, turbulent flow jets appear as a mosaic mix of colors. CFD also can be superimposed onto M-mode tracings (Fig. 13-32, Plate 56), often termed *M/Q imaging,* and is helpful in clarifying the timing of flow phenomena. Given the time constraints imposed by collecting the large volume of data required by CFD, velocity estimates are performed by autocorrelation techniques that are less accurate than fast Fourier transform analysis.[62] Nevertheless, CFD technology is a major advance that has improved the rapid detection of cardiac pathology, especially valvular regurgitation and intracardiac shunts.

Normal and Abnormal Flow Dynamics

The clinical application of Doppler recordings is based on the fundamental differences between normal and disturbed blood flow. Normal flow is laminar, with all RBCs exhibiting the same velocity and direction of

flow. Although some abnormalities, such as atrial septal defects, involve laminar flow, most pathologic conditions involve disturbed or turbulent flow and share a common hydrodynamic basis for the resultant flow dynamics. Specifically, nearly all circulatory disturbances (stenosis, regurgitation, shunt) involve blood flow from a high-pressure chamber to a lower-pressure chamber through a restricted orifice.[53] Aortic valve disease is a perfect example. Aortic stenosis is a forward flow disturbance in which turbulent blood travels from a high-pressure LV to a lower-pressure aorta through a restricted aortic orifice in systole. Aortic regurgitation is a retrograde flow disturbance in which turbulent blood regurgitates from a high-pressure aorta to a lower-pressure left ventricle through a small regurgitant orifice in diastole. In each case, the pressure gradient results in a high-velocity jet coursing through a restricted orifice, reaching its maximal velocity at a site just distal to the orifice, designated the *vena contracta*, at which time shear forces produce vortices resulting in flow of varying direction and velocity (Fig. 13-33). In each case, the velocity of the jet is related to the pressure gradient across the orifice. Thus, the hallmark of disturbed flow is a very high velocity jet with adjacent vortices of varying direction and velocity of flow. On pulsed Doppler recordings, these hemodynamic abnormalities cause broadening of the spectral signal and aliasing. On CW recordings, high velocity represents the primary abnormality. By color-flow imaging, the disturbance is manifest by the increased variance and higher velocities in the signal. With any of these techniques, of course, inappropriate timing of flow serves to highlight the abnormality (e.g., high-velocity LA flow during systole in mitral regurgitation).

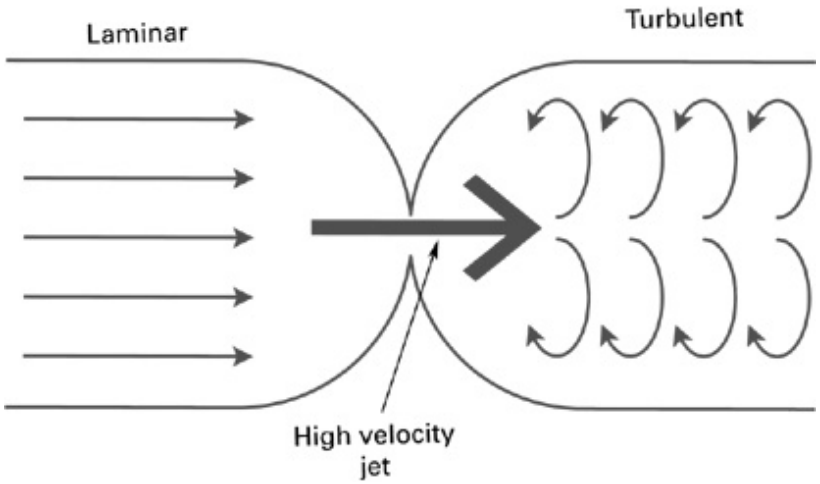


Figure 13-33: Flow characteristics through a stenotic orifice. Proximal to the stenosis, the flow is laminar. Near the point of maximal stenosis, the flow velocity is markedly increased. Turbulent flow is present distal to the stenosis.

The Standard Doppler Examination

A clinical Doppler examination must be performed with full consideration of the three different Doppler modalities available, the types of information each can provide, the multiple sites for flow interrogation, and the spectrum of pathologic lesions that produces flow disturbances. In light of these considerations, it is understandable that the Doppler examination may not be as standardized as the format for 2D cardiac imaging; however, a number of usual practices have emerged. A vast majority of echocardiographic examinations include screening for flow disturbances by CFD. Since Doppler signals are best recorded with the ultrasound beam parallel to flow, screening is typically performed in long-axis or apical views. Any flow disturbances visualized are subsequently examined by CW spectral recordings and, in most laboratories, by pulsed-wave Doppler. Although CW examination is typically reserved for flow disturbances, pulsed-wave Doppler also may be of value in quantifying flow dynamics in the setting of laminar flow. In this regard, pulsed Doppler recordings obtained at the mitral, tricuspid, and aortic valve orifices, pulmonary artery, and pulmonary veins constitute part of a standard echocardiogram in many laboratories (Figs. 13-26, 13-34, 13-35, 13-36 and 13-37).

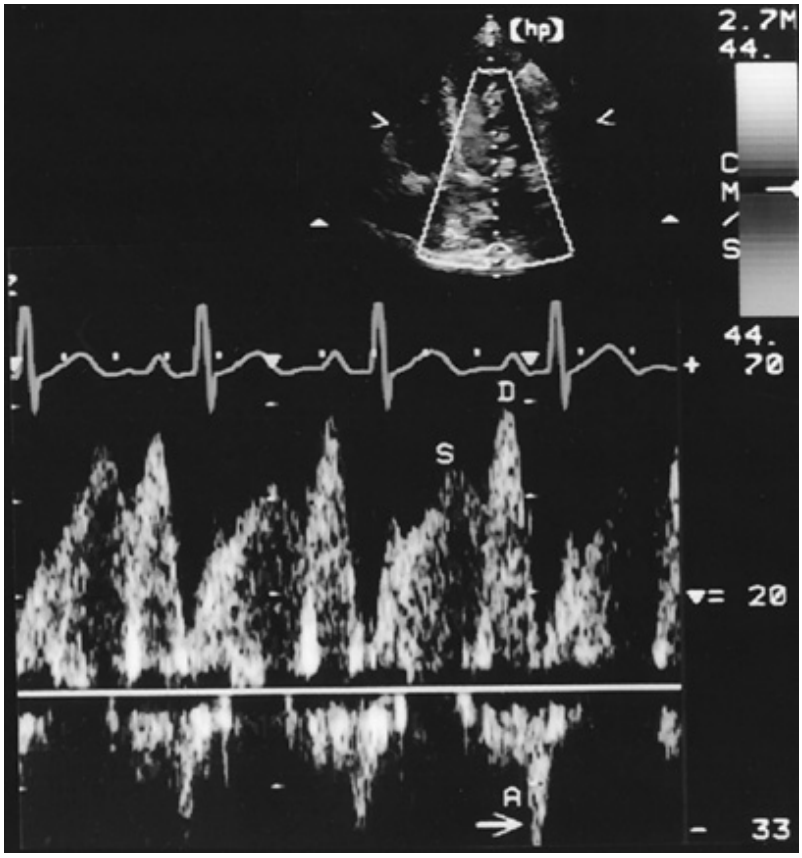


Figure 13-36: Pulsed-wave Doppler tracing from the right upper pulmonary vein (recorded from the apical transducer position). Flow toward the heart is biphasic, with peaks in systole (S) and diastole (D). A small amount of reversed flow is seen during atrial contraction (A).

The normal Doppler examination is characterized by uniformity of flow velocity and the absence of high-velocity turbulent flow. CFD recordings demonstrate laminar flow through the atrioventricular valves in diastole and the semilunar valves in systole. Since the Doppler examination is usually performed with a long-axis or apical transducer orientation, diastolic filling is characteristically encoded in red and ejection in blue (Fig. 13-30, Plate 54). Color aliasing is often observed at the levels of the mitral annulus and LV outflow tract as an abrupt change from bright red to bright blue or vice versa, usually in the center of the flow stream. Pulsed Doppler recordings of transmitral flow velocities are often recorded at the level of both the leaflet tips and annulus. Velocities are higher at the tips, while recordings at the annulus offer the ability to calculate flow through a cross-sectional area that is relatively uniform throughout the cardiac cycle. A sample volume positioned in the right upper pulmonary vein reveals systolic and diastolic emptying flow of nearly equal magnitude followed by a short, low-velocity reversal of flow into the pulmonary veins following atrial contraction (Fig. 13-36). Flow in the LV outflow tract and aortic annulus area is characterized by a progressive increase of velocity peaking in early systole, followed by a more gradual deceleration of flow (Fig. 13-35). Minimal if any flow velocities are detected in the mitral valve orifice and LV outflow tract in systole and diastole, respectively, in normal examinations. Examinations of the tricuspid and pulmonic valves give qualitatively similar results to those of the mitral and aortic valves (Figs. 13-26 and 13-37). Normal values for forward flow velocity are given in Table 13-4. As can be seen, velocity in normal individuals is highest in the aorta and is less than 2 m/s.[63] Other commonly made measurements include the acceleration time (from the beginning of flow to peak velocity of flow in the ascendingaorta or pulmonary artery); and the deceleration time, from LV inflow peak E-wave velocity extrapolated to baseline zero velocity.

Table 13-4: Normal Intracardiac Doppler Velocities

	Velocity, m/s
Right ventricle	
Tricuspid flow	0.3-0.7
Pulmonary artery	0.6-0.9
Left ventricle	
Mitral flow	0.6-1.3
Aorta	1.0-1.7

SOURCE: Hatle L, Angelsen B. *Doppler Ultrasound in Cardiology*, 2d ed. Philadelphia: Lea & Febiger; 1985.

Doppler Assessment of Diastolic Function

In recent years, there has been a great deal of interest in using mitral inflow velocity patterns to evaluate LV diastolic properties.[6474-74a] Transmitral filling velocities reflect the pressure gradient between the LA and LV during diastole[65] (Fig. 13-34). In early diastole, pressure in the LV normally falls below that in the LA, producing an increase in velocity due to rapid transmitral inflow (E wave). Flow decelerates as the pressures equilibrate in middiastole. In late diastole, LA contraction restores a small gradient, causing transmitral flow to accelerate to a second peak (A wave) that is of less magnitude than the E wave. In individuals in whom early LV relaxation is impaired, the transmitral pressure gradient is blunted, resulting in a decrease in both the velocity of early filling and rate of E-wave deceleration[66,68,70] (Fig. 13-38). Conversely, in patients with marked increases of LA pressure and LV stiffness, early diastolic filling velocities are high, deceleration is rapid, and late filling following atrial contraction is markedly reduced. This is the so-called restrictive pattern of LV filling (Fig. 13-39). Accordingly, an E-wave velocity that is substantially less than the A-wave velocity and is accompanied by a prolonged deceleration time represents evidence of impaired early diastolic relaxation by Doppler, while an increased E-wave velocity and decreased A-wave velocity (E/A ratio greater than 2.5 or 3 to 1) accompanied by a diminished deceleration time (less than 100 ms) is indicative of a noncompliant LV with markedly elevated lef atrial pressures.[69,70,73,73a] Although a restrictive pattern can be seen with restrictive cardiomyopathy or advanced LV dysfunction of any cause, it also occurs in pericardial disease.[75] Of significance, a restrictive pattern of LV filling has been associated with an increased mortality rate in patients with advanced congestive heart failure,[76] and persistence of this pattern despite changes in loading condition is an additional poor prognostic sign.[76a,76b]

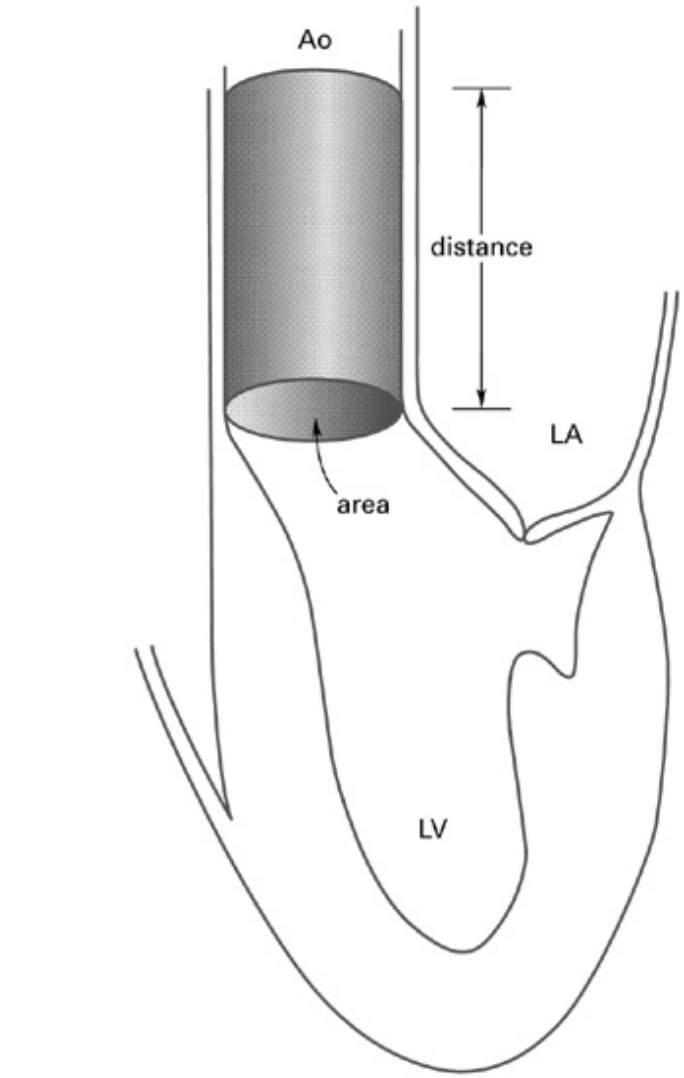
These abnormal mitral inflow patterns can be clinically useful and, when they are markedly distorted, are generally reliable in identifying and characterizing diastolic dysfunction. A number of variables other than diastolic function, however, are capable of influencing transmitral filling velocities. It has been shown that transmitral Doppler filling dynamics are affected by the age of the patient,[77,78] changes in heart rate,[79,80] respiration,[81] and even the position of the Doppler sample volume within the mitral valve orifice.[82-84] Of greatest significance, transmitral inflow is very sensitive to loading conditions, and reductions in LV preload induced by nitroglycerin and/or lower-body negative pressure can induce a striking decrease in early transmitral filling velocities independent of changes in diastolic properties.[85,86] The influence of LV loading upon transmitral filling is most striking when an increase in LA pressure due to cardiac dysfunction restores early diastolic filling velocities and obscures impaired relaxation, thus inducing "pseudonormalization."[68] Therefore, as Doppler transmitral filling dynamics have many limitations in assessing diastolic function, particular filling patterns should not be interpreted as "pathognomonic" findings of diastolic dysfunction but rather as a component of a complete clinical and echocardiographic evaluation.

Recently, attention has focused upon ancillary Doppler techniques to evaluate LV diastolic dysfunction and LA pressure. An impaired systolic filling wave and increased A-wave flow reversal in the velocity recordings from pulmonary veins in the setting of a relatively normal transmitral pattern of diastolic filling suggests elevated LV filling pressures and may be useful in distinguishing normal from pseudonormal mitral inflow pattern (Fig. 13-36). In addition, an increased amplitude of the pulmonary vein A-wave reversal in comparison with the forward transmitral A-wave velocity, especially in regard to duration, has been found to be of value in detecting elevated LV filling pressures by Doppler.[87,88] Tissue Doppler recordings also yield early diastolic and late atrial velocity signals which are altered in a similar fashion to transmitral filling in the setting of diastolic dysfunction.[53a] Tissue Doppler recordings are less influenced by LV loading, and may be of value in distinguishing pseudonormalization.[53c] The rate of propagation of the transmitral LV filling stream into the LV may also be utilized to detect impaired diastolic function as well as constrictive pericarditis.[53a]

Doppler Assessment of Systolic Function and Cardiac Output

Although measurements of LV volumes and ejection fraction can be obtained by 2D echocardiography, Doppler interrogation provides a unique and complementary noninvasive assessment of systolic function. Thus, LV systolic dysfunction often results in decreased aortic velocity and acceleration time.[89-91] As discussed below, in the presence of *mitral regurgitation* (MR), the acceleration of the MR jet can provide information regarding contractile function.[92]

One of the most important applications of Doppler is in the calculation of the stroke volume.[93] The theory involved is relatively simple. The volume of flow through any orifice or tube can be calculated as the product of the cross-sectional area through which flow occurs and the velocity of that flow (Fig. 13-40). Measures of anatomic cross-sectional area can be derived from echocardiographic images, while velocity can be determined by Doppler. As the annulus of the aortic valve is nearly circular, its cross-sectional area can be estimated from a measurement of diameter, as $\pi(\text{diameter}/2)^2$. The pulsed-wave Doppler envelope also can be recorded at the same level. The *mean* flow velocity through the orifice is calculated by integrating velocity over time. (that is, by measuring the area under the Doppler curve). This velocity-time integral, often called the *stroke distance*, is then multiplied by the cross-sectional area at the level of the Doppler interrogation to obtain the stroke volume.[93-96] The product of the stroke volume and heart rate then yields cardiac output.



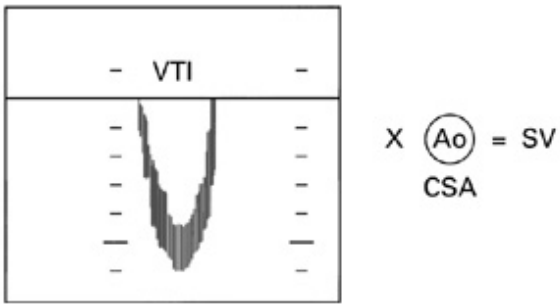


Figure 13-40: Calculation of stroke volume. Multiplying the cross-sectional area (CSA) of the blood column in the ascending aorta by the distance the column moves during a single cardiac contraction yields the stroke volume (SV). The velocity-time integral (VTI), expressed in units of length, represents the "stroke distance." (Modified from Pearlman AS. Technique of Doppler and color flow Doppler in the evaluation of cardiac disorders and function. In: Schlant RC, Alexander RW, eds. *The Heart, Arteries, and Veins*, 8th ed. New York: McGraw-Hill; 1994:2229, with permission.)

Calculation of stroke volume by the Doppler method involves a number of assumptions. The orifice must be circular and constant in size, and the flow velocity must be uniform throughout the cross-sectional area. In addition, the angle between flow and the interrogating beam must be less than 20 degrees. Despite the uncertainty of these assumptions, Doppler-derived measurements of cardiac output and stroke volume have been shown to correspond well with thermodilution, Fick, and the angiographic calculations, though the correlation is not perfect.[93-99]

Theoretically, stroke volume can be calculated at any valve annulus.[96,97,100-102] In clinical practice, however, this is not always possible (e.g., it is difficult to obtain an accurate diameter of the pulmonary artery in every patient). Because the measurement of annular radius is squared in the computation of area, it is the most important source of error of Doppler stroke-volume analyses. Stroke-volume analysis through the mitral annulus is cumbersome; it is uncertain whether the mitral annulus is best described as a circle or an ellipse, and the cross-sectional area of the annulus probably changes slightly during diastole. Calculations using the tricuspid annulus are hampered by similar problems. Despite these limitations, measurements of stroke volume through the various cardiac valves are clinically useful and can be used to calculate pulmonary-to-systemic shunt ratios, regurgitant volumes,[103-110] and orifice areas of stenotic valves by the continuity equation[111-115] (see below).

The Bernoulli Equation

An important application of Doppler echocardiography is the calculation of pressure gradients within the cardiovascular system using a modification of the Bernoulli equation.[116-118] This theorem states that the pressure drop across a discrete stenosis in the heart or vasculature occurs because of energy loss due to three processes: (1) acceleration of blood through the orifice (*convective acceleration*), (2) inertial forces (*flow acceleration*), and (3) resistance to flow at the interfaces between blood and the orifice (*viscous friction*).[119] Therefore, the pressure drop across any orifice can be calculated as the sum of these three variables (Fig. 13-41). In most clinical situations, the contribution of inertial forces and viscous friction are minimal and can be discounted. Since convective acceleration is determined by velocity, the pressure gradient can be calculated from the velocities of blood proximal to and at the level of an orifice as gradient = 4[(orifice velocity)^2 - (proximal velocity)^2]. If the blood velocity proximal to the stenosis is low (<1.0 m/s), this term can be ignored as well. The resulting modified equation states that the pressure gradient across a discrete orifice is equal to four times the square of the peak velocity (V) through the stenosis (PG = $4V^2$).[116-119]

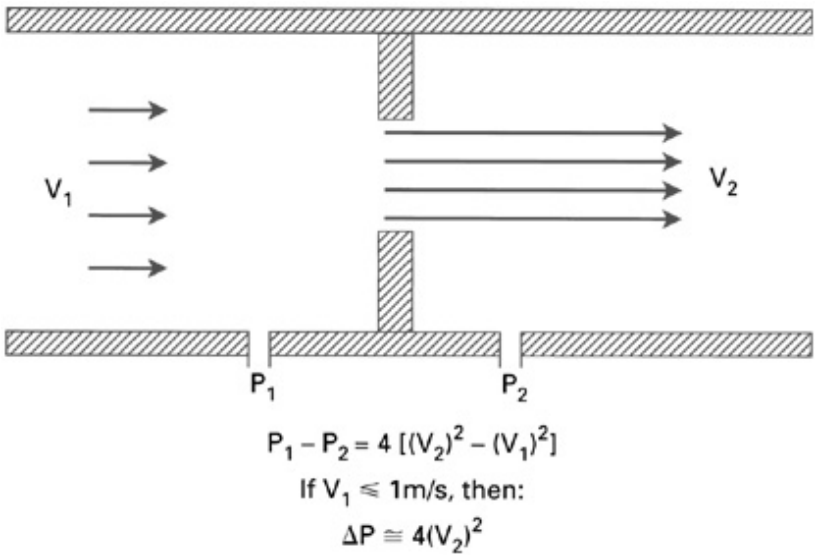


Figure 13-41: The modified Bernoulli equation. Pressure drop across a small orifice can be estimated as four times the square of the peak velocity (if the proximal velocity is less than 1 m/s). V_1 and P_1 = proximal velocity and pressure; V_2 and P_2 = distal velocity and pressure. (Modified from Pearlman AS. Technique of Doppler and color flow Doppler in the evaluation of cardiac disorders and function. In: Schlant RC, Alexander RW, eds. *The Heart, Arteries, and Veins*, 8th ed. New York: McGraw-Hill; 1994:2229, with permission.)

The modified Bernoulli equation can be used to calculate pressure gradients across any flow-limiting orifice and has been validated against invasive measurements.[116-122] The method was originally applied to aortic,

mitral, and pulmonic stenosis, but further uses have been identified. If at least trivial valvular regurgitation is present, systolic gradients across the tricuspid and end-diastolic gradients across the pulmonic valve can be calculated.[123,124] If the RV diastolic pressure is known (or estimated as the right atrial or central venous pressure), peak RV and pulmonary artery pressure (assuming pulmonic stenosis is absent) can be computed as follows[125,126]:

$$\text{Peak pulmonary artery pressure} = 4(\text{TR velocity})^2 + \text{RA pressure}$$

End-diastolic pulmonary artery pressure (PAD) also can be calculated:

$$\text{PAD} = 4(\text{end-diastolic pulmonary regurgitation velocity})^2 + \text{RA pressure}$$

In the presence of mitral regurgitation, a variety of calculations can be made. With measurement of peak systolic arterial pressure, systolic left atrial pressure can be estimated[127]:

$$\text{Left atrial systolic pressure} = \text{systolic blood pressure} - 4(\text{MR velocity})^2$$

Further, the acceleration of the MR jet can be used to estimate LV systolic *dP/dt*.[128] Thus, from the Bernoulli equation, the LA-to-LV pressure gradients at regurgitant velocities of 1 and 3 m/s are 4 and 36 mmHg, respectively. Therefore, *dP/dt* can be calculated as 32 mmHg divided by the time (in seconds) required for the mitral regurgitant jet to accelerate from 1 to 3 m/s. In the case of ventricular septal defects or aortopulmonary shunts, measurements of the peak systolic arterial pressure and the peak Doppler velocity across the defect allows calculation of the right ventricular (or pulmonary arterial) systolic pressure.

The Continuity Equation

Although transvalvular pressure gradients can be calculated from CW Doppler recordings using the modified Bernoulli equation, gradients sometimes can be misleading in the evaluation of valvular stenosis. The transvalvular gradient is determined by both the size of the stenotic orifice and the stroke volume traversing it. Severe aortic stenosis and accompanying LV systolic dysfunction may produce a low transvalvular gradient despite a small valve area, while coexistent aortic regurgitation may result in a large gradient with only mild aortic stenosis. The calculation of orifice area by Doppler echocardiography employs the *continuity equation*, which is derived from the law of the conservation of mass and states that the product of cross-sectional area and velocity is constant in a closed system of flow[129] (Fig. 13-42). Thus, in the case of aortic stenosis, the product of the area and velocity of the left LV outflow tract equals the product of the area and velocity of the aortic valve orifice. Annulus diameter and integrated velocity measurements are derived by the standard volumetric approach, while the velocity across the stenotic orifice is derived by CW Doppler. The equation is then solved for the valve area.[111-116]

$$(A_1) = \pi r^2 = \pi\left(\frac{D}{2}\right)^2 = 0.785\,(D^2)$$

$$(A_2)(V_2) = (A_1)(V_1) \text{ or } (A_2) = \frac{(A_1)(V_1)}{(V_2)}$$

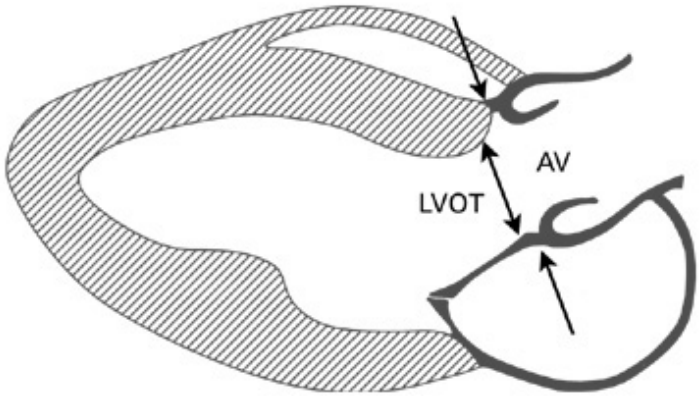


Figure 13-42: The continuity equation. In a closed system (*top*) with constant flow, $Q_1 = Q_2$. Therefore, $A_1 \times V_1$ must equal $A_2 \times V_2$. Determination of any three of the variables allows calculation of the fourth. Clinically (*bottom*), the area of the left ventricular outflow tract (LVOT) can be estimated and used to determine aortic valve area. (From Hagan AD, DeMaria AN. *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler.* Boston: Little, Brown; 1989, with permission.)

The continuity equation is simple and the constituent factors are readily measured, but a number of potential errors can occur. The most common pitfall is an inaccurate estimation of the cross-sectional area proximal to the stenosis. In addition, it is essential that blood velocity proximal to a stenosis be measured outside the area of flow acceleration. Finally, the continuity equation actually solves for the area of the vena contracta, which is usually just distal to the stenotic orifice. Although this area is very similar to the area of the stenotic orifice, occasional discrepancies occur.

Determinants of the Size of Flow Disturbances

Although CFD yields primarily qualitative information, it is unique in its ability to provide measurements of the size of flow disturbances. It is logical that the size of a turbulent jet should correlate with the volume of blood contained within the flow disturbance. Regardless of the lesion, however, the area of turbulence recorded by CFD has multiple determinants.[130-134] The volume of flow present in the disturbance is, of course, a major factor in its size. The pressure gradient operative in any flow disturbance is also an important determinant of the spatial distribution or "spray area" of turbulence.[134] In addition, the size of a flow disturbance is influenced by the orifice through which flow occurs as well as the size and compliance of the receiving chamber.[130-136] Finally, a number of technical factors can influence jet size as imaged by CFD, including instrument gain, the angle of incidence of the interrogating beam, the frequency and pulse repetition rate of the transducer, and the temporal sampling rate.[137] Therefore, measurements derived from the size of the turbulent jet recorded by color Doppler, are at best semiquantitative and should not be expected to correlate with the volume of blood contained in the flow disturbance.

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Chapter 13: THE ECHOCARDIOGRAM

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) usually defines cardiac anatomy and function satisfactorily, often obviating the need for further cardiac imaging. Occasionally, however, TTE does not provide complete or adequately detailed information. This is especially true in the evaluation of posterior cardiac structures (e.g., the LA, the left atrial appendage, the interatrial septum, the aorta distal to the root), in the assessment of prosthetic cardiac valves, and in the delineation of cardiac structures less than 3 mm in size (e.g., small vegetations or thrombi). Ultrasonic imaging from the esophagus is uniquely suited to these situations, as the esophagus is adjacent to the LA and the thoracic aorta for much of its course[138,139] and affords excellent access of the interrogating beam to these structures.

Over the past decade, a number of technologic advances have occurred in the field of *transesophageal echocardiography* (TEE), and flexible transesophageal ultrasound probes capable of multiplanar imaging of the heart are now widely available.[140-142] The current generation of probes also provide full pulsed-wave, CW, and CFD capabilities.

Although images can be recorded from a variety of probe positions most authorities recommend three basic positions: (1) posterior to the base of the heart, (2) posterior to the left atrium, and (3) inferior to the heart (transgastric position; Fig. 13-43). Figures 13-44 through 13-47 show TEE images obtained in various planes through the heart. It must be emphasized that, with the transducer in the esophagus, posterior structures appear at the top of the image. With the transducer in the stomach, a short-axis view is standardly obtained, with long-axis and apical views available to a variable degree. Upon withdrawing the transducer to the esophagus, one usually obtains apical-equivalent four-chamber and long-axis views, with multiple intermediate projections. Further withdrawal of the probe to the base yields excellent views of the atria, great vessels and semilunar valves, and pulmonary veins. Of particular value are views that delineate the LA appendage, all three leaflets of the aortic valve in short axis, and the transverse and descending aorta.[143]

TEE has become an important imaging modality for the diagnosis and management of infective endocarditis and its complications, including valvular vegetations, chordal rupture, fistulas, perivalvular abscesses, and mycotic aneurysms.[143-148] TEE is more accurate in detecting vegetations and abscesses than TTE[143,149,150] and provides prognostic information as well[150] (Fig. 13-48). In addition, TEE imaging may aid in accurate quantification of valvular disease (particularly mitral regurgitation) if TTE is inconclusive[151] (Fig. 13-49, Plate 57). TEE is especially useful for Doppler interrogation of the pulmonary veins (Fig. 13-50, Plate 58). Flow patterns in these vessels reflect LA pressure, and systolic reversal of pulmonary venous flow has been identified as an accurate marker of mitral regurgitation.[152,153] Although mitral regurgitant color jets are easier to see with TEE than TTE, they are usually larger, and care must be exercised not to overestimate severity of the regurgitation.[154] Multiplane TEE can be used to planimeter the orifice area in AS.[155,155a] The technique is also quite helpful in detection of aortic disease, including dissection, aneurysm, congenital malformations, and atherosclerosis.[139,156,157] Because of its portability, accuracy, and short preparation and procedural times, TEE is now recommended as the preferred diagnostic study in many cases of suspected aortic dissection (Fig. 13-51, Plate 59).[139,158]

Thromboemboli may originate from posterior cardiac structures such as the left atrium (LA) and appendage, interatrial septum, and aorta[159-168]; therefore, TEE has received wide application in the evaluation of possible cardiogenic embolization. Since the most common site of LA thrombi is the appendage, the ability of TEE to visualize this structure is of particular value (Fig. 13-52). TEE can also detect spontaneous contrast signals (that appear to represent transient rouleaux formation and predispose to thromboemboli).[169] In addition, TEE has provided unique real-time images of mobile, pedunculated, atherosclerotic "debris" in the thoracic aorta (Fig. 13-53). Although the optimal therapy for this disorder is currently unknown, warfarin may be helpful and mobile or protruding aortic atheromas appear to be significant risk factors for embolic events.[167,168,170,171171a-171b] The optimal role for TEE in the detection of intracardiac sources of emboli is controversial, and clinical trials are ongoing to evaluate the effect of treatment after discovery of potential embolic sources.

One of the proven applications of TEE is the evaluation of prosthetic valve dysfunction, particularly mechanical valves in the mitral position.[172-174] Since the materials used in artificial valves are strong reflectors and often cause ultrasonic shadowing, the areas behind prosthetic valves are usually hidden from view when transthoracic imaging is used. Because of its unique window on the heart, TEE is clearly superior to TTE imaging for detection of prosthetic regurgitation, infection, tissue ingrowth, and thrombosis[172,174] (Fig. 13-54).

TEE has also become an important intraoperative tool for the detection of cardiac ischemia, the evaluation of valve function after repair or replacement, and the delineation of congenital heart disease.[175-183] Cardiac surgeons often request intraoperative TEE for evaluation of cardiac anatomy and confirmation of a success of surgical repair before closing the chest. In this regard, TEE has almost completely replaced epicardial echocardiography. When TEE images are inadequate, TEE is helpful in managing critically ill patients[184-187] and also can be used to monitor or guide interventional procedures, such as transseptal catheterization,[185-190] mitral valvuloplasty, pericardiocentesis, and endomyocardial biopsy.[191]

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Chapter 13: THE ECHOCARDIOGRAM

CONTRAST ECHOCARDIOGRAPHY

Opacification of the right heart cavities with dense ultrasonic reflectances during intravenous contrast injection was first applied clinically in 1968.[192] Subsequently, it became clear that the origin of the dense intracavitary echoes were microbubbles within the injectate, and that any agitated liquid injected intravenously caused the effect.[193] Since room-air microbubbles with the diameter of pulmonary capillaries persist in blood for less than 1 s before dissolving, agitated agents injected intravenously cannot cross the lungs and enter the left-sided cardiac chambers. Thus, the presence of echocardiographic contrast entering left heart chambers after intravenous injection of an agitated liquid indicates the presence of a right-to-left shunt.[194,195]

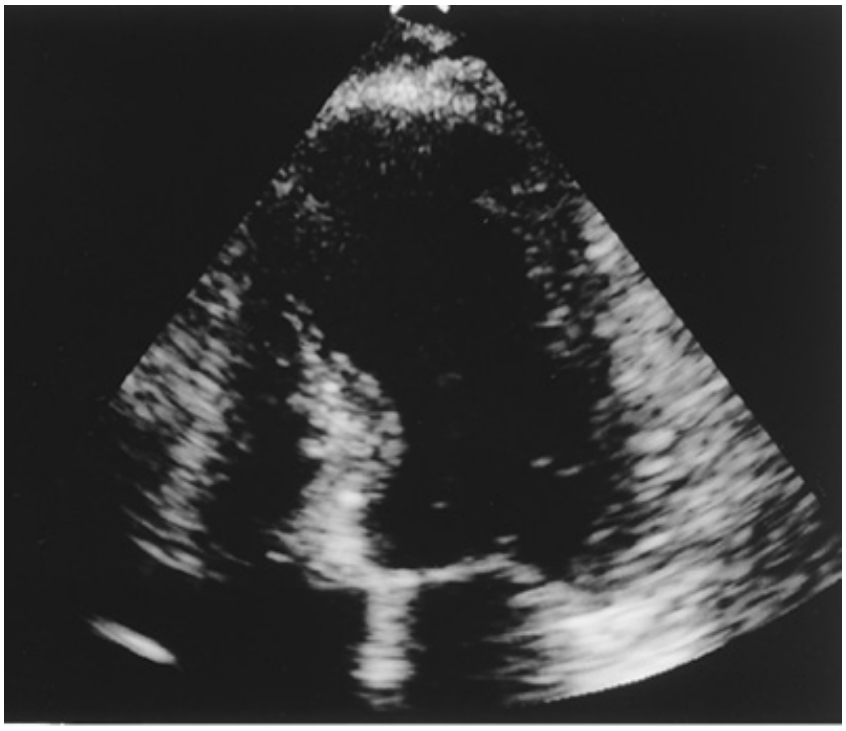
Identification of intracardiac shunts, particularly patent foramen ovale in patients with unexplained cerebral ischemia (Fig. 13-55), remains the most frequent indication for contrast echocardiography.[196] Simple agitated normal saline solution remains the most commonly used contrast agent for such studies.

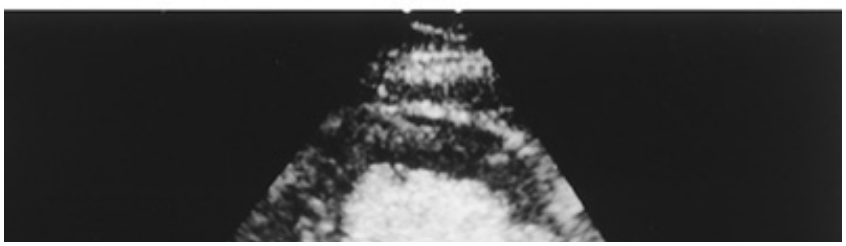
In recent years, many attempts have been made to achieve echocardiographic opacification of the LV cavity and myocardium.[197-200] Initial attempts utilized direct left-sided administration. Injection of agitated saline or other fluids into the LV or aorta causes echocardiographic opacification of those chambers and has been used as an alternative to angiography to evaluate mitral and aortic regurgitation.[194] In addition, injection of sonicated radiographic contrast agents into the aortic root or coronary arteries can produce myocardial opacification[201] (Fig. 13-56). The presence of echocardiographic contrast within the myocardium after such injections reflects the spatial distribution of coronary blood flow (CBF)[198] and is valuable in identifying collateral CBF and the absence of reflow following reperfusion therapy of acute myocardial infarction (MI).[202-210] Of significance, the presence of microcirculatory flow and integrity in these studies was a reliable predictor of viable myocardium.[207-209]

Direct injection of coronary contrast into the left heart is limited by its invasive nature. Therefore, stabilized solutions of microbubbles have been developed which can traverse the pulmonary capillary bed in high concentration after intravenous injection. These new ultrasonic contrast agents have been designed to achieve prolonged bubble persistence or survival after injection into blood. The persistence time of a bubble prior to disolving in blood can be increased by utilizing a shell or surface modifying of gas across the bubble surface. Alternatively, prolonged bubble survival can be achieved by utilizing a dense, high-molecular-weight gas with a reduced capacity to diffuse across the bubble shell and a low saturation constant in blood, which favors return of gas back into the bubble. Therefore, the new ultrasonic contrast agents utilize shells made of human serum albumin, liposomes, or even biodegradable poliment materials, and the fluorocarbon gases, which are dense and poorly soluble. These new microbubble agents are all capable of producing dense, high-intensity signals not only within the LV but also within the myocardium following intravenous injection.[210a,210b]

Efforts to produce stabilized solutions of microbubbles have now resulted in a commercially available agent, Optison, which is composed of a perfluorocarbon gas in an albumin shell. Intravenous injection of Optison opacifies the left ventricle in nearly all patients, thereby facilitating identification of the endomyocardial border. This capacity has found its greatest application in stress echocardiography, where detection of the endocardium is of fundamental

importance in recognizing abnormal contraction produced by ischemia. By intensifying backscatter within the intracardiac cavities, new ultrasonic agents also enhance Doppler recording of flow abnormalities.[211] Marginal Doppler spectral tracings in cases of mitral regurgitation, tricuspid regurgitation, and aortic stenosis often improved dramatically after contrast injection, facilitating the quantitation of valvular lesions and pulmonary hypertension.[212-216] In addition to new contrast agents, novel imaging technology directed to the amplification of contrast signals are also available. Second harmonic imaging enhances the ultrasonic backscatter from contrast microbubbles (which resonate in an ultrasonic field) while decreasing the returning signal from myocardium (which does not resonate).[217-219] (Fig. 13-57). Power Doppler imaging is a method that correlates signals between successfully transmitted pulses to derive images of moving blood or cardiac structures. Power Doppler techniques are especially well delineated to detect the changing signals produced by movement and/or dissolution of contrast microbubbles.[46] Finally, since exposure to ultrasound energy can produce microbubble destruction, intermittent electrocardiography (ECG) gated rather than continuous ultrasound transmission can also prolong microbubble persistence and amplify contrast signals.[220,221] When combined with the new ultrasonic contrast agents, these refined imaging modalities can achieve visualization of myocardial opacification following intravenous drug administration, thereby delineating myocardial perfusion. Initial studies indicate that myocardial contrast echocardiography can yield information regarding myocardial perfusion comparable to that obtainable by radionuclide techniques and can be of value in delineating coronary artery stenoses.[221a,221b] Intravenous injection of new contrast agents may actually permit visualization of intramyocardial vessels (Fig. 13-58).[214-217,221c] The ability to delineate regional myocardial perfusion is a major step forward in noninvasive imaging and can be expected to provide important information regarding coronary artery disease (CAD) in the near future.





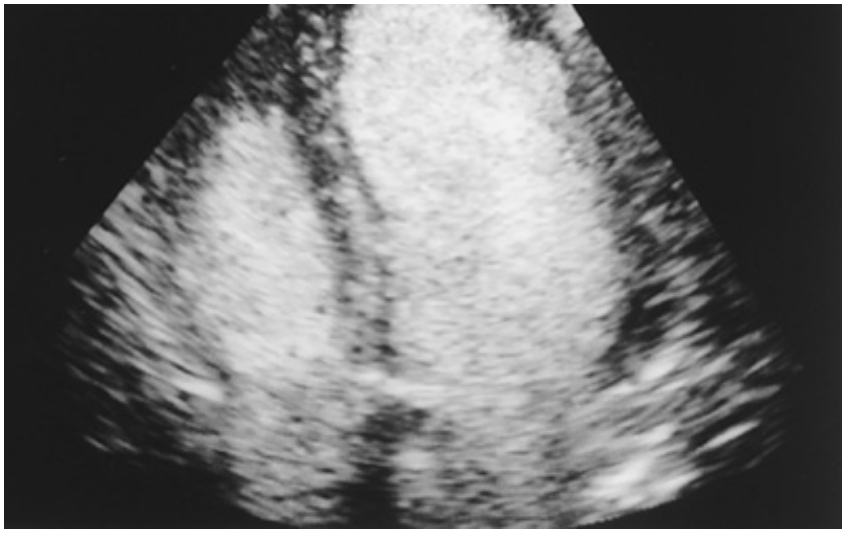


Figure 13-57: Harmonic imaging with second-generation echocardiographic contrast. Endocardial border definition before injection is fair (*upper panel*) but is markedly improved with harmonic imaging following contrast injection (*lower panel*).

In addition to new contrast agents, novel imaging technologies directed to the amplification of contrast signals are also available. For example, second-harmonic imaging enhances the ultrasonic backscatter from contrast microbubbles (which resonate in an ultrasonic field) while decreasing the returning signal from myocardium (which does not resonate)[217-219] (Fig. 13-57). Early after contrast injection, second-harmonic imaging increases the cavity-to-myocardium contrast intensity ratio, improving visualization of the left ventricular cavity. Second-harmonic imaging may also enhance the myocardial contrast phase, which follows LV cavity opacification with second-generation contrast agents.[217-219] As exposure to ultrasound energy can produce microbubble destruction, intermittent rather than continuous ultrasound transmission can also prolong microbubble persistence and amplify contrast signals.[220,221,210b] In recent years, harmonic imaging has been used to visualize cardiac structures in the absence of contrast injection. This tissue harmonic imaging decreases clutter and other artifacts, often improving endocardial definition (Fig. 13-58*A*).

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Chapter 13: THE ECHOCARDIOGRAM

DISEASES OF THE AORTIC VALVE AND AORTA

Aortic Stenosis

The aortic valve is best imaged in the parasternal views.[222] The leaflets are thin, linear structures. All three can be visualized in the short-axis view and produce a triangular orifice during systolic opening. The long-axis view exhibits the right and usually the noncoronary leaflets, which normally open to the walls of the aorta. Mild thickening and reduction of mobility is often observed in the elderly (aortic sclerosis) and is associated with an increased risk of CAD. In older adults, acquired aortic stenosis (AS) is manifested by markedly thickened, often calcified, immobile aortic valve leaflets,[223] while doming of the leaflets suggests congenital aortic stenosis and is usually encountered in younger patients (Fig. 13-59).[224] Echocardiography can distinguish valvular from sub- and supravalvular AS, can accurately identify bicuspid valves, and can delineate the presence of LV hypertrophy.[225,226] Subaortic stenosis may be caused by asymmetrical septal hypertrophy with systolic anterior mitral motion, a subaortic membrane, or (less commonly) a subaortic tunnel. Bicuspid valves exhibit an oval rather than triangular orifice (Fig. 13-60). Although the severity of stenosis can be assessed semiquantitatively by 2D and M-mode image echocardiography, valvular calcification may shadow the leaflets or produce reverberations and obscure their motion.[223] Therefore, attempts to measure valve area by transthoracic planimetry have been unsuccessful, although multiplane TEE has been of greater value[155] (Fig. 13-61). Thus, 2D-echocardiographic imaging accurately detects the presence and etiology of AS but not the severity. Likewise, CFD demonstrates turbulent flow through the aortic valve and may guide continuous wave interrogation but provides little quantitative data.[227] The use of Doppler echocardiography and the modified Bernoulli and continuity equations have now made noninvasive calculation of aortic gradients and valve area routine and have affected utilization of cardiac catheterization in AS patients.[228] (See also Chap. 56).

The cornerstone of the ultrasound evaluation of AS is CW Doppler interrogation through the aortic valve. The calculated gradient using the peak Doppler velocity [4(AS velocity)^2] correlates closely with the peak instantaneous gradient measured at catheterization[117-119] (Fig. 13-62). In interpreting echocardiographic studies, it is important to distinguish between the peak instantaneous pressure gradient, the mean gradient, and the peak-to-peak gradient. The first two physiologic parameters represent simultaneous pressure differences between LV and aorta and can be measured accurately by Doppler echocardiography. The *peak-to-peak gradient,* commonly used in the catheterization laboratory, compares the highest pressures reached in the LV and aorta (even though not simultaneous) and is uniformly lower than the peak instantaneous gradient recorded by Doppler. Therefore, the maximal Doppler gradient does not correlate with the peak-to-peak catheterization gradient, and comparisons between the two should be avoided (Chap. 56).

A number of potential sources of error exist in the estimation of the transvalvular aortic gradient by CW Doppler recordings. It is imperative that Doppler signals from the stenotic jet be obtained with an angle of incidence of less than 20 degrees. Since the direction of the jet rarely can be known with precision from 2D techniques, each examination must employ all possible windows and angulations, including apical, parasternal, and suprasternal transducer positions. Also, one must be careful to account for the proximal flow velocity in the Bernoulli equation if it is 1.5 m/s or greater. Finally, since some degree of pressure recovery occurs distal to the aortic valve

leaflets, it is important to record continuous wave signals as close to these structures as possible.

Values for aortic valve area can be calculated using the continuity equation by measuring the velocity of the jet across the aortic valve with CW Doppler, the velocity in the LV outflow tract just proximal to the valve with PW Doppler, and by deriving the area of the outflow tract from the diameter of the aortic annulus. Results from the continuity equation have been found to correlate well with the area calculations based on catheterization data and the Gorlin formula.[111-115] As both AS jet velocity and aortic annulus radius are squared in the continuity equation, accurate determination of these parameters is essential for reliable measurements. When atrial fibrillation is present, the peak Doppler velocity still correlates with peak instantaneous gradient through the aortic valve, but *calculations of valve area may be problematic*, as the outflow tract and peak aortic velocities are not measured simultaneously.

In summary, a comprehensive echocardiographic examination in a patient with AS should establish both the presence and severity of disease. Echocardiographic imaging should identify the structural abnormality involving either the subvalvular, valvular, or supravalvular area; distinguish congenital from acquired etiologies; and evaluate the state of LV hypertrophy and function. CW Doppler recordings should provide accurate measurements of instantaneous and mean transaortic valvular gradients, and the continuity equation should provide reliable estimates of aortic valve area. In cases where the relative roles of orifice stenosis and LV dysfunction are uncertain, TEE imaging or Doppler recordings during inotropic stimulation with dobutamine may be of value.[155,229] Cardiac catheterization is still necessary for the delineation of coronary anatomy.

Aortic Regurgitation

In contrast to AS, the aortic valve leaflets are often anatomically normal by echocardiography in patients with aortic regurgitation (AR).[230,231] 2D and M-mode echocardiography often provide indirect evidence of the presence of AR, including signs of LV volume overload, diastolic fluttering of the anterior mitral valve leaflet, aortic root enlargement, and incomplete coaptation of the aortic valve leaflets.[232,233] The important M-mode finding of premature diastolic closure of the mitral valve prior to the onset of systole due to LV filling by the regurgitant jet signifies acute, severe AR[234] (Fig. 13-63) and the need for surgery (Chap. 56).

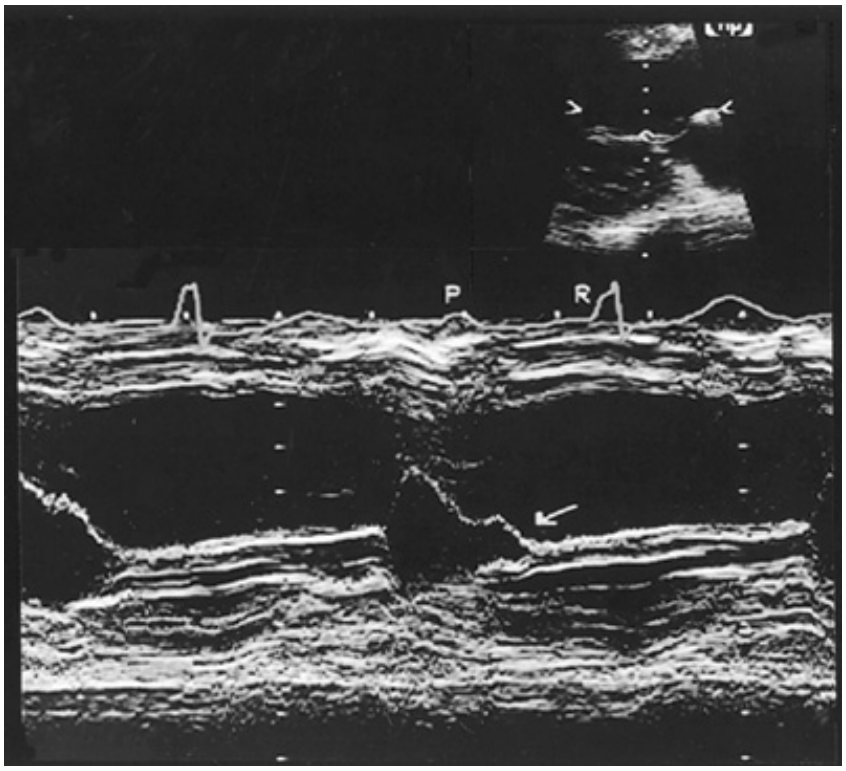

Figure 13-63: M-mode tracing (from the parasternal position) in a patient with acute severe aortic regurgitation. The mitral valve leaflets close (*arrow*) before ventricular contraction begins. P = p wave, R = QRS complex.

Perhaps the most important contribution of echocardiographic tissue imaging to the assessment of AR is in identifying the etiology.[235] Thus, thickened leaflets that are restricted in movement are observed in patients with acquired AS, while oval doming of two functional leaflets will be observed in the presence of a bicuspid aortic valve (Fig. 13-60). AR due to infectious endocarditis can be identified by the presence of valvular vegetations, while regurgitation due to diseases of the aorta are manifest by anatomic changes of the vessel. Less common etiologies of AR, such as those associated with subvalvular pathology or ventricular septal defect, may also be recognized by echocardiographic imaging.

Although the findings yielded by echocardiographic imaging are useful, Doppler interrogation is necessary to obtain direct evidence of the presence and severity of AR. Screening with CFD demonstrates turbulent flow in the LV outflow tract during diastole in virtually all views[236] (Fig. 13-64*A*, *B*, and *C*, Plate 60). The jet is typically elliptical and may be located anywhere in the LV outflow tract. CW Doppler spectral recordings from this jet yield a high-velocity diastolic signal directed toward the apex[237] (Fig. 13-62). Since AR jet velocity accurately reflects the diastolic pressure gradient between aorta and LV, it is maximum at the point of valve closure and decreases throughout diastole.[238] The flow pattern of AR may be readily distinguished from mitral inflow in that it is higher in velocity, begins immediately after aortic valve closure, generally has a much slower deceleration, and does not have an increased velocity following atrial contraction.

Several approaches exist for the quantitation of AR by echocardiography. Conventional echocardiographic imaging can provide evidence of the presence and extent of LV volume overload. More direct evidence of the severity of AR can be derived from the deceleration rate of the jet recorded by CW Doppler (Fig. 13-65).[237-240] In the presence of mild degrees of AR, the transvalvular pressure gradient will be maintained throughout diastole, creating a high-velocity jet with a minimal deceleration rate. Conversely, severe AR reduces aortic pressures and increases

LV pressures in diastole, eliminating the pressure gradient and creating a rapid jet deceleration to a low velocity (Fig. 13-65). Severe, acute AR can also cause diastolic MR (Fig. 13-64*C*, Plate 60). The most common approach to assessing the deceleration rate of the AR jet is by calculating the time required for the velocity to fall to one-half of the maximal pressure equivalent, a technique similar to the pressure half-time measurements performed in the quantitation of mitral stenosis (MS). Previous studies have demonstrated that a pressure half-time of less than 250 ms reliably identifies patients with severe degrees of aortic regurgitation as assessed by invasive methods.[240] Application of the pressure half-time approach to quantifying AR must take into account that, since the deceleration rate is a reflection of pressure gradient, it is determined by both the volume of AR and the compliance of the left ventricle. Accordingly, ventricles that vary greatly in stiffness or distensibility will yield different AR deceleration rates for the same regurgitant volume.

The estimate of severity most commonly derived from echocardiography is the size of the AR jet by CFD.[236] Conceptually, jets that are distributed over a small area of the LV outflow tract represent lesser degrees of AR than jets that penetrate widely and to the level of the papillary muscles. Some studies have demonstrated a general correlation between jet length and severity of AR.[241] The optimal results have been obtained when the width of the AR jet just proximal to the valve was expressed as a percentage of the width of the LV outflow tract; a jet occupying 50 percent or more of the outflow tract correlates with severe regurgitation by angiography.[236] Quantitation of AR based upon the size of the flow disturbance is subject to errors induced by the other factors that influence jet area: transvalvular pressure gradient, volume and compliance of the receiving chamber, regurgitant orifice, the Coanda effect (wall effect), and technical factors relating to the operator and instrument settings. In addition, entrainment and displacement of RBCs in the LV outflow tract also influence the size of the regurgitant jet. Finally, convergence of AR with normal transmitral filling may obscure the flow disturbance. Therefore, assessment of the severity of AR by analysis of the size and shape of the flow disturbance *is at best semiquantitative.*

The AR volume can be estimated by comparing volumetric measurements of LV inflow and LV outflow calculated from annular velocity and cross-sectional area (derived from pulsed Doppler and 2D images respectively).[110] This method is contingent upon the absence of valvular stenosis and of other regurgitant lesions. In the setting of AR, the volume ejected through the aortic annulus represents both systemic flow and regurgitant volume, while the volume coursing through the mitral annulus represents only systemic flow. Thereby, LV outflow will exceed LV inflow by the amount of the regurgitant volume.[110,242-244] This technique can provide useful estimates of regurgitant volume, but with any flow volume calculation by echocardiography, errors in technique and the assumptions involved in volume calculation can result in significant errors. An alternate *quantitative approach* derives estimates of regurgitant fraction from reverse diastolic flow in the aorta.[245] Assuming a constant cross-sectional aortic area, comparison of integrated flow velocities during forward systolic flow and retrograde diastolic flow should yield an estimate of regurgitant fraction. Although this is somewhat imprecise, the presence of a significant flow reversal in the aorta visualized by color or spectral Doppler is a reliable marker of severe AR (Fig. 13-66).

Determination of the optimal timing of surgical intervention in patients with AR remains a difficult problem in clinical medicine (see also Chap. 56). Several criteria derived from echocardiographic recordings have been proposed to guide this decision.[246-249] Most prominently, an LV end-systolic dimension of 55 mm or greater with a shortening fraction of 25 percent or less have been advocated as sufficient criteria for surgical intervention in the absence of symptoms.[250] Considerable debate continues regarding this issue, however, and no universally accepted echocardiographic criteria exist by which to determine the optimal role for surgical treatment.

Diseases of the Aorta

The thoracic aorta is best visualized from the left and right parasternal positions and from the suprasternal notch.[251] The descending aorta may also be imaged from subcostal and modified apical views. Normally, short-axis images of the aortic root yield a circular structure, while long-axis images exhibit two parallel linear walls with a maximal diameter of 35 mm.[252] Although 2D imaging is used most commonly, M-mode recordings of the aortic root facilitate precise measurement of its dimensions.

AORTIC DISSECTION

In recent years, 2D echocardiography has dramatically changed the diagnostic approach to aortic dissection. TTE is a convenient screening test (Fig. 13-67) and often enables accurate detection of ascending aortic dissection.[253] The diagnostic findings include a dilated aorta with a mobile intimal flap that presents as a thin, linear signal within the lumen. Transthoracic imaging is unreliable for detection of descending aortic dissection,[254] although it occasionally visualizes the complete length of the thoracic aorta (see also Chap. 88).

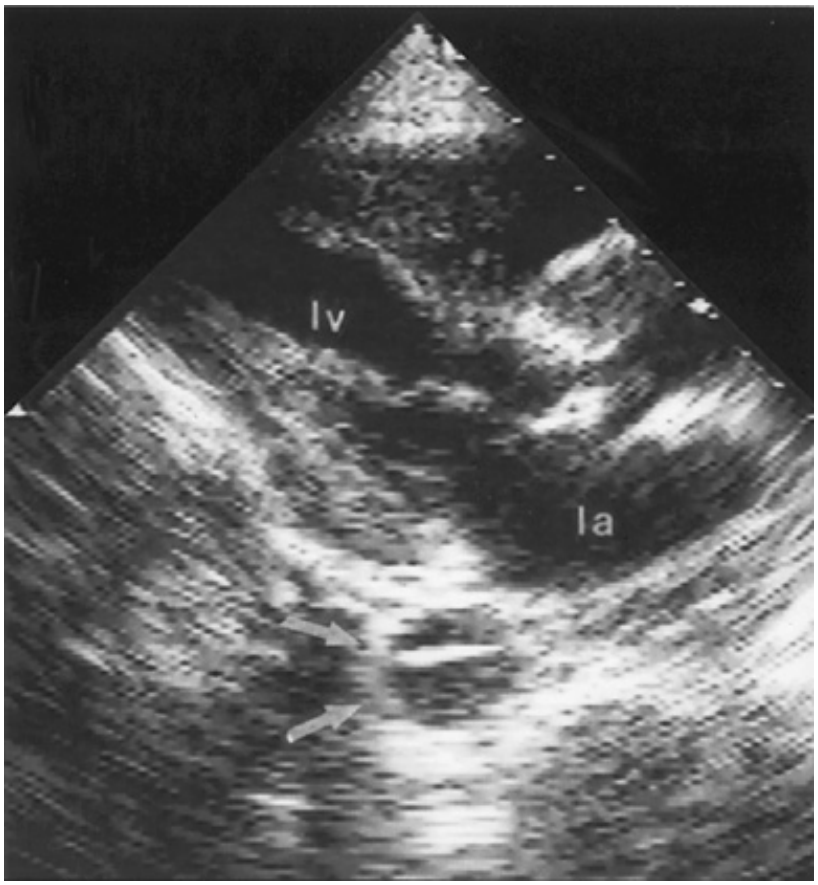

Figure 13-67: Transthoracic parasternal long-axis plane demonstrating a dissection of the descending thoracic aorta. The aortic root is dilated, the aortic valve is thickened, and an intimal flap is present in the descending aorta (*arrows*). LV = left ventricle; LA = left atrium.

Although several noninvasive methods exist to diagnose aortic dissection, TEE has become the procedure of choice in many hospitals because of its accuracy, portability, rapid procedural time, and ability to provide data regarding valvular regurgitation and LV function.[139,158,255-257] Except for *a short portion of the proximal aortic arch*, which is obscured by the bronchus, multiplane TEE provides excellent visualization of the entire thoracic aorta and high accuracy in detecting

aortic enlargement, intimal tears, and false lumen thrombus (Fig. 13-68). CFD may reveal communications between true and false channels (Fig. 13-51, Plate 59; Fig. 13-69, Plate 61). TEE also appears useful for the diagnosis of aortic intramural hematoma, an increasingly recognized disorder which has a clinical prognosis similar to that of classic dissection.[258,259]

AORTIC ANEURYSM

Aneurysms of the aorta may be saccular or fusiform and are recognized as localized or circumferential areas of aortic enlargement, often with thin walls. TTE is especially useful in detecting ascending aortic dilatation but can also visualize descending thoracic and abdominal aortic aneurysms.[252,260] Echocardiography has been used extensively to assess aortic pathology in patients with Marfan syndrome.[261] The nature of the lesion is relatively specific in that there is symmetrical dilatation of the annulus, sinuses of Valsalva, and aortic root (Fig. 13-70, Plate 62). Aortic leaflet coaptation may be compromised leading to AR. Echocardiography is helpful in determining prognosis and optimal timing of aortic root replacement.[262-264]

Sinus of Valsalva aneurysms are also well visualized by both TTE and TEE.[265,266] These lesions cause asymmetrical dilatation of the aortic root and seem to affect the right coronary sinus most frequently. They are prone to rupture, often into the right heart[267] (Fig. 13-70*A*). Doppler echocardiography in such settings demonstrates fluttering of the tricuspid valve, a color jet crossing from the aortic root into the right heart, and occasionally diastolic opening of the pulmonic valve.

Congenital aortic disease, such as supravalvular aortic stenosis (SAS), aortic coarctation, patent ductus arteriosus, and truncus arteriosus also can be detected with echocardiography (see Chaps. 63 and 64).[225,268] In these conditions, suprasternal and transesophageal imaging are often helpful. SAS is recognized as an "hourglass" narrowing just distal to the leaflets, while coarctation presents a more localized, abrupt luminal reduction in the descending aorta. Patent ductus arteriosus and truncus arteriosis are often best identified by virtue of the accompanying flow disturbance on CFD.[269,270]

AORTIC ATHEROSCLEROSIS

As mentioned in the section on TEE, recent studies suggest that aortic atherosclerosis is an important cause of stroke and embolic events.[167,168] Mobile and protruding intimal plaques have been detected by TEE (Fig. 13-53) in patients with stroke with a prevalence greater than in controls, a finding not previously appreciated by other imaging techniques.[271] Optimal treatment for extensive aortic atherosclerosis is currently unknown; although warfarin appears useful.[171b] It appears that detection of large aortic arch plaques prior to cardiopulmonary bypass should prompt adjustment of cannula placement to avoid dislodging the aortic debris.[272]

Penetrating aortic ulceration, which affects the descending aorta and mimics the clinical syndrome of acute aortic dissection, may also be diagnosed by TEE (Fig. 13-71, Plate 63).[273,273a] The diagnosis is based upon visualization of a localized defect with protrusion of the ulcer into the vessel wall (in the absence of dissection). This disease entity, which occurs in the setting of atherosclerosis, warrants urgent surgery to avoid aortic rupture. Aortic tears induced by trauma are also accurately detected by TEE[273b,273c] (Fig. 13-72).

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Chapter 13: THE ECHOCARDIOGRAM

DISEASES OF THE MITRAL VALVE

Mitral Stenosis

Detection of *mitral stenosis* (MS) was one of the earliest clinical applications of echocardiography[274] (see Chap. 57). In most individuals, the mitral valve leaflets are easily visualized and yield thin linear echoes that exhibit wide bipeaked excursions as they open in early and late diastole.[24] The characteristic 2D ultrasound findings of MS are seen clearly in nearly all patients with this disorder.[275] The mitral valve leaflets are thickened and often present bright high-intensity reflections indicating calcification. The process may involve thickening and shortening of the chordal apparatus as well. There are varying degrees of commissural fusion restricting mitral leaflet separation, especially at the distal tips.[276,277] This leads to diastolic "doming" or a right-angle bend of the anterior mitral valve leaflet, as high LA pressure creates a bulge in the leaflet's midportion (which is generally more pliable than the distal portion) (Fig. 13-73). The posterior leaflet actually may be pulled anteriorly during diastole because of commissural fusion with the longer anterior leaflet.[278] Mitral doming may also occur in congenital valvular disease, but it is not seen when mitral leaflet opening is reduced due to low-flow states[32] or AR jets. The LA is nearly always enlarged with MS.

The effects of stenosis upon mitral valve motion are often best demonstrated by M-mode recordings (Fig. 13-74). In addition to leaflet thickening and reduced excursion, M-mode tracings also depict a characteristic decrease in the reclosure rate of the anterior mitral leaflet in early diastole (reduced E-F slope) due to a persistent LA-LV pressure gradient and a slow rate of LV filling.[276-279] The decrease of the E-F slope has been found to correlate grossly with the severity of mitral stenosis. This finding is not specific for MS, however, and may occur whenever early diastolic filling is reduced.[24,280] Attempts to calculate mitral valve orifice area using the E-F slope have proved unsatisfactory.[281]

The entire perimeter of the mitral valve orifice can be visualized in the 2D parasternal short-axis view, and mitral leaflet excursion normally approaches the endocardial borders of the LV at the mitral tip level. In the setting of MS, the thickened leaflets form a fish-mouth orifice, which occupies only a small portion of the cross-sectional area of the left ventricle (see also Chap. 57).[275,282] Measurements of mitral valve area may be obtained by planimetry of the orifice visualized in the parasternal short-axis view and correlate well with those obtained by cardiac catheterization (Fig. 13-73).[282-284] Since the shape of the mitral valve resembles a funnel, it is crucial to identify the smallest cross-sectional area and obtain recordings with orthogonal beam orientation at that point in order to avoid overestimation. Optimal gain settings must be employed to avoid encroachment of tissue signals upon the orifice.[285]

Doppler examination provides additional quantitation of MS.[286,287] Interrogation of mitral inflow with either PW or CW modes (depending on velocity and Nyquist limit) reveals elevated diastolic velocities, with a reduction in the rate of deceleration in early diastole yielding a pattern similar to decreased E-F slope seen with M-mode in MS (Fig. 13-75). In a fashion similar to that of AS, the maximal gradient across the mitral valve can be calculated from the peak diastolic velocity utilizing the Bernoulli equation.[286,288] But since the maximal transmitral gradient is very sensitive to changes in heart rate and loading, the mean transmitral gradient obtained as the

average of a number of individual gradients derived throughout diastole is customarily utilized to assess the severity of MS.[288] In addition, Doppler technique may provide estimates of mitral valve area (MVA) by means of the calculation of the pressure half-time.[284,287] The pressure half-time represents the interval required for transmitral velocity to decelerate from its highest point (E) to a velocity that yields one-half of the pressure equivalent (Fig. 13-75). As the severity of MS increases, the rate of deceleration decreases, prolonging the pressure half-time. Further, dividing an empiric constant of 220[289] by the pressure half-time yields an estimate of MVA, which correlates with values obtained during cardiac catheterization. Since Doppler estimates of mitral valve area are indirect and involve the use of empiric constants, they are considered less accurate than direct measurements of MVA derived by planimetry of the mitral valve orifice.[290] The pressure half-time method is inaccurate immediately following mitral commissurotomy.[291,292]

Echocardiography can help assess the feasibility and appropriateness of percutaneous catheter balloon mitral commissurotomy (CBMC) to treat individual patients with MS[293,294,294a] (Chap. 37). An echocardiographic scoring system based on evaluation of mitral valvular thickening, calcification, mobility, and subvalvular involvement has been devised. Each variable is assigned a grade of 1 (minimal involvement) to 4 (severe), with a maximal score of 16. Although the prognostic capability of this method is limited, the outcome of balloon valvuloplasty in patients with higher scores, particularly greater than 12, is less satisfactory and involves a higher risk of complications than in patients with lower scores.[293,294,294b] Therefore, echocardiographic analysis is an important part of the decision-making process prior to CBMC. Preprocedural TEE is also often performed to detect left atrial thrombi, which can embolize during transseptal catheterization.[295,296] Following CBMC, echocardiography can identify complications including mitral regurgitation[297] and atrial septal defect.[298]

Mitral Regurgitation

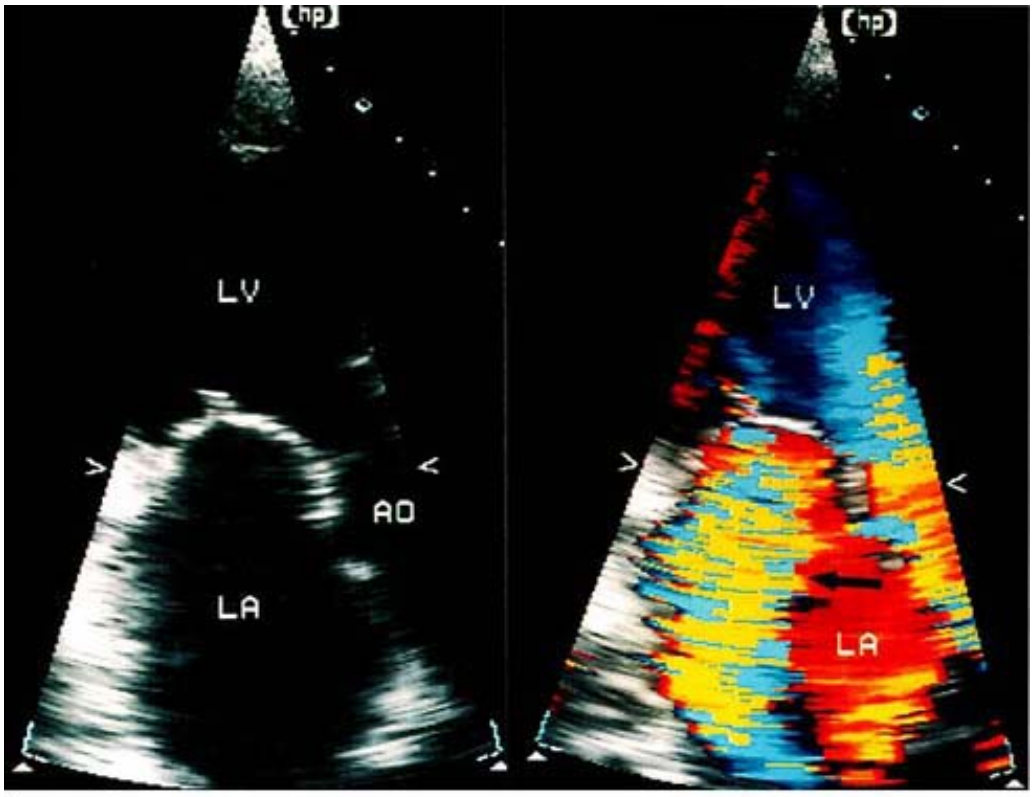
Although echocardiography is extremely accurate in the detection of mitral (and aortic) regurgitation, *quantitation* is more difficult. 2D imaging alone does not provide direct evidence of mitral regurgitation (MR) but usually reveals the etiology of the lesion.[299] Thus, 2D echocardiography reveals thickened, restricted leaflets in rheumatic disease, vegetations in infective endocarditis, flail mitral leaflets with torn chordae, and redundant leaflets with abnormal coaptation in mitral valve prolapse.[300] 2D echocardiography can also detect LA and LV abnormalities associated with MR, such as myxoma, papillary muscle dysfunction, and dilated cardiomyopathy. In addition, enlargement of these chambers offers indirect evidence of MR severity. In cases of chronic, severe MR, 2D echocardiography can also discern the presence of depressed LV function and decreased ejection fraction (see also Chap. 57).

Doppler echocardiography is the primary method for the detection and evaluation of MR[301-303] and reveals a disturbed flow jet in the LA during systole. Spectral Doppler recordings provide several indexes of severity which are of semiquantitative value. Since the intensity of the Doppler signal is a function of the number of RBCs in the sample volume, the videodensity of the jet correlates in a general way with regurgitant volume.[304] Similarly, an increase in transmitral filling velocities reflects increased forward flow and suggests a large regurgitant volume.[304a] Measurements obtainable from the envelope of the CW Doppler recording of the MR jet include a slow rate of acceleration, indicative of a diminished LV *dP/dt*[305] (Fig. 13-76). Early peaking followed by rapid deceleration of the MR jet suggests a large V wave, increased left atrial pressure, and usually acute severe MR.[306]

As in the case of AR, volumetric calculations of LV inflow and outflow by combined pulsed Doppler and 2D-echocardiographic imaging techniques can be used to derive measurements of regurgitant volume.[307,308] In the case of MR, transmitral filling represents both systemic and regurgitant volume, while aortic outflow represents only systemic flow. Therefore, mitral filling

should exceed left ventricular ejection, and the difference will be regurgitant volume.

The most commonly applied method for evaluation of MR is assessment of jet size by CFD.[303,309,310] Imaging of the left atrium in systole reveals a turbulent, mosaic jet of varying direction, size, and configuration (Fig. 13-77*A* and *B*, Plate 64). Previous studies have demonstrated that a mitral regurgitant jet whose absolute area exceeds 8 cm^2 [303,310] or fills at least 40 percent of the area of the LA[309] is predictive of finding 3+ to 4+ MR by LV angiography. Unfortunately, neither jet size nor angiographic grade correlates closely with measurements of actual regurgitant volume.[310] The lack of correlation between CFD jet area and regurgitant volume is attributable to the additional variables that influence the distribution of the flow disturbance, such as pressure gradient and the volume and compliance of the LA, as well as technical limitations. The Coanda effect is of particular significance in regard to MR, since jets into the left atrium are often eccentric (for example, in cases of mitral valve prolapse and torn chordae tendineae). Due to differential frictional forces and resistance to flow, eccentric MR jets are drawn along the walls of the LA, resulting in cross-sectional jet areas that are smaller than centrally directed flow disturbances of comparable regurgitant volume (Figs. 13-77 and 13-78). This effect can lead to underestimation of severity of regurgitation.[311,312]



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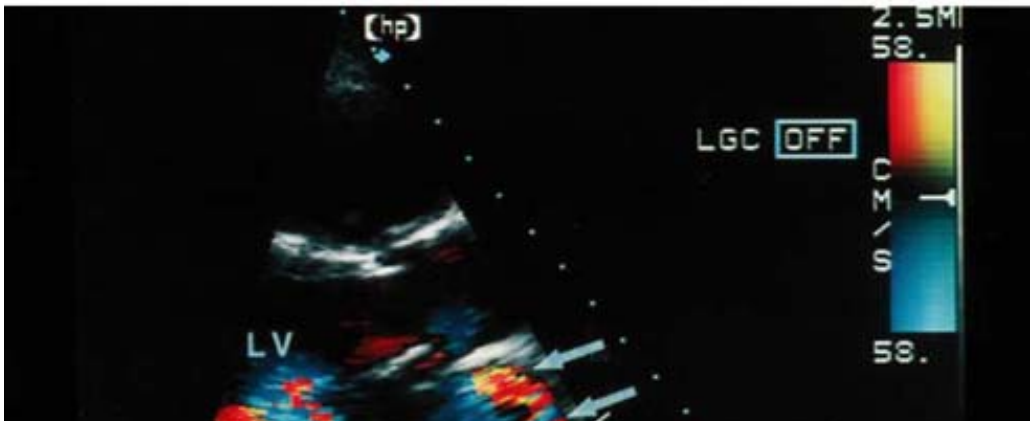

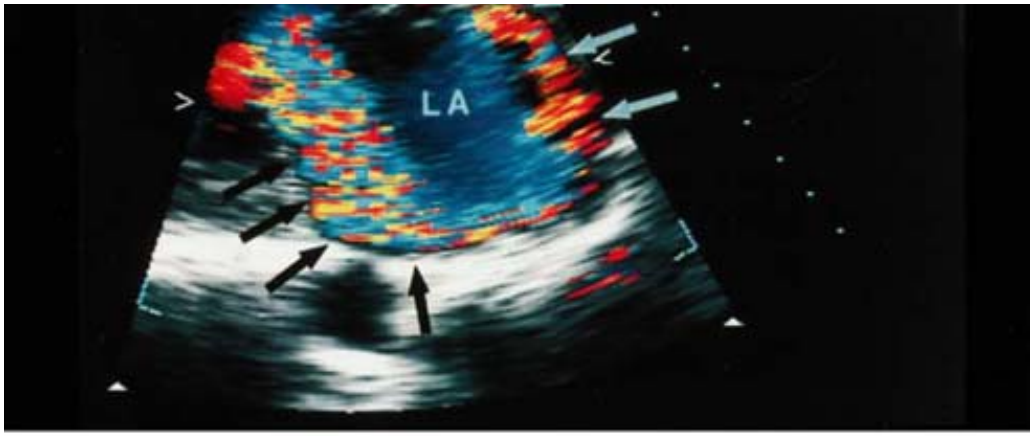

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Figure 13-77: (Plate 64) *A.* Mitral regurgitation. *Left:* apical three-chamber plane. Right: same plane with color Doppler imaging. A large jet of mitral regurgitation (*arrow*) is present. AO = aorta; LA = left atrium; LV = left ventricle. *B.* Parasternal long-axis view from a patient with angiographically proved severe mitral regurgitation. The color Doppler jet in this case is directed posteriorly and eccentric (*black arrows*). The jet hugs the wall of the left atrium (LA) and wraps around all the way to the aortic root (*white arrows*). LV = left ventricle.

TEE is also useful for assessment of MR, as the close proximity of the probe and its higher-frequency interrogating beam permit imaging of regurgitant jets in greater detail than TTE.[313-315] Eccentric jets and mitral valvular anatomy are well visualized (Fig. 13-78*A* and *B*, Plate 65), and rightward bulging of the interatrial septum with severe MR is also sometimes apparent. As the regurgitant jets often appear larger with TEE than with TTE, one must avoid overestimation of MR severity.[154] TEE often yields Doppler interrogation of the pulmonary veins that is superior to TTE, and several recent studies have shown that systolic reversal of flow into the pulmonary veins is a reliable sign of severe MR[152,315a,315b] (Fig. 13-79).

Another color Doppler method of flow quantitation involves measurement of the zone of flow convergence proximal to the regurgitant orifice (or the *proximal isovelocity surface area, referred to as PISA*).[316-319] The mechanism for this phenomenon is derived from the hydrodynamic principle that blood flow accelerates before passing through a small orifice under high pressure. If this increase in flow velocity exceeds the Nyquist limit, color aliasing occurs and the velocity aliasing border is equal to the Nyquist limit (Fig. 13-31 and Fig. 13-80*A* and *B*; Plate 66). If one assumes that the aliasing border conforms to the geometry of a hemisphere around the mitral orifice, then the instantaneous flow rate of blood through the orifice can be calculated as:

$$\text{Flow} = 2\pi r^2 \cdot V_r$$

where r is the radius of the hemisphere shell (distance from alias border to orifice) and V_r is the velocity of blood at distance r (the Nyquist limit velocity).[316] If the maximal calculated flow rate is divided by the peak regurgitant flow velocity (measured with CW Doppler), the regurgitant orifice area is then obtained.[320] The product of regurgitant orifice area and integrated velocity of the MR jet by CW yields regurgitant volume.

The PISA method avoids the variables associated with jet size and the assumptions and technical limitations of volumetric calculations. Numerous studies have shown a correlation between both flow rate and regurgitant orifice area calculated by PISA and the severity of MR assessed by standard methods.[316,320] In addition, flow convergence calculations have been applied to other valvular lesions, including AR and MS[321,322] (Fig. 13-81, Plate 67), ventricular septal

defect,[323] and prosthetic heart valves.[324] The proximal flow convergence assumes a hemispheric geometry for the PISA signal and that the plane of the mitral leaflets is flat, two sources of potential error.[325] Despite these limitations, the method holds considerable promise for the clinical evaluation of valvular regurgitation.

Mitral Valve Prolapse

As is true of so many aspects of mitral valve prolapse (MVP),[326] the echocardiographic findings in this disorder have been controversial for many years.[327] Recent insights into the anatomy of the mitral annulus and the significance of abnormal leaflet structure have established a central role for echocardiography in the diagnosis and prognosis of MVP.[328] The classic echocardiographic findings in overt MVP syndrome consists of mid- to late-systolic bulging of one or both mitral leaflets across the plane of the mitral valve annulus into the LA (Fig. 13-82*A* to *C*).[329] The leaflets are often observed to be structurally abnormal, with thickening, elongation, and hooding.[330] Mid- to late-systolic MR is sometimes present, often eccentric, and generally directed away from the prolapsing leaflet.[326] The chordae tendineae may be thickened and elongated, the aortic root may be dilated, and the tricuspid valve leaflets may prolapse as well. LV function is usually normal, although the LA and LV may be enlarged if MR is significant. The greater temporal resolution of M-mode over 2D echocardiography often yields striking evidence of abrupt midsystolic posterior/superior motion of the mitral valve leaflets in prolapse patients[331] (Fig. 13-82*C*). Although such M-mode findings, which resemble a question mark on its side, are specific for mitral valve prolapse, patients with classic MVP occasionally may demonstrate diagnostic findings only with 2D imaging (Chap. 58).

Although the diagnosis of classic, fully expressed MVP is straightforward by echocardiography, identification of mild prolapse is more difficult, and no absolute diagnostic criteria currently exist.[329] This is largely related to the absence of any "gold standard" with which to validate findings, including auscultation, angiography, and even pathology.[326] For prolapse to be present, the mitral valve leaflets must cross the plane of the mitral valve annulus after initial systolic coaptation. Recent studies have established that the mitral valve annulus is not flat but rather saddle-shaped.[332] The annulus reaches its nadir in the apical four-chamber view, and even normally coapting mitral valve leaflets may appear to prolapse in this projection. Therefore, current criteria require that MVP be diagnosed only when one or both of the mitral leaflets clearly bulge past the plane of the mitral valve annulus in the parasternal long-axis view.[328] Unfortunately, the degree to which the mitral leaflets must break the plane of the annulus is unclear. The greater the portion of the mitral valve leaflets entering the LA, the more likely the existence of signs and symptoms related to this disorder; a peak distance behind the annulus of 2 mm almost invariably establishes the presence of MVP.[329] The diagnosis of mild MVP may be assisted by examination of the structure of the leaflets and chordae tendineae, since it has been demonstrated that patients with redundant or thickening valve leaflets (greater than 5 mm in midleaflet) are at increased risk of complications, including severe MR and infective endocarditis[333] (Chap. 73).

Torn Chordae Tendineae

Rupture of chordae tendineae may occur spontaneously or in conjunction with MVP or endocarditis. This can result in a flail mitral leaflet and severe MR. Although TTE often detects these lesions, TEE is especially sensitive and accurate and often demonstrates free motion of the leaflet and ruptured chord into the LA even when the TTE is equivocal (Fig. 13-83*A* and *B*).[334] As with MVP, the MR jet in this condition is usually eccentric and directed away from the affected leaflet, often "hugging" the adjacent left atrial wall (Coanda effect). Therefore, the jet's cross-sectional area may be misleadingly small. The findings of mitral valvular anatomy on TEE may also be helpful in predicting the feasibility and success of valve repair surgery.[335]

In the setting of ischemic heart disease, both LV enlargement and papillary muscle dysfunction (from infarction or transient ischemia) may cause MR.[336] Both the MR and the contractile abnormality responsible for it are usually well visualized by 2D echocardiography. In rare cases, papillary muscle rupture (partial or complete) occurs in the postinfarction period.[337] Rapid echocardiographic diagnosis often requires TEE and may be lifesaving in these cases.[334]

Mitral Annular Calcification

The finding of mitral annular calcification (MAC) is fairly common in adults and occurs more frequently with advancing age. Although ultrasound cannot discern histology, calcification typically appears as thickened, extremely high-intensity ("bright") signals (Fig. 13-84). The posterior portion of the mitral annulus is affected much more commonly than the anterior segment, and calcification often extends into the posterior mitral leaflet, sometimes restricting its motion.[338-340] The abnormality, best visualized in the parasternal long- and short-axis views, is seen as a bright calcific density at the junction of the posterior mitral leaflet and the annulus. In the short-axis view, the posterior band of calcification often appears crescentic. Rarely, the calcification is extensive enough to cause marked valvular thickening and clinically significant mitral stenosis.[339] MAC has also been implicated as a source of cardiogenic embolization.[341]

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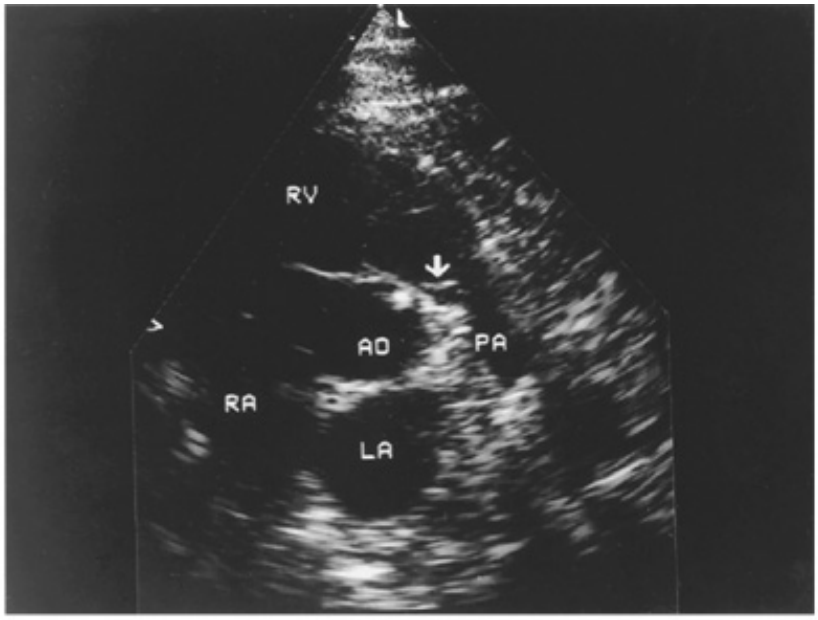
Chapter 13: THE ECHOCARDIOGRAM

RIGHT-SIDED VALVULAR DISEASE ANDPULMONARY HYPERTENSION

Pulmonic Valve

Major structural abnormalities of the pulmonic valve are relatively rare. *Pulmonic stenosis* (PS) is usually congenital in origin and resembles congenital AS in many respects. The stenotic valve does not open fully and exhibits characteristic thickening and systolic doming on 2D imaging[342] (Fig. 13-85). M-mode recordings of the pulmonic valve often show a large a wave, since right ventricular diastolic pressure is often so high and pulmonary artery (PA) pressure so low that the atrial "kick" is sufficient to open the pulmonic valve.[343] Doppler interrogation reveals turbulent flow distal to the valve, and CW measurements can be used to calculate gradients and valve areas with the Bernoulli and continuity equations much as in aortic stenosis.[344]



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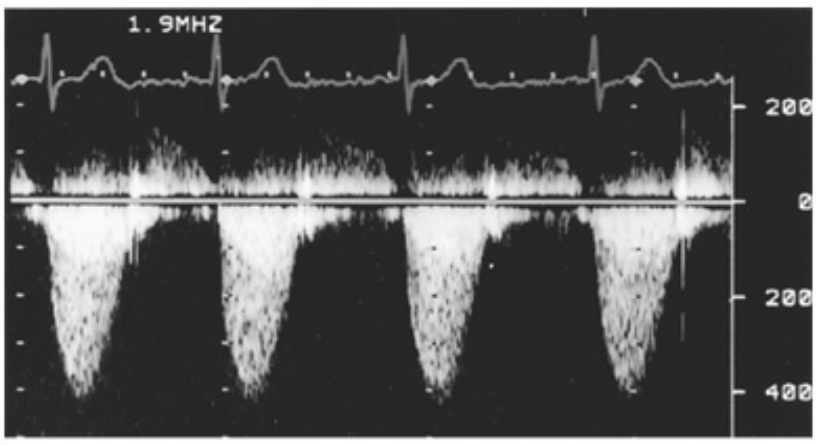

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Figure 13-85: *A.* Pulmonic stenosis. The pulmonic valve leaflet is thickened and echo-reflective (*arrow*). RA = right atrium; LA = left atrium; AO = aorta; PA = pulmonary artery; RV = right ventricle. *B.* Doppler interrogation reveals increased flow velocity (4 m/s) through the valve orifice.

Although severe *pulmonic regurgitation* (PR) is rare, mild PR is common and appears as a flame shaped flow disturbance in the *right ventricular outflow tract* (RVOT) in diastole.[345] Many individuals have trivial PR on color Doppler examination; this is a physiologic, normal variant (Fig. 13-86). Hemodynamically significant PR is uncommon; when present, it is usually due to congenital heart disease, valvular tumors, endocarditis, or carcinoid heart disease (Chap. 59). The echocardiographic grading of PR is semiquantitative, based on the density of the CW envelope, area of the color Doppler jet, and width of the jet at the valve.[346,347] The PR pressure half-time by CW Doppler may be shorter with more severe PR, but this is not as well investigated as in the case of aortic regurgitation. Measurements derived from the CW Doppler recording also provide estimates of end-diastolic pulmonary artery pressure using the Bernoulli equation as follows[348]: [4(PR end-diastolic velocity)^2 + central venous pressure (CVP).

Tricuspid Valve

Tricuspid stenosis (TS) is usually rheumatic in origin, and coexistent mitral and aortic valvular disease is the rule. Congenital or acquired (nonrheumatic) causes of TS are quite uncommon. On rare occasions, tricuspid stenosis may be caused by carcinoid heart disease or by leaflet adhesions to permanent pacemaker leads. Because of the large size of the tricuspid annulus, obstruction by masses, even multiple vegetations, is unlikely to cause stenosis (Chap. 59).

Regardless of the etiology, diastolic doming of the valve leaflets suggests stenosis.[349,350] CW Doppler interrogation is also helpful and mimics the findings of MS (high diastolic velocity with prolonged pressure half-time).[349] The pressure half-time equation of mitral valve area calculation cannot be applied directly to the tricuspid valve, and large studies comparing Doppler echocardiography with right heart catheterization in TS are not available.

Tricuspid regurgitation (TR) is much more common than TS, and like PR is present to a mild degree in many normal individuals (Chap. 59). Hemodynamically significant TR may be caused by endocarditis, rheumatic valvular disease, pulmonary hypertension, congenital heart disease (for example, Ebstein's anomaly), carcinoid heart disease, flail TR leaflet (which can occur as a complication of cardiac trauma or endomyocardial biopsy), and tricuspid valve prolapse. Echocardiographic findings in patients with TR generally mirror those found in MR.[351] Although 2D imaging can detect abnormalities associated with TR, such as incomplete leaflet coaptation, flail leaflet, and right-sided chamber enlargement, the technique cannot accurately quantify TR grade. Doppler echocardiography, especially color-flow mapping, has become the procedure of choice to detect TR, and has reasonable accuracy for semiquantitation of severity.[352,353] As with MR, severity of TR can be estimated by regurgitant jet area, ratio of jet area to right atrial area, and size of proximal flow convergence zones[354] (Fig. 13-31). Doppler interrogation of the hepatic vein is also useful, as systolic flow reversal within the vein suggests severe TR[355] (Fig. 13-87). Peak right ventricular (and pulmonary artery) pressure can be estimated using measurements of peak TR velocity by CW Doppler (see section on Bernoulli equation, above). If necessary, intravenous echocardiographic contrast agents can be injected to accentuate the TR Doppler jet and facilitate more accurate measurements of pulmonary artery pressure.[352-354]

Right Ventricular Function and Pulmonary Hypertension

Right ventricular (RV) enlargement and pulmonary hypertension can be diagnosed and assessed by echocardiography[355,356] (Fig. 13-88*A* and *B*). Because of the asymmetrical and crescentic shape of the RV, accurate volume calculations are difficult.[357,358] Nonetheless, 2D imaging provides useful general information regarding RV size and function. In the apical four-chamber view, the RV should appear somewhat smaller than the LV; therefore RV enlargement can be diagnosed qualitatively when the RV cross-sectional area exceeds that of the LV. RV chamber area measurements in the apical four-chamber imaging plane can also be compared to standardized normal values.[359] Although not well standardized, measurements of RV wall thickness can be performed from the parasternal view; a value of 5 mm is generally accepted as the upper limit of normal.[360,361] Systolic motion of the RV free wall and LV lateral wall toward the interventricular septum should be similar and roughly symmetrical in normal situations. Asymmetrical hypokinesis of the RV free wall indicates RV dysfunction.[362]

RV volume overload can lead to RV hypertrophy, chamber enlargement, and, in advanced stages, depressed RV systolic function. TR can result from or cause RV overload, and the TR Doppler velocity allows estimation of the peak RV systolic pressure. The interventricular septum also becomes abnormal in RV overload and tends to flatten or even bulge toward the LV (Fig. 13-89).[363] The pattern of septal movement can help distinguish between volume and pressure overload: in pure volume overload, the RV diastolic pressure may equal or exceed that of the LV, while the systolic pressure of the LV greatly exceeds that of the RV. Therefore, the interventricular septum flattens during diastole and returns to its normal curvature during systole.[363,364] With RV pressure overload, however, the abnormally high RV pressures persist through the entire cardiac cycle and the interventricular septum remains deformed during both systole and diastole.[364]

The hallmark of pulmonary hypertension by Doppler echocardiography is a high-velocity TR jet in the absence of PS. Peak TR jet velocity can be converted to peak systolic PA pressure as follows[365]:

$$4(\text{TR velocity})^2 + \text{CVP}$$

In the setting of severe pulmonary hypertension, the main PA and the inferior vena cava are often dilated. If RA pressure is elevated, the inferior vena cava (IVC) does not decrease in diameter with inspiration as normally expected.[366] M-mode examination of the pulmonic valve in pulmonary hypertension may show a characteristic W-shaped motion of the valve leaflet during systole[367-369] (Fig. 13-90) and loss of the normal a dip caused by partial opening of the valve during atrial contraction. The loss of the a wave is probably due to the large pressure difference between the RV and pulmonary artery during late diastole and the resulting inability of the atrial contraction to partially open the pulmonic valve. The midsystolic closure of the valve and partial reopening in late systole (sometimes called the *flying W*) may be caused by elevated pulmonary vascular resistance and oscillation of a pressure wavefront within the pulmonary artery.[370]

Characteristic pulsed-wave Doppler abnormalities in pulmonary hypertension include a decrease in the velocity-time integral of flow through the pulmonic valve (secondary to depressed RV stroke volume) and a shortening of the acceleration time (measured from beginning of flow through the pulmonic valve to peak velocity). The acceleration time (in milliseconds) can be used to estimate the mean pulmonary artery (PA) pressure[371] as:

$$\text{Mean PA pressure} = 80 = (\text{acceleration time}/2)$$

Pulmonic regurgitation is also common in the setting of pulmonary hypertension and is usually

well recorded by pulsed Doppler. As discussed above, the end-diastolic PR velocity can be used to estimate PA end-diastolic pressure by the Bernoulli equation.

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Chapter 13: THE ECHOCARDIOGRAM

PROSTHETIC CARDIAC VALVES

Echocardiography is a critically important tool in the evaluation and serial follow-up of mechanical and bioprosthetic valves.[372] Unfortunately, the increased echo reflectivity of prosthetic valves (especially the mechanical models) causes extensive distal shadowing and reverberations that markedly limit the utility of transthoracic 2D echocardiography (Figs. 13-91 and 13-92). TTE imaging may detect partial ring dehiscence manifest as abnormal "rocking" motion of a prosthetic valve. TTE may also identify reduced movement of the valve disks or leaflets and may occasionally visualize adherent thrombi, tissue ingrowth, and vegetations.[373-375] Leaflet thickening, detachment, and flail motion also may be visualized for bioprosthetic valves.

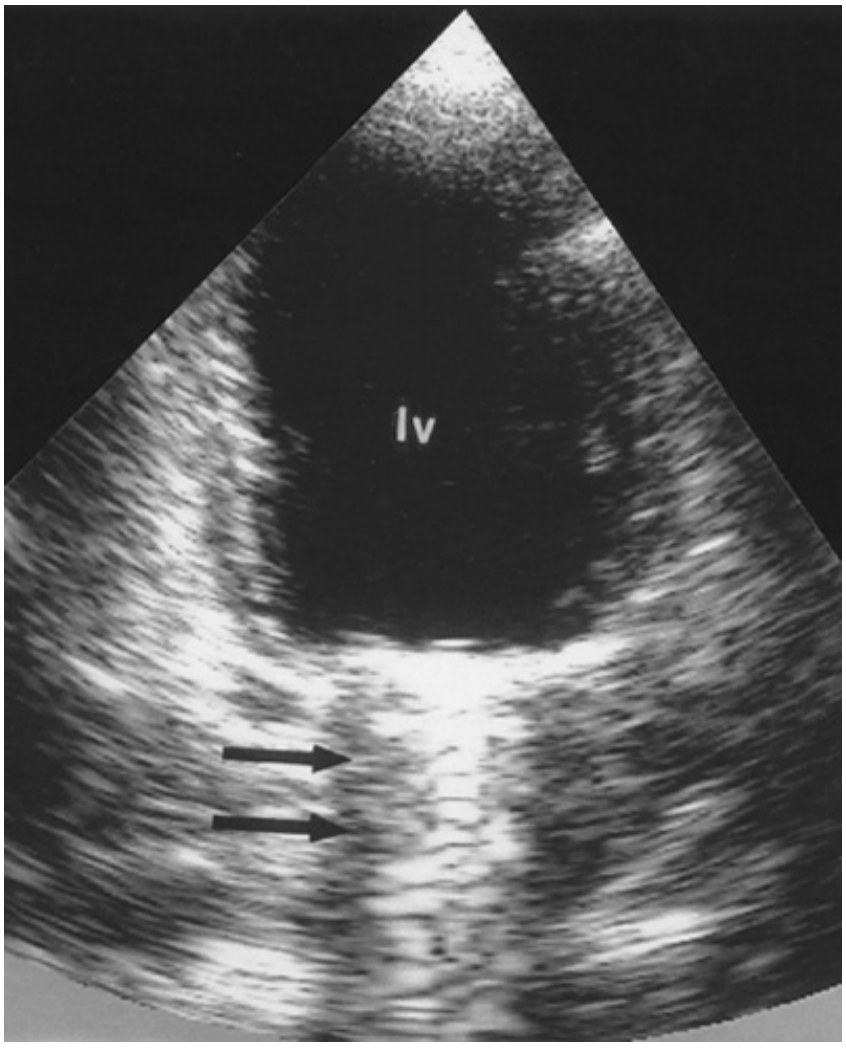

Figure 13-91: Apical two-chamber view of a mechanical prosthetic valve (mitral position) during systole. The left atrium is completely obscured by ultrasonic shadowing (*arrows*). LV = left ventricle.

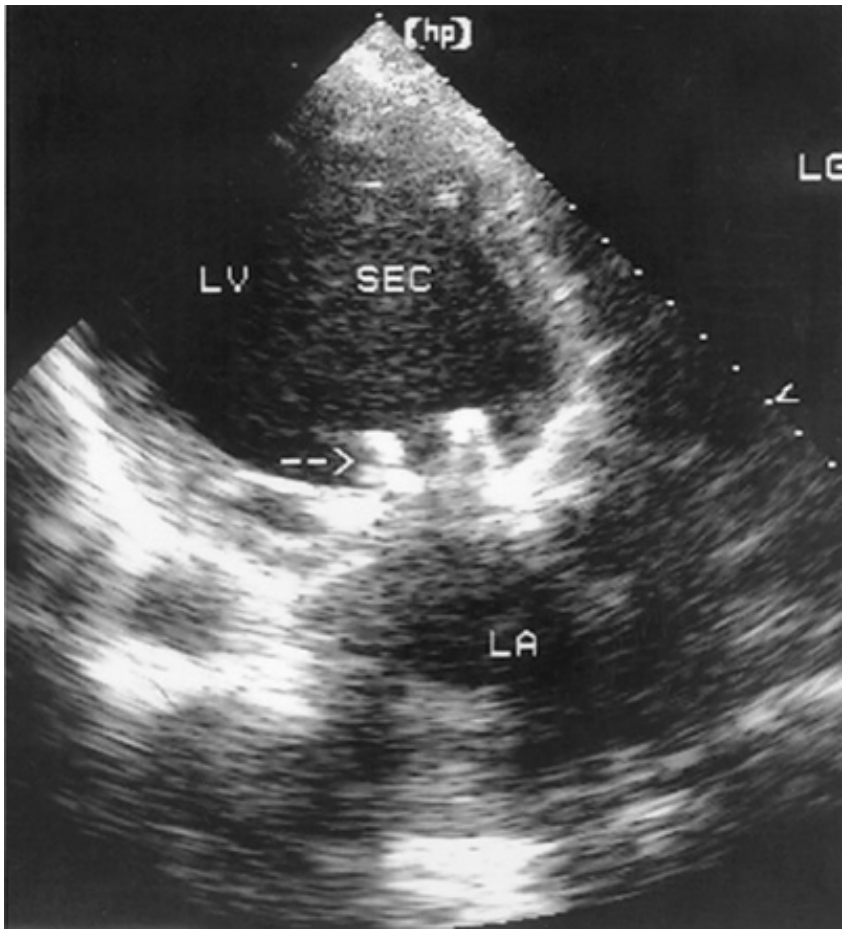

Figure 13-92: Apical view of a bioprosthetic valve (*arrow*) in the mitral position (two of the three prosthetic valve struts are apparent). Spontaneous echo contrast (SEC) is also present, secondary to systolic dysfunction and enlargement of the left ventricle (LV); LA = left atrium.

Doppler interrogation is the cornerstone of the echocardiographic assessment of prosthetic valvular stenosis and regurgitation.[376-379] Color-flow imaging can document the presence, direction, and size of the forward flow stream. Color-flow Doppler can also detect regurgitant flow jets, but like 2D imaging, is limited by acoustic shadowing distal to the prosthesis. Doppler color jets due to prosthetic AR can be readily visualized from the transthoracic apical view, but jets produced by prosthetic mitral and tricuspid regurgitation are often obscured.[380,381] Therefore, although detection of prosthetic regurgitation by transthoracic Doppler is usually feasible, quantitation is often difficult. A small flow signal shortly after valve closure may be observed frequently with prosthetic valves and is likely related to the blood caught behind the occluder as it closes.[382]

Doppler flow velocities and gradients (calculated by the Bernoulli equation) through normal prosthetic valves vary depending upon the type, position, and diameter of the prosthesis.[376-379] The velocities and gradients across prosthetic valves are flow-dependent as well[383] and therefore related to LV function. Given these variables, it is not surprising that a wide range of transvalvular gradients exists for normally functioning prosthetic valves. Nevertheless, "normal" ranges have been reported for various valve types and can be used as a guide to recognize malfunction. High prosthetic valvular gradients due to increased flow volume rather than stenosis can be recognized by high flow velocity across the remaining native valves, a short pressure half-time for mitral prostheses, and a short ejection time for aortic prostheses. With aortic valve prostheses, peak systolic Doppler velocities may indicate higher systolic pressure gradients than those actually

found during cardiac catheterization.[384,385] This problem may be more prevalent with StarrEdwards (ball-in-cage) and St. Jude (bileaflet tilting disks) valves than with Medtronic-Hall (single tilting disk) and bioprosthetic valves. The inaccuracies with Starr-Edwards and St. Jude valves are probably due to the presence of multiple flow channels (with various orifice areas) and the phenomenon of flow recovery.[385,386] Because of these variabilities, an echocardiographic examination is warranted following prosthetic valve implantation to establish its baseline Doppler characteristics.[387] As opposed to peak gradients, mean transvalvular gradients calculated by Doppler correlate reasonably well with direct catheter measurements.

TEE has dramatically changed the diagnostic approach to prosthetic valve dysfunction,[380,381] and is especially useful for assessing mitral prostheses, as it overcomes the problem of left atrial shadowing and reverberation (Fig. 13-93). TEE is extremely accurate in the detection of prosthetic regurgitation and impaired movement of the valve occluder, and it is the diagnostic procedure of choice in most cases of suspected prosthetic valve endocarditis.[388-390] Small thrombi, tissue ingrowth, infected or sterile vegetations, and even sutures in the sewing ring usually can be readily visualized. The enhanced sensitivity of TEE requires operator experience and judgment, as nearly all mechanical prostheses exhibit a normal small amount of regurgitation, which should not be misinterpreted as pathologic.[382] TEE may also visualize thin fibrinous strands sometimes attached to prosthetic valves; these structures appear to be a potential source of cardiogenic embolization.[391,392] The technique is quite accurate in the diagnosis of prosthetic valve thrombosis, a potentially fatal medical emergency, and can assist clinical decision making in this disorder.[393-395]

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Chapter 13: THE ECHOCARDIOGRAM

INFECTIVE ENDOCARDITIS

Infective endocarditis remains an all too common illness, with a significant risk of morbidity and mortality (see also Chap. 78). Traditionally, the diagnosis has been based on either the cumulative results of blood cultures, physical examination, and laboratory findings or on pathologic proof of infected valvular vegetations at surgery or autopsy. Echocardiography may play an important role in infective endocarditis in regard to diagnosis, detection of associated cardiac abnormalities and hemodynamic dysfunction, prognosis, and the need for surgery. Vegetations can now be visualized noninvasively in many (but not all) cases of endocarditis and have become the echocardiographic hallmark of this disorder.[396-398] Thus, even though TTE cannot exclude endocarditis, abnormal findings may strongly suggest the disorder, even in the presence of negative blood cultures. Since no single abnormality has 100 percent diagnostic accuracy for infective endocarditis, strategies for diagnosis have been devised based upon a number of criteria,[399399a-399b] and definite echocardiographic vegetations are designated as a major criterion. Both TTE and TEE are valuable in the detection of perivalvular abscesses and prosthetic-valve endocarditis.[147,400] Although there is considerable debate concerning the most accurate diagnostic criteria for endocarditis, echocardiography has become one of the most commonly used techniques for the evaluation of potentially affected patients.[401] Echocardiography (both TTE and TEE) is also useful for evaluation of patients with systemic lupus erythematosus complicated by Libman-Sacks endocarditis.[402,403]

Even though M-mode recordings produced the first echocardiographic description of vegetations,[396] this modality has gradually been largely replaced by 2D imaging. With 2D echocardiography, valvular vegetations typically appear as irregular, usually localized masses of varying echocardiographic density attached to valvular or perivalvular structures (Figs. 13-94 and 13-95) without significantly altering their mobility. The vegetations may be small or quite large and may attach directly to the valve leaflets or the supporting chordal apparatus.[397,398,404,405] Both small, nonmobile vegetations on a normal valve and large vegetations on a markedly abnormal valve may be difficult or impossible to identify with certainty. Aggressive infections often cause perforation or distortion of the affected leaflet, leading to varying degrees of valvular regurgitation. This is distinctly different from most cases of nonbacterial thrombotic (marantic) endocarditis, where the valvular vegetations are usually nondestructive.[406] In cases of infective endocarditis, the presence of vegetations by TTE increases the risk of heart failure, embolic events, and the ultimate necessity of valve replacement.[407-411] Unfortunately, TTE is not 100 percent sensitive in detecting vegetations, and up to 20 percent of patients with proved native-valve endocarditis may have unremarkable examinations.[412] The sensitivity of TTE in prosthetic valve endocarditis has been found to be even lower (approximately 60 percent) due to technical limitations in imaging.[400]

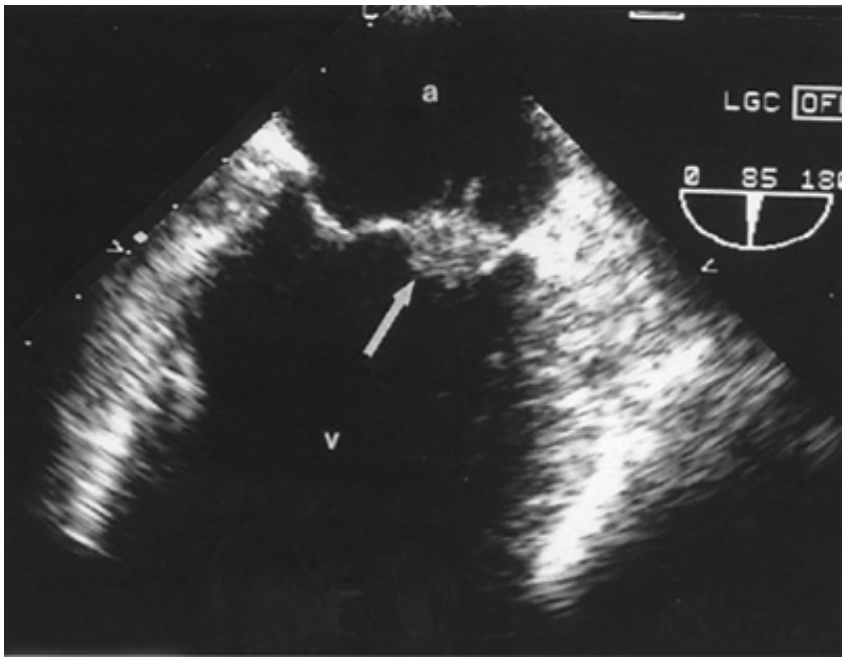

Figure 13-95: Longitudinal TEE view of a large mitral valve vegetation (*arrow*). a = left atrium; v = left ventricle. (Courtesy of William D. Keen, Jr., MD.)

TEE has proved significantly more sensitive than TTE for detection of infective vegetations and is extremely helpful for the diagnosis of perivalvular abscesses, mycotic diverticula, and prosthetic valve involvement.[147,413] The technique is also useful for assessing valvular regurgitation, fistulas (Fig. 13-96), and other hemodynamic complications of endocarditis.[414] Although a negative TEE examination cannot completely exclude infective endocarditis, it confers a relatively good prognosis in those cases where the diagnosis is eventually confirmed.

The optimal use of TEE in suspected endocarditis remains controversial: some authorities recommend routine TEE in all cases, but many do not.[415] A reasonable approach may be to perform TTE as the first screening test in patients with suspected endocarditis. If the study is technically difficult, equivocal, or detects vegetations in patients at high risk for perivalvular complications or hemodynamic compromise, TEE should be performed. If TTE is unremarkable or detects vegetations in patients at low risk for complications, TEE may not be necessary.[149] Exceptions to this last recommendation might include patients with prior antibiotic treatment or those with persistent bacteremia or fever of unknown etiology. In high-risk patients (i.e., with possible prosthetic valve involvement, congenital heart disease, or infection with especially virulent organisms), TEE is recommended even if TTE is normal.[149]

Echocardiographic evaluation of suspected endocarditis is not without pitfalls. It may be quite difficult to detect active vegetations in patients with preexisting valvular abnormalities such as calcification, myxomatous change, rheumatic involvement, and healed vegetations. Despite recent technologic advances, the diagnosis of infective endocarditis remains a clinical one, and over-reliance on echocardiography may cause mistakes. Therefore, *echocardiographic results should be integrated with other clinical information* to diagnose this disorder accurately.[416]

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Chapter 13: THE ECHOCARDIOGRAM

ISCHEMIC HEART DISEASE

Echocardiography in Coronary Heart Disease

Although originally of greatest value in valvular heart disease and cardiomyopathy, echocardiography has now become one of the most important techniques for the detection and quantitative assessment of myocardial ischemia and infarction. Cardiac ultrasound-because it is rapid, portable, noninvasive, and inexpensive-is especially well suited to the evaluation of ischemic heart disease. Although visualization of coronary artery structure and flow has been achieved by echocardiography,[417-420] the application of this technique in ischemic heart disease continues to revolve primarily about the assessment of LV function.

Currently, the primary application of echocardiography in patients with coronary heart disease is based upon the detection of the effects of myocardial ischemia and/or infarction upon LV structure and function. Interruption of coronary flow or imposition of an oxygen demand that exceeds oxygen supply quickly leads to impaired systolic thickening and excursion of the affected myocardium. If flow is not restored and transmural infarction occurs, the affected myocardium may become akinetic or dyskinetic and eventually thinned and fibrotic. In addition, myocardial ischemia produces diastolic dysfunction, which may be detected by analysis of transmitral Doppler flow recordings or endocardial expansion profiles. These changes in the structure, contraction, and relaxation of myocardium are often readily detected by echocardiography.

The echocardiographic detection of myocardial ischemia was initially described using M-mode echocardiography, and this modality remains useful because of its excellent sensitivity and temporal resolution.[421] 2D imaging, however, has now become the primary technique for the examination of LV size, wall thickness, myocardial thickening, and regional wall motion, since it enables visualization of all LV wall segments. Thereby, in patients with CAD, standard echocardiographic approaches can be utilized to calculate LV diastolic and systolic volumes as well as ejection fraction.

The echocardiographic manifestations of CAD consist of one or more of the following: reduction in systolic thickening, abnormal segmental wall motion during systole or diastole, and alterations in the acoustic properties of the myocardium (usually termed *tissue characterization*).[422] These abnormalities may be expressed as a disturbance in global LV size and function, an increase in LV volume, and a decrease in LVEF calculated by standard approaches. In addition, using the standard tomographic planes, the LV can be divided into 16 wall segments according to the format recommended by the American Society of Echocardiography (Fig. 13-97).[423] By grading the contraction of each of the 16 segments as hyperkinetic, normal, hypokinetic, akinetic, or dyskinetic (and assigning a numerical value to each grade), a semiquantitative wall motion score can be calculated as the mean numerical value for all segments. Wall motion scores of this kind have been used to assess prognosis in both acute myocardial infarction[424] and chronic coronary artery disease.[425] When LV dysfunction is detected echocardiographically, the specific coronary artery responsible can often be inferred based upon the dyssynergy region(s).[426,427] The echocardiographic findings of akinesis with segmental myocardial thinning can also be used to distinguish CAD from dilated cardiomyopathy, which typically manifests global hypokinesis and decreased wall thickness. There is overlap in the echocardiographic findings between these two groups, however, as severe ischemic disease may cause global hypokinesis and nonischemic

cardiomyopathy may sometimes cause heterogeneous dysfunction.[428]

Myocardial Infarction and Postinfarction Complications

Cardiac ultrasound has achieved an important role in the evaluation of patients with acute myocardial infarction (MI) and is frequently used for diagnosis, quantitative functional assessment, risk stratification, and detection of complications[424429-432] (see also Chap. 47). Echocardiography is especially valuable in *excluding* transmural infarctions, as these are almost always associated with regional akinesis or dyskinesis (Figs. 13-98, 13-99 and 13-100).[433,434] Non-Q-wave infarctions are more difficult to diagnose with certainty, however, as the echocardiogram may show subtle regional hypokinesis or even normal wall motion in some cases. Thus, echocardiography has been used to evaluate chest pain in the emergency department and appears to have a reasonable sensitivity and specificity in the diagnosis of MI.[433,434] It may also help select patients for thrombolytic therapy.[435] In addition, patients without contractile abnormalities who ultimately exhibit signs of MI have a low incidence of complications.[434]

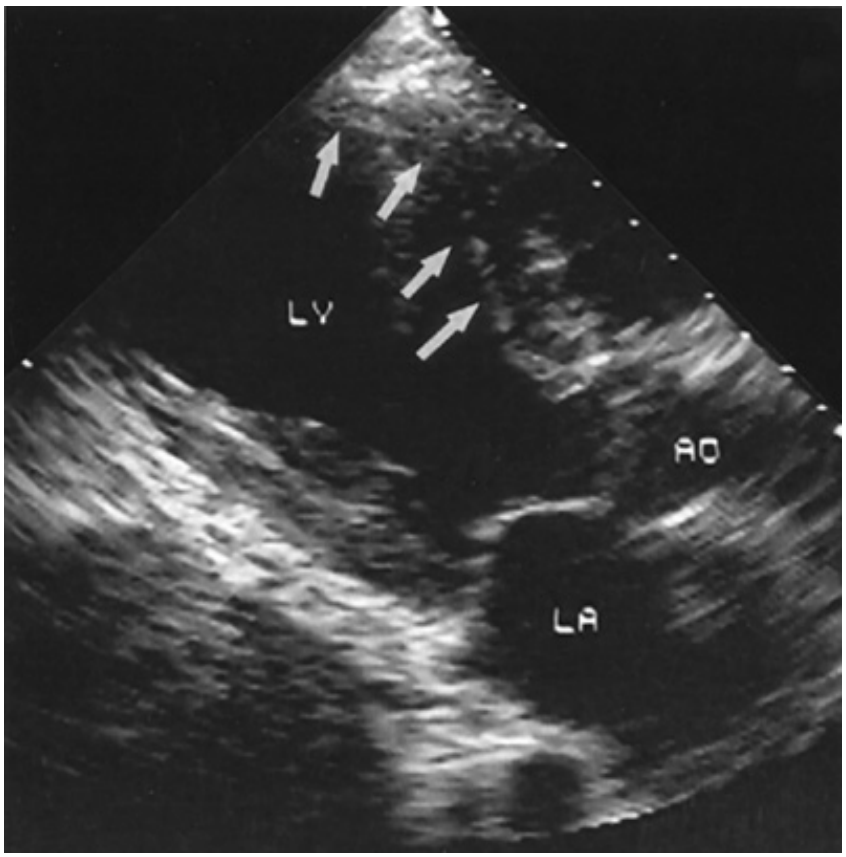

Figure 13-99: Parasternal long-axis view of a large anteroseptal myocardial infarction, with thinning and dyskinesis of the anteroseptal wall (*arrows*). LV = left ventricle; LA = left atrium; AO = aorta.

Echocardiography is now the most commonly utilized approach to assess the effects of MI upon LV function. Ultrasound imaging studies of LV remodeling have demonstrated that infarct expansion occurs commonly with anterior infarctions, often beginning within the first 10 days, and conveys an adverse prognosis.[436,437] Similarly, calculation of the wall motion score has identified a cohort of post-MI patients at markedly increased risk for in-hospital complications.[434] This prognostic marker appears superior to conventional clinical criteria in predicting events.[434]

Echocardiography is probably of greatest value in the assessment of complications associated with acute MI. Most such complications are quickly detected by echocardiography, and the fact that it is portable, rapid, and noninvasive render the technique extremely valuable in these circumstances. As indicated above, severe LV dysfunction resulting in advanced heart failure or shock can be readily identified by echocardiography. In addition, aneurysm formation is usually quite apparent in ultrasonic images.[438] By definition, postinfarction LV aneurysms are recognized as wide-mouthed, thinned-walled myocardial segments that display dyskinetic expansion during systole. Aneurysms are a favored site for development of LV thrombi, which are discussed in detail in the discussion of cardiac masses, below. A less frequent complication is rupture of the LV free wall, which is usually rapidly fatal and therefore rarely imaged by echocardiography.[439] However, the presence of significant pericardial effusion on echocardiography in patients with hemodynamic compromise in the postinfarction period should suggest this condition. If a free wall rupture is sealed off by clot and pericardial inflammation, a pseudoaneurysm is formed[440,441] (Fig. 13-101). This lesion is distinguished from a true aneurysm by its highly localized nature and the presence of a narrow neck connecting it with the ventricle. Pseudoaneurysms frequently have multilayered thrombi within them and exhibit characteristic Doppler flow signals at the junction with the ventricle.[441] Since the risk of rupture is high, accurate diagnosis and prompt surgical repair of pseudoaneurysms is important.

Although postinfarction free wall rupture does not lend itself well to echocardiographic detection, acquired defects of the interventricular septum are more commonly delineated by cardiac ultrasound.[442,443] Acquired ventricular septal defects often consist of a latticework of tissue rather than a discrete orifice, but nevertheless echocardiographic images can depict absence of myocardium and distinct flow jets communicating between the LV and RVs (Fig. 13-102, Plate 68).[444] These color jets are typically high-velocity and aliased, coursing from the septum into the RV. The echocardiographic location of the defect and jet correlate well with the location by cineangiography, surgery, or autopsy, and an apical location is most amenable to surgical correction.[444]

MR is a common sequela of acute MI; if severe, it may result in profound congestive heart failure and shock. Several mechanisms may be responsible for the occurrence of postinfarction MR including dilation of the LV cavity and mitral annulus, papillary muscle dysfunction, and partial or complete rupture of a papillary muscle (Fig. 13-103).[445-447] MR from papillary dysfunction may lead to eccentric color jets within the LA. In general, the recognition and quantitation of MR occurring in the postinfarction period is no different from that of any other type of MR. Acute ischemic MR, however may cause a smaller flow disturbance by color Doppler than comparable grades of chronic MR, particularly with transthoracic imaging. Therefore, TEE may play an important role in the identification and quantitative assessment of this complication, as well as in ensuring adequate operative repair.[447]

In the setting of inferior wall infarction due to occlusion of the proximal right coronary artery, right ventricular MI may occur. The most specific echocardiographic sign of right ventricular infarction is a regional wall motion abnormality, which is usually best visualized in the RV free wall (Fig. 13-104).[448] RV infarction is typically accompanied by RV enlargement and tricuspid regurgitation; associated inferior or posterior left ventricular wall motion abnormalities are virtually always present.

Pericarditis is a common complication of acute MI, typically occurring during the acute phase of the illness and much less often in the late phases as part of Dressler syndrome. Postinfarction pericarditis, however, is not typically associated with marked echocardiographic abnormalities. If a pericardial effusion is present at all, the amount of fluid is usually quite small. Therefore, the absence of pericardial fluid on ECG cannot rule out pericarditis, and the presence of a large effusion with tamponade should raise the suspicion of a LV free wall rupture.

TEE has recently assumed a central role in the evaluation of patients with significant hemodynamic abnormalities in the postinfarction period. When TTE is technically suboptimal, transesophageal images can rapidly identify LV dyssynergy, valvular dysfunction, and other abnormalities associated with infarction. TEE may enable direct visualization of acquired ventricular septal defects when the lesion is not obvious or seen only as a disturbed flow stream in the RV with transthoracic imaging. Perhaps of greatest significance, TEE can provide definitive identification of a ruptured papillary muscle and a quantitative assessment of postinfarction mitral regurgitation.

Echocardiography has been used to evaluate the extent of reperfusion after thrombolytic or interventional therapy for acute MI. Several reports have demonstrated that LV systolic function assessed by 2D imaging improved within 24 h to 10 days of successful thrombolysis.[449,450] More recently, contrast echocardiograms obtained by direct intracoronary injection have shown that reperfusion of the infarct-related epicardial coronary artery by angiography is not necessarily accompanied by evidence of normal flow in the downstream microcirculation. In addition, this "no-reflow" phenomenon on echocardiography heralds a poor prognosis, including failure of improvement of LV performance as well as increased late complications.[208-210,450a]

Stress Echocardiography

Recently, the combination of stress testing and echocardiography (stress echocardiography) has found an important role in the diagnosis of CAD[451-453] (see also Chap. 42). The utility of this technique improved dramatically when technologic advances permitted side-by-side viewing of rest and stress images together in a cine-loop format.[454] The application of stress echocardiography is based upon the concept that a stress-induced imbalance in the myocardial supply/demand ratio will produce regional ischemia and resultant abnormalities of regional contraction, which can be readily identified by echocardiography (Fig. 13-105). The location of wall motion abnormalities may be used to predict the stenosed coronary vessel(s), while the ratio of dyssynergic to normal myocardium can provide a quantitative assessment of LV ischemia.[426,427] Although the digital techniques currently employed limit the number of views available and restrict the examination to eight frames during systole, this process does not seem to impair the ability to identify contractile dysfunction.[455,456]

The types of stress employed fall into two basic groups, exercise and pharmacologic.[426,427] Other forms, such as mental stress and atrial pacing, are not widely used. Exercise testing can be performed either on a treadmill or a stationary bicycle (either upright or supine).[457] Treadmill testing involves a familiar activity, uses equipment that is widely available, and achieves a greater oxygen consumption than bicycle ergometry. Echo imaging usually can be accomplished only before and after treadmill exercise, however, whereas bicycle exertion facilitates the acquisition of images during the exercise protocol. Thus far, treadmill has been the preferred exercise modality. Of importance, all postexertional images should be obtained within a 2-min window following exercise to avoid recording normal contractile function after recovery from ischemia.

Pharmacologic stress has the advantages of reducing the motion artifact of exercise, enabling continuous imaging throughout the protocol, and assessing myocardial viability.[458-469] Pharmacologic stress echocardiography can employ vasodilator agents such as dipyridamole or adenosine, which induce a heterogeneity of myocardial perfusion in ischemic heart disease, or inotropic agents such as dobutamine and arbutamine, which increase myocardial oxygen demand and directly produce ischemia.[458-469] As with exercise stress, diagnostic criteria include induction of regional wall motion abnormalities and LV dilatation. It is important to recognize that the normal response to exercise is hyperkinesis, and wall motion abnormalities may take the form of a lesser degree of hyperkinesis of a given segment in comparison with the rest of the LV myocardium. Dobutamine stress echocardiography appears to be of particular value in detecting

myocardial viability.[455-463,466-469,469a,469b]

The safety and accuracy of stress echocardiography for the diagnosis of myocardial ischemia has been examined in a number of studies.[453,469-472] Both exercise and pharmacologic stress carry an extremely low risk of arrhythmia or infarction, although dobutamine can result in hypotension or *systolic anterior motion of the mitral valve* (SAM) with resultant LV outflow obstruction.[453,473,474] In general, stress echocardiography and nuclear scintigraphy yield similar results, although stress echocardiography may be slightly less sensitive and slightly more specific than scintigraphy.[455,464,475] In a study performed in an institution with high volumes and expertise in both ultrasound and radionuclide stress imaging, the two techniques were found to be comparable in their accuracy of detecting coronary artery disease.[455]

The most common clinical application of stress echocardiography is in the diagnosis of CAD, and it appears especially useful in cases where exercise *electrocardiography* (ECG) may be inaccurate or falsely positive (e.g., abnormal baseline ECG, LV hypertrophy, or chronic digitalis administration).[453,472,476,477] In this regard, stress echocardiography appears especially useful for detection of ischemia in women,[478,478a,478b] in whom stress ECG yields a high incidence of false-positive results. Stress echocardiography also adds independent prognostic information to exercise ECG, even in multivessel CAD.[479] Dobutamine echocardiography may aid in the detection of ischemia in patients with cardiac transplantation and allograft vasculopathy (chronic rejection).[480] In patients with known CAD, exercise echocardiography may facilitate localization and quantitation of ischemia, guide revascularization procedures, and assess the functional severity of coronary artery stenoses.[481] Stress echocardiography can also demonstrate resolution of regional ischemia after successful coronary artery bypass surgery or angioplasty.[482-485]

Stress echocardiography can play an important role in determining the prognosis of patients with CAD.[486-494,494a,494b,494c] Both exercise and pharmacologic stress echocardiography appear superior to exercise ECG for identification of patients at high risk of recurrent ischemic events after MI.[486-491] In addition, dobutamine stress echocardiography is useful in predicting perioperative ischemic complications in patients undergoing noncardiac surgery and appears to have a very strong negative predictive value.[492-494]

In patients with chronic CHD, dobutamine stress echocardiography can identify hypokinetic yet viable myocardium and predicts improvement in function after successful revascularization.[457-463,467,469a,469b,470] Functional improvement in a hypokinetic segment with low-dose dobutamine infusion which then progresses to hypokinesis or akinesis with higher dobutamine dose (the so-called biphasic response) correlates well with the presence of ischemic yet viable ("hibernating") myocardium. Studies have suggested that dobutamine stress echocardiography compares well with positron emission tomography and thallium single-photon emission computed tomography (SPECT) imaging in this regard.[466-468,495-505,501a,501b] It is likely that this application of echocardiography will continue to evolve over time, particularly for pharmacologic stress testing (Chap. 48).

There is evidence that exercise echocardiography can provide useful information regarding the hemodynamic status and functional severity of valvular heart disease.[502-505] Specifically, stress echocardiography has been used to assess the degree of obstruction in patients with MS[503] and to quantitate the severity of AS in patients with advanced LV dysfunction.[505] These data may help guide the timing of surgical valve repair or replacement.

As is true of all diagnostic modalities, stress echocardiography has certain limitations. High-quality ultrasound images may be difficult to acquire in some patients-a situation that may be exacerbated by exertion and the time constraints inherent to exercise stress testing. In addition, considerable expertise is required to interpret stress echocardiographic images accurately, and this

learning curve precludes the use of stress echocardiography by all but experienced echocardiographers. Nevertheless, stress echocardiography has many advantages over alternate diagnostic approaches such as radionuclide scintigraphy and coronary angiography, including its noninvasive and relatively inexpensive nature, rapid acquisition and interpretation times, and freedom from ionizing radiation. Harmonic imaging (both with and without intravenous echocardiographic contrast) has also enhanced endocardial border definition, facilitating stress echo studies in many patients with suboptimal fundamental (nonharmonic) echo images.Therefore it is anticipated that the use of stress echocardiography will continue to increase in the foreseeable future.

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Chapter 13: THE ECHOCARDIOGRAM

THE CARDIOMYOPATHIES

The evaluation of cardiomyopathy is complicated by the fact that few specific diagnostic criteria exist, and identification is often a process of exclusion. Further, many potential etiologies may be responsible for the myopathic process, and it may be possible to identify a specific etiology in only the minority of patients. Accordingly, a diagnostic strategy has evolved that initially seeks to place patients into one of three pathophysiologic categories: dilated, hypertrophic, or restrictive; then, the specific etiologies recognized as producing the individual pathophysiologic state are pursued.[506] Thus, dilated cardiomyopathies are associated with myocyte loss and necrosis, a marked increase in LV volume, thinning of the myocardium, and profound systolic dysfunction.[507] *Hypertrophic cardiomyopathy* (HCM) is recognized by increased myocardial thickness, particularly involving the interventricular septum, with preserved systolic function.[508] Restrictive cardiomyopathies may be due to infiltration of the myocardium by abnormal substances or fibrotic tissue; these cause symmetrical degrees of wall thickening with modest or no diminution of systolic function and little change in cavity size.[509] Echocardiography customarily serves as the cornerstone of such evaluations and provides data on cavity size, wall thickness, and systolic function. Thus, on echocardiogram, patients with dilated cardiomyopathy exhibit a marked increase in left LV and volume, little change in wall thickness, and severe contractile dysfunction.[507] Patients with HCM exhibit a dramatic increase in LV wall thickness, with the septum characteristically disproportionate to the posterior wall, and often subaortic stenosis induced by systolic anterior motion of the anterior mitral valve leaflet. Patients with restrictive cardiomyopathy are identified by a symmetrical increase in wall thickness accompanied by modest changes in contractile function and LV cavity size.[509]

Hypertrophic Cardiomyopathy

HCM is a primary abnormality of the myocardium that exhibits myocyte disarray and unprovoked hypertrophy, often affecting the septum disproportionately[508] (see also Chap. 74). The disorder, which is often transmitted in an autosomal dominant pattern, has been linked to a number of abnormalities in genes that code for myocardial proteins.[510,511] A number of classic echocardiographic findings occur in HCM (Fig. 13-106). The fundamental abnormality on echocardiogram in HCM is LV hypertrophy, which is often severe. Although the hypertrophy may be confined to the septum, it may be concentric or involve any other portion of the LV.[512] The customary classic finding is *asymmetrical septal hypertrophy* (ASH), defined as a disproportionate thickness of the interventricular septum compared to the posterobasal wall with a ratio of greater than 1.3 to 1.[513,514] In some cases the entire septum is hypertrophied, while in others the thickening may be localized to the proximal, mid-, or distal (apical) septum.[515] Asymmetric hypertrophy of the proximal interventricular septum may lead to dynamic LV outflow tract obstruction-*hypertrophic obstructive cardiomyopathy* (HOCM) or *idiopathic hypertrophic subaortic stenosis* (IHSS). Although ASH is almost always present in cases of dynamic LV outflow tract obstruction, it is not a specific marker for HCM and may occur in some patients with RV hypertrophy, inferior MI, and a minority with hypertensive LV hypertrophy.[516] In general, the more extensive the hypertrophic process, the more severe the symptoms. Extent of hypertrophy, however, does not appear to correlate well with risk of sudden death, as patients with minimal hypertrophy may still be at significant risk.[517]

The second characteristic finding of HCM is systolic anterior motion of the mitral valve, or SAM,

which usually involves the anterior mitral valve leaflet. Posterior-leaflet SAM also has been reported in HCM, as have a variety of mitral valve deformities.[518,519] Encroachment of the pathologically thickened septum upon the LV outflow tract creates a pressure drop by a Venturi effect, which draws the mitral leaflets toward the septum, creating dynamic (subaortic) LV outflow obstruction (Fig. 13-106). Recent work has also demonstrated the important effects of papillary muscle position and chordal tension on systolic mitral morphology and SAM.[520] Because of distorted mitral coaptation during systole, SAM generally causes MR of variable severity. The severity and duration of SAM directly influence the degree of both outflow tract obstruction and mitral regurgitation.[521] Like asymmetrical septal hypertrophy, SAM (especially systolic motion of the chordae) is not pathognomonic for HCM, having been reported in other conditions such as hypovolemia, anemia, and states where LV outflow tract narrowing and hyperdynamic contraction are present.[522,523]

The third manifestation of classic HCM is midsystolic closure of the aortic valve.[524] This finding is best seen on M-mode recordings, occurs only in the presence of outflow tract obstruction, and is probably a manifestation of the sudden pressure drop during mid- and late systole caused by SAM. As with ASH and SAM, midsystolic aortic closure is not specific for HCM and can occur in MR, aortic root dilatation, ventricular septal defect, and discrete subaortic stenosis.[525,526] When HCM is present, however, midsystolic aortic valve closure suggests significant outflow tract obstruction.

The fourth important abnormality of HCM is observed on Doppler examination of the LV outflow tract (LVOT). Normally, Doppler interrogation of this area produces a spectral tracing that peaks early in systole and has a maximum velocity of less than 1.7 m/s. In many patients, HCM creates a high-pressure gradient coincident with SAM, which is detected by Doppler as a high-velocity systolic jet in the LVOT. As opposed to valvular aortic stenosis, however, the maximal velocity in obstructive HCM peaks late in systole, creating a characteristic "saber-tooth" pattern (Fig. 13-107).[527-530] Although the subaortic gradient can be estimated using the modified Bernoulli equation,[529,530] the assumptions used in this equation may not apply to HCM, as intraventricular gradient calculations can be spuriously high because of the phenomenon of pressure recovery.[531] Similar Doppler patterns also may be seen occasionally within the LV in patients with HCM if systolic obliteration of the hypertrophied LV causes localized areas of high flow velocity in the more distal portions of the ventricular cavity.[527]

Diastolic dysfunction has been long recognized in HCM. Doppler interrogation of LV inflow often reveals a relaxation abnormality, with a reduced early diastolic (E) velocity, a prolonged deceleration slope of the E wave, and an increased velocity of the atrial systolic (A) component.[532,533] Color Doppler imaging can be used to demonstrate intraventricular flow characteristics.[534]

Dilated Cardiomyopathy

In cases of *dilated cardiomyopathy* (DCM), the heart is typically greatly enlarged and systolic function is markedly depressed (see also Chap. 66).[535] Four-chamber dilatation is a common but not uniform finding, as some patients may have relatively preserved RV size (this may confer an improved prognosis).[536] Marked LV enlargement and generalized dysfunction can also be caused by severe ischemic heart disease, chronic alcohol abuse, various infectious myocarditides, anthracyclines and other cardiotoxic agents, nutritional deficiencies, and hereditary myopathies.[537,538] Severe ischemic disease is often segmental and has been reported to spare the posterior wall frequently,[539] while the LV dysfunction of DCM is usually global. The typical constellation of echocardiographic findings in DCM include an increased LV end-diastolic diameter and volume with decreased fractional shortening, thinning of the LV walls (Fig. 13-108), increased E point-septal separation, LA enlargement, and limited mitral and aortic valve opening

(due to low stroke volume).[535,540] Intracardiac thrombi are frequently observed and are most often found in the LV apex.[540] M-mode imaging of the mitral leaflets may demonstrate a "B bump," or notch just before systolic valve closure, indicating elevated LV diastolic pressure (Fig. 13-8). The cardiac valves are usually normal, but mitral annular dilatation and secondary MR are common.

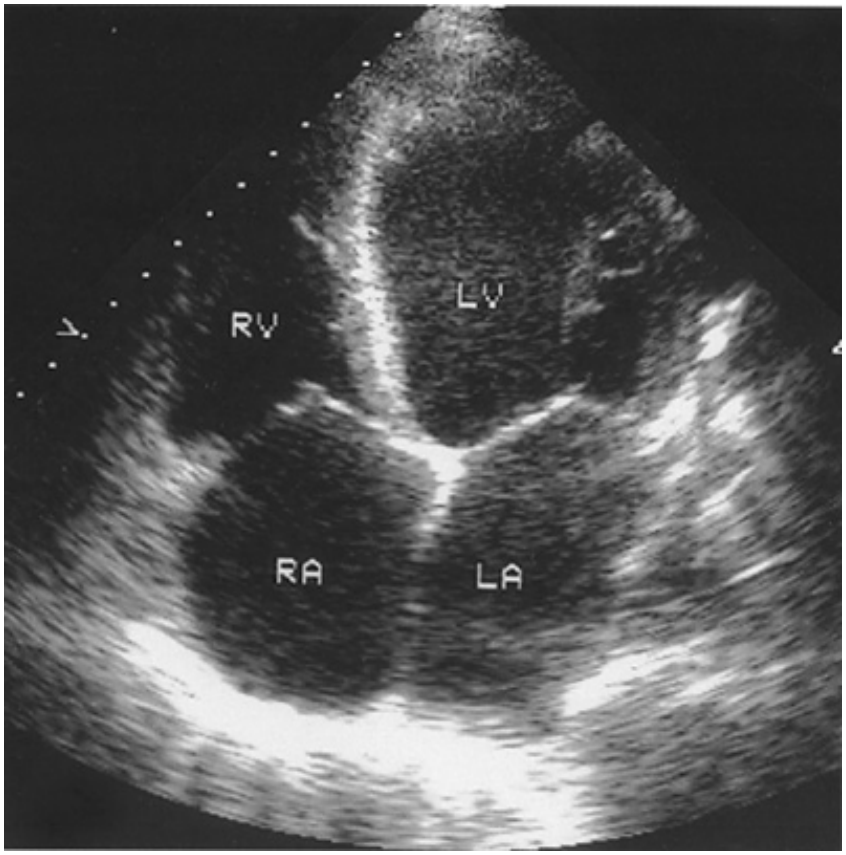

Figure 13-108: Apical four-chamber image of dilated cardiomyopathy. There is four-chamber enlargement as well as left ventricular (LV) spontaneous echo contrast. RV = right ventricle; RA = right atrium; LA = left atrium.

Doppler echocardiography often reveals an abnormally low-velocity time integral in the LV outflow or inflow tracts.[541] Diastolic MR due to elevated LV diastolic pressure also may be present. Diastolic dysfunction is common, and pulsed-wave Doppler interrogation of mitral inflow may show an abnormal relaxation, restrictive, or pseudonormal pattern depending on LV diastolic pressures and loading conditions.[541,541a] A restrictive pattern of mitral inflow Doppler confers a poor prognosis in patients with DCM.[542,543]

Restrictive Cardiomyopathy

Restrictive cardiomyopathy may be idiopathic or secondary to infiltrative diseases such as amyloidosis, hemochromatosis, hypereosinophilic syndrome and Loeffler endocarditis, sarcoidosis, radiation toxicity, glycogen storage diseases, and Gaucher disease[544] (see also Chap. 75). Typical 2D echocardiographic features of these diseases include (1) a diffuse increase of ventricular thickness in the absence of marked ventricular chamber dilation and (2) marked biatrial enlargement[509,545-549] (Fig. 13-109). Systolic function is often modestly decreased. As with the other cardiomyopathies, these echocardiographic findings are nonspecific. Doppler

examination may show a mitral inflow relaxation abnormality early in the course of restrictive cardiomyopathy, but restrictive pattern (E much greater than A, with shortened E deceleration time) is a more classic finding, which often evolves with time and indicates both a high LA pressure and poor prognosis.[550]

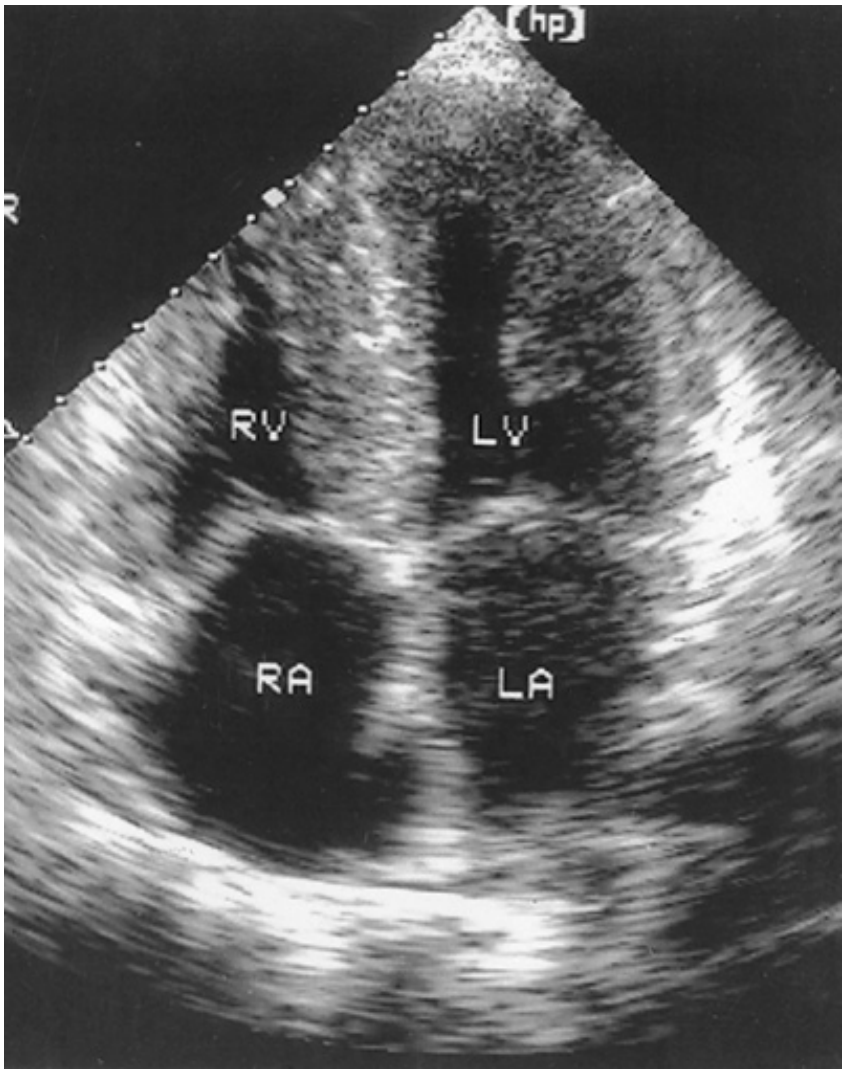

Figure 13-109: Apical four-chamber image of cardiac amyloid. RV = right ventricle; RA = right atrium; LA = left atrium; LV = left ventricle.

Amyloidosis is generally the most commonly encountered restrictive cardiac disease. In addition to biventricular hypertrophy, amyloidosis is also associated with diffuse thickening of the interatrial septum and cardiac valves.[549] In advanced disease, depressed systolic function is also common. An abnormal "speckled" pattern or "ground-glass" appearance of the myocardium has been described on 2D echocardiography, but this sign is absent in many cases and therefore has minimal clinical usefulness.[547,549] The finding of a restrictive mitral inflow pattern (and an abnormally high diastolic component of pulmonary vein inflow) on Doppler echocardiography has been identified as a marker of advanced disease and poor prognosis.[551,552] In addition to increased myocardial thickness, endocardial thickening and fibrosis and restricted atrioventricular leaflet motion are common features of Loeffler endocarditis and endomyocardial fibroelastosis.[548] Intraventricular thrombi are also common in these processes.[553]

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Chapter 13: THE ECHOCARDIOGRAM

CONGENITAL HEART DISEASE

Echocardiographic Identification of Congenital Cardiac Anomalies

2D and Doppler echocardiography has had a major impact on the diagnosis and management of patients with congenital heart disease (see also Chaps. 63 and 64). From isolated congenital lesions to complex, extensive cardiac malformations, echocardiographic imaging (often with intravenous contrast injection) is usually sufficient to delineate cardiac anatomy. TEE is an important adjunctive technique as well[554]; in many cases, a thorough echocardiographic evaluation may obviate the need for cardiac catheterization and angiography.[555-557]

The ultrasound diagnosis of a simple intracardiac shunt is usually straightforward, but the task of defining complex congenital cardiac abnormalities can be daunting. In these cases, it is useful to remember a few basic anatomic rules. The venae cavae and pulmonary veins generally empty into the morphologic right atrium and LA, respectively. The atrioventricular valves uniformly follow their ventricles through embryologic development: a tricuspid valve accompanies the morphologic right ventricle and a mitral valve accompanies the left. Similarly, the semilunar valves follow the great vessels. The aorta and pulmonary artery can be distinguished, regardless of their position, by the bifurcation of the pulmonary artery.

Several features aid identification of the morphologic right and left ventricles. The right ventricle has a tricuspid atrioventricular valve; in comparison with the mitral annulus, the tricuspid annulus is positioned slightly closer to the cardiac apex.[558] The right ventricle also has a moderator band, coarser trabeculations than those in the left ventricle, and an infundibulum that separates the inlet area from the right ventricular outflow tract.

Cardiovascular Shunts

ATRIAL SEPTAL DEFECT

Most secundum and primum *atrial septal defects* (ASD) are easily visualized by echocardiography, although sinus venous defects are often difficult to detect without TEE.[559,560] Apical echocardiographic views often show artifactual "dropout" in the region of the fossa ovalis, since the interatrial septum is thin in this area and runs parallel to the ultrasound beam. Therefore, the subcostal view provides the optimal imaging plane to detect lesions of the atrial septum.[561] Ostium secundum defects are the most common form of ASD, and 2D imaging shows a localized absence of septal tissue in the midportion of the interatrial septum (Fig. 13-110*A*, Plate 69). Lack of any interatrial septal tissue between the defect and the base of the interventricular septum characterizes an ostium primum defect (Figure 13-110*B*). Although ostium secundum defects are usually isolated, ostium primum (or partial AV canal) defects are often accompanied by other lesions, such as cleft anterior mitral valve leaflet, MR, and atrioventricular canal ventricular septal defect.[562] Sinus venosus defects are strongly associated with partial anomalous pulmonary venous return (for example, drainage of the right upper pulmonary vein into the right atrium or superior vena cava) (Fig. 13-111). Rarely, the atrial septum may be completely absent (Fig. 13-112). With all but small ASDs, the right atrium is enlarged and RV volume overload is present, with a dilated RV and paradoxical septal motion.[563]

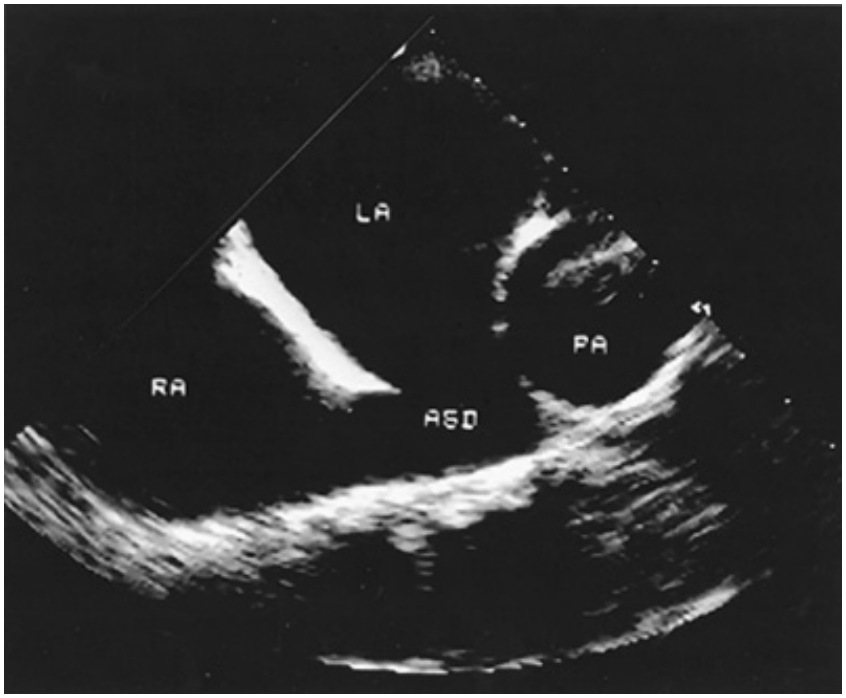


Figure 13-111: Transesophageal image of a sinus venosus atrial septal defect (ASD) (longitudinal plane). The defect is present in the superior portion of the interatrial septum. RA = right atrium; LA = left atrium; ASD = atrial septal defect; PA = pulmonary artery.

Intravenous contrast injection generally demonstrates shunting across the ASD, frequently with bidirectional flow.[564] Therefore, "negative jets" of unopacified flow from the left atrium into the contrast-filled right atrium may alternate with the appearance of contrast bubbles flowing through the defect into the LA. When an ASD is present, contrast should appear quickly (within three to five heartbeats) in the LA after entering the right atrium. Delayed appearance of contrast in the LA may indicate an intrapulmonary shunt rather than an ASD.

Color Doppler imaging is also useful for detecting flow through ASDs (Fig. 13-110*A*, Plate 69), although the pressure drop between atria often does not produce turbulence. Inflow from the inferior vena cava and right-sided pulmonary veins may be prominent in normals and can be misinterpreted as a shunt.[565,566] Pulsed-wave Doppler recordings usually reveal continuous flow, which peaks in late systole. Pulmonary-to-systemic flow ratios can be estimated in ASD (and ventricular septal defects) by comparing volumetric flow measurements through the LV and RV outflow tracts. Such calculations are only moderately accurate in adults.[567,568]

VENTRICULAR SEPTAL DEFECT

Ventricular septal defects (VSDs) may be classified as perimembranous, inlet, outlet, or trabecular. Echocardiography is quite useful for the detection and classification of VSDs.[569-571] The defect itself is sometimes visible with 2D imaging alone (Fig. 13-113*A*), but smaller VSDs are easily missed. Complete absence of the interventricular septum (single ventricle) is quite rare (Fig. 13-113*B*). Pulsed- or continuous-wave Doppler interrogation often reveals discrete areas of high-velocity flow across the interventricular septum. Measurement of the peak CW velocity through the shunt allows calculation of the interventricular pressure gradient (via the modified Bernoulli equation); subtraction of this gradient from the systolic blood pressure (in the absence of aortic valve disease) approximates the RV systolic pressure.

Overall, color-flow imaging is the most useful Doppler technique for the diagnosis of VSDs.[571] Typically, a high-velocity systolic color jet is seen traversing the interventricular septum, although the velocity is lower with large defects and in the presence of pulmonary hypertension (Fig. 13-114, Plate 70). The appearance of the color jet in the standard imaging planes can be used to determine the type of VSD. Intravenous contrast injection may reveal a negative contrast jet in the right ventricle, and contrast may cross the defect and partially opacify the left ventricle. In the absence of MR, contrast will not enter the left atrium, distinguishing an isolated VSD from an ASD. Doppler echocardiography can also be used to detect abnormalities associated with VSDs, such as ventricular septal aneurysm, MR and TR, ASD (especially with inlet VSDs), aortic insufficiency-with outlet (supracristal) VSDs-and "straddling" of the defect by the mitral or tricuspid valve.[572,573] Accurate detection of such lesions is especially critical before surgical intervention.

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus originates just to the left of the PA bifurcation and inserts into the aorta slightly distal to and opposite from the ostium of the left subclavian artery. Given this posterior location, it is difficult to image a *patent ductus arteriosus* (PDA) itself with 2D TTE alone, and TEE is usually superior for direct visualization of the lesion[574] (Fig. 13-115*A* and *B*, Plate 71). In most cases, 2D imaging of the communication is not essential, as color-flow Doppler reliably detects high-velocity diastolic flow within the PA in nearly all non-Eisenmenger patients.[575-577] The flow jet characteristically enters the distal left region of the main PA and streams anterior along the medial wall of the vessel (Fig. 13-115*B*, Plate 42*B*). With large shunts, volume overload and subsequent dilation of the left ventricle occurs. Aortopulmonary window is a much rarer shunt involving the great vessels which presents as a communication anteriorly between the ascending aorta and proximal PA.[578,579] It is embryologically distinct from a PDA and more closely related to a truncus arteriosus defect.

Venous Inflow Abnormalities

Anomalous pulmonary venous return (APVR) may be partial or total. Partial APVR is present in 80 percent of sinus venosus ASD cases and is a feature of the Scimitar syndrome.[580,581] The usual finding on TTE is RV volume overload. TEE is quite useful in detecting these abnormal venous connections. In total APVR, the pulmonary veins may empty directly into the right atrium or into a common posterior chamber or vein. This structure and its connection with the right atrium may be visualized echocardiographically, along with the obligatory ASD.[582-585] In some cases, the collecting chamber posterior to the left atrium may mimic the appearance of *cor triatriatum*, an entity characterized by a membrane in the posterior left atrium which may obstruct pulmonary venous inflow, causing symptoms similar to those of mitral stenosis[586] (Fig. 13-116).

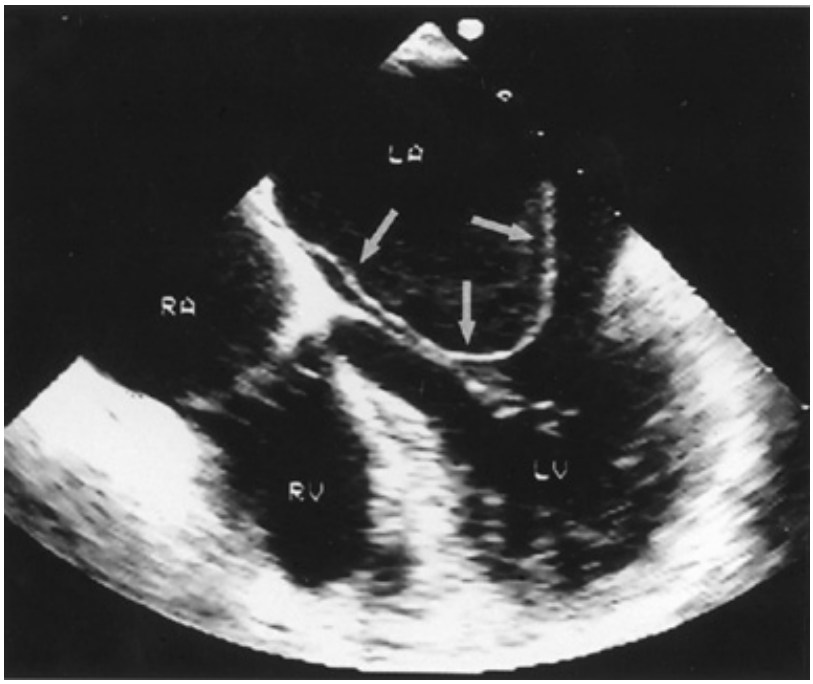
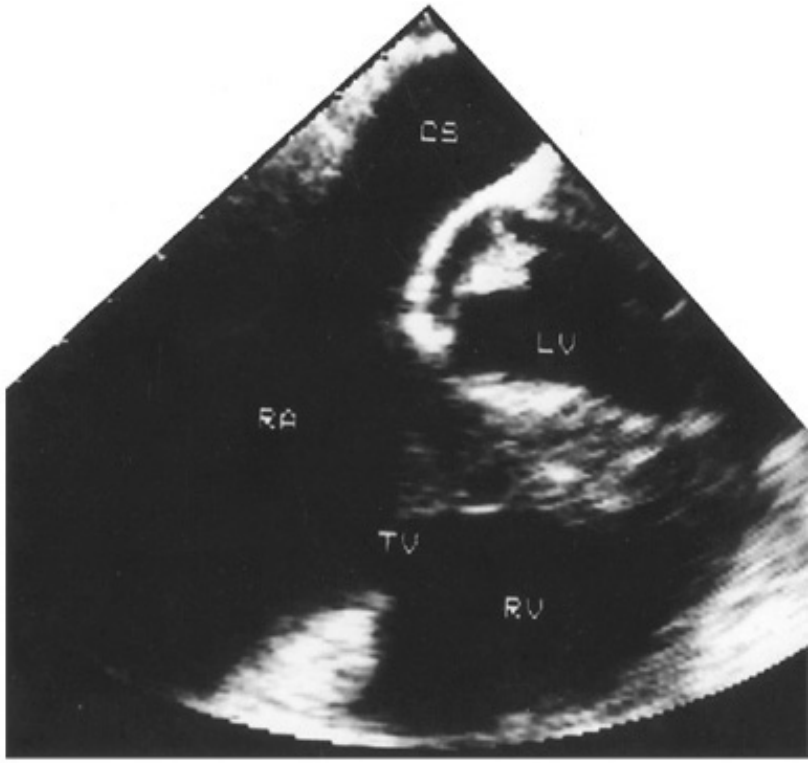


Figure 13-116: Transverse transesophageal image of cor triatriatum. A membrane (*arrows*) is present in the left atrium. RV = right ventricle; RA = right atrium; LA = left atrium; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Persistent left superior vena cava occurs in 0.5 percent of the normal population.[587,588] In most cases, the anomalous vein empties into the coronary sinus, which then drains into the right atrium (Fig. 13-117). Unless the coronary sinus is unroofed and drains into the left atrium, no shunting occurs. The typical echocardiographic finding is a large coronary sinus, which is especially well seen on transesophageal or parasternal transthoracic views. The diagnosis may be confirmed by intravenous contrast injection from the left arm, as this will opacify the coronary sinus shortly before filling the right atrium.[587,588]



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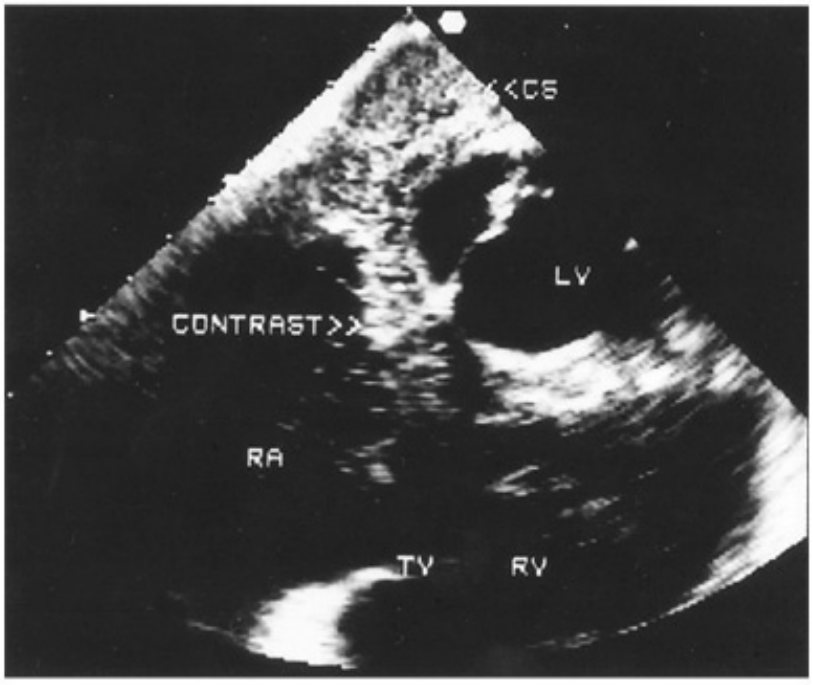
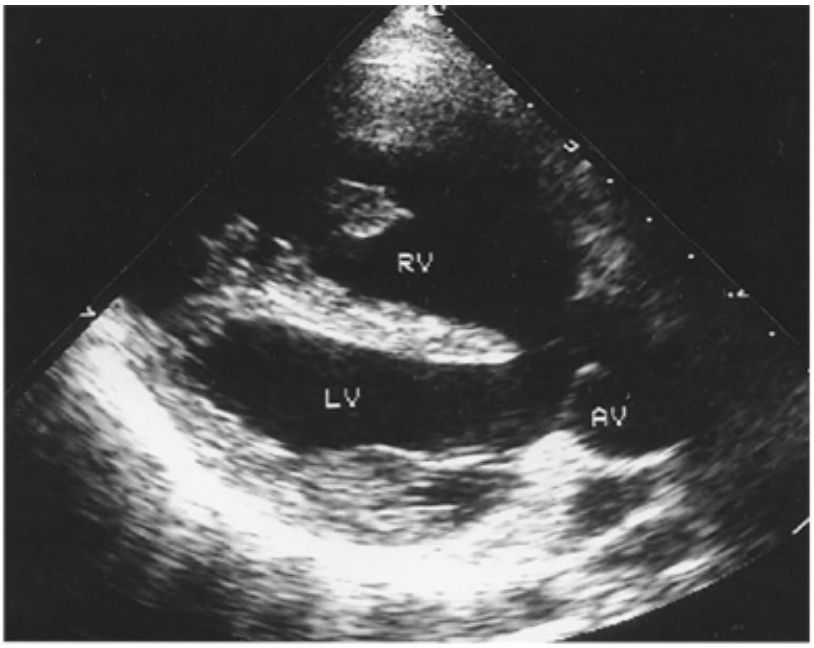


B

Figure 13-117: *A.* Transesophageal image (transverse plane) from a patient with persistent left superior vena cava. The coronary sinus (CS) is dilated. *B.* After injection of agitated saline into the left antecubital vein, contrast is seen entering the right atrium (RA) via the CS. TV = tricuspid valve; RV = right ventricle; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Conotruncal and Aortic Abnormalities

Tetralogy of Fallot is one of the more common conotruncal abnormalities, and affected individuals may sometimes survive to adulthood without surgical intervention. The classic echocardiographic features include a large perimembranous VSD, an anteriorly displaced aorta which overrides the VSD, RV enlargement and dysfunction, and pulmonic stenosis (either infundibular, valvular, or suprevalvular) (Fig. 13-118).[589,590] The VSD and aorta are well visualized in the parasternal long-axis view, while the RV outflow tract and proximal PA are best seen in the parasternal short-axis view at the base of the heart. Doppler interrogation can provide evaluation of the severity of pulmonic stenosis, both before and after surgery. Echocardiography may aid detection of infants with tetralogy who will require early surgical intervention as well as patients who are at high risk for sudden death after surgical repair.[591,592]



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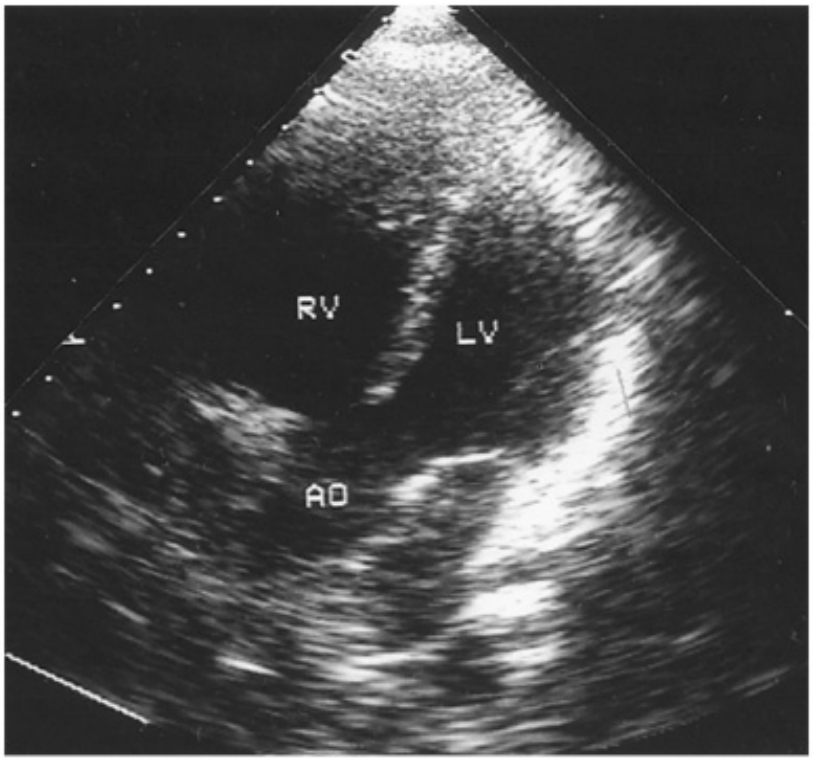

B

B

Figure 13-118: Parasternal long-axis (*A*) and apical four-chamber (*B*) images of tetralogy of Fallot. The right ventricle (RV) is enlarged, and a large VSD is present. The aorta (AO) overrides the interventricular septum. LV = left ventricle. (Courtesy of Reinaldo W. Beyer, MD.)

Although *double-outlet right ventricle* (DORV) shares several clinical characteristics with tetralogy of Fallot (VSD and anterior aortic displacement are invariably present, and pulmonic valvular stenosis and ASD are common in both), it is morphologically distinct (Fig. 13-119). Normal continuity of the posterior aortic wall with the anterior mitral valve leaflet (always present in tetralogy of Fallot) is absent in DORV, and an interposed mass of fibrous tissue between the left atrium and the nearest great vessel is seen on 2D imaging.[593,594] In addition, the great vessels may be transposed in DORV, resulting in a characteristic side-by-side appearance of the aorta and PA on parasternal short-axis images.[595]

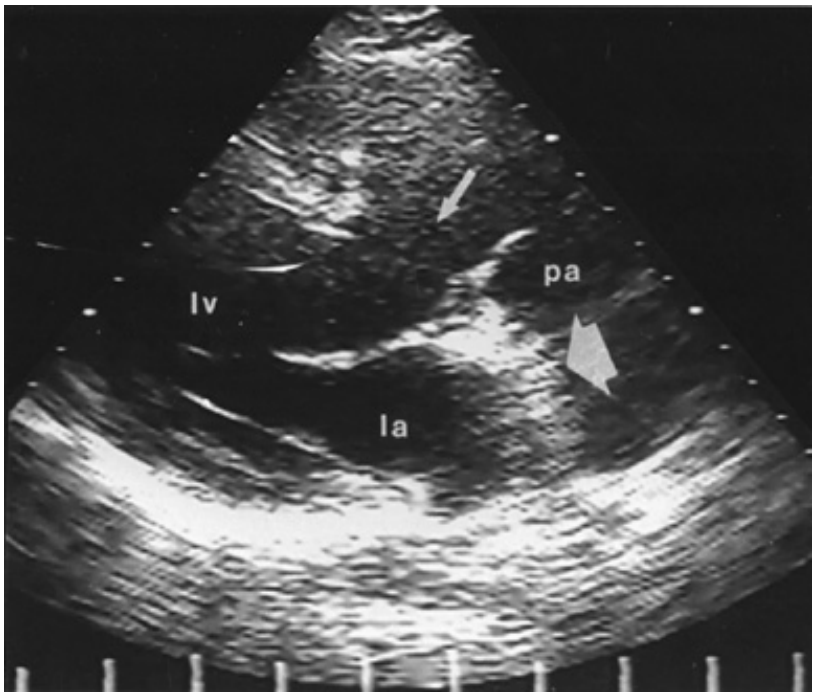

Figure 13-119: Parasternal long-axis image of double-outlet right ventricle. A large VSD is present (*small arrow*) and the normal continuity between the posterior aortic wall and the anterior mitral leaflet is absent. Fibrous tissue is seen (*large arrow*) between the left atrium (LA) and the nearest great vessel (in this case, the pulmonary artery (PA). LV = left ventricle.

Echocardiography has become a valuable tool for detection, management, and postoperative follow-up of patients with *transposition of the great arteries.* Attention to the anatomic rules mentioned earlier is essential for accurate diagnosis of both D (classic) and L ("congenitally corrected") transposition. In D-transposition, the aorta arises from the RV, the PA arises from the LV, and one or more obligatory shunts are present. With L-transposition, the morphologic right and left ventricles are switched, and associated anomalies such as VSD and pulmonic stenosis are common. In both types of transposition, the normal echocardiographic orientation of the great vessels on parasternal short-axis images (a sausage-shaped RVOT and PA draped over a circular aorta) is no longer present, and the two great vessels are typically side by side and parallel (Fig. 13-120).[596,597] In general, the aorta is anterior and to the right of the PA in D-transposition and anterior and to the left in L-transposition. Both TTE and TEE are an important part of continuing

care after surgical repair or palliation of transposition; they can detect valvular regurgitation, outflow tract narrowing, and stenosis of the atrial baffle systems used to palliate D-transposition surgically.[598-600]

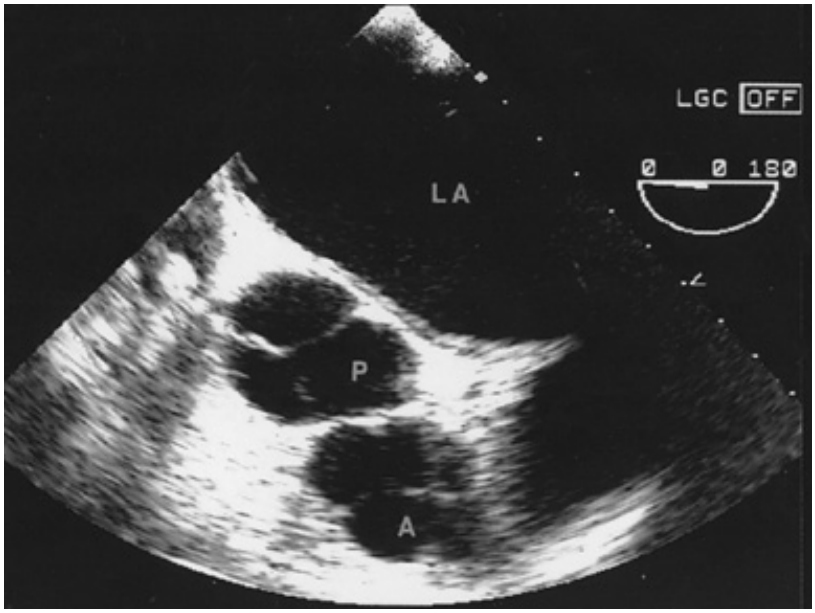

Figure 13-120: Transverse transesophageal image through the semilunar valves in L-transposition. The aortic valve (A) is anterior and to the left of the pulmonic valve (P). LA = left atrium.

Truncus arteriosus is a rare anomaly characterized by a large VSD, a single semilunar valve, and a single great vessel that divides into the ascending aorta and PA.[601,602] Ultrasound imaging can determine the anatomy of the great vessels and assist in defining the various subsets of truncus arteriosus.

Coarctation of the aorta is associated with a bicuspid aortic valve and is best visualized from the suprasternal position. 2D imaging may identify the site of coarctation, but the natural mild curving of the descending aorta can occasionally lead to a false-positive diagnosis. Clear visualization of narrowing in the proximal descending aorta with poststenotic dilatation, however, is pathognomonic of coarctation.[603,604] Doppler interrogation from the suprasternal notch demonstrates increased systolic velocity in the descending aorta and may also reveal a persistent flow gradient throughout diastole in cases of severe coarctation (Fig. 13-121).[605] Color imaging often displays flow acceleration and aliasing proximal to the site of coarctation. The maximum velocity through the coarctation can be used to estimate the pressure gradient, and this measurement can be particularly valuable for the detection of restenosis after surgical repair or percutaneous balloon aortic dilatation.[606,607]

Supravalvular aortic stenosis, either isolated or associated with Williams syndrome (Chap. 10), is generally imaged best from the suprasternal and superior parasternal positions. Echocardiography reveals either an hourglass-shaped stenosis of the aorta above the sinuses of Valsalva, diffuse hypoplasia of the ascending aorta, or a focal fibrous ridge at the sinotubular junction.[608] Doppler imaging can help estimate the gradient across the stenosis, and marked aliasing of color-flow imaging in the ascending aorta should raise suspicion of the diagnosis. Thickening of the aortic valve leaflets and stenoses of the coronary ostia are important associated findings that may be detectable by echocardiography.

Ventricular Outflow Tract and Semilunar Valve Abnormalities

RIGHT VENTRICLE

Infundibular stenosis is rare outside the setting of tetralogy of Fallot and is much less common than valvular PS. On 2D imaging, muscular hypertrophy is often visualized proximal to the pulmonary artery, while Doppler interrogation reveals increased flow velocities through the infundibulum.[609] PS is reasonably common and may be either isolated or associated with other congenital lesions (such as VSD, transposition, and tetralogy of Fallot). Typical echocardiographic features include thickening of the leaflets, restricted leaflet motion, systolic doming of the valve, and elevated systolic flow velocity on Doppler[610] (Fig. 13-85). As with other stenotic lesions, the gradient can be estimated using the modified Bernoulli equation. The pulmonic valve is best visualized in the parasternal short-axis view through the base (or a modified parasternal view of the RVOT). In children, the subcostal position frequently provides excellent visualization of the RVOT and pulmonic valve. When TTE is suboptimal, TEE can provide detailed images of the pulmonic valve. In pulmonic stenosis, the valve leaflets may calcify over time, and poststenotic dilatation of the pulmonary artery is often present.

LEFT VENTRICLE

Subvalvular obstruction may be dynamic or fixed. *Hypertrophic cardiomyopathy*, which may present at any age, is discussed earlier in this chapter. Discrete *subaortic stenosis* may be caused by a thin membrane in the LV outflow tract, a fibromuscular ridge, or diffuse muscular narrowing of the outflow tract (Figs. 13-122*A* and *B*, Plate 72).[611] 2D echocardiographic imaging can distinguish these various forms of discrete subvalvular stenosis, and Doppler analysis permits estimation of the systolic gradient.[612] Color-flow imaging demonstrates increased turbulence in the LVOT as well as aortic valvular regurgitation in about 50 percent of cases. Apical views are sometimes more useful for detecting thin subaortic membranes, as these structures are parallel to the ultrasound beam on parasternal images (Fig. 13-122). Subaortic fibromuscular ridges are sometimes associated with anomalous mitral valve chordae connecting the papillary muscles or the anterior mitral valve leaflet to the septum.[613,614] M-mode imaging may reveal midsystolic partial closure of the aortic valve, differentiating subvalvular from valvular AS.

Bicuspid aortic valve is the most common congenital cardiac lesion in adults and is present in 1 to 2 percent of all individuals (men are affected more often than women).[615,616] Initially, eccentric diastolic coaptation of the aortic cusps was reported on M-mode in patients with bicuspid valves. However, M-mode findings are less accurate than 2D imaging, and the parasternal short-axis view is generally best for defining the fish-mouthed systolic aortic valvular anatomy (Figs. 13-60 and 13-61). Bicuspid valves are sometimes easy to detect in diastole as well, but raphes and remnants of commissures may obscure the diagnosis and mimic a trileaflet valve. In general, asymmetry of the aortic leaflets suggests congenital deformation. In equivocal cases, multiplane TEE is usually diagnostic (Fig. 13-61).

Ventricular Inflow Tract Abnormalities

Ebstein's anomaly is a congenital deformity of the tricuspid valve in which the leaflets are displaced into the right ventricle. Associated findings include TR, right atrial enlargement, and ASD.[617,618] 2D imaging typically shows abnormal apical displacement of the septal leaflet insertion, with variable deformity of the leaflet (Fig. 13-123). The anterior leaflet originates from the tricuspid annulus but is elongated and often tethered to the RV free wall by abnormal chordal attachments. The tricuspid deformity and regurgitation are best visualized in the apical four-chamber view, although the subcostal and modified parasternal views also may be helpful.

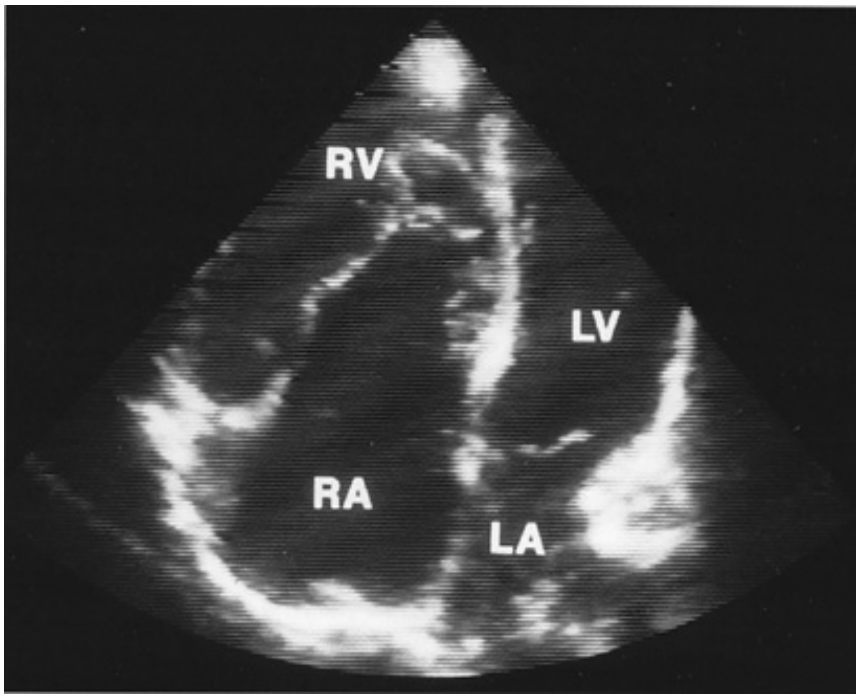

Figure 13-123: Apical four-chamber image of Ebstein's anomaly. The right heart is enlarged, and the insertion of the septal leaflet of the tricuspid valve is displaced apically. The anterior tricuspid leaflet (to the patient's right) is abnormally elongated. RV = right ventricle; RA = right atrium; LA = left atrium; LV = left ventricle. (Reproduced with permission of Joseph A. Kisslo, MD.)

Atrioventricular valvular atresia is usually accompanied by hypoplasia of the corresponding ventricle. Echocardiographic images of tricuspid atresia characteristically show a small, nonfunctional right ventricle, an interatrial communication of variable size, and a normally developed left ventricle. Associated lesions include VSD, transposition, and RV outflow obstruction. Echocardiography is an important tool in the management of patients with tricuspid atresia after palliation with the Fontan procedure. Mitral atresia is associated with a hypoplastic LV. Additional rare congenital mitral anomalies imaged by echocardiography include parachute mitral valve and congenital MS.

Fetal Echocardiography

The average risk for significant heart disease in the fetus is approximately 0.4 to 0.8 percent. Fetal echocardiography has evolved over the past 14 years into a sophisticated method for intrauterine detection of cardiac abnormalities[619] (Fig. 13-124). The technique has been advocated for the preterm diagnosis of congenital heart disease, especially in higher-risk cases [for example, maternal congenital heart disease or diabetes mellitus, maternal teratogen exposure or *t*oxoplasmosis, *o*ther intrauterine infections, *r*ubella, *c*ytomegalovirus, and *h*erpes virus (TORCH) infection, and familial syndromes that may affect the heart].[620] Fetal echocardiography has successfully identified a variety of congenital lesions including atrial and ventricular septal defect, pulmonic stenosis, transposition, tetralogy of Fallot, hypoplastic left heart, Ebstein's anomaly, and tricuspid atresia.[621] Prenatal detection of these lesions may improve prognosis and guide therapy. Although some have recommended routine limited fetal echocardiography during the second or third trimester,[620] recent reports have suggested a low yield and limited diagnostic accuracy.[622-624] Like many imaging techniques, fetal echocardiography is evolving, and further study is required to define its optimal clinical use.

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Chapter 13: THE ECHOCARDIOGRAM

CARDIAC MASSES, THROMBI, AND TUMORS

Normal Variants and Masses of Uncertain Significance

When an abnormally localized accumulation of dense reflectances appears on the echocardiogram, it is said to represent a mass. Echocardiographic masses may be caused by technical artifacts or anomalous structures, but they are of greatest significance in representing true lesions of the heart such as tumors, thrombi, and vegetations. Echocardiography is the procedure of choice for the detection and evaluation of cardiac mass lesions; often, it is the only modality capable of delineating small lesions such as papillary fibroelastomas.[625] Accordingly, echocardiographic examinations are commonly performed to search for embolic sources, particularly in patients with cerebral ischemic events.

A number of technical artifacts are capable of appearing as masses on echocardiogram. For example, side lobe signals, reverberations, and noise artifact may lead to accumulations of ultrasonic reflectance within the cavities or adjacent to the myocardium of the heart.[20,21] Such structures usually lack distinct borders, do not move appropriately through the cardiac cycle, lack identifiable attachments to endocardial surfaces, and cannot be visualized in all views and at all depth settings. In seeking a way to distinguish artifacts from LV thrombi (a common clinical dilemma) the absence of wall motion abnormalities is of particular value.[626]

Several benign normal variant findings can be observed during echocardiographic examination and must be distinguished from pathologic lesions. Thus, many adults manifest persistence of the eustachian valve (Fig. 13-125), a thin ridge of tissue at the junction of the inferior vena cava and right atrium.[627,628] The eustachian valve appears as a long, linear, freely mobile structure in the right atrium at the mouth of the inferior vena cava and is nearly always benign (although infective involvement has been reported).[629,630] An additional embryonic remnant that may be seen in the posterior right atrium is the Chiari network, which typically appears as a weblike mobile structure.[631,632] In some individuals, RV hypertrophy may produce significant enlargement of the RV moderator band coursing along the interventricular septum to the apex of the RV.[633] Similarly, false chordae tendineae ("heartstrings") can occasionally be visualized as linear structures spanning the LV cavity attached to endomyocardium at both ends (Fig. 13-126).[634,635] Neither of the foregoing lesions has been conclusively associated with morbidity or mortality. On occasion, LV hypertrophy or hypertrophied papillary muscles may simulate cardiac mass lesions.[633] Although TEE provides enhanced sensitivity and resolution in the delineation of cardiac mass lesions, this technique may be associated with variants and artifacts of its own.[636,637]

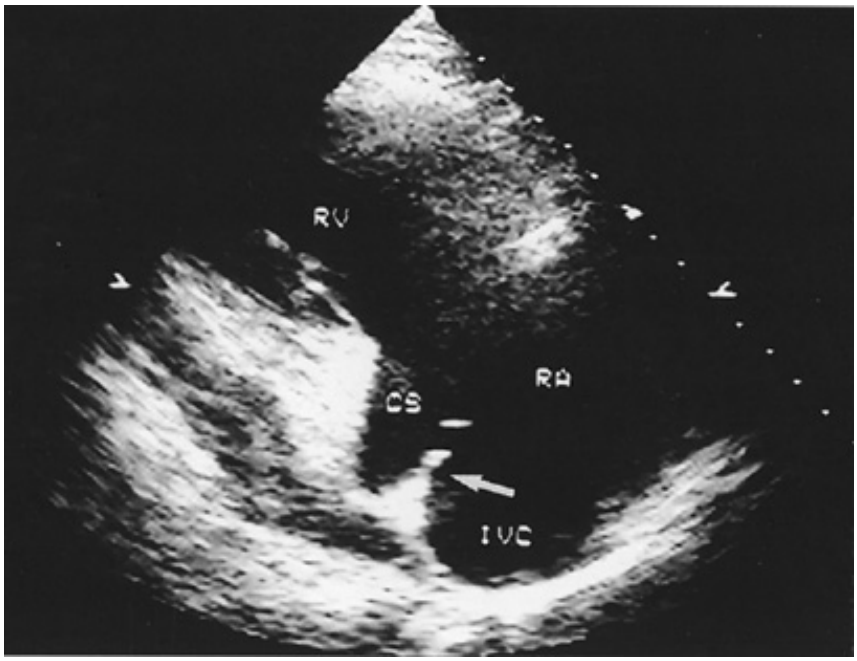

Figure 13-125: Right ventricular inflow view showing a prominent eustachian valve (*arrow*) at the junction of the inferior vena cava (IVC) and the right atrium (RA). RV = right ventricle; CS = coronary sinus. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging,* 2d ed. Philadelphia; Saunders; 1996:452-480, with permission.)

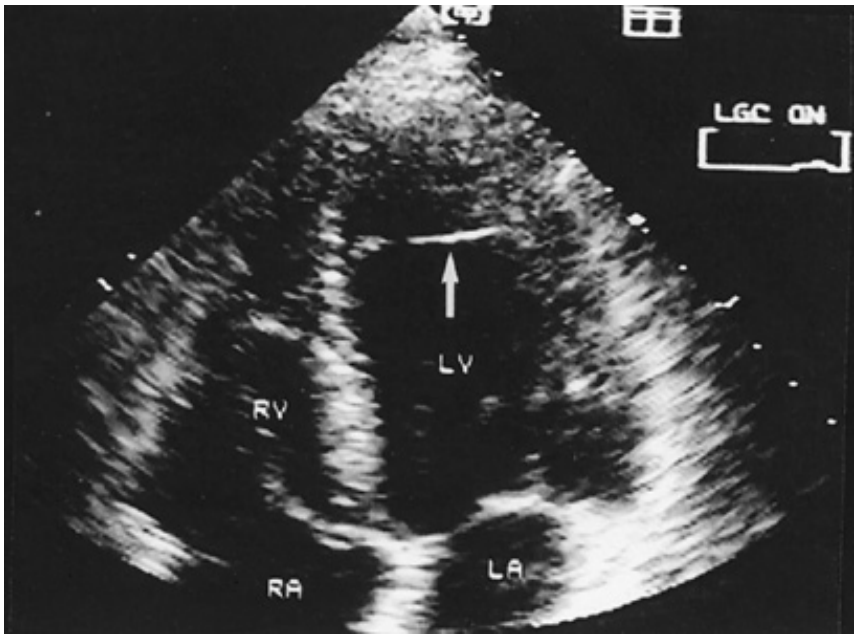

Figure 13-126: Apical four-chamber view demonstrating a false chord (*arrow*) within the left ventricle (LV). LA = left atrium; RA = right atrium; RV = right ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

A variety of foreign bodies and iatrogenically induced anatomic alterations may be visualized on echocardiogram and must be distinguished from pathologic lesions. Intracardiac catheters,

pacemaker leads (Fig. 13-127), prosthetic valves or patches, and atrial suture lines after cardiac transplantation can be visualized during echocardiographic examination.[638,639] These structures are usually easily recognized due to the highly reflective properties of the foreign material, which result in bright echoes, reverberations, and shadowing behind the structures. In this regard, endomyocardial biotomes and pericardiocentesis catheters can be readily visualized by cardiac ultrasound, and echocardiography can be employed to guide procedures utilizing these instruments in lieu of fluoroscopy.[640,641] Last, a variety of manufactured objects that have penetrated the heart have been described on echocardiography, including bullets, pellets, and nails.[642]

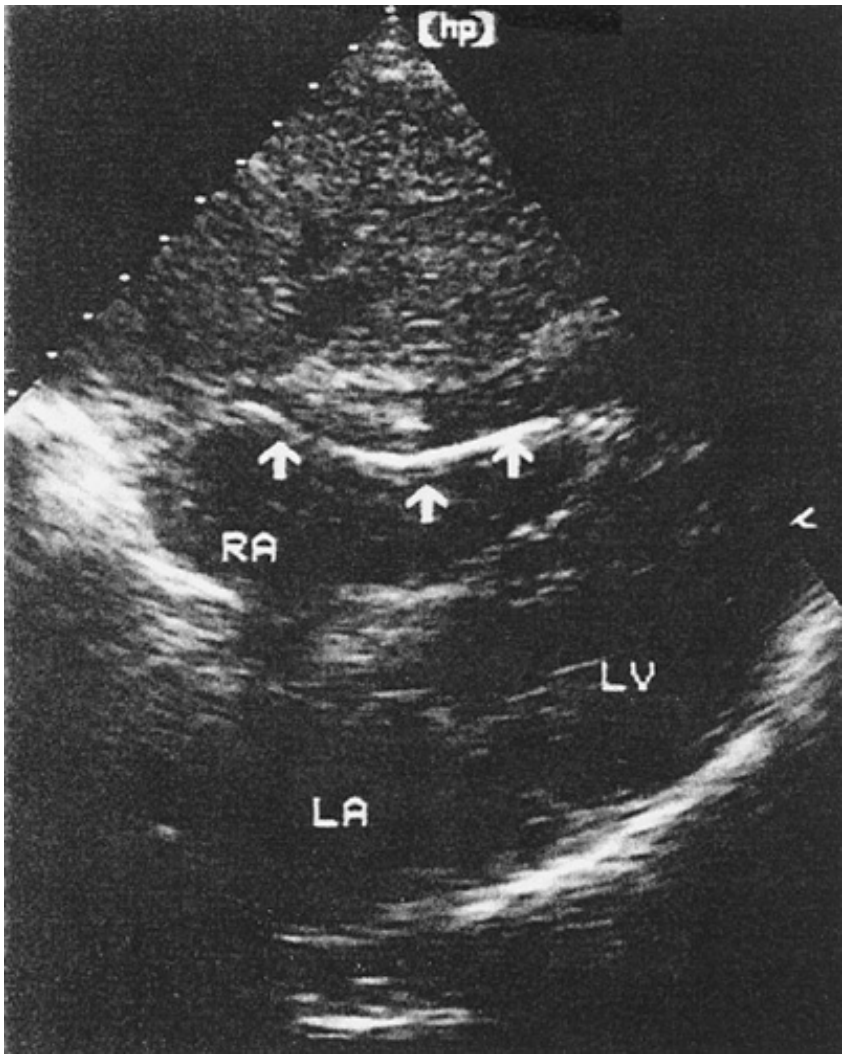

Figure 13-127: Subcostal four-chamber image demonstrating a pacemaker wire (*arrows*) in the right heart. RA = right atrium; LA = left atrium; LV = left ventricle.

Several morphologic changes involving the interatrial septum are often considered under the classification of cardiac mass lesions of uncertain significance. Aneurysms of the interatrial septum have been reported in about 1 percent of the population and are recognized on echocardiogram as a protrusion of the interatrial septum of at least 1.5 cm from its longitudinal plane dividing the left and right atrium (Fig. 13-128).[643,644] Although usually benign, interatrial septal aneurysms are often associated with a patent foramen ovale and have been implicated as a source of cardiogenic emboli.[645] Interatrial septal aneurysms may be detected by TTE, but they are more readily imaged by the transesophageal approach.[644] Lipomatous

hypertrophy of the interatrial septum, or accumulation of adipose tissue within this structure, is not an uncommon finding in elderly individuals. Lipomatous hypertrophy appears as a highly reflective thickening of the interatrial septum that typically spares the foramen ovale, thereby creating a characteristic dumbbell echocardiographic appearance.[646,647] No significant consequences or sequelae have been attributed to lipomatous infiltration of the interatrial septum.

Intracardiac Thrombi

Intracardiac thrombi occur commonly in a variety of cardiovascular disorders, may be visualized in any chamber of the heart, and frequently result in embolic events.[648] The major factors that predispose to the formation of intracardiac thrombi include localized stasis of flow, low cardiac output, and cardiac injury. In addition, migration of venous thrombi may also result in intracardiac clots.[649,650] The appearance of intracardiac thrombi may vary considerably, and although they are typically attached to the endocardium, unrestricted and freely mobile thrombi occasionally may be encountered (particularly in the setting of valvular stenosis which prevents exit of the thrombus from the heart).[651] Thrombi typically have identifiable borders and may be layered and homogeneous or heterogeneous, with areas of central liquefaction (Figs. 13-129 and 13-130).[651,652]

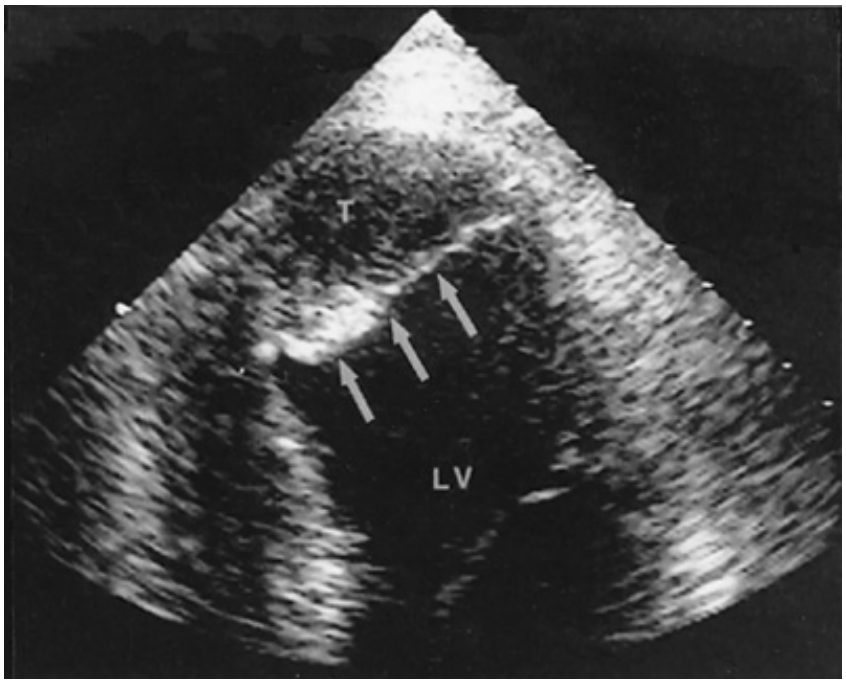

Figure 13-129: Magnified apical view of a large thrombus (T) in the apex of the left ventricle (LV). Although the thrombus is fairly homogeneous, its border is more echo-dense (*arrows*).

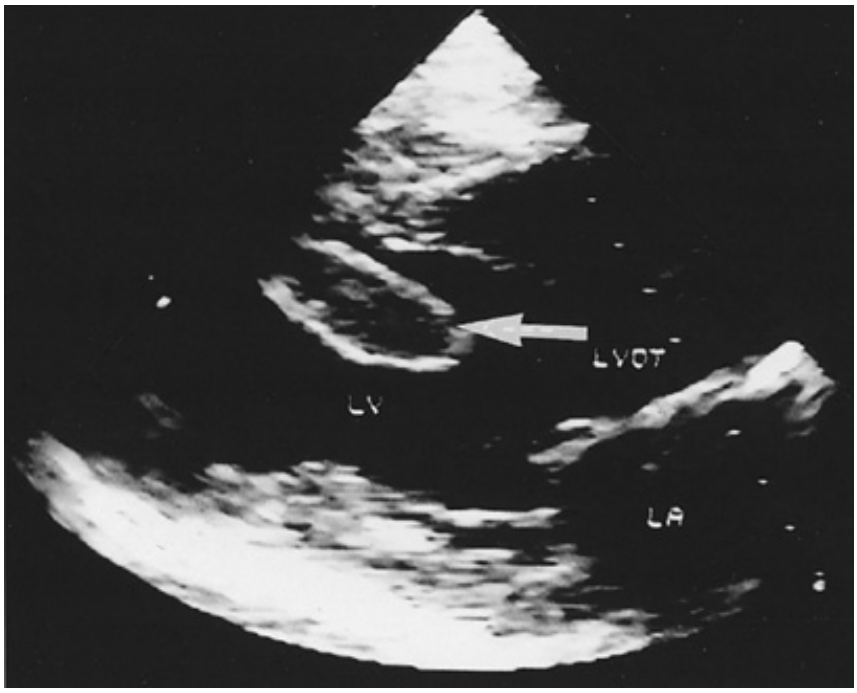

Figure 13-130: Parasternal long-axis view of a large mobile thrombus (*arrow*) attached to the anteroseptal segment of the left ventricle (LV). LVOT = left ventricular outflow tract; LA = left atrium. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

RIGHT HEART

Thrombi within the right heart chambers may form locally or migrate from the venous circulation; they are found most commonly in the RA.[653] As opposed to the laminar, relatively immobile nature of RA thrombi that form in situ, venous thromboemboli trapped in the RA tend to be serpentine and mobile.[649] The potential for pulmonary embolism is high.[654] Thrombi also can be seen within the main pulmonary arteries, although they are less well visualized by TTE than TEE.[655] RV thrombi are rare but may occur with RV infarction and endomyocardial fibrosis.[656,657] Their appearance is similar to that of LV thrombi.

LEFT ATRIUM

Left atrial thrombi occur in the setting of low cardiac output, mitral valvular disease (particularly mitral stenosis), atrial fibrillation, and LA enlargement. Both TTE and TEE can detect thrombi within the main cavity of the left atrium (Fig. 13-131), but TEE is clearly superior for visualizing thrombi within the left atrial appendage.[658-660] Since approximately 50 percent of LA thrombi are limited to the appendage, TEE is the diagnostic procedure of choice to detect this lesion.[652,661] LA thrombi appear as discrete masses, either fixed or mobile, and are usually of homogeneous echo density[659] (Fig. 13-52). On TEE, normal pectinate muscular ridges in the appendage must be distinguished from small thrombi. In addition, the left atrial appendage may occasionally be multilobed. Although this anatomic variant may be a risk factor for appendage thrombi, the atrial tissue separating the lobes should not be mistaken for clot.[662]

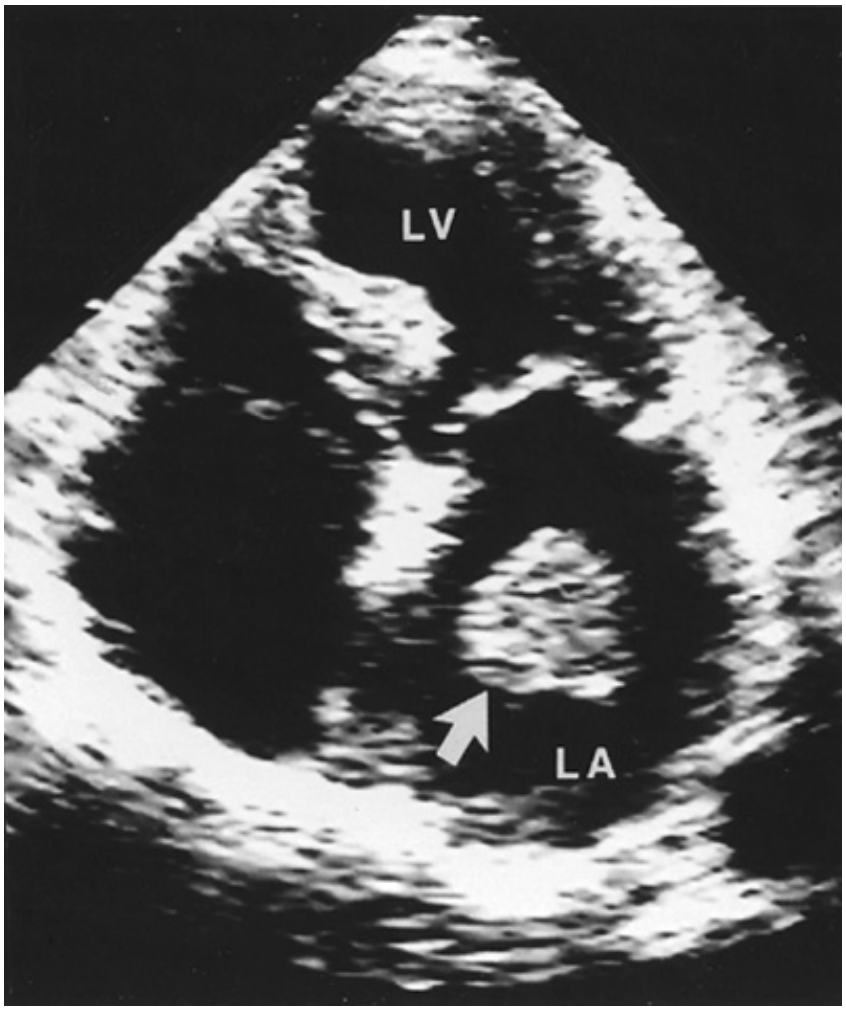

Figure 13-131: Apical four-chamber image of a large mobile "ball" thrombus (*arrow*) in the left atrium (LA). LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Left atrial thrombi are often accompanied by spontaneous echo contrast (or "smoke") within the LA. This finding, probably produced by transient aggregation of erythrocytes and plasma proteins,[663] indicates stagnant blood flow and can occur in any cardiac chamber or the aorta. Left atrial spontaneous echo contrast, like LA thrombus, has been associated with embolic events[664,665] and may be a marker of regional prothrombotic activity.[666] On 2D imaging, the contrast signals are in constant motion and can be missed if gain settings are inappropriately low.

LEFT VENTRICLE

Most LV thrombi occur in settings of abnormal systolic contraction (dilated cardiomyopathy, acute myocardial infarction, and chronic LV ventricular aneurysm).[667-669] LV thrombi have been reported in up to one-half of patients with large myocardial infarctions and occur more frequently in anterior infarctions (up to 30 to 40 percent of such patients).[668] Most thrombi are located in the apex[626] and thus are best visualized in the apical views (Fig. 13-129). Although echocardiography is the procedure of choice for detecting LV thrombi,[669] the technique's true sensitivity and specificity remains uncertain, since most patients included in validating studies had LV aneurysms and the echocardiographic criteria applied were subjective.[668-670]

LV thrombi may be laminar and fixed or protruding and mobile, and they may have a

heterogeneous echo density (Figs. 13-129 and 13-130). Studies suggest that "immature" thrombi are often filamentous, with irregular borders, while older thrombi tend to be echodense and fixed.[626,648,671] The echocardiographic characteristics of thrombi may influence the risk of cardiogenic embolization, as irregularly shaped, mobile, and protruding thrombi are more likely to embolize than laminar, immobile clots.[648] True LV thrombi have a density distinct from the underlying myocardium, appear in multiple imaging planes, and move concordantly with the underlying myocardium.[669] Suspected masses in areas of normally functioning myocardium are rarely thrombi.

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CARDIAC TUMORS

Although diagnosed infrequently, cardiac tumors often are included in the differential diagnosis of cardiac problems because of their protean clinical manifestations. Cardiac tumors may be intracavitary or intramural, and the location determines their echocardiographic appearance. Intracavitary tumors appear as sessile or mobile echo densities attached to the mural endocardium while intramural tumors appear as localized thickening of the LV wall.[672] The pericardium also may be involved with cardiac tumors, with or without the presence of concomitant effusion (Chap. 77).

Myxomas

Myxomas are the most common primary cardiac tumors, accounting for about 25 percent of all such lesions.[673-675] Myxomas can occur in any cardiac chamber, but 75 percent are found in the LA.[675] On 2D imaging, myxomas usually appear as gelatinous, speckled, sometimes globular masses with frond-like projections (Figs. 13-132 and 13-133). Tissue heterogeneity is common, but calcification is rare.[673] Although they may be sessile, myxomas are usually attached to the endocardial surface by a pedicle. Typically, they are attached to the interatrial septum, but they can originate from the posterior or anterior atrial wall, the appendage, or even the cardiac valves.[676,677] Large tumors are almost always mobile to some degree, and a sizable left atrial mass that appears fixed in position is therefore less likely to be a myxoma. Large left atrial myxomas may move back and forth into the mitral valve annulus during the cardiac cycle, entering the orifice in diastole and the left atrium in systole. Accordingly, Doppler interrogation may demonstrate either obstruction of flow, valvular regurgitation, or both.[678,679] Most myxomas are visible on TTE, but TEE is superior for the delineation of tumor attachments and detection of small myxomas.[680] Since approximately 5 percent of myxomas are biatrial, careful evaluation of the RA is mandatory.[675]

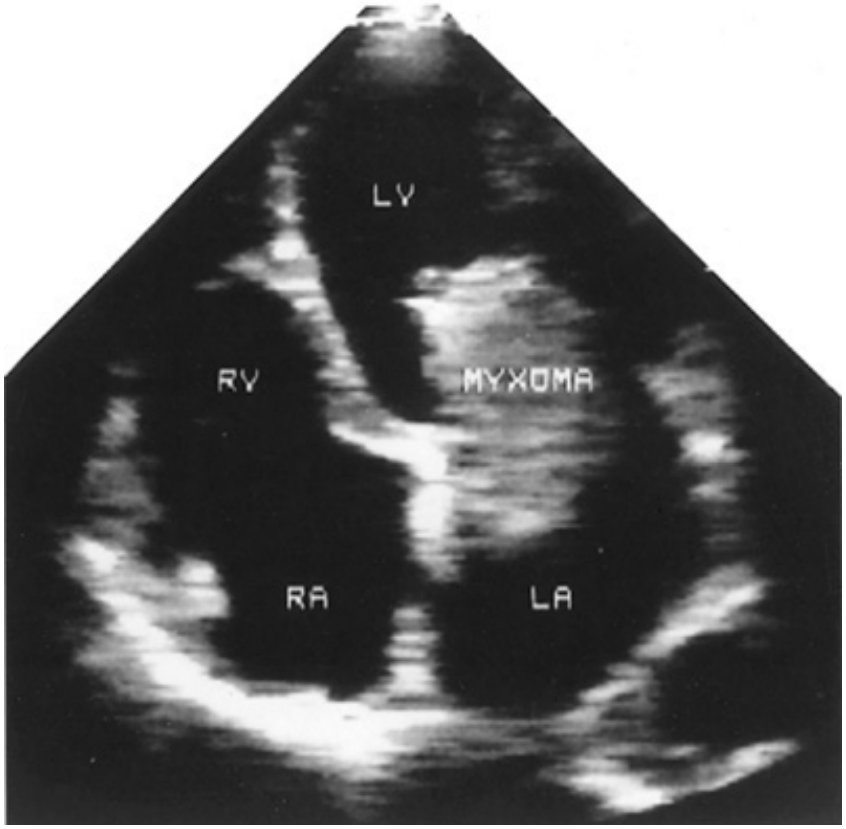

Figure 13-132: Apical four-chamber image of a left atrial myxoma which is attached to the interatrial septum and prolapses through the mitral valve. LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging,* 2d ed. Philadelphia: Saunders, 1996:452-480, with permission.)

Additional Primary Tumors

Benign

Rhabdomyomas are rare cardiac tumors associated with tuberous sclerosis.[681,682] There is a strong tendency for multiple tumors to occur within an affected heart (90 percent of cases).[681,683] Fibromas are found most often in children and affect the left ventricle most frequently. The tumor may grow within the myocardium rather than expanding into a cardiac chamber.[684,685] Papillary fibroelastomas are usually quite small in size (less than 1 cm in diameter) and often grow on cardiac valves or chordae. These rare tumors typically have multiple small fronds that tend to embolize.[625,686,687] Echocardiographic differentiation from vegetations can be difficult (Chap. 77).

Malignant

Primary malignant cardiac tumors are quite rare and confer a very poor prognosis. Angiosarcoma is the most common and occurs most often in the right atrium. Rhabdomyosarcoma is an additional primary cardiac malignancy.[688] Echocardiography can be useful in monitoring response to therapy, but its diagnostic utility is limited, as most findings are nonspecific.

Metastatic and Secondary Tumors of the Heart and Pericardium

Metastatic tumors to the pericardium and heart occur 20 to 40 times more often than primary cardiac tumors (Fig. 13-134).[689] Tumors that commonly involve the heart and pericardium include breast and lung carcinoma, melanoma, and lymphoma. Involvement may be secondary to hematogenous, lymphatic, or contiguous spread. Tumors such as hepatoma and renal carcinoma can also extend to the heart via the venae cavae.[690] In these cases, tumor is often visible in the inferior vena cava and RA. Metastatic disease affects the pericardium more frequently than the heart itself, and pericardial effusion is the most common echocardiographic manifestation in patients with cardiac metastases.[689,691,692] Intracavitary and pericardial masses are easily visualized with 2D imaging, although intramural tumors are sometimes difficult to image. Echocardiographic findings are nonspecific, and metastatic tumors may be mistaken for primary cardiac neoplasms, vegetations, thrombi, or even prominent muscular trabeculations (Chap. 77).

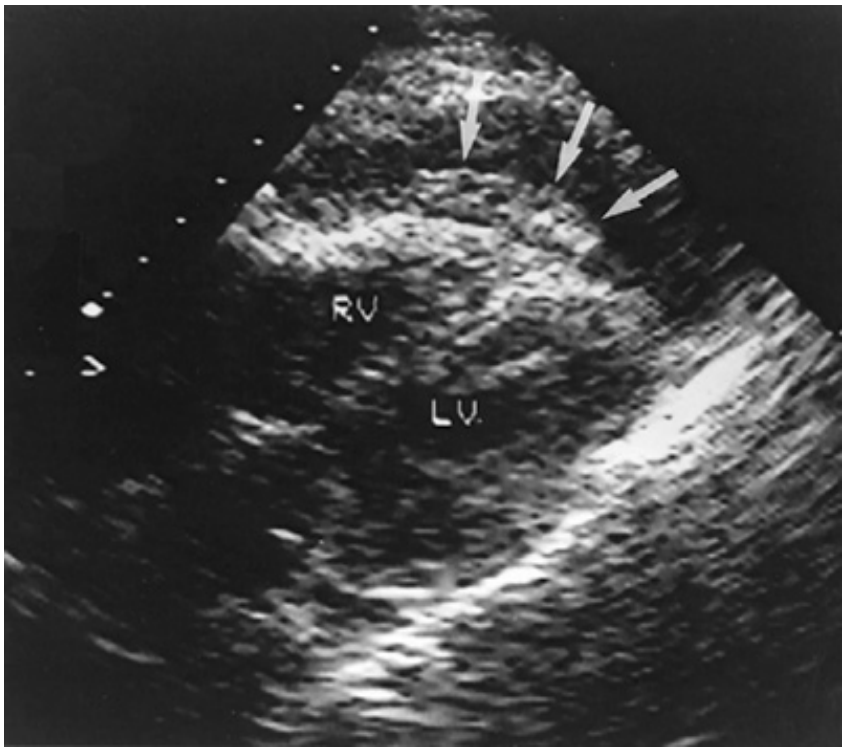

Figure 13-134: Modified subcostal image showing a metastatic tumor on the epicardium (*arrows*) and a malignant pericardial effusion. RV = right ventricle; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Additional Cardiac Masses

The heart is rarely involved in echinococcal disease (<2 percent of cases), but intracardiac or intrapericardial rupture of a cyst can lead to anaphylaxis and cardiac tamponade, respectively.[693] Echocardiographic detection of a multiseptated cyst in the left ventricle or interventricular septum suggests cardiac echinococcal disease.[694]

Simple pericardial cysts usually occur in the right costophrenic angle (posterior to the right atrium) and have a benign prognosis. The structures are nonseptated and fluid-filled; they do not compress the cardiac chambers.[695]

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PERICARDIAL DISEASE

In normal subjects, the pericardium is difficult to visualize since the pericardial cavity is only a potential space and visceral and parietal pericardial layers appear as a single echo.[696] In the setting of pericardial effusion, the fluid appears as a sonolucent area (or clear space) separating epicardium from pericardium.[697] Pericarditis may be unaccompanied by pericardial effusion and in such cases may be undetectable by echocardiography.[698] In addition, although thickening and/or calcification of the pericardium may be detectable by echocardiography in patients with constrictive pericarditis, cardiac ultrasound is limited in this capability.[699-700a] Therefore, the evaluation of constrictive pericarditis by echocardiography, primarily involves Doppler flow recordings.[701]

Pericardial Effusion

Echocardiography is the diagnostic procedure of choice for detection of pericardial fluid[696,697] (Fig. 13-135), and early M-mode studies demonstrated that volumes as small as 20 to 30 mL could be detected reliably.[702] As both myocardium and pericardium are echo-reflective and pericardial fluid is not, a sonolucent area between the epicardium and pericardium is diagnostic of a pericardial effusion. Although epicardial-pericardial separation may be seen during systole in normal cases, separation throughout the cardiac cycle is abnormal.[702] Descending aorta, coronary sinus, pleural effusion, pericardial cyst, and LV pseudoaneurysm occasionally may be mistaken for pericardial effusion.[703]

Echocardiography can be used to identify pericardial loculations, fibrous strands, and pericardial tumors as well as to assess the size of effusions[692,696,697,699,700] (Fig. 13-136). Pericardial effusions may be concentric or loculated (the latter type is especially common with postoperative, infective, and malignant effusions). As pericardial tissue reflects upon itself behind the left atrium between the pulmonary veins (the oblique sinus), fluid is rarely seen in this area. Small, nonloculated effusions may move depending on patient position and thus are often drawn posteriorly and inferiorly by gravity during routine imaging. A rim of pericardial fluid surrounding the heart is evidence of a moderate or large effusion, and the heart can sometimes be seen "swinging" back and forth within the pericardial space, creating the mechanism of *electrical alternans.*[704] In general, small effusions are seen posteriorly rather than anteriorly on supine imaging.[696] Moderate-sized (100 to 500 mL) nonloculated effusions are present both anterior and posterior to the heart.[696] Large nonloculated effusions (>500 mL) are circumferential and frequently allow free motion of the heart within the fluid-filled space.[696,697]

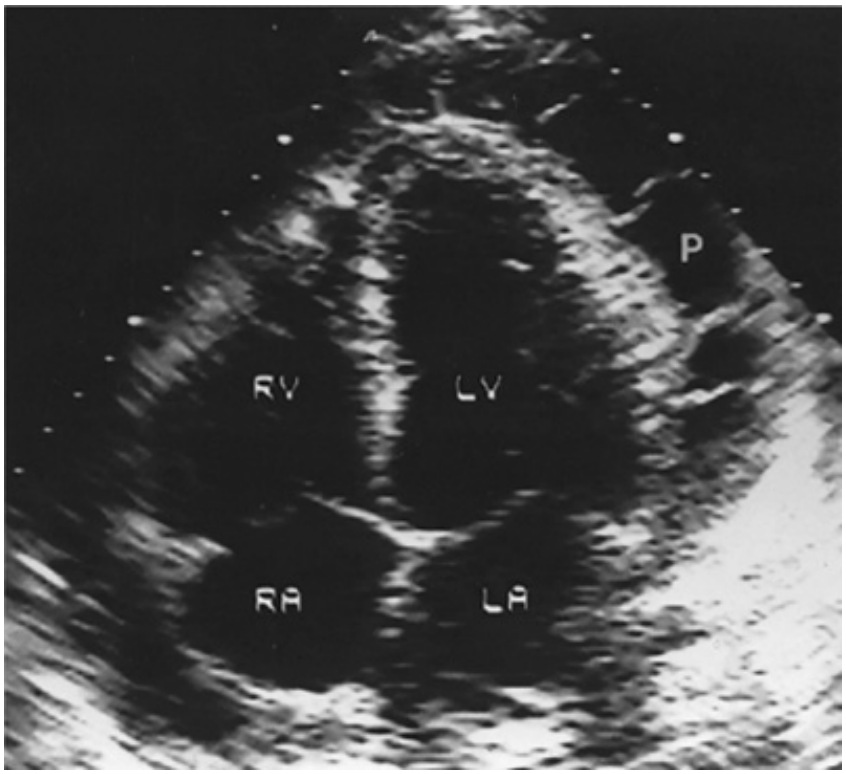

Figure 13-136: Apical four-chamber image in a case of malignant pericardial effusion (P). Numerous fibrinous strands are seen within the effusion. LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders, 1996:452-480, with permission.)

Distinguishing between pericardial and pleural effusions is occasionally difficult with echocardiography.[705] If these conditions coexist, the pericardium usually can be identified as a linear density separating fluid in the two spaces. The parasternal long-axis view is often helpful in differentiating the disorders. The descending aorta is a mediastinal structure; therefore pericardial effusions will often separate the heart and descending aorta, while pleural effusions are seen inferior and posterior to the aorta[705] (Fig. 13-137). In cases of large pleural effusions, atelectatic lung tissue also may be present (Fig. 13-137). Subcostal views are often valuable and may yield the only satisfactory transthoracic images in postoperative or posttraumatic cases. The inferior vena cava also can be imaged in this view; if the vessel does not display inspiratory collapse greater than 50 percent of its maximum diameter, elevated RA pressure is present.[366]

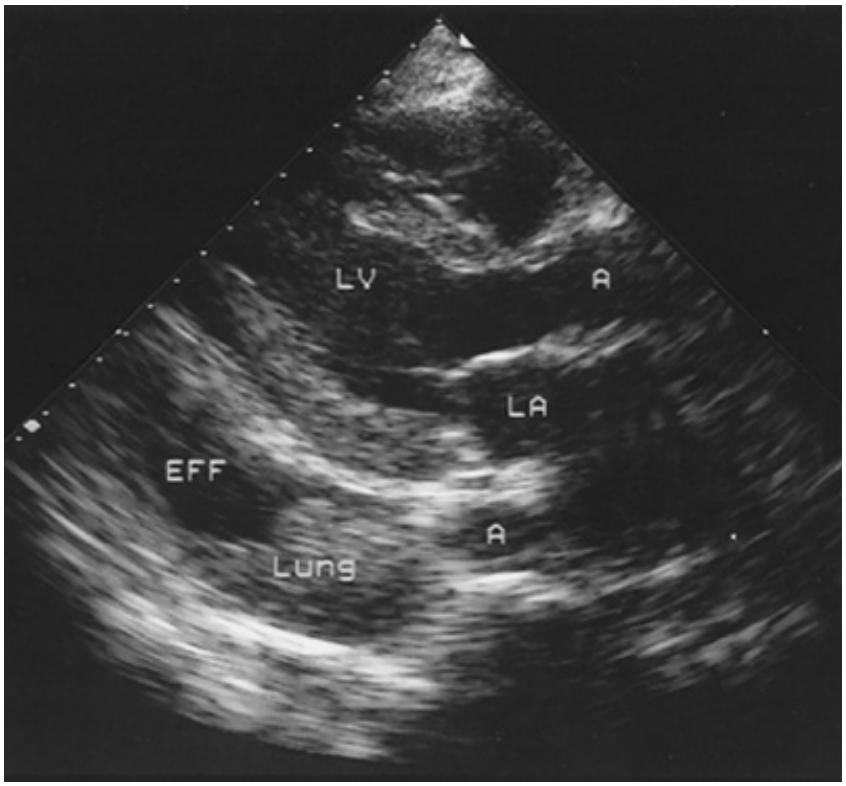

Figure 13-137: Parasternal long-axis view in a patient with a pleural effusion (EFF) posterior to the heart. Atelectatic lung tissue is present within the effusion. LA = left atrium; LV = left ventricle; A = aorta.

On parasternal images, an echolucent space is sometimes visualized anterior to the RV.[706] Although this finding may represent pericardial fluid, it usually is caused by epicardial fat (without effusion) and has no pathologic significance. Therefore the diagnosis of pericardial effusion based solely on the presence of this anterior clear space should be avoided.

Cardiac Tamponade

As the pericardium is a relatively noncompliant membrane that adapts slowly to volume changes, pericardial effusions (especially those that accumulate rapidly) may limit cardiac filling and cause cardiac tamponade. Echocardiography can help diagnose this condition by detecting (1) morphologic signs of increased intrapericardial pressure and (2) abnormal intracardiac flow patterns caused by tamponade and enhanced ventricular interdependence.[707,708]

As diastolic pressures are slightly lower in the right heart than the left, the RA and RV are usually the first chambers to exhibit evidence of increased intrapericardial pressure. High intrapericardial pressure can cause compression or collapse of right heart chambers.[707,709,710] Invagination of the right atrial wall during atrial systole is a sensitive (but not specific) sign of tamponade (Fig. 13-138).[709] Diastolic collapse or "buckling" of the RV free wall is a more specific sign of tamponade, and can be visualized both on 2D and M-mode imaging[707,710] (Fig. 13-135*B* and *C*). In cases of localized tamponade or severe RV hypertrophy, left atrial or ventricular diastolic collapse may be the first sign of tamponade.[711,712]

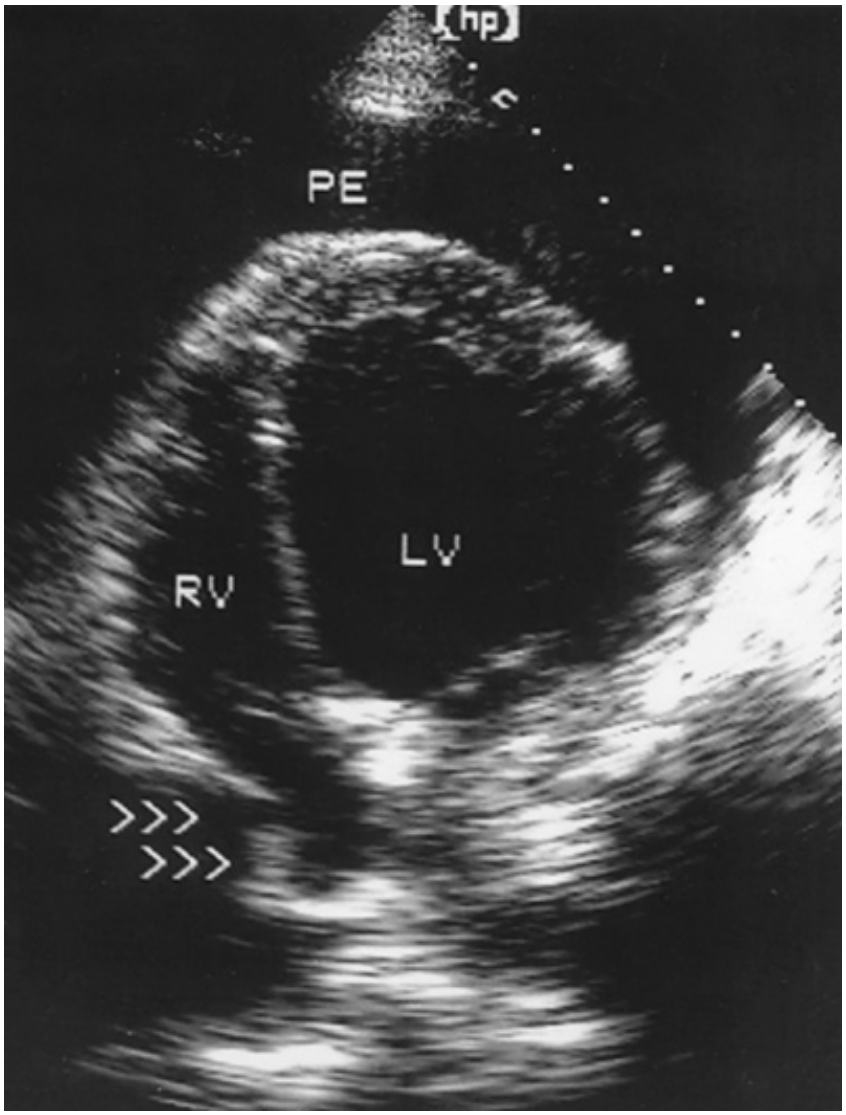

Figure 13-138: Right atrial collapse (*arrows*) in cardiac tamponade. PE = pericardial effusion; LV = left ventricle; RV = right ventricle.

Doppler echocardiographic recordings in patients with tamponade have demonstrated an enhancement or exaggeration of the normal respiratory variation in ventricular inflow and outflow.[708,713] Thus, transmitral and LVOT velocities decrease significantly with inspiration, probably because of enhanced ventricular interdependence and a marked decrease in the transmitral diastolic gradient during inspiration (Fig. 13-139). The latter is caused both by high intrapericardial pressure as well as leftward motion of the interventricular septum from increased RV filling.[708] Although cardiac tamponade remains a clinical diagnosis, echocardiography has significantly improved the detection of hemodynamic effects from pericardial fluid, especially in early and equivocal cases. Studies have also indicated that when echocardiography is used to direct pericardiocentesis to the site of greatest fluid accumulation, the risks associated with blind pericardial puncture are decreased.[714]

Constrictive Pericarditis

The diagnosis of constrictive pericarditis is sometimes difficult to establish, even by cardiac catheterization. 2D and M-mode echocardiography may provide evidence of thickened pericardial tissue by demonstrating increased reflectivity and multiple parallel moving echoes in the area of the pericardium.[699,700] The criteria for pericardial thickening on echocardiogram are imperfect, however, as the normal pericardium is an echodense, highly reflective structure with a gain-

dependent signal.[715] Paradoxical septal motion may be seen on M-mode with constriction, as can an abnormal inspiratory interventricular septal "bounce"[716] and limited diastolic motion of the posterior LV wall.[717] A dilated inferior vena cava that does not collapse on deep inspiration is indicative of high RA pressure and may be observed on 2D imaging in constrictive pericarditis.[716]

The utility of Doppler recordings in evaluating constrictive pericarditis has been shown in several recent studies.[550,701,718-723a,723b] As with cardiac tamponade, pericardial constriction produces exaggerated respiratory variation in the isovolumic relaxation time and in flow velocities within right and left ventricles, pulmonary veins, and hepatic vein.[701,718,722] A respiratory variation of >20 percent in peak mitral E velocity favors the diagnosis of constriction over restrictive cardiomyopathy, while little respiratory variation and a shortened E deceleration time favor restrictive physiology.[701] Doppler echocardiographic criteria for constriction have been validated prospectively and may help predict clinical response to pericardiectomy.[721] Unfortunately, exaggerated respiratory flow variation is not specific for pericardial constriction and also can be seen in chronic obstructive pulmonary disease and asthma.[724] In these cases, Doppler examination of superior vena cava flow is useful: patients with asthma will have increased flow toward the heart during inspiration, while limited forward flow will be seen in constriction (the echocardiographic equivalent of Kussmaul's sign).[724,724a] Recently, respiratory variation in the peak velocity and duration of continuous-wave Doppler TR spectral envelopes has been shown to reflect accurately the enhanced ventricular interaction seen in constrictive pericarditis.[725]

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IMAGING OF THE CORONARY ARTERIES

The ability to visualize the proximal segments of the left and right coronary arteries was initially demonstrated by Weyman et al.[417] Subsequent studies established the ability of color and spectral Doppler examination to image and record the velocity of flow from TTE and TEE approaches, particularly with regard to the left anterior descending coronary artery.[418-420] However, visualization of the coronary arteries by echocardiography has not achieved a significant role in clinical practice because the resolution of the technique is at the limit of vessel size and the vessels are circuitous and move vigorously, often coursing in and out of the beam path. Despite these limitations, transthoracic imaging has proven useful for the diagnosis and follow-up of patients with Kawasaki disease and coronary involvement[726-728] (Fig. 13-140) and may also help distinguish normal from atherosclerotic coronary arteries.[729]

The coronary arteries are routinely imaged with TEE, which can detect proximal stenoses, atherosclerosis, and congenital abnormalities of the coronaries more accurately than surface imaging.[730-732] Doppler TEE analysis also has been used to determine coronary low reserve.[733,734]

Visualization of mid- and distal coronary arteries is problematic with both TTE and TEE. Recent advances in technology and contrast agents, however, may significantly improve capabilities in this area. Figure 13-141 (Plate 73) shows color flow within a septal coronary artery. This image was produced by an instrument utilizing a carrier frequency range of 5 to 7 MHz, rather than the more commonly used range of 2.5 to 3.5 MHz. This area of echocardiography is expanding rapidly and clinical applications will grow in the future.[735,736]

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Figure 13-5: Formation of A-mode, B-mode, and M-mode echocardiograms. The transducer emits an ultrasound beam, which reflects at each anatomic interface. The reflected wavefronts can be represented as dots (B mode) or spikes (A mode). The dot brightness and spike magnitude vary with the amplitude of the reflected wave. If the B-mode scan is swept from left to right with time, an M-mode image is produced. CW = chest wall; RV = right ventricle; IVS = interventricular septum; AML = anterior mitral leaflet; PML = posterior mitral leaflet; and PW = posterior wall. (Modified from Hagan AD, DeMaria AN. *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*. Boston: Little, Brown; 1989, with permission.)

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Figure 13-108: Apical four-chamber image of dilated cardiomyopathy. There is four-chamber enlargement as well as left ventricular (LV) spontaneous echo contrast. RV = right ventricle; RA = right atrium; LA = left atrium.

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Figure 13-110: (Plate 00) *A.* Apical four-chamber view of an ostium secundum atrial septal defect (ASD). On the left, a defect in the mid atrial septum is apparent (*arrow*). On the right, there is color flow through the shunt. RV = right ventricle; RA = right atrium; LA = left atrium; LV = left ventricle. *B.* Subcostal four-chamber view of a large ostium primum atrial septal defect (*arrow*). RA = right atrium; LA = left atrium; LV = left ventricle; RV = right ventricle. (Reproduced with permission of Joseph A. Kisslo, MD.)

Figure 13-111: Transesophageal image of a sinus venosus atrial septal defect (ASD) (longitudinal plane). The defect is present in the superior portion of the interatrial septum. RA = right atrium; LA = left atrium; ASD = atrial septal defect; PA = pulmonary artery.

Figure 13-112: Transverse transesophageal image of single atrium. RV = right ventricle; LV = left ventricle. (From Blanchard DG, Scott ED. Single atrium. *Circulation* 1997; 95:273, with permission.)

Figure 13-113: *A.* Apical four-chamber image of an inlet ventricular septal defect (VSD). The defect (*arrows*) is situated more inferiorly than the typical position of a perimembranous VSD. RV = right ventricle; RA = right atrium; LA = left atrium; LV = left ventricle. *B.* Apical image of single ventricle. RA = right atrium; LA = left atrium.

Figure 13-114: (Plate 70) Parasternal short-axis images of a large perimembranous ventricular septal defect (VSD) (*arrow*) without (*left*) and with (*right*) superimposed color flow Doppler. A large, turbulent color jet crosses the VSD during systole (*right*). RVOT = right ventricular outflow tract; RA = right atrium; LA = left atrium; LVOT = left ventricular outflow tract.

Figure 13-115: (Plate 71) *A.* Transesophageal image of a patent ductus arteriosus (PDA). Color Doppler imaging shows flow from the descending aorta (DESC AO) into the PDA. (Courtesy of Bruce J. Kimura, M.D.) *B.* Parasternal short-axis images at the aortic valve level. On the left, the pulmonary artery (PA) is somewhat enlarged. On the right, color imaging reveals diastolic flow within the PA, consistent with a patent ductus arteriosus. RV = right ventricle; RA = right atrium; LA = left atrium; AO = aorta.

Figure 13-116: Transverse transesophageal image of cor triatriatum. A membrane (*arrows*) is present in the left atrium. RV = right ventricle; RA = right atrium; LA = left atrium; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Figure 13-117: *A.* Transesophageal image (transverse plane) from a patient with persistent left superior vena cava. The coronary sinus (CS) is dilated. *B.* After injection of agitated saline into the left antecubital vein, contrast is seen entering the right atrium (RA) via the CS. TV = tricuspid valve; RV = right ventricle; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Figure 13-118: Parasternal long-axis (*A*) and apical four-chamber (*B*) images of tetralogy of Fallot. The right ventricle (RV) is enlarged, and a large VSD is present. The aorta (AO) overrides the interventricular septum. LV = left ventricle. (Courtesy of Reinaldo W. Beyer, MD.)

Figure 13-119: Parasternal long-axis image of double-outlet right ventricle. A large VSD is present (*small arrow*) and the normal continuity between the posterior aortic wall and the anterior mitral leaflet is absent. Fibrous tissue is seen (*large arrow*) between the left atrium (LA) and the nearest great vessel (in this case, the pulmonary artery (PA). LV = left ventricle.

Figure 13-120: Transverse transesophageal image through the semilunar valves in L-transposition. The aortic valve (A) is anterior and to the left of the pulmonic valve (P). LA = left atrium.

Figure 13-121: Continuous-wave Doppler tracing of the descending aorta (from the suprasternal position) in aortic coarctation. Peak systolic velocity is approximately 3.6 m/s, and there is persistent flow during diastole, suggesting severe coarctation. D Ao = descending aorta.

Figure 13-122: (Plate 72) Apical three-chamber view of discrete subaortic stenosis. *A.* Fibromuscular ridge (*arrow*) is present in the left ventricular outflow tract. LV = left ventricle; LA = left atrium; A = aortic root. *B.* Apical five-chamber view of discrete subaortic stenosis with color-flow Doppler, demonstrating aliasing and proximal flow convergence in the left ventricular outflow tract. LV = left ventricle; LA = left atrium.

Figure 13-123: Apical four-chamber image of Ebstein's anomaly. The right heart is enlarged, and the insertion of the septal leaflet of the tricuspid valve is displaced apically. The anterior tricuspid leaflet (to the patient's right) is abnormally elongated. RV = right ventricle; RA = right atrium; LA = left atrium; LV = left ventricle. (Reproduced with permission of Joseph A. Kisslo, MD.)

Figure 13-124: Fetal echocardiogram (four-chamber view). LV = left ventricle; RV = right ventricle.

Figure 13-125: Right ventricular inflow view showing a prominent eustachian valve (*arrow*) at the junction of the inferior vena cava (IVC) and the right atrium (RA). RV = right ventricle; CS = coronary sinus. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia; Saunders; 1996:452-480, with permission.)

Figure 13-126: Apical four-chamber view demonstrating a false chord (*arrow*) within the left ventricle (LV). LA = left atrium; RA = right atrium; RV = right ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Figure 13-127: Subcostal four-chamber image demonstrating a pacemaker wire (*arrows*) in the right heart. RA = right atrium; LA = left atrium; LV = left ventricle.

Figure 13-128: Transverse transesophageal image of an interatrial septal aneurysm (*arrow*). RA = right atrium; LA = left atrium. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Figure 13-129: Magnified apical view of a large thrombus (T) in the apex of the left ventricle (LV). Although the thrombus is fairly homogeneous, its border is more echo-dense (*arrows*).

Figure 13-130: Parasternal long-axis view of a large mobile thrombus (*arrow*) attached to the anteroseptal segment of the left ventricle (LV). LVOT = left ventricular outflow tract; LA = left atrium. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Figure 13-131: Apical four-chamber image of a large mobile "ball" thrombus (*arrow*) in the left atrium (LA). LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Figure 13-132: Apical four-chamber image of a left atrial myxoma which is attached to the interatrial septum and prolapses through the mitral valve. LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging*, 2d ed. Philadelphia: Saunders, 1996:452-480, with permission.)

Figure 13-133: Apical four-chamber image of a large left atrial myxoma (*arrows*), which is attached to the lateral wall of the atrium. LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle; PE = pericardial effusion; PL = pleural.

Figure 13-134: Modified subcostal image showing a metastatic tumor on the epicardium (*arrows*) and a malignant pericardial effusion. RV = right ventricle; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging,* 2d ed. Philadelphia: Saunders; 1996:452-480, with permission.)

Figure 13-135: *A.* Moderate pericardial effusion (PE) on parasternal long-axis imaging. AO = aorta; LV = left ventricle; LA = left atrium. *B.* Right ventricular compression in cardiac tamponade (subcostal plane). RA = right atrium; LV = left ventricle; PE = pericardial effusion. *C.* M-mode image of cardiac tamponade and right ventricular diastolic collapse. The right ventricular (RV) free wall (*arrows*) moves posteriorly toward the interventricular septum during diastole. E = effusion; LV = left ventricle.

Figure 13-136: Apical four-chamber image in a case of malignant pericardial effusion (P). Numerous fibrinous strands are seen within the effusion. LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle. (From Blanchard DG, DeMaria AN. Cardiac and extracardiac masses: Echocardiographic evaluation. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. *Marcus' Cardiac Imaging,* 2d ed. Philadelphia: Saunders, 1996:452-480, with permission.)

Figure 13-137: Parasternal long-axis view in a patient with a pleural effusion (EFF) posterior to the heart. Atelectatic lung tissue is present within the effusion. LA = left atrium; LV = left ventricle; A = aorta.

Figure 13-138: Right atrial collapse (*arrows*) in cardiac tamponade. PE = pericardial effusion; LV = left ventricle; RV = right ventricle.

Figure 13-139: Pulsed-wave Doppler tracing of left ventricular inflow in cardiac tamponade (apical transducer position). There is abnormal respiratory variation in the peak E wave velocity (which varies from 60 to 80 cm/s). E = expiration; I = inspiration.

Figure 13-140: Parasternal short-axis images of coronary artery aneurysms associated with Kawasaki's disease. *A.* The proximal left coronary artery (LCA) is seen to be diffusely dilated and aneurysmal. *B.* A proximal right coronary artery aneurysm (*arrow*) is shown. AO = aorta, LA = left atrium. (Courtesy of Victor Lucas, MD and Paul Grossfeld, MD.)

Figure 13-141: (Plate 73) Transthoracic short-axis image of a coronary artery within the interventricular septum (*arrows*). LV= left ventricle; RV = right ventricle.

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Chapter 13: THE ECHOCARDIOGRAM

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 14:

ECG EXERCISE TESTING

Author: Victor F. Froelicher

The exercise test continues to have an integral place in cardiovascular medicine because of its high yield of diagnostic, prognostic, and functional information.[1] When conducting an exercise test, the method and analysis of the data should be determined by the objective of the test. In the clinical setting, the major indications for exercise testing are the diagnosis and prognostication of heart disease. The determination of exercise capacity is helpful in quantifying disability, estimating prognosis, and monitoring the disease state of patients with chronic obstructive pulmonary disease, chronic heart disease, and known coronary heart disease. However, the major emphasis is on the analysis of the electrocardiogram (ECG) in the majority of clinical tests. Also, the reproduction of symptoms such as angina or presyncope is vital for clinical purposes.

METHODS

Excellent guidelines have been updated by organizations such as the American Heart Association, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the American College of Sports Medicine that are based on a multitude of research studies over the last 20 years and have led to greater uniformity in methods.[2-4] These should be followed as closely as possible. General concerns prior to performing an exercise test include safety precautions and equipment needs, patient preparation, choosing a test type, choosing a test protocol, patient monitoring, reasons to terminate a test, and posttest monitoring.

Safety Precautions and Equipment

The safety precautions outlined by the American Heart Association are very explicit in regard to the requirements for exercise testing. Everything necessary for cardiopulmonary resuscitation must be available, and regular drills should be performed to ascertain that both personnel and equipment are ready for a cardiac emergency. The first survey of clinical exercise facilities by Rochmis and Blackburn[5] showed exercise testing to be a safe procedure, with approximately 1 death and 5 nonfatal complications per 10,000 tests. Perhaps due to an expanded knowledge concerning indications, contraindications, and end points, maximal exercise testing appears safer today than 20 years ago.[6] Gibbons et al.[7] reported the safety of exercise testing in 71,914 tests conducted over a 16-year period. The complication rate was 0.8 per 10,000 tests. The authors suggested that the low complication rate may be due to a cool-down walk, but we have observed a low complication rate despite laying patients supine immediately after the test and exercising higher-risk patients.[7]

Besides emergency equipment, the safety and accuracy of the testing equipment should be considered. The treadmill should have front and side rails for subjects to steady themselves. It should be calibrated monthly. Some models can be greatly affected by the weight of the subject and will not deliver the appropriate workload to heavy individuals. An emergency stop button should be readily available to the staff only. A small platform or stepping area at the level of the belt is advisable so that the subject can start the test by "pedaling" the belt with one foot prior to stepping on.

Although numerous clever devices have been developed to automate blood pressure measurement during exercise, none can be recommended. The time-proven method of holding the subject's arm with a stethoscope placed over the brachial artery remains most reliable. The subject's arm should be free of the handrails so that noise is not transmitted up the arm. It is sometimes helpful to mark the brachial artery. An anesthesiologist's auscultatory piece or an electronic microphone can be fastened to the arm. A device that

inflates and deflates the cuff on the push of a button can be helpful also.

Exercise Testing

PRETEST PREPARATIONS

During the pretest evaluation, the physician should establish an understanding of any patterns of cardiopulmonary compromise associated with exercise and the patient's usual level of exercise tolerance. The patient should be asked whether he or she has ever become light-headed or fainted while exercising and whether anyone in the family has died suddenly during exercise. The physician also should ask about family history and general medical history, making note of any conditions that may increase the risk of sudden death.

A brief physical examination always should be performed prior to testing to rule out significant outflow obstruction. In some instances, such as when asymptomatic, apparently healthy subjects are being tested for exercise capacity or a repeat treadmill test is being done on a patient whose condition is stable and established, a physician need not be present but should be in close proximity and prepared to respond promptly. The response to signs or symptoms should be moderated by the information the patient gives regarding his or her usual activity. If abnormal findings occur at levels of exercise that the patient usually performs, then it may not be necessary to stop the test because of them. Also, the patient's activity history should help determine appropriate target workload for testing.

Table 14-1 lists the absolute and relative contraindications to performing an exercise test, as well as the factors to consider in assessing the degree of exercise.

Table 14-1: Contraindications to Exercise Testing

ABSOLUTE
Acute myocardial infarction (within 2 d)
Unstable angina not previously stabilized by medical therapy*
Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
Symptomatic severe aortic stenosis
Uncontrolled symptomatic heart failure
Acute pulmonary embolus or pulmonary infarction
Acute myocarditis or pericarditis
Acute aortic dissection
RELATIVE†
Left main coronary artery stenosis
Moderate stenotic valvular heart disease
Electrolyte abnormalities
Severe arterial hypertension‡
Tachyarrhythmias or bradyarrhythmias
Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Mental or physical impairment leading to inability to exercise adequately

High-degree atrioventricular block

*Appropriate timing of testing depends on level of risk of unstable angina, as defined by the Agency for Health Care Policy and Research Unstable Angina Guidelines.
†Relative contraindications can be superseded if the benefits of exercise outweigh the risks.
‡In the absence of definitive evidence, the committee suggests a systolic blood pressure of >200mmHg and/or diastolic blood pressure of >110 mmHg.

SOURCE: Modified from Fletcher GF, Balady G, Froelicher VF, et al. Exercise standards: A statement for healthcare professionals from the American Heart Association. Special report. *Circulation* 1995; 91:580-615.

Preparations for exercise testing include the following:

1. The subject should be instructed not to eat or smoke at least 2 hours prior to the test and to come dressed for exercise.
2. A brief history and physical examination (particularly noting systolic murmurs) should be accomplished to rule out any contraindications to testing (see Table 14-1).
3. Specific questioning should determine which drugs are being taken, and potential electrolyte abnormalities should be considered. The labeled medication bottles should be brought along so that medications can be identified and recorded. Because of a greater potential for cardiac events with the sudden cessation of β blockers, they should not be automatically stopped prior to testing but done so gradually under physician guidance, only after consideration of the purpose of the test.
4. Pretest standard 12-lead ECGs are necessary in both the supine and standing positions. Good skin preparation must cause some discomfort but is necessary for good conductance and to avoid artifacts. The changes caused by exercise electrode placement can be kept to a minimum by keeping the arm electrodes off the chest, placing them on the shoulders, and by recording the baseline ECG supine[8] (Fig. 14-1). In this situation, the modified exercise limb lead placement can serve well as the reference resting ECG prior to an exercise test.
5. Hyperventilation is not necessary prior to testing. Subjects both with and without disease may or may not exhibit **ST**-segment changes with hyperventilation; the value of this procedure in lessening the number of false-positive responders is no longer considered useful.

DURING THE TEST

Most problems can be avoided by having an experienced physician, nurse, or exercise physiologist standing next to the subject, measuring blood pressure, and assessing appearance during the test. The exercise technician should operate the recorder and treadmill, take the appropriate tracings, enter data on a form, and alert the physician to any abnormalities that may appear on the monitor scope.

Subjects should be reminded not to grasp the front or side rails because this decreases the work performed and creates noise in the ECG. Hanging on increases exercise time, resulting in an overestimation of exercise capacity.

Target heart rates based on age should not be used because the relationship between maximal heart rate and age is poor, and a wide scatter exists around the many different recommended regression lines. Such heart rate targets result in a submaximal test for some individuals, a maximal test for some, and an unrealistic goal for others. The Borg scales are an excellent means of quantifying an individual's effort. At 1- to 2-min intervals, subjects should be monitored for perceived effort level by using the 6 to 20 Borg scale or the nonlinear 1 to 10 scale of perceived exertion.[9,10]

INDICATIONS FOR TEST TERMINATION

The absolute and relative indications for termination of an exercise test listed in Table 14-2 have been derived from clinical experience. Absolute indications are clear-cut, whereas relative indications sometimes

can be disregarded if good clinical judgment is used. Absolute indications include a drop in systolic blood pressure despite an increase in workload, anginal chest pain becoming worse than usual, central nervous system symptoms, signs of poor perfusion (such as pallor, cyanosis, and cold skin), serious dysrhythmias, technical problems with monitoring the patient, patient's request to stop, and marked electrocardiographic changes, e.g., more than 0.3 mV of horizontal or downsloping ST-segment depression or 0.2 mV of ST-segment elevation. Relative indications for termination include other worrisome ST-segment or QRS changes such as excessive junctional depression; increasing chest pain; fatigue, shortness of breath, wheezing, leg cramps, or intermittent claudication; and worrisome appearance, hypertensive response (systolic pressure >260 mmHg, diastolic pressure >115 mmHg), and less serious dysrhythmias including supraventricular tachycardias. If more information is required, the test can be repeated later after symptoms have been stabilized.

Table 14-2: Indications for Terminating Exercise Testing

ABSOLUTE INDICATIONS
Drop in systolic blood pressure (persistently below (baseline) despite an increase in workload
Onset of new or increasing anginal chest discomfort
Central nervous system symptoms (ataxia, dizziness, or near syncope)
Evidence of poor peripheral perfusion (cyanosis or pallor)
Serious arrhythmias (i.e., high-grade ventricular, such as multiform complexes, triplets, and runs)
Technical difficulties in monitoring the ECG or systolic blood pressure
Patient's request to stop
RELATIVE INDICATIONS
ST or QRS changes such as excessive (≥3-4 mm) St-segment displacement, junctional depression, or marked QRS axis shift
Increasing chest discomfort
Fatigue, shortness of breath, wheezing, leg cramps, or intermittent claudication
General appearance (see discussion)
Less serious arrhythmias, including supraventricular tachycardias
Development of bundle branch block thar cannot be distinguished from ventricular tachycardia

AFTER EXERCISE

If maximal sensitivity for ischemic markers is to be achieved with an exercise test, patients should be supine during the postexercise period. It is advisable to record about 10 s of electrocardiographic data while the patient is standing motionless but still experiencing near-maximal heart rate and then have the patient lie down. Having the patient perform a cool-down walk after the test can delay or eliminate the appearance of ST-segment depression.[11] According to the law of LaPlace, the increase in venous return and thus ventricular volume in the supine position increases myocardial oxygen demand. Data from our laboratory[12] demonstrate that having patients lie down enhances ST-segment abnormalities in recovery.

Monitoring should continue for at least 5 min after exercise or until changes stabilize. An abnormal response occurring only in the recovery period is not unusual. All such responses are not false-positive results, as has been suggested. Experiments confirm mechanical dysfunction and electrophysiologic abnormalities in the ischemic ventricle following exercise. A cool-down walk can be helpful when performing tests on patients with an established diagnosis undergoing testing for other than diagnostic

reasons, when testing athletes, or when testing patients with dangerous dysrhythmias. When this is the case, it may be preferable to walk slowly (1.0-1.5 mi/h) or continue cycling against zero or minimal resistance (0-25 W when testing with a cycle ergometer) for several minutes following the test.

Exercise Test Modalities

Three types of exercise can be used to stress the cardiovascular system: isometric, dynamic, and a combination of the two. *Isometric exercise*, defined as constant muscular contraction without movement (such as handgrip), imposes a disproportionate pressure load on the left ventricle relative to the body's ability to supply oxygen. *Dynamic exercise* is defined as rhythmic muscular activity resulting in movement, and it initiates a more appropriate increase in cardiac output and oxygen exchange. Since a delivered workload can be calibrated accurately and the physiologic response measured easily, dynamic exercise is preferred for clinical testing.

Numerous modalities have been used to provide dynamic exercise for exercise testing, including steps, escalators, and ladder mills. Today, however, the bicycle ergometer and the treadmill are the most commonly used dynamic exercise devices. In cases of spinal cord injury, peripheral neuropathy, or orthopedic disorders, arm ergometry is also performed for exercise testing. A wheelchair ergometer has been developed for spinal cord-injured patients.[13]

BICYCLE ERGOMETER VERSUS TREADMILL

The bicycle ergometer is usually cheaper, takes up less space, and makes less noise. Although bicycling is a dynamic exercise, most individuals perform more work on a treadmill because a greater muscle mass is involved, and most subjects are more familiar with walking than cycling. Upper body motion is usually reduced, but care must be taken so that the arms do not perform isometric exercise. The workload administered by the simple bicycle ergometer is not well-calibrated and depends on pedaling speed. It is too easy for a subject to slow pedaling speed during exercise testing and decrease the administered workload. More expensive electronically braked bicycle ergometers keep the workload at a specified level over a wide range of pedaling speeds.

In most studies comparing upright cycle ergometer with treadmill exercise, maximal heart rate values have been demonstrated to be roughly similar, whereas maximal oxygen uptake has been shown to be 6 to 25 percent greater during treadmill exercise.[14-16]

ARM ERGOMETRY

For a given submaximal workload, arm exercise requires a greater myocardial oxygen demand than leg exercise. At maximal effort, however, physiologic responses generally are greater in leg exercise than in arm exercise. At a given power output [expressed as kilopound-meters per minute (kpm/min) or watts (W)], heart rate, systolic and diastolic blood pressure, the product of heart rate times systolic blood pressure, minute ventilation (V_E), and blood lactate concentration are higher during arm exercise. In contrast, stroke volume and the ventilatory threshold (the latter expressed as a percentage of aerobic capacity) are lower during arm exercise compared with leg exercise.[17-20] Since cardiac output is nearly the same in arm and leg exercise at a given oxygen uptake,[21] the elevated blood pressure during arm exercise is due to increased peripheral vascular resistance. Maximal oxygen uptake ($_{O_2max}$) during arm ergometry in men generally varies between 64 and 80 percent of leg ergometry Vdot;$_{O_2max}$. Similarly, maximal cardiac output is lower during arm exercise compared with leg exercise, whereas maximal heart rate, systolic blood pressure, and rate-pressure product are comparable[22] or slightly lower[23] during arm exercise.

Exercise Protocols

The many different exercise protocols in use have led to some confusion regarding how physicians compare tests between patients and serial tests in the same patient. The most common protocols, their stages, and the predicted oxygen cost of each stage are illustrated in Fig. 14-2. When treadmill and cycle ergometer testing were first introduced into clinical practice, practitioners adopted protocols used by major researchers.[24-28] The large and uneven work increments in some of these protocols have been shown to

result in a tendency to overestimate exercise capacity.[29] Investigators have since recommended protocols with smaller and more equal increments.[30,31] Recent guidelines suggest that protocols should be individualized for each subject such that test duration is approximately 8 to 12 min.

RAMP TESTING

An approach to exercise testing that has gained interest is the ramp protocol, in which work increases constantly and continuously (Fig. 14-3). The recent call for "optimizing" exercise testing would appear to be facilitated by the ramp approach, since work increments are small, and since it allows for increases in work to be individualized, a given test duration can be targeted.

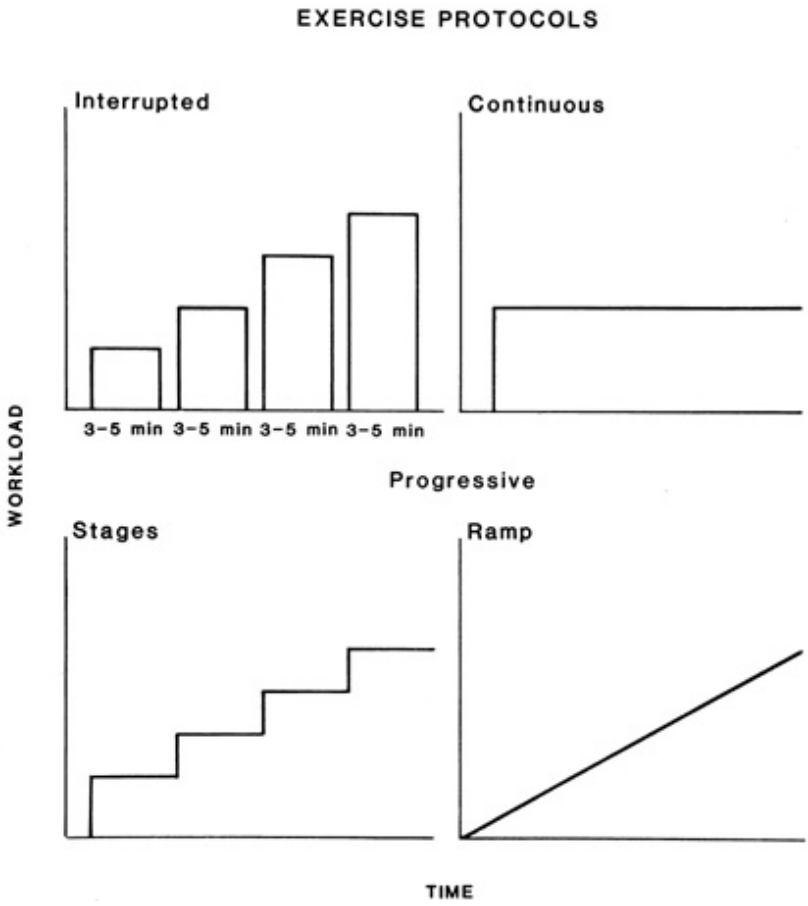

Figure 14-3: An approach to exercise testing that has gained interest is the ramp protocol, in which work increases constantly and continuously, as shown in this illustration.

To investigate this, our laboratory compared ramp treadmill and bicycle tests with protocols used more commonly clinically.[32] Ten patients with chronic heart failure, 10 with coronary artery disease who were limited by angina during exercise, 10 with coronary artery disease who were asymptomatic during exercise, and 10 age-matched normal subjects performed three bicycle tests (25 W/2-min stage, 50 W/2-min stage, and ramp) and three treadmill tests (Bruce, Balke, and ramp) in randomized order on different days. Maximal oxygen uptake was significantly higher (18 percent) on the treadmill protocols versus the bicycle protocols collectively, confirming previous observations. Only minor differences in maximal oxygen uptake, however, were observed among the treadmill protocols themselves or among the cycle ergometer protocols themselves. Our observations suggest that (1) oxygen uptake is overestimated from tests that contain large increments in work, and (2) the variability in estimating oxygen uptake from work rate is markedly greater on these tests than for an individualized ramp treadmill test.

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Chapter 14: ECG EXERCISE TESTING

HEMODYNAMIC RESPONSES

Monitoring hemodynamic responses while conducting a treadmill test is vital to assessing the patient's response to exercise. Measurements are used for diagnosis and prognosis and can necessitate test termination.

Maximal Heart Rate

METHODS OF RECORDING

Although measuring a patient's maximal heart rate (HR_{max}) should be a simple matter, the different ways of recording rate and differences in the type of exercise used may affect its measurement. Heart rate drops quickly in recovery and can climb steeply even in the last seconds of exercise. Premature beats can affect averaging and must be eliminated in order to obtain the actual heart rate. Cardiotachometers are incorporated into most exercise test devices but may fail to trigger or may trigger inappropriately on T waves, artifacts, or aberrant beats, thus yielding inaccurate results.

FACTORS LIMITING MAXIMAL HEART RATE

Several factors may affect the HR_{max} during dynamic exercise. HR_{max} declines with advancing years and is affected by gender. Height, weight, and even lean body weight apparently do not affect HR_{max} very much. The physiologic limits on HR_{max} in normal men are determined by rapidity of sinus node recovery, cardiac dimensions, left ventricular filling, and contractile state. Systole has a relatively fixed time interval; in contrast, relatively less time of the cardiac cycle is spent in diastole when heart rate increases. Many studies have reported HR_{max} during treadmill testing in a variety of patients. Regressions with age have varied depending on the population studied and other factors. Figure 14-4 summarizes these studies of HR_{max}.[33,34] In an effort to clarify the relationship between HR_{max} and age, Londeree and Moeschberger[35] performed a comprehensive review of the literature compiling over 23,000 subjects aged 5 to 81 years. A stepwise multiple regression revealed that age alone accounted for 75 percent of the variability; other factors added only about 5 percent and included mode of exercise, level of fitness, and continent of origin but not sex. The 95 percent confidence interval, even when accounting for these factors, was 45 beats per minute (Fig. 14-5). Heart rates at maximal exercise were lower on bicycle ergometry than on the treadmill and lower still with swimming. Their analysis revealed that trained individuals had significantly lowered maximal heart rates. Graettinger et al.[36] from our laboratory presented clinical, echocardiographic and functional determinants of HR_{max}. Despite controlling for age, activity status, sex, and hypertension, measures of cardiac size and function added little to the prediction of HR_{max}. Most of the variance in HR_{max} was accounted for simply by age. Given the large degree of individual variability in cardiac variables, as well as the HR_{max}/age relationship, HR_{max} always may be a difficult variable to explain.

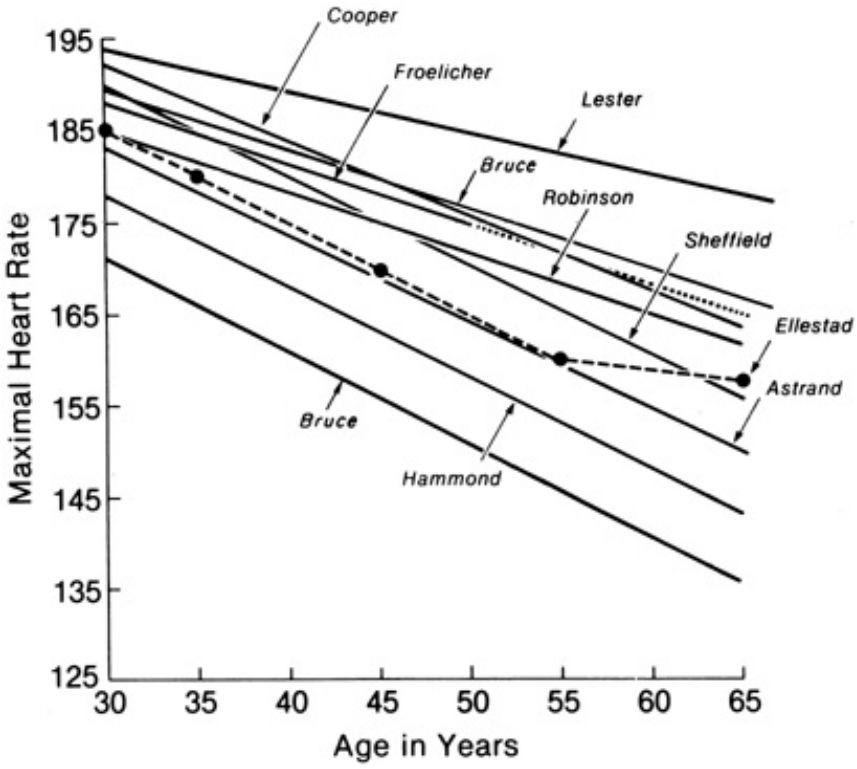

Figure 14-4: Many studies, as shown in this illustration, have reported HR_{max} during treadmill testing in a variety of patients. Regressions with age have varied depending on the population studied and other factors.

Another factor that affects HR_{max} and which is important to clinical medicine is bed rest.[37] Altitude may affect the heart rate response to exercise.[38] Some investigators report substantially lower maximal heart rates in well-trained athletes. A final factor determining maximal exercise heart rate is motivation to exert oneself maximally. Older patients may be restrained by poor muscle tone, pulmonary disease, claudication, orthopedic problems, and other noncardiac causes of limitation. The usual decline in HR_{max} with age is not as steep in people who are free from myocardial disease and stay active, but it still occurs. Recent work from the Cleveland Clinic emphasizes the prognostic importance of chronotropic incompetence or heart rate impairment and demonstrates that such a response does not make a test "inadequate."[39]

Blood Pressure Response

Systolic blood pressure should rise with increasing treadmill workload, whereas diastolic blood pressure usually remains about the same (Fig. 14-6). A rising diastolic blood pressure can be associated with coronary heart disease; however, it is more likely a marker for labile hypertension, which leads to coronary disease. A drop in systolic blood pressure below preexercise values is the most ominous criterion, whereas a drop of 20 mmHg or more without a fall below preexercise values appears to have less predictive value.[40] Exercise-induced hypotension (EIH) can be due to either left ventricular dysfunction (as reflected by myocardial infarction status), ischemia, or outflow obstruction. When EIH occurs without association with either of these two factors, EIH appears to be benign.

The highest systolic blood pressure should be achieved at maximal workload. When exercise is stopped, approximately 10 percent of people tested will abruptly drop their systolic blood pressure owing to peripheral pooling. To avoid fainting, patients should not be left standing on the treadmill. The systolic blood pressure usually normalizes on resuming the supine position during recovery but may remain below normal for several hours after the test. Irving et al.[41] examined

variations in clinical noninvasive systolic pressure at the point of symptom-limited exercise on a treadmill. Lower maximal systolic pressures often were associated with two- or three-vessel disease or reduced ejection fraction or both. The annual rate of sudden cardiac death decreased from 98 per 1000 men to 25 and 7 per 1000 men as the range of maximal systolic pressure increased from less than 140 to 140 to 199 to 200 mmHg or more, respectively.

The 3-min systolic blood pressure ratio is a useful and readily obtainable measure that can be applied in all patients who are undergoing exercise testing for the evaluation of known or suspected ischemic heart disease.[42] The ratio is calculated by dividing the systolic blood pressure 3 min into the recovery phase of a treadmill exercise test by the systolic blood pressure at peak exercise. A 3-min systolic blood pressure ratio greater than 0.90 is considered abnormal. Higher values for the ratio are associated with more extensive coronary artery disease, as well as an adverse prognosis after myocardial infarction.

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Chapter 14: ECG EXERCISE TESTING

EXERCISE CAPACITY

Maximal ventilatory oxygen uptake (Vdot;$_{O_2max}$) is the greatest amount of oxygen that a person can extract from inspired air while performing dynamic exercise involving a large part of the total-body muscle mass. Since maximal ventilatory oxygen uptake is equal to the product of cardiac output and arteriovenous oxygen difference (aV_{O_2}), it is a measure of the functional limits of the cardiovascular system. Maximal a V_{O_2} difference is physiologically limited to roughly 15 to 17 mL/dL. Thus maximal a V_{O_2} difference behaves more or less as a constant, making maximal oxygen uptake an indirect estimate of maximal cardiac output.

Maximal oxygen uptake depends on many factors, including natural physical endowment, activity status, age, and sex, but it is the best index of exercise capacity and maximal cardiovascular function. As a rough reference, the maximal oxygen uptake of the normal sedentary adult is often considered approximately 30 mL O_2/kg per minute, and the minimal level for physical fitness is often considered roughly 40 mL O_2/kg per minute. In general, aerobic training can increase maximal oxygen uptake by up to 25 percent. This increase depends on the initial level of fitness and age as well as the intensity, frequency, and length of training sessions. Individuals performing aerobic training such as distance running can have maximal oxygen uptakes as high as 60 to 90 mL O_2/kg per minute. For convenience, oxygen consumption is often expressed in multiples of basal resting requirements. The metabolic equivalent (MET) is a unit of basal oxygen consumption equal to approximately 3.5 mL O_2 per kilogram of body weight per minute. This is the amount of oxygen required to sustain life in the resting state. Table 14-3 lists clinically meaningful METs for exercise, prognosis, and maximal performance.

Table 14-3: Clinically Significant Metabolic Equivalents for Maximum Exercise

1 MET*	Resting
2 METs	Level walking at 2 mi/h
4 METs	Level walking at 4 mi/h
<5 METs	Poor prognosis; usual limit immediately after myocardial infarction, peak cost of basic activities of daily living
10 METs	Prognosis with medical therapy as good as coronary artery bypass surgery
13 METs	Excellent prognosis regardless of other exercise responses
18 METs	Elite endurance athletes
20 METs	World-class athletes

*MET = metabolic equivalent, or a unit of sitting resting oxygen uptake. 1 MET = 3.5 mL/kg/min oxygen uptake.

SOURCE: From Fletcher GF, Balady G, Froelicher VF, et al. Exercise standards: A statement for health professionals from the American Heart Association Writing Group. *Circulation* 1995; 91:580-615. Reproduced with permission from the publisher and authors.

It is preferable to estimate an individual's maximal oxygen uptake from the workload reached while performing an exercise test. Maximal oxygen uptake is, of course, most precisely determined by direct measurement using ventilatory gas-exchange techniques. Thus, if quantifying work with precision is an important objective, such as in athletics, research studies, and patients considered for cardiac transplantation, a direct measurement is essential. *Clinical exercise test results always should be reported in METs and not minutes of exercise.* In this way, the results from different protocols and exercise modalities can be compared directly.

NORMAL VALUES FOR EXERCISE CAPACITY

Maximal oxygen uptake declines with increasing age, and higher values are observed among men compared with women. Thus, when measuring or estimating maximal oxygen uptake, it is useful to have reference values for comparison. Many clever attempts have been made to improve the prediction of what represents a "normal" exercise capacity by including height, weight, body composition, activity status, exercise mode, and such clinical and demographic factors as smoking history, heart disease, and medications.[43] It is important to note that a "normal" value is only a number that has been inferred from some population. A predicted normal value usually refers to age and gender, but many other factors affect one's exercise capacity. In addition to those just mentioned, such factors include some that are not so easily measured, such as genetics and the type and extent of disease.

Regression Equations

The following are commonly used generalized equations based on data published[44-47] in North America and Europe in the 1950s, 1960s, and 1970s:

Males:

$$\dot{V}O_2max\ (L/min) = 4.2 - 0.032\ (age)\ (SD \pm 0.4)$$
$$\dot{V}O_2max\ (mL/kg/min) = 60 - 0.55\ (age)\ (SD \pm 7.5)$$

Females:

$$\dot{V}O_2max\ (L/min) = 2.6 - 0.014\ (age)\ (SD \pm 0.4)$$
$$\dot{V}O_2max\ (mL/kg/min) = 48 - 0.37\ (age)\ (SD \pm 7.0)$$

Application of Nomograms

Morris et al.[48] developed a nomogram from 1388 male veteran patients (Fig. 14-7). The regression equations derived from the group were:

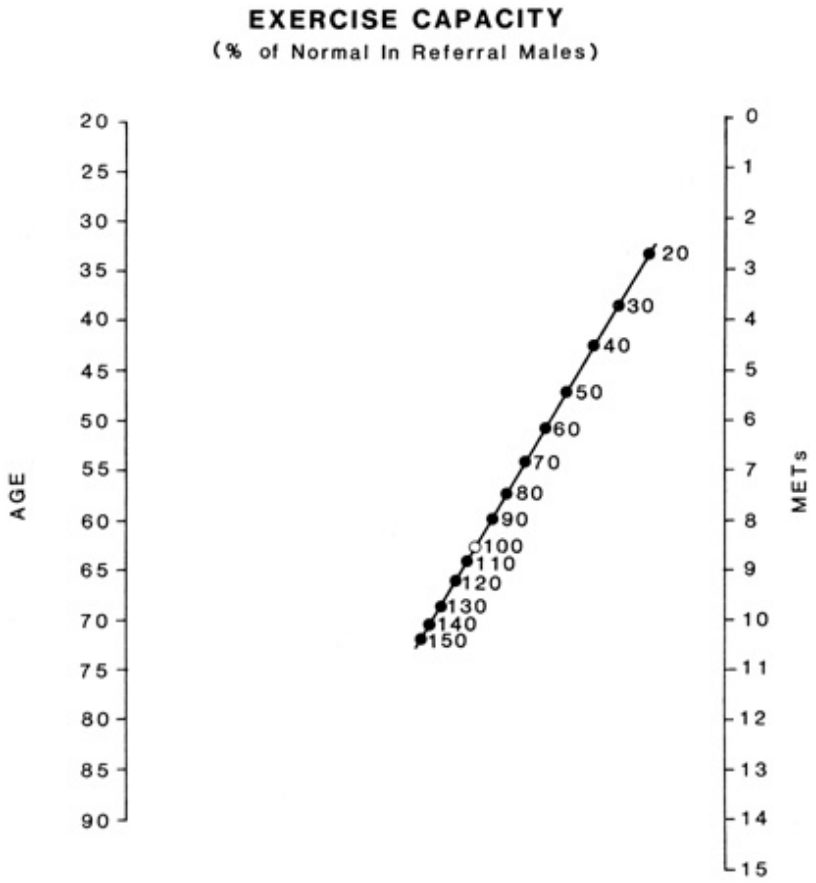

Figure 14-7: The exercise capacity nomogram providing a relative estimate of normal for age, with 100 percent being as expected for age in a clinical population.

All subjects:

$$\text{METs} = 18.0 - 0.15(\text{age}), \text{SEE} = 3.3, r = -0.46, p < 0.001$$

Active subjects:"

$$\text{METs} = 18.7 - 0.15(\text{age}), \text{SEE} = 3.0, r = -0.49, p < 0.001$$

Sedentary subjects:

$$\text{METs} = 16.6 - 0.16(\text{age}), \text{SEE} = 3.2, r = -0.43, p < 0.001$$

When using regression equations or nomograms for reference purposes, it is important to consider several points. First, as mentioned, the relationship between exercise capacity and age is rather poor (r = 0.30 to 0.60). Second, nearly all equations are derived from different populations using different protocols. Thus, to some extent, they are both population- and protocol-specific. Moreover, since treadmill time or workload tends to overpredict maximal METs, it is important to consider whether gas-exchange techniques were used in developing the equations. For example, the equations developed by Morris et al.[48] were derived from a large group of veterans referred for testing for clinical reasons. Thus they had a greater prevalence of heart disease than patients in the other studies, and it is not surprising that a steeper slope was present with a faster decline in $_{O_2max}$ with age.

To account for the differences in measured versus predicted oxygen uptake, a nomogram also was developed using measured oxygen uptake among 244 active or sedentary apparently healthy males (Fig. 14-

8). The MET values are shifted downward roughly 1.0 to 1.5 METs for any given age, reflecting the lower but more precise measures of exercise capacity:

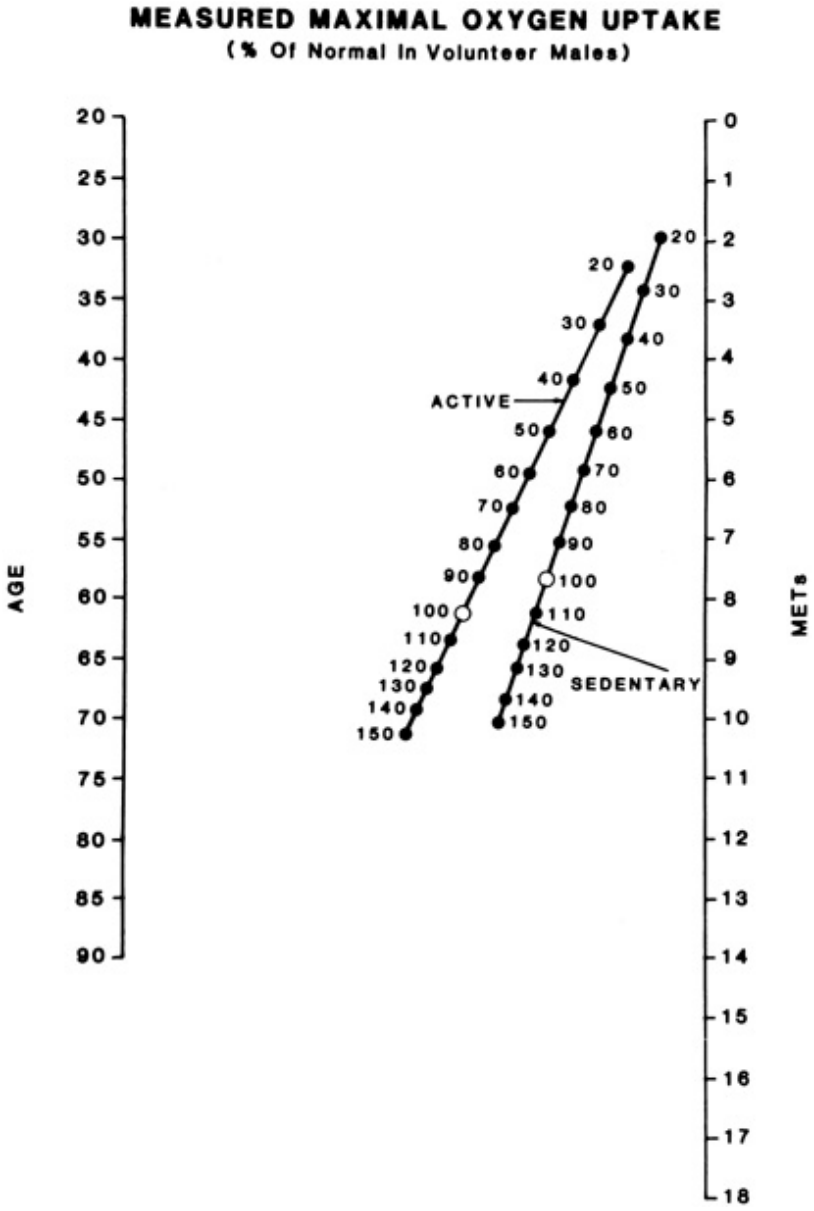

Figure 14-8: The exercise capacity nomogram for estimating aerobic impairment in normal male volunteers.

All subjects:

$$METs = 14.7 - 0.11(age)$$

Active subjects:"

$$METs = 16.4 - 0.13(age)$$

Sedentary subjects:

$$METs = 11.9 - (-0.07)(age)$$

Thus such scales are specific to both the population tested and to whether oxygen uptake was measured directly or predicted. Within these limitations, these equations and the nomograms derived from them can provide reasonable references for normal values and can facilitate communication with patients and between physicians regarding their level of exercise capacity in relation to their peers.

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ECG INTERPRETATION

ST Analysis

ST-segment depression is a representation of global subendocardial ischemia, with a direction determined largely by the placement of the heart in the chest. ST-segment depression does not localize coronary artery lesions. V_5 is the lead predominating in significant ST-segment depression. Depression isolated to other leads is usually due to Q-wave distortion of the resting ECG. ST-segment depression in the inferior leads (II, aV_F) is most often due to the atrial repolarization wave that begins in the PR segment and can extend to the beginning of the ST segment. When ST-segment depression is isolated to these leads and there are no diagnostic Q waves, it is usually a false-positive response.[48] ST-segment depression limited to the recovery period does not generally represent a false-positive response. Inclusion of analysis during this time period increases the diagnostic yield of the exercise test.

When the resting ECG shows Q waves of an old myocardial infarction, ST-segment elevation is due to wall-motion abnormalities, whereas accompanying ST-segment depression can be due to a second area of ischemia or reciprocal changes. When the resting ECG is normal, exercise-induced ST-segment elevation is due to severe ischemia (spasm or a critical lesion), although accompanying ST-segment depression is reciprocal. Such ST-segment elevation is uncommon and very arrhythmogenic, and it localizes the involved coronary artery. Exercise induced ST-segment elevation (not over diagnostic Q waves) and ST-segment depression both represent ischemia, but they are quite distinctive: Elevation is due to transmural ischemia, is arrhythmogenic, has a 0.1 percent prevalence, and localizes the artery where there is spasm or a tight lesion, whereas depression is due to subendocardial ischemia, is not arrhythmogenic, has a 5 to 50 percent prevalence, is rarely due to spasm, and does not localize. Figure 14-9 illustrates the various patterns. The standard criterion for abnormal is 1 mm of horizontal or downsloping ST-segment depression below the PR isoelectric line or 1 mm further depression if there is baseline depression. While computer analysis can help interpretation, the raw data always should be considered first because processing can cause artifacts.[49] Also, though numerous computerized ST-segment scores have been recommended, they only appear to be equivalent to visual interpretation using standard criteria. Most information is available in lead V_5, with maximal exercise and 3 min of recovery being the most important times to look for ST-segment depression.[50] ECG recordings should continue for 5 min in recovery or until any new changes from baseline stabilize.

Nonsustained ventricular tachycardia is uncommon during routine clinical treadmill testing (prevalence <2 percent) and is well tolerated, and its prognosis is determined by the accompanying ischemia and left ventricular damage.[51]

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THE ACC/AHA GUIDELINES FOR THE USE OF THE STANDARD EXERCISE TEST

The task force to establish guidelines for the use of exercise testing produced guidelines in 1986 and 1997.[52] The most recent publication had some dramatic changes from the first, including the recommendation that the standard exercise test be the first diagnostic procedure in women and in most patients with resting ECG abnormalities rather than performing imaging studies. The following classifications were used to summarize the indications for exercise testing:

- *Class I:* Conditions for which there is evidence and/or general agreement that the exercise test is useful and effective (appropriate).
- *Class II:* Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the exercise test.
- *Class IIa:* Weight of evidence/opinion is in favor of usefulness/efficacy (probably appropriate).
- *Class IIb:* Usefulness/efficacy is less well established by evidence/opinion (maybe appropriate).
- *Class III:* Conditions for which there is evidence and/or general agreement that the exercise test is not useful/effective and in some cases may be harmful (not appropriate).

Patients who are candidates for exercise testing may have stable symptoms of chest pain, may be stabilized by medical therapy following symptoms of unstable chest pain, or may be postmyocardial infarction or postrevascularization patients. The indications provided in the guidelines are summarized below.

For Diagnosis of Coronary **Artery** Disease

Exercise testing for the diagnosis of obstructive coronary artery disease is one of the most common uses of exercise testing. Most relative evidence for this use has been gathered in patients presenting with chest pain, although it has been logically extended to those with other symptomology or ECG changes possibly due to coronary artery disease. Appropriate evidence-based use of the test for this application (class I) is in adult patients (including those with complete right bundle branch block or less than 1 mm of resting ST-segment depression) with an intermediate pretest probability of coronary artery disease based on gender, age, and symptoms (Table 14-4) (see also Chap. 40). A probable diagnostic use of the test (less evidence) is in patients with vasospastic angina (class IIa). The efficacy is less well established by evidence/opinion (class IIb) in patients with a low or high pretest probability of coronary artery disease by age, symptoms, and gender and in patients with less than 1 mm of baseline ST-segment depression and taking digoxin or with left ventricular hypertrophy. The exercise ST-segment analysis should not be used for diagnosis (class III) in patients with Wolff-Parkinson-White syndrome, left bundle-branch block, electronic pacemakers, or greater than 1 mm of resting ST-segment depression. Patients with a documented myocardial infarction or prior coronary angiography or intervention demonstrating significant disease should not be tested for diagnosis because they have an established diagnosis of coronary artery disease; however, ischemia and risk can be determined by testing.

Table 14-4: Pretest Probability of Coronary Artery Disease by Symptoms, Gender, and Age

Age	Gender	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30-39	Males	Intermediate	Intermediate	Low (<10%)	Very low (<5%)
	Females	Intermediate	Very low (<5%)	Very low	Very low
40-49	Males	High	Intermediate	Intermediate	Low
	Females	Intermediate	Low	Very low	Very low
50-59	Males	High (>90%)	Intermediate	Intermediate	Low
	Females	Intermediate	Intermediate	Low	Very low
60-69	Males	High	Intermediate	Intermediate	Low
	Females	High	Intermediate	Intermediate	Low
High = >90%		Intermediate = 10-90%		Low =<10%	Very Low = <5%

NOTE: There are no data for patients or athletes younger than age 30 or older than age 69, but it can be assumed that coronary artery disease prevalence increases with age.

Diagnostic testing is most valuable in patients with an intermediate pretest probability. Exercise testing for the diagnosis of coronary artery disease is expressed most commonly by sensitivity and specificity. Results of correlative studies have been divided over the use of 50 or 70 percent luminal diameter occlusion. Metaanalysis of 58 consecutively published reports involving 11,691 patients without prior myocardial infarction who underwent coronary angiography and exercise testing revealed a wide variability in sensitivity and specificity.[53] Mean sensitivity was 67 percent, and mean specificity was 72 percent. In the studies where workup bias was avoided by having the patients with chest pain agree to undergo both procedures, the approximate sensitivity and specificity of 1 mm of horizontal or downsloping ST-segment depression for diagnosis of coronary artery disease were 50 and 90 percent, respectively.[54] The true diagnostic value of the exercise ECG lay in its relatively high specificity, but the sensitivity can be enhanced by consideration of clinical and hemodynamic variables in scores.

Screening for Silent Coronary Artery Disease in Asymptomatic Individuals

A diagnostic test such as the exercise ECG can be used to screen asymptomatic individuals for coronary artery disease. As mentioned previously, there are 12 studies using the exercise test to do such.[55] Patients were screened for silent heart disease using the exercise test and followed for 5 to 10 years for cardiac events. Considerably different results were obtained in these studies according to the end points considered. When angina is included as an end point, nonspecific symptoms in a subject with an abnormal test are more likely to be called coronary artery disease during the follow-up period. Hard end points, such as death or myocardial infarction, eliminate this misclassification and are more appropriate. The first eight screening studies included angina as an end point; the last four have used only hard end points. In Table 14-5, the first eight studies tested 5000 subjects and ranged in size from 113 to 1390 individuals. Sensitivity was 50 percent, specificity was 90 percent, the risk ratio was 9, and the predictive value of a positive response was 25 percent. This means that 1 of 4 patients with abnormal tests went on to have a cardiac event. Remember that some of these events will be angina, which probably was not actually due to coronary artery disease or truly angina. The last four studies have been larger in size and have included only hard end points. The sensitivity of the test has been about 25 percent, specificity about 90 percent, the risk ratio was 4, and the predictive value of a positive response was only 5 percent. This means that only 1 of 20 people with an abnormal test went on to a cardiac event. Because of this very limited predictive value, in any asymptomatic population, screening has not been recommended. It will lead to many other unnecessary tests. Attempts to raise the pretest probability by considering risk factors have not been able to limit the

false-positive results and improve the predictive value. Theoretically, this should be possible by using a risk factor score.

Table 14-5: The Twelve Screening Studies

Study	No. of Patients	Sensitivity	Specificity	Relative Risk	Predictive Value (+)
First 8 (soft end points)	5526	50%	90%	9×	25%
Last 4 (hard end points)	12,212	25%	90%	4×	5%

Using soft end points exaggerates the sensitivity and predictive value of the test. This could be avoided by blinding all parties to the test result, but this has been considered unethical. Since some of the asymptomatic individuals developing chest pain really have angina due to coronary artery disease, the sensitivity probably lies between the 25 and 50 percent obtained in the studies that used respectively hard and hard plus soft end points. While soft end points are very appropriate for intervention studies, they can result in important prediction errors in studies of diagnostic procedures.

Screening studies have other important population selection considerations. First, the population should truly be asymptomatic and should represent a random sample of the target population. Volunteers are not appropriate because they usually represent the extremes of the population: the healthiest and those who are concerned for personal reasons regarding their health (i.e., family history, symptoms they chose to deny, etc.). Volunteers represent a subtle form of limited challenge.

There is no class I indication for the use of the exercise test in asymptomatic persons without known coronary artery disease because the available evidence demonstrates a large number of false-positive results in low-prevalence populations.

The efficacy of using the exercise test in evaluation of persons with multiple risk factors or of asymptomatic men older than 40 years and women older than 50 years who plan to start vigorous exercise (especially if sedentary) or who are involved in occupations in which impairment may have an impact on public safety or who are at high risk for coronary artery disease due to other diseases (e.g., chronic renal failure) is possibly but not definitely supported by evidence (class IIb).

The test should not be used for routine screening (class III) of asymptomatic men or women.

COMPARISON WITH OTHER DIAGNOSTIC TESTS

While the studies of the standard exercise test have been helpful in illustrating the problems in demonstrating test characteristics, newer technologies often have been evaluated by studies with the same limitations. Nonetheless, it is appropriate to compare the newer diagnostic modalities with the standard exercise test because it is a mature, established technology. The equipment and personnel for performing it are readily available. Exercise testing equipment is relatively inexpensive, so replacement or updating is not a major limitation. The exercise test can be performed in the doctor's office and does not require injections or exposure to radiation. It can be an extension of the medical history and physical examination, providing more than simply diagnostic information. Furthermore, it can determine the degree of disability and impairment to quality of life as well as be the first step in rehabilitation and altering a major risk factor (physical inactivity).

Some of the newer add-ons or substitutes for the exercise test have the advantage of being able to localize ischemia as well as diagnose coronary artery disease when the baseline ECG negates ST-segment analysis (more than 1 mm of ST-segment depression, left bundle branch block, Wolff-Parkinson-White syndrome). The substitutes for exercise also have the advantage of not requiring the patient to exercise and are particularly valuable clinically for those unable to ambulate. However, while the newer technologies appear to have better diagnostic characteristics, this is not always the case, particularly when more than the ST segments from the exercise test are used in scores.

Test evaluation has been advanced by the critical analysis of Feinstein[56,57] and Guyatt.[58] A number of researchers have applied these guidelines along with meta-analyses to reach a consensus on the diagnostic characteristics of the available tests for angiographic coronary **artery** disease.[59,60] Table 14-6 presents some of the results from meta-analyses and from multicenter studies. Techniques listed include electron-beam computed tomography (EBCT), a radiographic technique that can make a quantitative measurement of coronary artery calcification.[61,62] Nuclear perfusion imaging includes both the early studies mainly using thallium radiographic images and the more modern use of single-photon-emission computed tomography (SPECT), which requires computer enhancement of the emissions of thallium and other agents.

Table 14-6: Comparison of Exercise Testing and Add-Ons or Other Test Modalities

Grouping	No. of Studies	Total No. of Patients	Sensitivity	Specificity	Predictive Accuracy
Meta-analysis of standard exercise ECG	147	24,047	68%	77%	73%
Excluding myocardial infarction patients	58	11,691	67%	72%	69%
Limiting workup bias	2	>1,000	50%	90%	69%
Meta-analysis of exercise test scores	24	11,788			80%
Thallium scintigraphy	59	6,038	85%	85%	85%
SPECT without myocardial infarction	27	2,136	86%	62%	74%
Exercise ECHO	58	5,000	84%	75%	80%
Exercise ECHO excluding myocardial infarction patients	24	2,109	87%	84%	85%
Nonexercise stress tests					
Persantine thallium	11	<1,000	85%	91%	87%
Dobutamine ECHO	5	<1,000	88%	84%	86%
Electron-beam computed tomography (EBCT)	5	2,373	90%	45%	61%

Since sensitivity and specificity are inversely related and altered by the chosen cut point for normal/abnormal, the predictive accuracy (percentage of patients correctly classified as normal and abnormal) is a convenient way to compare tests. For instance, while the sensitivity and specificity for exercise testing and EBCT are nearly opposite, the predictive accuracy of the tests is similar. This means that altering their cut points (i.e., lowering the amount of ST-segment depression or raising the calcium score) would result in similar sensitivities and specificities. Since predictive accuracy can be thought of as the number of individuals correctly classified out of 100 tested, simply subtracting predictive accuracy provides an estimate of how many more patients are classified by substituting one test for another test. However, this does assume a disease prevalence of 50 percent that is the intermediate probability for appropriateuse of diagnostic tests (i.e., predictive accuracy is affected by disease prevalence).

While the nonexercise stress tests are very useful, the results shown in Table 14-6 are probably better than their actual performance because of patient selection. For studies of diagnostic characteristics, patients with

a prior myocardial infarction should be excluded because diagnosis of coronary artery disease is already known to be present.

EXERCISE TEST SCORES

The exercise testing studies that have considered additional information besides the ST-segment response have been reviewed and demonstrate the improved test characteristics obtained using this approach.[63] Recent publications have extended the Duke prognostic score to diagnosis,[64] and a consensus approach that uses a number of equations appears to make the scores more applicable to other populations.[65]

EXERCISE NUCLEAR PERFUSION AND ECHOCARDIOGRAPHY

A review of the contemporary literature compared the diagnostic performance of exercise echocardiography and exercise nuclear perfusion scanning in the diagnosis of coronary artery disease (see Chaps. 13 and 16).[66] Studies published between January 1990 and October 1997 were identified from MEDLINE search, bibliographies of reviews and original articles, and suggestions from experts in each area. Articles were included if they discussed exercise echocardiography and/or exercise perfusion imaging for detection and/or evaluation of coronary artery disease, if data on coronary angiography were presented as the reference test, and if the absolute numbers of true-positive, false-negative, true-negative, and false-positive observations were available or derivable from the data presented. Studies performed exclusively in patients after myocardial infarction, with coronary interventions, or with recent unstable coronary syndromes were excluded. Two reviewers used a standardized spreadsheet to independently extract data with discrepancies and resolve them by consensus. Forty-four articles met inclusion criteria: 24 reported exercise echocardiography results in 2637 patients with a weighted mean age of 59 years, 69 percent men, 66 percent with angiographic coronary artery disease, and 20 percent with prior myocardial infarction, and 27 reported exercise SPECT in 3237 patients, 70 percent men, 78 percent with angiographic coronary artery disease, and 33 percent with prior myocardial infarction. In pooled data weighted by the sample size of each study, exercise echocardiography had a sensitivity of 85 percent (95% CI, 83-87 percent) with a specificity of 77 percent (95% CI, 74-80 percent). Exercise perfusion yielded a similar sensitivity of 87 percent (95% CI, 86-88 percent) but a lower specificity of 64 percent (95% CI, 60-68 percent).

ELECTRON-BEAM COMPUTED TOMOGRAPHY

Of the angiographic correlative studies of EBCT, we selected the five with more than 200 subjects without overlapping populations. One hundred and sixty men and women with coronary artery disease (45-62 years of age), of whom 138 had obstructive coronary artery disease and 22 had normal coronary arteries, and 56 age-matched healthy control subjects underwent double-helix CT.[67] Sensitivity in detecting obstructive coronary artery disease was high (91 percent); however, specificity was low (52 percent) because of calcification in nonobstructive lesions. A multicenter study evaluated patients referred for angiography.[68] Four hundred and ninety-one symptomatic patients underwent coronary angiography and EBCT at five different centers between 1989 and 1993. Sensitivity of any detectable calcification by EBCT as an indicator of significant stenosis (>50 percent narrowing) was 92 percent, and specificity 43 percent. When these CT images were reinterpreted in a blinded and standardized manner, however, specificity was only 31 percent. In another multicenter study[69] of 710 enrolled patients, 427 had significant angiographic coronary artery disease, and coronary artery calcification was detected in 404, yielding a sensitivity of 95 percent. Of the 283 patients without angiographically significant disease, 124 had negative EBCT studies, for a specificity of 44 percent. Ultrafast CT was used to detect and quantify coronary artery calcium levels in 584 subjects, 19 percent of whom had clinical coronary artery disease.[70] Sensitivity, specificity, and predictive values for clinical coronary artery disease were calculated for several total calcium scores in each decade. For age groups 40 to 49 and 50 to 59 years, a total score of 50 resulted in sensitivities of 71 and 74 percent, respectively, and specificities of 91 and 70 percent, respectively. For the age group 60 to 69 years, a total score of 300 gave a sensitivity of 74 percent and a specificity of 81 percent. Three hundred and sixty-eight symptomatic patients underwent coronary angiography and EBCT at four different centers between April 1989 and December 1993.[71] One hundred and fifty-eight patients (43 percent) had angiographically obstructive coronary artery disease (>50 percent), and 297 (81 percent) had coronary calcification. It appears that even the best studies of EBCT suffer from limited challenge and workup bias so that the true characteristics of this procedure are not known. However, the five studies averaged in the table

demonstrated a high sensitivity and a low specificity, with a predictive accuracy of about 61 percent. While adjusting the cut point for calcium density can alter the sensitivity and specificity, EBCT is not more diagnostic for angiographic coronary artery disease than the standard exercise test (see Chaps. 17 and 40).

For Risk Assessment and Prognosis

Risk assessment (prognostication) and postmyocardial infarction are the next two applications of the standard exercise ECG. The test should not be performed in these situations in patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularization (class III).

The second major application of the exercise ECG test is for assessment of risk and prognosis in patients with symptoms or a prior history of coronary artery disease. Appropriate evidence-based use of the test for this application (class I) is in patients undergoing initial evaluation or in patients with significant change in clinical status with suspected or known coronary artery disease.

Exercise testing may be useful for prognostic assessment of patients on digoxin or with abnormal resting ECGs, but its usefulness is less well established in this setting (class IIb). Also, the exercise test may still provide prognostic information (particularly exercise capacity) in patients with preexcitation, ventricular paced rhythm, more than 1 mm of ST-segment depression, and left bundle-branch block but cannot be used to identify ischemia. The test also may be used in patients with a stable clinical course who undergo periodic monitoring to guide treatment. The Duke treadmill score (see nomogram in Fig. 14-10) incorporates two of the major prognostic markers (i.e., exercise capacity[72] and exercise-induced ischemia) and was strongly recommended.[73]

After Myocardial Infarction

The third major application of the exercise ECG is for patients within 2 months of a myocardial infarction.[74] Appropriate evidence-based uses of the test for prognostic assessment, activity prescription, evaluation of medical therapy, and cardiac rehabilitation of these patients (class I) are (1) before discharge for prognostic assessment, activity prescription, or evaluation of medical therapy (submaximal at about 4-7 days), (2) early after discharge if the predischarge exercise test was not done (symptom-limited, about 14-21 days), and (3) late after discharge if the early exercise test was submaximal (symptom-limited, about 3-6 weeks). A probable postmyocardial infarction use of the test (less evidence) is for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone coronary revascularization (class IIa). The efficacy is less well established by evidence/opinion (class IIb) before discharge in patients who have undergone cardiac catheterization to identify ischemia in the distribution of a coronary lesion of borderline severity or in those with the above-mentioned ECG abnormalities that interfere with the recognition of ischemia or for periodic monitoring in patients who continue to participate in exercise training or cardiac rehabilitation.

A meta-analysis of 28 studies involving 15,613 patients found that markers of ventricular dysfunction were more accurate predictors of adverse cardiac events after myocardial infarction than measures of exercise-induced ischemia.[75] A similar study in the postthrombotic age considered other test modalities and validated these conclusions.[76-78]

Exercise Testing Using Ventilatory Gas Analysis

Evidence supports the addition of ventilatory gas analysis to the exercise test (class I) for the evaluation of exercise capacity and response to therapy in patients with heart failure who are being considered for heart transplantation and when assistance is needed in differentiating cardiac versus pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity.

A probable reason to add gas analysis to the exercise test (less evidence, class IIa) is for the evaluation of exercise capacity when indicated for medical reasons in patients in whom subjective assessment of maximal exercise is unreliable.

The efficacy of adding gas analysis is less well established by evidence/opinion (class IIb) for evaluation of the patient's response to specific therapeutic interventions in which improvement of exercise tolerance is an important goal or end point or for determination of the intensity for exercise training as part of comprehensive cardiac rehabilitation.

Expired gas analysis is not indicated (class III) routinely to evaluate exercise capacity.

Valvular Heart Disease

There is no evidence-based class I indication for testing patients with valvular heart disease. The test possibly can be used, although there are no convincing data to evaluate exercise capacity in patients with valvular heart disease (class IIb). The exercise ECG should not be used to diagnose coronary artery disease in patients with valvular heart disease (class III).

Before and After Revascularization

The evidence supports the use of the exercise ECG test to demonstrate ischemia before revascularization and to evaluate patients with recurrent symptoms suggesting ischemia after revascularization (class I).

A probable use of the test (less evidence) is after discharge for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone coronary revascularization (class IIa). The efficacy is less well established by evidence/opinion (class IIb) for detection of restenosis in selected high-risk asymptomatic patients within the first months after angioplasty or for periodic monitoring of selected high-risk asymptomatic patients for restenosis, graft occlusion, or disease progression.

The test should not be used to localize ischemia for determining the site of intervention or for routine periodic monitoring of asymptomatic patients after percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting without specific indications (class III).

Since the guidelines were published, investigators have found nuclear perfusion exercise testing to be important in prognostication in patients after coronary artery bypass grafting.[78]

Investigation of Heart Rhythm Disorders

The exercise test should be used to identify the appropriate settings in patients with rate-adaptive pacemakers (class I).

A probable use of the test (less evidence) is for evaluation of patients with known or suspected exercise-induced arrhythmias or for evaluation of medical, surgical, or ablative therapy in patients with exercise-induced arrhythmias (including atrial fibrillation) (class IIa). The efficacy is less well established by evidence/opinion for investigation of isolated ventricular ectopic beats in middle-aged patients without other evidence of coronary artery disease (class IIb).

The test should not be used to investigate isolated ectopic beats in young patients (class III).

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Chapter 14: ECG EXERCISE TESTING

SUMMARY

While cardiologists are frequently relinquishing the performance of the standard exercise test to internists and family practitioners, it is important that the latter be properly trained to do it correctly and have expertise in its interpretation. However, the addition of echocardiography or myocardial perfusion imaging does not negate the importance of the ECG or clinical and hemodynamic responses to exercise. The exercise test complements the medical history and the physical examination, and it remains the second most commonly performed cardiologic procedure next to the routine ECG. The renewed efforts to control costs undoubtedly will support the role of the exercise test. Convincing evidence that treadmill scores enhance the diagnostic and prognostic power of the exercise test certainly has cost-efficacy implications. In addition, there is also evidence that measurement of expired gases improves the prognostic power of the test in certain groups of patients and helps to determine if exercise intolerance is due to the heart or the lungs.

Use of proper methodology is critical for safety and obtaining accurate and comparable results. The use of specific criteria for exclusion and termination, interaction with the subject, and appropriate emergency equipment are essential. The exercise protocol should be progressive, with even increments in speed and grade whenever possible.

The following rules are important to follow for getting the most information from the standard exercise test:

- The treadmill protocol should be adjusted to the patient, and one protocol is not appropriate for all patients; consider using a manual or automated ramp protocol.
- Report exercise capacity in METs, not minutes of exercise.
- Hyperventilation prior to testing is not indicated.
- ST-segment measurements should be made at ST0 (J-junction) and ST-segment depression should only be considered abnormal if horizontal or downsloping.
- Raw ECG waveforms should be considered first and then supplemented by computer-enhanced (filtered and averaged) waveforms when the raw data are acceptable.
- Patients should be placed supine as soon as possible after exercise, with a cool-down walk avoided in order for the test to have its greatest diagnostic value.
- The 3-min recovery period is critical to include in analysis of the ST-segment response.
- Measurement of systolic blood pressure during exercise is extremely important, and exertional hypotension is ominous; at this point, only manual blood pressure measurement techniques are valid.
- Age-predicted heart rate targets are largely useless because of the wide scatter for any age; a relatively low heart rate can be maximal for a patient of a given age and submaximal for another. Thus a test should not be considered nondiagnostic if a percentage of age-predicted maximal heart rate (i.e., 85 percent) is not reached. In fact, chronotropic incompetence or heart rate impairment has important prognostic implications.
- Calculation of the Duke treadmill score for every patient should be considered.
- Other predictive equations should also be considered as part of the treadmill report.

To ensure the safety of exercise testing, the following list of the most dangerous circumstances in the exercise testing laboratory should be recognized:

- Testing patients with aortic valvular disease should be done with great care because they may develop severe cardiovascular complications. Thus, a physical examination including assessment of systolic murmurs should be done before all exercise tests. If a significant murmur is heard, an echocardiogram should be considered.
- When patients exhibit ST-segment elevation without diagnostic Q waves due to transmural ischemia, this can be associated with dangerous arrhythmias and infarction. The incidence is about 1 in 1000 clinical tests and usually occurs in V_2 or aV_F rather than V_5.
- When a patient with an ischemic cardiomyopathy exhibits severe chest pain due to ischemia (angina pectoris), a cool-down walk is advisable because the ischemia can worsen in the recovery period.
- When a patient develops exertional hypotension accompanied by ischemia (angina or ST-segment depression) or when it occurs in a patient with a history of congestive heart failure, cardiomyopathy, or recent myocardial infarction, safety is a serious issue.
- When a patient with a history of sudden death or collapse during exercise develops premature ventricular contractions that become frequent, a cool-down walk is advisable because the premature ventricular contractions can increase in recovery, particularly after an abrupt cessation of exercise.

The ACC/AHA guidelines for exercise testing clearly indicate the correct uses of exercise testing. Since the last guidelines, it has been extended as the first diagnostic test in women and in individuals with right bundle branch block and resting ST-segment depression. The Duke prognostic nomogram and scores increase the value of the exercise test. In fact, the use of scores results in test characteristics that approach the nuclear and echocardiographic add-ons to the exercise test.

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 15:

CARDIAC CATHETERIZATION, CORONARY ARTERIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

Authors: Robert H. Franch, John S. Douglas, Jr., Spencer B. King III, Morton J. Kern

In 1929, Werner Forssman, a resident surgeon at Eberswalde, catheterized his right atrium from a left antecubital vein cutdown using self-fluoroscopy with a mirror. The position of the catheter tip was verified by a roentgenogram.[1] The extensive use of the right heart catheter by Cournand in the early 1940s in the study of human cardiovascular physiology led his group and others to explore the use of this technique for the study of heart disease.[2] In 1945, Brannon, Weens, and Warren described the hemodynamics of atrial septal defect in four patients. From these beginnings, steady advances in methods occurred.[3,4] Catheterization then spread from the laboratory to the bedside, to yield physiologic data and to guide treatment.[5] Now, palliative and corrective interventions involving valves, arteries, veins, and septal defects may accompany the catheterization study.[6]

PREPARATIONS FOR CARDIAC CATHETERIZATION

A relaxed meeting with the patient and the patient's family serves to lessen apprehension, correct any misunderstanding, and establish rapport. Since catheterization is frequently the first major step on the road to cardiac surgery, a tolerable experience fosters an optimistic attitude in the patient and family toward future events. The patient should be examined, and the history, a current chest x-ray, an electrocardiogram, and past catheterizations should be reviewed, along with surgical records, angiocardiograms, and echocardiograms. The site of optimal vascular access is chosen. Nearly all balloon catheters and many gloves contain latex, and it should be added to the list of allergens sought in the history.[7] Old operative notes are examined, especially for complex palliation or repair. A clinical diagnosis is made, and a catheterization protocol is designed to answer pertinent specific questions. The catheterization protocol also may be modified as data become available during the procedure. The patient's education booklet about the procedure is usually read by the patient and the family prior to securing informed consent. Absolute contraindications include the refusal of a competent adult or the absence of a qualified operator and/or a suitable facility[8] (Table 15-1). Anticoagulants are stopped, and the prothrombin time is brought to less than 18 s (INR <2) before a percutaneous arterial catheterization. Dimethyl biguanide, an oral hypoglycemic drug, is not given for 2 days prior to angiography. Serum levels of creatinine, urea nitrogen, and potassium are noted. A patient with chronic renal disease is hydrated; prophylaxis for past allergy to contrast material is given.[9] Breakfast is withheld for a morning procedure; for an afternoon procedure, coffee or juice is permitted, and lunch is withheld. In our experience, prophylactic antibiotics are not necessary. Conscious sedation for diagnostic catheterization involves the incremental use of intravenous drugs that are titrated to each patient's response. Pulse oximeter monitors require accuracy to within 3 percent in the 70 to 100 percent saturation range. Diazepam (Valium) or midazolam (Versed) is given intravenously; intravenous fentanyl may be added for more sedation. Intravenous hydromorphone (Dilaudid) is used if analgesia is required. Subcutaneous 1% lidocaine (Xylocaine) is used locally. If there is a history of allergy, intradermal or subcutaneous testing is done with serial dilutions of a preservative-free local anesthetic agent.[10] Occasionally, particularly in adults, vagal slowing of the pulse, nausea, and perspiration are noted, for which intravenous atropine is the antidote. Systemic anticoagulation is achieved via a bolus of heparin at the start of a diagnostic study that uses the brachial artery but not routinely if the femoral artery is used.

Table 15-1: Contraindications to Cardiac Catheterization

THE ONLY ABSOLUTE CONTRAINDICATIONS
1. Refusal of a mentally competent adult (>16 years of age) patient, or of the parent(s) (guardians) of children, infants, or neonates to consent to the procedure
2. Absence of an experienced cardiac angiography and/or suitable laboratory facilities
RELATIVE CONTRAINDICATIONS TO BE CAUTIOUSLY APPLIED TO INDIVIDUAL PATIENT
1. Significant electrolyte abnormalities or digitalis toxicity
2. Uncontrolled hypertension
3. Febrile illness (not related to endocarditis)
4. Decompensated congestive heart failure
5. Bleeding diathesis: includes patients receiving anticoagulation therapy whose prothrombin time is >18 s (INR >2)
6. Presence of a noncardiac disease that precludes long-term survival
7. Refusal to undergo surgical or interventional curvative or palliative procedures regardless of the outcome of the catheterization (angiogram)
8. Previous history of severe contrast reaction
9. Active gastrointestinal bleeding
10. Pregnancy, especially during first trimester

SOURCE: From Ruiz et al.,[8] with permission from the authors and publisher.

It is desirable that the laboratory be fully involved daily in diagnostic work. General efficiency is increased, costly equipment and space are used, and most important, all personnel become confident and knowledgeable with experience. Certainly the most important ingredient in the laboratory is the thoroughly experienced technical-professional team. The primary objective is to make an accurate diagnosis at one sitting, with the least possible risk and discomfort to the patient. After the procedure, a preliminary, labeled single-page diagram in the patient's chart can accurately present the essence of the catheterization findings.

Outpatient left-sided heart and coronary artery studies require careful selection of patients and an experienced support team.[11,12] The clinical profiles of patients who are not suitable candidates for outpatient catheterization have been published.[13] Others have stated that if a patient is stable enough to be at home before cardiac catheterization, an outpatient catheterization can be considered and a decision following the procedure can be made based on the patient's tolerance of the procedure and the catheterization findings. This approach is most relevant when a catheterization laboratory is in or adjacent to a hospital. The cost savings per patient with outpatient procedures remain significant. Although some physicians have performed cardiac catheterization of stable, low-risk patients in freestanding facilities, the lack of support in this environment is a potential liability, and thus the procedure is not recommended.

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Chapter 15: CARDIAC CATHETERIZATION, CORONARY ARTERIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

TECHNIQUES

Catheterization of the Right Side of the Heart: Percutaneous Venous

Percutaneous femoral or median cubital vein catheterization usually permits reuse of the vein. The femoral vein is entered medial to the common femoral artery pulse. Puncture may be facilitated by a Valsalva maneuver to increase femoral vein size. To extend the range of the percutaneous technique, a thin tubular sheath is advanced over a short introducer catheter into the lumen of the vein. This temporary conduit then may be used to introduce a variety of catheters. Two catheters can be inserted through a single femoral vein puncture site by initially placing two guidewires through the femoral vein sheath; the maneuver is repeated to insert an additional catheter. If the hepatic portion of the inferior vena cava (IVC) is absent, the azygos vein channels the catheter tip into the right superior vena cava (SVC) and then into the right atrium (Fig. 15-1), or the azygos vein may enter a persistent left SVC and then through the coronary sinus to the right atrium (Fig. 15-2). In order to cross the tricuspid valve from the IVC, bending the catheter tip against the right atrial wall may be required. If atrial ectopy occurs, the catheter tip can be looped in a hepatic vein and then advanced into the right atrium. The tip is then rotated from the lateral right atrial wall clockwise across the anterior atrial wall and through the tricuspid valve, followed by a slight counterclockwise turn to the anterolateral position in the right ventricle and then clockwise to place the tip via the outflow tract into the main pulmonary artery and then into the left pulmonary artery, its direct continuation. The foramen ovale is entered with the tip pointed leftward and 45° posteriorly. The SVC lies posteriorly and is entered by making a 60° counterclockwise turn from the lateral right atrial border with a straight catheter tip. The foramen ovale is probe-patent in approximately 20 to 35 percent of adults.

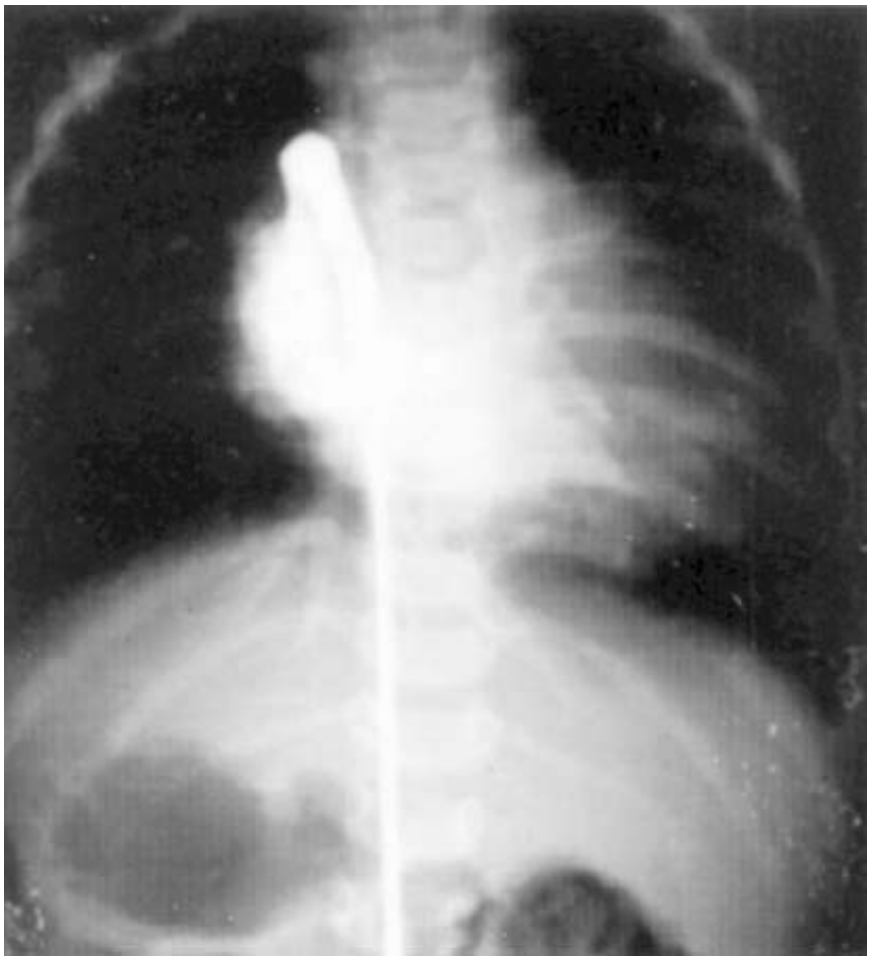

Figure 15-1: Selective injection of a right azygos vein. The hepatic portion of the IVC is absent. The catheter tip enters the right atrium superiorly through the right SVC via the azygos vein.

The internal jugular vein or the subclavian vein also may be used to insert a balloon catheter percutaneously. The latter catheter produces little ectopy because the advancing force is distributed over the surface of the balloon. The tricuspid valve is crossed easily with this approach. If a right-to-left shunt is present, the balloon should be filled with CO_2 and the sidearm of the sheath flushed regularly. In children who lack conventional venous access, transhepatic venous catheterization via a right midaxillary approach is safe and effective.[14]

Rarely, if a venous cutdown is necessary, the right basilic or right median cubital (but not the cephalic) vein is preferred. Care should be taken not to mistake the superficial radial, ulnar, or accessory brachial arteries for veins. From the left arm, the catheter tip may enter a persistent left SVC, exiting via the coronary sinus into the right atrium in an awkward position for entering the right ventricle. A deep inspiration often enables the catheter tip to pass the subclavian vein-brachiocephalic vein junction. The seating of a conventional catheter tip in the pulmonary artery wedge position may be difficult if severe pulmonary artery hypertension or extreme enlargement of the right side of the heart is present. A flow-directed balloon catheter may then be used. Clues to inadvertent coronary sinus catheterizations are (1) the acute angle that the catheter shaft makes as it enters the coronary sinus, especially in the right anterior oblique position, (2) the marked desaturation of coronary sinus blood, and (3) the posterior position of the catheter in the lateral view.

In order to enter the pulmonary artery in patients with transposition of the great arteries and an intact ventricular septum, a balloon catheter is passed across the inevitably present interarterial communication to the left atrium and then superiorly looped in the left ventricular (LV) outflow

tract, from which it enters the pulmonary artery readily. In postoperative patients with pulmonary valve atresia, the pulmonary artery also may be entered via a subclavian (Blalock) or aorticopulmonary (Waterston or Potts) shunt.

Catheterization of the Left Side of the Heart

PERCUTANEOUS TECHNIQUE

In 1953, Seldinger described the use of a flexible metal leader to introduce a polyethylene tube into the artery. The Seldinger technique is used in the common femoral and less often in the axillary radial or brachial arteries in carrying out catheterization of the left side of the heart.[15] The common femoral artery, 4 cm in length, begins at the inguinal ligament and ends at its bifurcation into the deep and superficial femoral arteries at the inferior cortical margin of the head of the femur. The inguinal crease, especially in an obese patient, tends to be inferior to the ligament. In this case, a puncture at or below the crease may involve the superficial femoral artery, and lack of posterior bony support results in poor compression with the chance of bleeding and pseudoaneurysm formation[16] (Fig. 15-3). A skin puncture site chosen 3 cm below the inguinal ligament (not the crease) allows the common femoral artery to be entered at a point where it is compressible against the head of the femur. External rotation of the leg and slight adduction help fixate the artery. The artery is punctured with a nonstylet needle at a 45° angle, transfixing the anterior wall. The guidewire is inserted only when the needle spurt is maximal. Resistance to insertion usually indicates an intramural or extravascular position of the needle or entry into a side branch artery by the guide. The catheter is inserted into the artery over the guidewire, or a sheath assembly may be used, facilitating catheter introduction in a very obese patient or if scar tissue is superficial to the artery. The catheter sheath reduces bleeding during manipulation and reduces discomfort during catheter changes. Arterial pressure may be monitored through a side port in the sheath. Guidewires with torsional control of a flexible distal tip aid passage through a tortuous iliac artery, as does a right Judkins catheter, alone or with a guide. The guide tip is kept at the level of the diaphragm, and the catheter is advanced to this level. The catheter is aspirated and then flushed with heparinized saline solution. To avoid added manipulation of the catheter tip in the transverse arch, the guidewire is placed in the aortic root.[17] The femoral and foot pulses are palpated prior to withdrawal. The artery is compressed for 10 to 15 min, maintaining normal ankle pulses. Devices deployed for sealing the femoral artery puncture site include a collagen plug, a collagen plug with anchor, thrombin with collagen or with fibrin, and a percutaneous suture technique.[18,19] The brachial artery is punctured with an 18-gauge needle, a sheath is inserted, and a no. 6 French 80-cm multipurpose catheter is advanced to the ascending aorta over a 0.032-in. J-guide. Then 5000 units of heparin is given. An arm board is applied for 6 h. Rarely, the right subclavian artery will rise aberrantly as the last root vessel of a left aortic arch, precluding access to the ascending aorta from the right brachial artery. Percutaneous left-sided heart catheterization via an aortofemoral or axillary-femoral synthetic bypass graft has been surprisingly free of complications.[20] A potential hazard is disruption of the pseudointima with subsequent thrombosis.

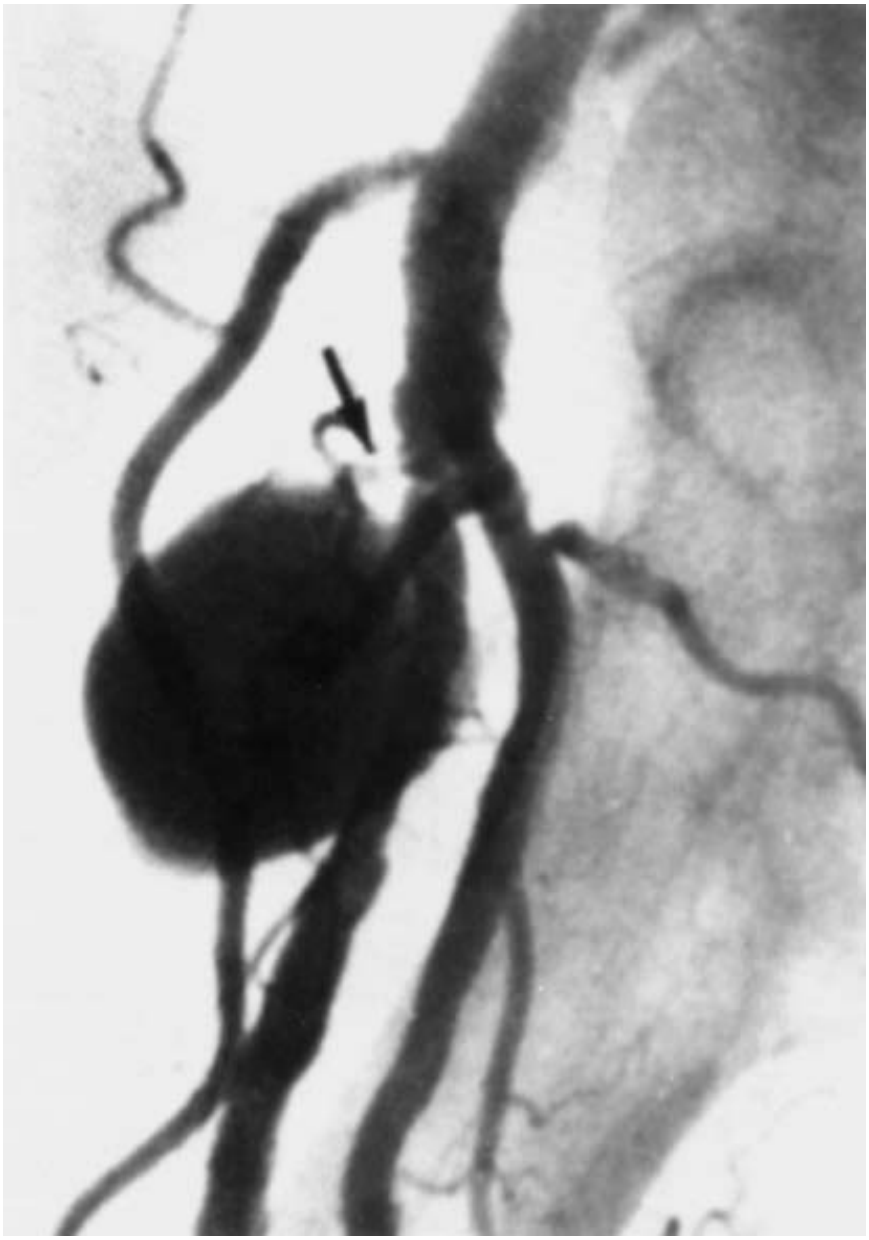

Figure 15-3: The femoral arteriogram shows the neck (*arrow*) of an oval pseudoaneurysm (pulsating hematoma) arising from the right superficial femoral artery (*arrow*) at the site of the previous catheter entry. (Reproduced with permission from Rapoport et al.[16] and the Radiological Society of North America, Inc.)

The normal aortic valve is easily crossed retrogradely with the catheter tip. Even in aortic valve stenosis, the left ventricle can be entered in nearly all cases. By slowly withdrawing the catheter tip from its looped position in the left aortic sinus, one may perform wall-to-wall exploration of the severely stenotic valve. A straight-tip guidewire may enhance this maneuver. Left and right Judkins, left Amplatz, and pigtail catheters have all been used to center the guidewire in the aortic root to achieve more effective probing of the stenotic orifice.[21,22]

In selected patients who have aortic and mitral valve disk or ball-valve prostheses, a brief direct percutaneous puncture through the palpable apex of the left ventricle is surprisingly free of complications.[23] LV angiography can be performed through the sheath or a catheter. Retrograde catheterization of the left ventricle via a prosthetic aortic disk valve should be avoided. Valvular incompetence is induced, and the catheter may become entrapped in the disk valve mechanism. In contrast, tissue valves can be crossed without significant hazard. In patients with both femoral and

axillary artery disease, selective coronary arteriography can be performed via a translumbar aortic approach, using a sheath,[24] or via a transseptal approach.[25]

ARTERIAL CUTDOWN

The cutdown technique for left-sided heart study usually uses the brachial artery. After the administration of 100 units/kg of heparin intravenously, the anterior wall of the exposed artery is punctured with the tip of an 18-gauge needle. The opening is enlarged slightly with a small forceps, permitting insertion of the tapered catheter. The arteriotomy is closed either by a previously placed, very small purse-string loop or by one or two interrupted sutures. If brisk bleeding does not occur from both proximal and distal artery segments, thrombectomy is performed with a balloon catheter.

Transseptal Approach

Transseptal catheterization may be used to enter the left atrium.[26] From the right femoral vein percutaneously, a 71-cm-long needle is advanced inside a dilator catheter-sheath system to a position beneath the ledge of the limbus fossae ovalis in the right atrium. The needle is then bared to puncture the atrial septum.[27-29] Entry into the left atrium is confirmed by a clear continuous pressure tracing. The dilator is then pushed across the septum. The needle tip is pulled back into the dilator, and when both are well in the left atrium (Fig. 15-4), the sheath is slid over them to also enter the left atrium; needle and dilator are then withdrawn. The sheath permits various preformed open- or closed-tip catheters or large guidewires to be passed into the left atrium and left ventricle. A CO_2-filled balloon catheter may be passed from the left atrium to the left ventricle to the ascending aorta. Biplane fluoroscopy, continuous pressure recording, a catheter in the aortic root, and knowledge of the size and position of the left atrium following pulmonary artery angiography are helpful in positioning the transseptal needle. The left atrium is difficult to enter if there is deformity of the thoracic or lumbar spine or if there is a very large right atrium. Other relative contraindications to transseptal catheterization include marked dilatation of the aortic root and other anatomic distortions of the IVC or atria. The procedure is not done if there is intraatrial thrombus or tumor.

Retrograde catheterization of the left atrium from the left ventricle in the right anterior oblique (RAO) projection uses a tapered flexible catheter that forms a clockwise loop in the left ventricle as it passes to the left atrium. A pigtail catheter has been used similarly.[29]

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Chapter 15: CARDIAC CATHETERIZATION, CORONARY ARTERIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

EQUIPMENT

Catheters

Disposable single-use catheters in a wide range of sizes, shapes, and lengths with end and/or side holes are available for diagnostic use. The ideal nonpreformed catheter is soft enough to permit bending as required, has "memory" to hold its shape, and has enough strength or body to permit the curve of the tip to be advanced intact. Torque control is improved by incorporating a thin wire braid in the walls. Transmission of torque to the catheter tip in the ascending aorta is damped by a tortuous iliac artery. The torque is received instead by the proximal part of the catheter, resulting in coiling or potential knotting in the iliac artery. Preformed catheters are made to serve a specific function with a minimum of manipulation. Catheters should have smooth, regular surfaces to reduce thrombogenicity. Atrial septostomy with a fluid-filled balloon catheter or with a controlled folding surgical blade at the catheter tip improves shunting and increases systemic arterial saturation in patients with transposition of the great arteries.[30] A precompressed Ivalon plug or thrombogenic coils inserted by catheter have been used to close the patent ductus arteriosus. Loop-snare or jawed biopsy catheters are used for nonthoracotomy retrieval of intraluminal cardiovascular foreign bodies. A small Doppler crystal mounted on a thin guidewire serves as an intraluminal probe to measure coronary artery blood flow velocity.[31] A catheter-tip electromagnetic probe can be used to measure aortic blood flow velocity. A Doppler pulmonary artery catheter can provide continuous instantaneous stroke output values,[32] assuming a flat velocity profile. An intracoronary artery ultrasound imaging catheter system can provide a cross-sectional, two-dimensional image of good anatomic detail (see Chap. 47). The coronary artery lumen also may be visualized by fiberoptic angioscopic catheters.[33] Inhaled hydrogen gas is detected within 4 s of inhalation with extreme sensitivity by a pacing catheter electrode positioned at the site of a left-to-right shunt or downstream from it.

Used in treating valvular pulmonic stenosis and coarctation of the aorta,[34,35] pulmonary valvuloplasty and aortic angioplasty balloons up to 4 cm long with an inflation diameter up to 20 mm are made of high-tensile-strength polyethylene. Inflation to 3 to 4 atm with a 20-mL plastic syringe is usual. The lumen between the no. 8 or 9 French catheter and the balloon is large, permitting deflation in less than 7 s, decreasing the occlusion time. A short bilobed balloon catheter (two layers with a polyester micromesh between) permits stable positioning across the stenotic valve, stepwise dilation, and a short deflation time.[36] A catheter can be used to deliver a device to close a secundum atrial septal defect as large as 2 cm. Test balloon occlusion of aortopulmonary collaterals mimics the effects of planned surgical closure. In patients with pulmonary atresia and **an** intact ventricular septum who have had surgical relief of the pulmonary atresia, the atrial septal defect can be closed temporarily with a balloon catheter in order to direct all the systemic venous return to the small right ventricle, testing its response. Transcatheter pulmonary artery dilation and stent implantation are especially useful in surgically inaccessible sites.[37]

Radiation Exposure

A qualified radiologic physicist should check the catheterization facilities, and secondary or scattered radiation should be minimized.[38-40] Radiation intensity varies inversely with the square

of the distance; i.e., if the distance to the source is doubled, the amount of radiation will be only one-quarter as much. One should select the smallest possible collimation and keep the image intensifier as close to the patient as possible. The U-arm position that places the x-ray tube to the examiner's side of the table causes the greatest exposure as a result of scattered radiation from the patient. Two film badges should be worn, one at the belt beneath the 0.5-mm equivalent lead apron and the other at the collar level outside the apron. The eyes, gonads, and red bone marrow have a whole-body limit of 5 rem (roentgen equivalent man) per year; any specific organ, such as the thyroid or skin, has a yearly limit of 15 rem. Lead glass spectacles and a thyroid collar reduce radiation to the eye and to the thyroid. Both a floating and a table-to-floor screen are needed for added shielding. The maximal permissible dose, or "safe" exposure, for catheterization laboratory personnel is 100 mrem per week monitored by an unshielded left collar badge. If possible, women of childbearing age should have studies done within 10 days after the onset of menstruation.

Pressure-Recording System

If the heart rate is 60 to 120 beats per minute, the fundamental frequency of the basic wave is 1 to 2 per s. The tenth harmonic or sine-wave component of the pressure wave then occurs at a frequency of 10 to 20 Hz; it is important to detect these components without phase lag or amplitude distortion because their sum represents the rising and falling contours of the native pressure curve. A properly responding pressure-recording system should have a high natural frequency and optimal damping. A high natural frequency is obtained by using a bubble-free, saline solution-filled system of minimum length whose catheter and connector tubings have stiff walls and wide bores. Many catheter-tubing transducer systems are underdamped. To achieve optimal damping, a damping needle or tube is placed between the catheter and the transducer. This extends the output-input ratio of the pressure wave in a nearly uniform manner (unity + 5 percent) to as close as possible to the natural frequency of the system. The values for both frequency response and damping coefficient are obtained by introducing a square-wave pressure input to the catheter system and by measuring the amplitude ratio of any two successive peak pressure amplitudes and the time interval between peaks (Fig. 15-5). For clinical cardiac catheterization, a manometer system with a uniform dynamic response of greater than 20 Hz is desirable.

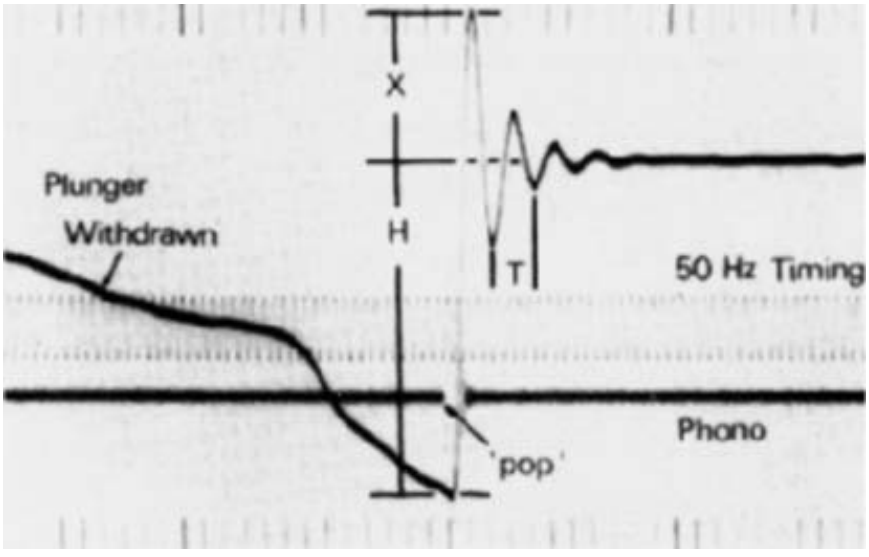

Figure 15-5: In order to measure the dynamic frequency response of a catheter transducer system, an abrupt transient input dynamic pressure is applied to the catheter tip (a plunger is pulled free of an air-filled syringe); the pressure oscillations are recorded at a fast paper speed and measured. X, height of the initial overshoot; H, end height of the recorded deflection; T, period of a free

oscillation, 0.08 s. The natural frequency is 13 Hz; the useful range is 4 Hz. The amplitude ratio of two successive peak amplitudes is 0.59, and the damping coefficient is 0.17. This underdamped system is optimally damped to a coefficient around 0.64 by the addition of a narrow-bore tube between catheter and transducer. (Reproduced with permission of Irex Corporation.)

Clinically, the zero position for an external pressure transducer is set at the lateral midchest level. Specifically, hydrostatic zero is considered to be at the level of most anterior surfaces of the LV blood pool.[41] An additional limiting factor in pressure recording is the superimposition of artifacts on the pressure pulse by the accelerating and decelerating movements imparted to the fluid-filled cardiac catheter by the beating heart. Distortion of the catheter-obtained phasic pressure waveform by motion or damping artifact can be avoided with the use of a catheter-tip, side-mounted, ultraminiature semiconductor gauge. This manometer system is required for first- or second-derivative measurements of the pressure curve.

Oxygen Analysis

The total oxygen content of the blood, once determined by the classic Van Slyke manometric technique, is now obtained by gas chromatography or mass spectrometry. The percent oxyhemoglobin saturation is measured from a small sample of whole blood in a disposable plastic curvette by direct photooximetry or, after hemolysis, by a precision spectrophotometer.[42] Analysis of expired air, from collecting bag or breath by breath, for oxygen and carbon dioxide may be made by gas analyzers or infrared or mass spectroscopy. Oxygen consumption also can be measured throughout the procedure using a flow-through hood technique.[43] Oxygen consumption also can be estimated with a 10 to 25 percent variation from measured values.

PREVIOUS | NEXT

Chapter 15: CARDIAC CATHETERIZATION, CORONARY ARTERIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

DATA OBTAINED AT CATHETERIZATION

Pressure Measurements

High-fidelity phasic pressure curves are not obtained from the ventricles or great arteries by fluid-filled catheter recording systems. The underdamped curve gives falsely high systolic and falsely low diastolic readings, and the overdamped curve has a smooth shape with disappearance of the incisura. The shape of the ventricular or great artery pressure trace is occasionally of diagnostic aid. An abrupt fall in pressure in early diastole (early diastolic dip) followed by a sudden rise to a high end-diastolic pressure plateau occurs in both ventricles in abnormal compliance states such as constrictive pericarditis and restrictive cardiomyopathy. In patients with constriction, the LV and right ventricular (RV) pressures have a respiratory reciprocal (discordant) relationship, whereas with heart failure, the relationship is concordant.[44,45] In isolated pulmonary stenosis, the configuration of the RV pressure curve is frequently peaked or triangular.

In valvular pulmonary stenosis, the pulse pressure is frequently greater in the left pulmonary artery than in the right pulmonary artery because flow is preferentially directed into the left pulmonary artery and kinetic energy is translated into lateral pressure. A systolic dip is noted in the main pulmonary artery due to pressure loss from the Bernoulli effect (Fig. 15-6). In bilateral branch pulmonary artery stenosis, the proximal main pulmonary artery shows a wide pulse pressure with a low dicrotic notch. In supravalvular aortic stenosis, the coanda effect makes the right brachial and right carotid artery peak pressures greater than those on the left. A large *a* wave in the right atrium is characteristic of valvular pulmonary stenosis but not of tetralogy of Fallot. A large *v* wave on the pulmonary artery wedge ("pulmonary capillary") pressure tracing may or may not mean that severe mitral regurgitation is present.[46]

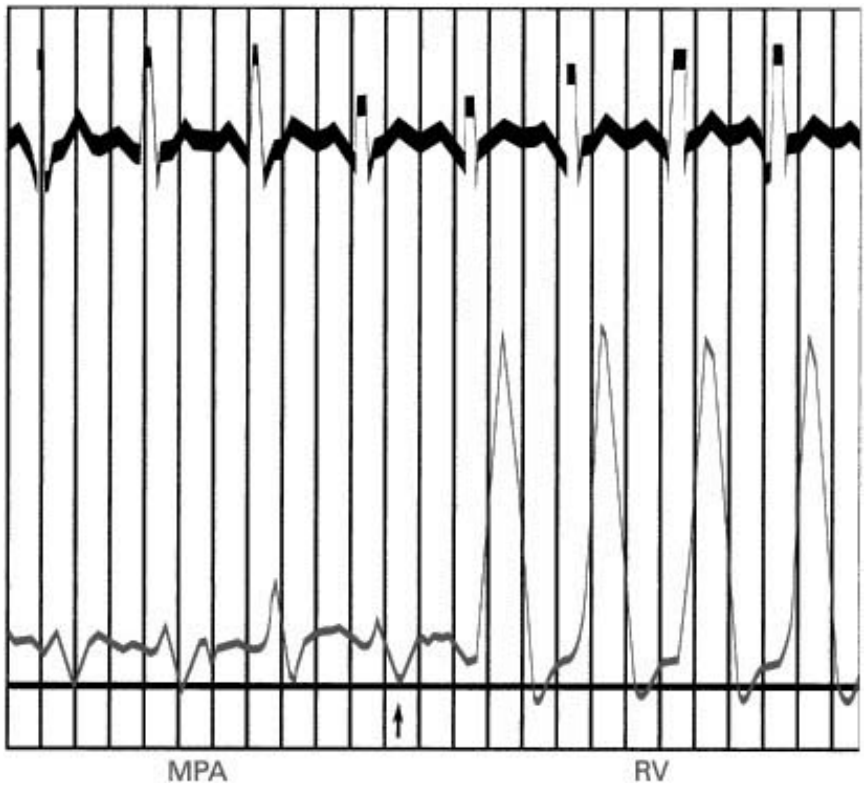

Figure 15-6: Pullback continuous pressure tracing from the main pulmonary artery (MPA) to the right ventricle (RV) recorded in a 27-year-old male with moderate valvular pulmonic stenosis. RV systolic pressure is 84 mmHg. MPA pressure is 16/7 mmHg. Note the systolic dip (*arrow*) in the MPA pressure tracing, due to the pressure loss from the Bernoulli effect. (From Franch RH. Recognition and management of valvular pulmonic stenosis. *Heart Dis Stroke* 1994; 3:365-370. Reproduced with permission from the author and publisher.)

Left ventricular end-diastolic pressure (LVEDP) is recorded on a high-sensitivity scale and is measured where the downslope of the *a* wave in the left ventricle coincides with the initial upstroke of the LV pressure. The LVEDP also may be measured at the peak of the R wave of the electrocardiogram. An elevated LVEDP reflects an alteration in the ventricular pressure-volume relation or a decrease in diastolic compliance of the ventricle. An increased LVEDP occurs commonly with a dilated failing left ventricle but also may be noted in a small ventricular cavity with thick walls or in a normal-size LV cavity during an acute ischemic attack.

In order to measure the maximal rate of rise of LV pressure, or peak *dP/dt*, a high-fidelity pressure record is needed, obtained ideally via a catheter-tip transducer. This value is influenced by preload and afterload in addition to the contractile state. The preejection phase index (*dP/dt*)/*P*, where *P* is the LV pressure during isovolumic systole, reflects the velocity of shortening of contractile elements but also responds to changes in preload. In daily practice, ejection-phase indexes derived from the conventional LV angiogram are used to assess LV function.[47] The ejection fraction is commonly employed as an index of ventricular contractility but is sensitive to changes in preload and afterload as well (see Chap. 22).

A satisfactory pulmonary artery wedge mean pressure provides a good estimate of left atrial mean pressure. Some damping in waveform and phase shift (0.06-s time delay) occurs in the transmitted wedge pressure when compared with the direct left atrial pressure record. During diastole, pulmonary artery wedge diastolic mean pressure tends to be higher than the left atrial diastolic mean pressure, especially in the presence of a prosthetic or abnormal mitral valve. End-expiratory pulmonary artery diastolic pressure agrees within 2 to 4 mmHg with mean pulmonary artery wedge pressure in the absence of increased pulmonary arteriolar resistance. In contrast, pulmonary

vein wedge pressure does not give an accurate estimate of the pulmonary artery pressure in the presence of pulmonary artery hypertension.

Pressure recording permits measurement of either the peak or the mean pressure differential across a stenotic semilunar or atrioventricular (AV) valve or a segmentally narrowed blood vessel. If possible, simultaneous pressure recordings across a valve should be obtained, especially if there is atrial fibrillation. If the pulmonary artery wedge is used as an estimate of left atrial mean pressure, the waveform and amplitude should be confirmed at a second site. The error in assessing the mitral valve area in mitral stenosis can be large when the measured pressure differential is small. Because of the slow fall of the *y* descent in the wedge position, the mitral valve gradient may be overestimated by 3 to 4 mmHg when compared with the gradient obtained with a direct left atrial pressure.[48,49] A pullback record across the semilunar valve performed with a catheter having multiple paired side holes may show a false zone of composite ventricular and great artery pulses resulting from the simultaneously recorded pressures through proximal and distal side holes. Occasionally, a gradient may be overlooked if the catheter tip cannot be advanced well into the ventricle so that it washes into the aorta in systole and falls into the left ventricle in diastole. The ascending aortic pressure should be recorded at the level of the coronary ostia to avoid the effects of pressure recovery,[50,51] i.e., the increase in lateral pressure downstream from a stenosis as the narrow, high-velocity flow field broadens and slows, losing kinetic energy.[52-54] The LV pressure in aortic valve stenosis is recorded well in the LV cavity to avoid systolic pressure loss due to tapering high-velocity flow in the subaortic area. In a case of proximal infundibular pulmonary stenosis, if the pullback is at the cranial aspect of the tricuspid valve, the catheter may fall back into the right atrium from the RV outflow tract very quickly, missing the gradient.

LV cavity obliteration with catheter entrapment may result in spurious pressure gradient. To detect an intraventricular gradient, the LV pressure should be checked in the inflow and outflow (i.e., submitral and subaortic) positions simultaneously and in the apical versus the inflow or outflow positions simultaneously. These recordings enable one to detect any delay in the fall of LV systolic pressure that may occur when the catheter is entrapped.

Interventions during Catheterization

We use a bicycle ergometer that provides loads of 0 to 450 W in steps of 5 W; the level of effort remains constant by maintaining a monitor pointer at a neutral position. The regression equation for oxygen consumption in milliliters per minute for a given load in watts on this ergometer is V_{O_2} = 13.16 W + 254 mL. An increase in cardiac output of 0.6 L/min or greater for each 100 mL of oxygen consumed presumes a normal response. If the oxygen consumption is increased 200 to 250 mL/min by supine use of a bicycle ergometer, an increase in arteriovenous oxygen content difference greater than 30 mL/L is considered abnormal. When the pulmonary artery oxygen saturation falls to substantially less than 30 percent during exercise, the upper limit of circulatory stress is being approached. Normally, during moderate exercise, LVEDP actually falls, and stroke work increases; if LV performance is only moderately impaired, LVEDP rises, and stroke work rises; but in severe dysfunction, stroke work fails to increase despite an increase in LVEDP. Isometric hand-grip exercise increases heart rate, systemic mean pressure, and cardiac output. A fall in LV stroke work and a sharp rise in LVEDP during the grip test is evidence of poor LV reserve. All patients with mitral stenosis who have normal or mildly increased pulmonary artery and wedge pressures at rest should have the mitral gradient and cardiac output rechecked during exercise. In normal patients during exercise, pulmonary artery pressure rises minimally, usually no higher than 25 mmHg mean. In a patient with a repaired ventricular septal defect and residual pulmonary vascular disease, the pulmonary artery pressure may be at the upper limits of normal or slightly increased at rest but may double with low-level exercise.

Rapid atrial pacing also may be used as a stress intervention. In normal individuals, LVEDP falls

as the heart rate is increased. If a paced patient with coronary artery disease is unable to meet the increased myocardial oxygen demand, the LVEDP rises in the early postpacing period, and excess lactate is noted in coronary sinus blood. In patients with tetralogy of Fallot, spontaneous or drug-induced increases in heart rate or atrial pacing produce a drop in arterial oxygen saturation and an increase in right-to-left shunting by increasing dynamic RV outflow tract obstruction.

In hypertrophic obstructive cardiomyopathy, isoproterenol, amyl nitrite, exercise, tilting, and the Valsalva maneuver, which tends to decrease diastolic ventricular volume, can intensify or provoke a systolic outflow tract pressure gradient, whereas a purely vasopressor amine, phenylephrine, which enlarges ventricular volume, tends to decrease the outflow tract pressure gradient[53] (see Chap. 67).

The response of cardiac output to vasodilator drugs in a patient with heart failure can be assessed. In patients with primary pulmonary artery hypertension (see Chap. 59), a 30 percent decrease in pulmonary vascular resistance and a 10 percent decrease in mean pulmonary artery pressure are the usual criteria for a positive response to pulmonary vasodilator drugs.[55]

Blood Oxygen Measurements

An increase in the oxygen content of blood from the chambers of the right side of the heart in excess of the normal variation in oxygen content on serial sampling is used as evidence of a left-to-right shunt.[56] Thus an oxygen step-up from the SVC to the right atrium of more than 1.9 vol% indicates shunting into the right atrium; a step-up from the right atrium to the right ventricle of 0.9 vol% or more and a step-up from the right ventricle to the pulmonary artery of 0.5 vol% or more indicates a left-to-right shunt at the RV and pulmonary artery levels, respectively. By these criteria, false-positive results are rare, but false-negative results can occur in patients with small shunts. In an anemic or polycythemic patient, the detection of shunting is best reflected by the step-up in percentage oxygen saturation rather than the step-up in volume percent, since the latter depends on the hemoglobin concentration.[57]

Studies show that sensitivity in detecting left-to-right shunts is improved if numerous serial blood samples are withdrawn in rapid succession for oximetry. If two sets of interrupted samples are taken from the SVC, right atrium, right ventricle, and pulmonary artery, a 9 percent saturation increase between the SVC and the right atrium indicates a large atrial shunt, a 5 percent saturation increase between the right atrium and the right ventricle indicates a ventricular shunt, and a 3 percent saturation increase between the right ventricle and the pulmonary artery indicates a pulmonary artery shunt. Sensitivity can be improved if blood samples are obtained in multiple pairs in a rapid serial sweep without flushing with saline solution between samples. The rise in oxygen saturation step-up for a given left-to-right shunt is related to the saturation of mixed venous blood (MVB). For example, if the MVB is 85 percent, a 5 percent step-up represents a 2:1 shunt; if MVB is 75 percent, a 10 percent step-up is needed; if the MVB is 65 percent, a 15 percent step-up indicates a 2:1 shunt. The results of the blood oxygen analysis should be reviewed before the catheterization is completed. Left-to-right shunts of less than 20 percent of pulmonary flow are not detectable by oximetry. Since no oximetric criteria exist for exclusion of a shunt, selective angiography and/or the use of a hydrogen (platinum) electrode provide maximal sensitivity and reliability in excluding small shunts.[58] The presence of an increased oxygen step-up in the right side of the heart should be correlated closely with angiographic findings.

Catheter Position

The catheter position may be useful in identifying the anatomic location of an intracardiac defect or an anomalous vein (Fig. 15-7). In crossing a membranous ventricular septal defect in the anteroposterior view, the catheter inserted from the arm passes into the ascending aorta from the

right ventricle in a hairpin loop and enters the pulmonary artery from the right ventricle in a wider U loop. A patent ductus arteriosus is entered by pointing the tip of the catheter toward the "roof" of the junction of the main and left pulmonary arteries. Failing direct catheter passage, a flexible-spring guidewire, introduced while the venous catheter tip rests in the main pulmonary artery, readily passes through the ductus into the descending aorta; in aorticopulmonary septal defect, the tip passes directly up the ascending aorta from the main pulmonary artery. When the catheter tip enters a pulmonary vein within the heart shadow, angiography is necessary to ascertain whether the pulmonary vein drains into the left or the right atrium. A secundum atrial septal defect is more easily crossed from the leg approach, a sinus venosus defect from an arm approach, and an ostium primum defect from either approach. If the tricuspid valve is congenitally displaced into the right ventricle, the pressure transition from the right ventricle to the right atrium may occur while the catheter tip is far to the left of the spine. Simultaneous intracardiac electrocardiography is confirmatory (see also Chap. 70).

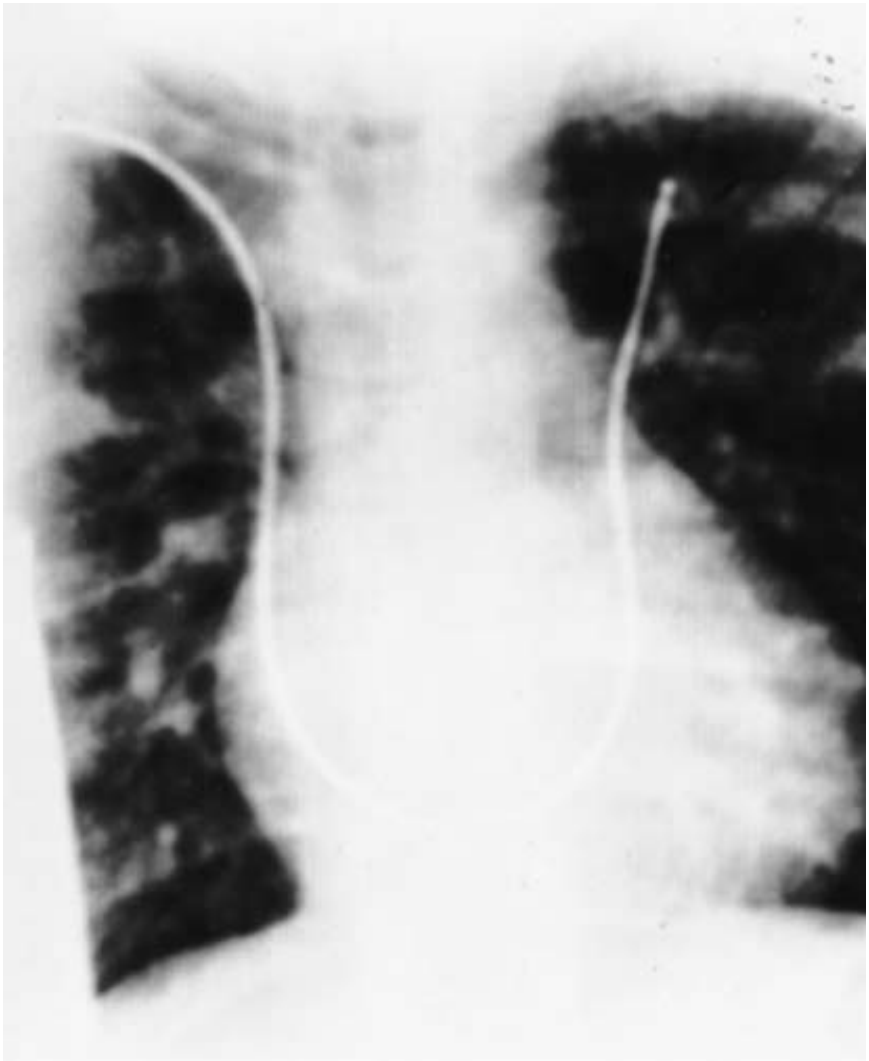

Figure 15-7: The catheter tip passes from the right SVC to the right atrium and then to the coronary sinus, the left SVC, and an anomalous left upper lobe pulmonary vein.

Flow and Shunt Calculations

FICK METHOD: CARDIAC OUTPUT

In 1870, Adolph Fick expounded a theory for the measurement of blood flow that he never used in the laboratory: "The total uptake or release of a substance by an organ is the product of the blood flow to the organ and of the arteriovenous concentration of the substance." In the following example, the cardiac output may be calculated given the following three values: total oxygen consumption of 300 mL/min, arterial blood oxygen content of 19 mL per 100 mL of blood, and mixed venous blood oxygen content of 14 mL per 100 mL of blood. The cardiac output, in liters per minute, is equal to the oxygen consumption divided by the arteriovenous oxygen difference multiplied by 10 (to convert the latter to liters). In this case, the cardiac output equals 6.0 L/min. Cardiac output may be related to the body surface area (BSA) as the *cardiac index*. If one assumes a BSA of 2.0 m^2, the cardiac index would be 3 L/min per square meter. Because of laminar flow from the coronary sinus and the cavae and in the right atrium, MVB is best obtained from the pulmonary artery. Under conditions of exercise, a minimum of 3 min is usually required to obtain a steady-state preliminary to expired air and blood collection. In a given person, repeated measurements of the cardiac output at rest by the Fick technique may vary to a maximum of ±17 percent, presuming a continued steady state.

SHUNT CALCULATIONS

Shunt calculations using the Fick principle tend to be approximations, since complete mixing of venous and shunted blood may not occur. Also, as the arteriovenous oxygen narrows, small errors in the analysis or in the collection of blood samples make large variations in the calculated pulmonary blood flow possible. The calculation of shunt flow, however, is useful; it provides a quantitative index that is combined with clinical findings to determine whether or not surgery is advisable.

Numerous formulas have been developed, but those listed below are the ones used most often. The *oxygen capacity* is the maximal amount of oxygen that will combine with hemoglobin and that will be dissolved in plasma at a high P_{O_2}. One gram of hemoglobin can combine with 1.36 mL of oxygen. The amount of oxygen dissolved in plasma depends on the solubility coefficient of oxygen, the temperature, and the partial pressure of oxygen. At 37°C, the solubility coefficient is such that the amount of oxygen dissolved in plasma is 0.03 mL/mmHg per liter. With an oxygen tension of about 100 mmHg, about 3 mL of oxygen is dissolved per liter of blood. This small amount is usually ignored, although when the patient is breathing 100% oxygen, a considerable amount of oxygen can be dissolved in plasma. Oxygen content is related to both the hemoglobin concentration and the oxygen saturation. The oxygen content equals 1.36 × Hb (g/dL) × Sa_{O_2} (%)/100.

1. A sample calculation of left-to-right shunt:

Total oxygen consumption (V_{O_2})	240 mL/min
Pulmonary artery blood oxygen content ($P_{A_{O_2}}$)	17 mL/100 mL
Mixed venous blood oxygen content (MV_{O_2})	15 mL/100 mL
Arterial blood oxygen content (Sa_{O_2}) (assumed to equal pulmonary venous oxygen content)	19 mL/100 mL

$$\text{Pulmonary flow } (Q_p) = \frac{V_{O_2}}{Sa_{O_2} - P_{AO_2}}$$

$$= \frac{240}{19 - 17(10)}$$

$$= 12 \text{ L/min}$$

$$\text{Systemic flow } (Q_s) = \frac{V_{O_2}}{Sa_{O_2} - MV_{O_2}}$$

$$= \frac{240}{19 - 15(10)}$$

$$= 6 \text{ L/min}$$

Pulmonary flow/systemic flow ratio = $Q_p/Q_s = 12/6 = 2$.

If one substitutes for Q_s and Q_p in the preceding formula and reduces to a common denominator, the *pulmonary flow-systemic flow* ratio is obtained from a formula requiring only the oxygen saturation. Assuming an oxygen capacity of 20 vol%, the following blood oxygen saturations for the preceding samples are Sa = 95 percent, P_A = 85 percent, and MV = 75 percent.

Left-to-right shunt also may be expressed as the percentage of total pulmonary flow that is shunted blood. The 2:1 Q_p/Q_s ratio above then represents a 50 percent left-to-right shunt.

2. Calculation of right-to-left shunt:

$$\frac{Q_p}{Q_s} = \frac{Sa_{O_2}\% - MV_{O_2}\%}{Sa_{O_2}\% - Pa_{O_2}\%} = \frac{95 - 75}{95 - 85} = 2$$

$$V_{O_2} = 240 \text{ mL/min}$$
$$MV_{O_2} = 13 \text{ mL/100 mL blood}$$
$$Sa_{O_2} = 17 \text{ mL/100 mL blood}$$

Pulmonary vein blood oxygen content is as follows:

$$PV_{O_2} = 19 \text{ mL/100 mL blood}$$

(assumed to be 98 percent of oxygen capacity + 0.3 mL of dissolved oxygen).

$$Q_p = \frac{V_{O_2}}{PV_{O_2} - MV_{O_2}} = \frac{240}{19 - 13(10)}$$

$$= 4 \text{ L/min}$$

$$Q_s = \frac{V_{O_2}}{Sa_{O_2} - MV_{O_2}} = \frac{240}{17 - 13(10)}$$

$$= 6 \text{ L/min}$$

Pulmonary/systemic flow ratio = Q_p/Q_s = 0.7. Right-to-left shunt also may be expressed as the percentage of total systemic flow that is shunted blood. The 0.66 Q_p/Q_s ratio above represents a 33 percent right-to-left shunt.

3. Calculation of bidirectional shunt:

$$V_{O_2} = 240 \text{ mL/min}$$
$$P_{AO_2} = 15 \text{ mL/100 mL blood}$$
$$MV_{O_2} = 13 \text{ mL/100 mL blood}$$
$$Sa_{O_2} = 18 \text{ mL/100 mL blood}$$
$$PV_{O_2} = 19 \text{ mL/100 mL blood}$$

$$Q_p = \frac{V_{O_2}}{PV_{O_2} - P_{AO_2}} = \frac{240}{19 - 15(10)}$$

$$Q_s = \frac{V_{O_2}}{Sa_{O_2} - MV_{O_2}} = \frac{240}{18 - 13(10)}$$

$$= 4.8 \text{ L/min}$$

$$Q_{ep} = \frac{V_{O_2}}{PV_{O_2} - MV_{O_2}} = \frac{240}{19 - 13(10)}$$

$$= 4.0 \text{ L/min}$$

$$\text{Left-to-right shunt} = Q_p - Q_{ep} = 6 - 4$$
$$= 2 \text{ L/min}$$
$$\text{Right-to-left shunt} = Q_s - Q_{es} = 4.8 - 4.0$$
$$= 0.8 \text{ L/min}$$

Note that effective pulmonary flow Q_{ep} is that volume of systemic venous blood which, after returning to the right atrium, actually reaches the pulmonary capillaries. It is equal to effective systemic blood flow Q_{es}.

INDICATOR-DILUTION TECHNIQUE

Cardiac Output: Dye Method

The cardiac output, or the mean volume rate of flow, may be determined by using a modification of the standard concentration equation employed for the determination of a static fluid volume

such as the blood volume:

$$V = \frac{I}{C}$$

where V = fluid volume, mL
I = indicator added to fluid, mg
C = concentration of indicator in each milliliter of fluid, mg/mL

For determination of a moving fluid volume,

$$\text{Cardiac output} = \frac{I}{Ct}$$

where t = time required for all indicator-fluid mixture to pass sampling site once

If the indicator particles are injected into the circulation as a bolus and measured in the initial passage at a downstream site, they distribute themselves in a time-concentration plot of grossly predictable form called an *indicator-dilution curve* (Fig. 15-8). The descending limb of the indicator-dilution curve is distorted by indicator-blood mixture that has begun a second circulation. To exclude recirculating indicator, the concentration is plotted logarithmically against time. The early portion of the disappearance slope is extrapolated linearly on semilogarithmic paper to obtain a primary curve, on the premise that if indicator-blood mixing is complete, the washout of indicator is an exponential function of time. A cuvette densitometer is used to obtain a continuous arterial time-concentration curve. Thus

$$\text{Cardiac output (in L/min)} = \frac{I \times 60\ \text{s}}{Ct}$$

where C = mean concentration of indicator in one circulator passage, mg/L
t = time, s

The cardiac output is falsely high if an indicator is lost. If an indicator is counted twice, i.e., if undetected recirculation occurs, the cardiac output is falsely low. An analogue computer provides rapid calculation of cardiac output from dye-dilution curves and detects whether or not logarithmic decay of indicator concentration has occurred. The Stewart-Hamilton formula assumes constant heart rate and stroke volume and a linear runoff in the pulmonary artery. Values for cardiac output obtained with the indicator-dilution technique compare closely with those obtained by the Fick method.[59]

In the absence of shunt, the indicator-dilution curve shows an uninterrupted buildup slope, a sharp concentration peak, a steep disappearance slope, and a prominent recirculation peak. Two major types of distortion are produced by central shunting. In a left-to-right shunt, there is decreased peak concentration of dye, a gentle disappearance slope (prolonged disappearance time), and absence of the recirculation peak. These alterations are produced by the recirculation of indicator particles through the lungs, resulting in a slow release of indicator to the peripheral circulation. The typical curve produced by a venoarterial, or right-to-left, shunt shows deformity of the buildup slope by an abnormal or early-appearing hump, or reflection, representing indicator that

has been shunted from right to left. The distortion in contour of the indicator-dilution curve in valvular regurgitation is similar to that occurring with left-to-right shunts. Efforts have been made to predict all or part of the curve from certain other curve components. The cardiac output obtained by the forward-triangle method compares favorably with the classic Hamilton method. In this technique, the initial portion of the indicator-dilution curve is considered to be a triangle. The area of this triangle multiplied by a constant gives the area of the primary dilution curve. Intracardiac shunts can be detected and quantified by indicator-dilution curves.[61]

Cardiac Output: Thermodilution Technique

The thermodilution technique was introduced by Fegler in 1953 to measure volume flow rate.[61,62] A multiple-lumen, balloon-tipped flow-directed thermistor catheter is placed in the pulmonary artery. Ten milliliters of room-temperature (22°C) 5% dextrose or normal saline solution is injected rapidly (<4 s) through a second lumen into the right atrium. As the injectate blood mixture initially passes from the right ventricle, the pulmonary artery blood temperature drops maximally and then progressively rises in a beat-to-beat disappearance slope as the residual injectate-blood mixture is washed out of the right ventricle. The recirculation phase is negligible. Recording the curve allows assessment of the technical adequacy of the study. The area under the time-temperature curve is electronically integrated, and the cardiac output is computed by the Stewart-Hamilton formula. The difference between successive determinations should be less than 10 percent. Since there is no "gold standard" for cardiac output, the results have been compared with the dye-dilution and Fick techniques and have been noted to correlate well, except in low cardiac output states, where the Fick method is preferable. If severe tricuspid or pulmonary regurgitation or significant left-to-right shunting is present, the peak is attenuated and the downslope of the curve is prolonged, so the thermal dilution cardiac output likely will be unreliable.[63] In general, when one uses thermal dilution, a true directional change in cardiac output is reflected by an observed change of ±10 percent.

Ventricular Volume Measurements

LV volume is estimated by selective injection of contrast medium into the left ventricle or left atrium. The image of the opacified LV cavity is obtained by cineventriculography. Biplane view image pairs used include frontal and lateral, right and left anterior oblique, or half-axial left anterior oblique and conventional RAO.[64,65] A single-plane mode using the frontal or RAO projection often is adequate.[66,67] In the classic biplane technique, each shadow of the LV cavity is treated as an ellipse. The long axis of the ventricle (L_m) and the two mutually perpendicular short axes at its midpoint (D_a and D_l) are measured, and the volume (V) is calculated from the formula for volume of an ellipsoid:

$$V = \frac{4}{3}\pi \times \frac{D_a}{2} \times \frac{D_l}{2} \times \frac{L_m}{2}$$

or

$$V = \frac{\pi}{6} \times D_a \times D_l \times L_m$$

In the single-plane method, the long axis and one short axis are measured; the second nonvisible short axis is assumed to equal the first; thus

$$V = \frac{\pi}{6} \times L_m \times D_l^2$$

More often, in either the biplane or single-plane method, the short-axis dimension is derived from the measured long axis and the area (*A*) of the LV shadow, treated as an ellipse (area-length method of Dodge) (Fig. 15-9):

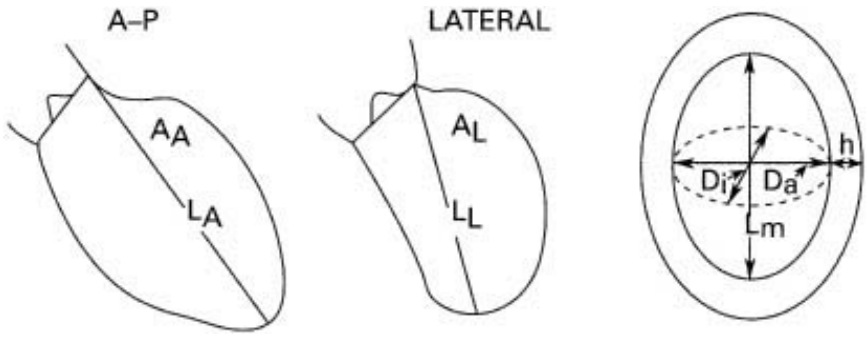

Figure 15-9: Dimensions of the left ventricular (LV) cavity in end-diastole used for the calculation of the ventricular volume by the area-length method, biplane technique. A-P, anteroposterior plane; A_a, A_l, area, A-P and area lateral plane (planimetry); L_a, L_l, length or long axis of the left ventricle (measured); D_a, D_l, diameter of short axis, A-P lateral plane (derived; L_m, maximum length or long axis whether from the lateral A-P or lateral plane; *h*, wall thickness, LV. See text for formulas. (Left and middle portion of figures from Sandler and Dodge.[66] Right portion of figure from Dodge HT. Hemodynamic aspects of cardiac failure. *Hosp Pract* 1971; January:91. Illustration by B. Tagawa and A. Miller. Reproduced with permission from the publishers and authors.)

$$A = \pi L_m \frac{D}{4}$$

Corrections are made for magnification due to the divergence of the x-ray beam.[68] A calibrated grid or circular reference marker is filmed at the estimated level of the left ventricle. The true grid size equals the size measured on the projected film times a correction factor. More magnification may occur in the periphery than in the center of the field (pincushion effect) due to spherical aberration in the lens system. Digital ventriculography provides rapid, computer-derived ventricular volumes. Geometric and nongeometric count-based radionuclide techniques for calculation of ventricular volumes are well validated.

By the use of magnetic resonance imaging (MRI) in each case, LV volume obtained by the biplane long-axis method and LV volume obtained from multiple short-axis plane images (using Simpson's rule) agree closely.[69] If the left ventricle of a postmortem heart specimen is filled with contrast material and filmed, the calculated estimate of the volume of the left ventricle is higher than the known volume of the left ventricle. An appropriate regression equation for both single-plane[66,67] and biplane[64,65] techniques has been derived to adjust for this initial overestimate. The LVEDV is normally 70 ± 20 mL/m^2, and the end-systolic volume is 24 ± 10 mL/m^2. The forward stroke volume obtained by left ventriculography agrees well with indicator-dilution and Fick determinations. The ejection fraction of the left ventricle is 0.67 ± 0.08; values below 0.55 are usually considered abnormal. Diastolic LV wall thickness measured by angiography is 9 mm for women and 12 mm for men, and LV wall mass is 76 g/m^2 for women and 99 g/m^2 for men.[70]

The total stroke volume obtained by left ventriculography is used to assess the severity of mitral and aortic valve regurgitation. Total stroke volume minus forward stroke volume equals regurgitant stroke volume. The regurgitant fraction equals regurgitant stroke volume divided by total stroke volume. Severe valvular regurgitation has a regurgitant fraction of 0.50 or greater. Direct measurement of aortic regurgitation in milliliters per stroke in a pulsatile circulation model agrees closely with MRI-derived phase velocity encoding data in the model. The technique is clinically applicable (Fig. 15-10).

RV volume is estimated by applying Simpson's rule or the area-length method to the cavity silhouettes after biplane angiography.[71] The end-diastolic volume of the right ventricle in normal persons is 81 ± 12 mL/m^2. The opacified left atrial shadow is represented as an ellipsoid, so the left atrial volume also can be calculated in the biplane mode; the normal left atrial maximal volume is 63 ± 16 mL with a mean volume of 35 ± 8.7 mL.

Resistance

By Poiseuille's law, the flow varies directly with the fourth power of the radius of a tube; resistance varies inversely with the fourth power of the radius. Vascular resistance to blood flow in systemic, pulmonary, or regional vascular beds is estimated by analogy to Ohm's law:

$$\text{Resistance} = \frac{\text{pressure (or volts)}}{\text{mean blood flow (or amperes)}}$$

or resistance = mean pressure differential across the vascular bed divided by the blood flow (see also Chap. 3).

To obtain the pressure difference across the pulmonary bed, subtract the pulmonary artery wedge (or left atrial) pressure from the pulmonary artery mean pressure; for the systemic pressure difference, subtract the mean central venous or right atrial pressure from the mean aortic pressure. Conversion into centimeter-gram-second (cgs) units (dyn·s/cm^5) is usual, but it does not add to the intrinsic significance of the measurements. Resistance also can be expressed simply as *R* in units = mean pressure difference (mean flow in millimeters of mercury) divided by the cardiac output (in liters per minute). In infants and children, the pressure drop is related to the flow index; thus *R* in units × m^2 = pressure difference divided by cardiac index. Pulmonary resistance calculations in adults are usually not indexed, although there is an increasing tendency to do so. The normal pulmonary vascular resistance index is 1 to 2 units. Generally, 1 resistance unit is approximately equal to 80 dyn·s/cm^5. In a physiologic sense, the term *resistance* avoids specific definition. A change in resistance usually implies a change in a cross-sectional area of the vascular bed but does not indicate the mechanism behind the change. Passive widening of the vessels by increases in intravascular flow as well as the opening of previously closed channels may produce changes in resistance similar to those of active vasomotion. Subnormal calculated pulmonary vascular resistance is found in the patient who has a large atrial septal defect with normal pulmonary artery pressure. Clinically, the resistance figure is useful in quantitating the extent of pulmonary vascular disease; thus a patient with a pulmonary vascular resistance of 10 units/m^2 probably would not benefit from closure of a septal defect (see Chap. 70). The total resistance to blood flow in a pulsatile system is defined as *impedance*. Its clinical use is limited, however, since the accurate calculation of impedance requires high-fidelity pressure and velocity or flow recordings.

Calculation of Valve Areas

The equation for calculation of valve area (Torricelli's orifice equation) uses a standard hydrokinetic formula for a rounded-edge orifice or a short tube. When flow occurs across a

narrow orifice, the pressure differential is related to the conversion of pressure energy into kinetic energy. The Gorlin formula for calculation of valve area is derived by combining two standard orifice formulas, one describing the volume rate of flow and the second, the velocity of flow.[72,73]

FORMULA I

$$F = AVC_c$$

where F = volume rate of flow during the time the valvular orifice is open, mL/s of diastole or systole
A = area of fixed orifice, cm^2
V = velocity flow, cm/s
C_c = coefficient of orifice contraction compensating for the physical phenomenon of reduction of the orifice stream to an area less than the area of the actual orifice

FORMULA II

$$V^2 = C_v^2 2gh \quad \text{or} \quad V = C_v\sqrt{2gh}$$

where V = as above
C_v = coefficient of velocity (allowing for some loss in conversion of pressure energy to velocity)
g = gravity acceleration (980 cm/s per second)
h = pressure head or differential across the orifice, cmH_2O

COMBINING I AND II

$$A = \frac{F}{C_c \times C_v\sqrt{2gh}} \qquad A = \frac{F}{C \times 44.3\sqrt{P_1 - P_2}}$$

where C = discharge coefficient (an orifice constant obtained by comparing calculated with measured valve areas at postmortem, which combines C_c, C_v, conversion factor, mmHg to cmH_2O, other unknown factors)

$44.3 = \sqrt{2g} = \sqrt{1960}$
$h = P_1 - P_2$
= pressure differential across the orifice, mmHg

The duration of ventricular filling or emptying is calculated in seconds per minute from pullback or simultaneous pressure records obtained immediately upstream and downstream from the valve. The systolic or diastolic time per beat multiplied by the heart rate gives the number of seconds in each minute during which either filling or emptying occurs across the AV or semilunar valve, respectively. Thus the volume rate of flow in milliliters per second of systole or diastole is the mean volume rate of flow (cardiac output in milliliters per minute) divided by the filling or

emptying time in seconds per minute. A sample calculation of mitral valve area is as follows:

$$\begin{aligned}\text{Cardiac output (CO)} &= 5000\ \text{mL/min}\\ \text{Diastolic filling period (DFP) beat} &= 0.38\ \text{s/beat}\\ \text{Pulse rate} &= 90\ \text{beats/min}\\ \text{DFP/min} &= 34\ \text{s/min}\\ \text{Left atrial mean diastolic pressure (LAP)} &= 30\ \text{mmHg}\end{aligned}$$

The calculation for the aortic valve area is as follows:

$$\begin{aligned}\text{Left ventricular mean diastolic pressure (LVDP)} &= 5\ \text{mmHg}\\ C &= 0.85\ \text{(orifice constant for the mitral valve)}^{77}\end{aligned}$$

$$\begin{aligned}\text{Mitral valve flow (MVF)} &= \frac{\text{CO}}{\text{DFP/min}}\\ &= \frac{5000\ \text{mL/min}}{34\ \text{s/min}}\\ &= 147\ \text{mL/s of diastole}\end{aligned}$$

$$\begin{aligned}\text{Mitral valve orifice area (MAV)} &= \frac{\text{MVF}}{0.85 \times 44.5\sqrt{\text{LAP} - \text{LVDP}}}\\ &= \frac{147}{38\sqrt{25}} = 0.8\ \text{cm}^2\end{aligned}$$

If the femoral artery is used, the aortic gradient from the simultaneous left ventricular-femoral artery pressure tracing should be averaged with the gradient obtained from the tracing that is realigned to correct for the central to peripheral time lag of the femoral pulse.[74] Other modifications also have been proposed.[75,76]

Similarly, orifice areas may be calculated for the tricuspid and pulmonary valves, using an orifice constant of 1.0. In a pulsatile flow model, the Gorlin valve area predicted the severity of aortic stenosis better than valvular resistance or stroke-work loss measurements.[77] The approximations and systemic errors in the formula do not detract from its usefulness in providing objectivity in the classification of patients with valvular disease.[78] The valve orifice, and thus the calculated valve area, may not be fixed and may be flow- and pressure-dependent. The orifice constant, too, may vary with the square root of the mean pressure gradient. Modifications of the widely used Gorlin formula have been made. To estimate aortic valve area, the Bache formula uses either the peak-to-peak or the maximum systolic gradient, thus avoiding planimetry.[79] Hakki omits the ejection or filling period and the empirical constant. He uses the square root of either the mitral mean, aortic mean, or aortic peak pressure gradients divided into the cardiac output. The Hakki mitral or aortic valve area generally agrees with the Gorlin areas[80]; a correction factor for heart rate has been proposed.[81] If flow is normal, reducing a valve orifice diameter to less than half or the cross-sectional area to one-fourth is generally required to offer significant obstruction. A significantly reduced mitral valve area is 1 cm^2; aortic valve area is 0.7 cm^2 (see Chap. 57). The transmitral pressure gradient is somewhat overestimated if the pulmonary artery wedge pressure is used rather than the left atrial pressure.[82] Calculation of the orifice area of a stenotic valve in the presence of associated valvular regurgitation must take into consideration the added regurgitant flow or the severity of the stenosis will be overestimated. To obtain an estimate of mitral or aortic regurgitant

volume, the forward stroke volume should be subtracted from total angiographic LV stroke volume.

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Chapter 15: CARDIAC CATHETERIZATION, CORONARY ARTERIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

SELECTIVE ANGIOGRAPHY

Contrast medium was first injected through a rubber catheter placed in the right ventricle by Chavez in 1947. The technique of selective angiography has been continually refined. In the patient with valvular or congenital heart disease, the diagnosis is often made initially by noninvasive imaging. Catheterization and angiography are then performed as directed studies to provide histologic data and additional anatomic detail. A catheter with a large lumen facilitates rapid low-pressure delivery of a single bolus of the contrast agent. A catheter with a coiled open tip and multiple laterally directed openings reduces recoil. A balloon-tipped angiographic catheter with proximal side holes is easy to manipulate and induces less ectopy than do conventional catheters. A power injector delivers the desired volume of contrast medium at a preselected maximal flow rate. In adults with complex cyanotic congenital heart disease, a large closed-end catheter with multiple side holes inserted via the femoral vein can deliver 70 mL of contrast medium in 2 s without recoil. Positioning the catheter in the apex of the right ventricle is done by using a guidewire or a tip deflector wire when a large-diameter catheter is used.

Contrast Media

In 1923, Osborn noted that the urinary bladder of luetic patients treated with oral and intravenous sodium iodide became opaque to x-rays because of the absorption of photons by iodine. All contrast media contain three iodine molecules attached to a fully substituted benzene ring. The fourth position in the standard ionic agent is taken up by sodium or methylglucamine as cation; the remaining two positions of the benzene ring have side chains of diatrizoate, metatrizoate, or iothalamate. All media are excreted predominantly by glomerular filtration. The normal half-time of excretion is 20 min; biliary excretion is 1 percent. A dose of 0.5 to 1.0 mL/kg of medium may be scaled up or down in relation to total body weight, size of the heart chambers, systemic blood flow, degree of left-to-right shunting, severity of pulmonary vascular disease, and clinical status of the patient. If significant hemodynamic changes rapidly follow the administration of contrast medium, subsequent large-volume injections ideally should be spaced in time as the clinical status of the patient dictates. The vasodilator effect and the transient decrease in systemic vascular resistance are directly related to the degree of osmolality of the contrast medium used. Transient hypervolemia and depressed contractility are in part responsible for the elevation of left atrial and LV end-diastolic pressure.

To reduce the osmotic effects of contrast medium, the number of dissolved particles must be decreased or the molal concentration of iodine per particle must be increased (Fig. 15-11). New-generation, nonionic, monomer, and ionic dimer contrast agents have approximately the same viscosity and iodine concentration but have only one-half or less of the osmolality of the ionic agents, e.g., iopamidol and ioxaglic acid (ioxaglate), 796 and 560 mosmol/kg H_2O, respectively, versus 1689 mosmol/kg H_2O for diatriozate sodium.[83] The advantages of the new agents include less hemodynamic loading,[84] patient discomfort, binding of ionic calcium, depression of myocardial function and blood pressure,[85] and possibly fewer anaphylactoid reactions. A disadvantage is the high cost that leads to a policy of selected use.[86] Also, while standard contrast media have a moderate anticoagulant effect, some nonionic media have only a slight anticoagulant effect, and the catheter and syringe containing them should thus be kept free of blood.[87] The principal use of the new agents may be in very ill patients, especially in adults with extremely

poor LV function, in patients with renal disease, especially those with diabetes, and in patients with a history of serious reaction to contrast media or with multiple allergies. If standard high-osmolality agents are used, those which are non-calcium binding may produce less negative inotropic effect and less ventricular fibrillation.[88]

CONTRAST MEDIA

	Standard Agents	New Generation Agents	
	High Osmolality	Low Osmolality	
Structure	Ionic Monoacid Monomer	Non-Ionic Monomer	Ionic Monoacid Dimer
Benzene Rings	One	One	Two
Cation	One	None	One
Moles of Iodine	Three	Three	Six
Particles in Solution	Two	One	Two
Molal Concentration Of Iodine Per Particle	1.5	3.0	3.0
Side Chains	Ditrizoate[1] Metrizoate[2] Iothalamate[3]	Metrizamide[4] Iopamidol[5] Iohexol[6]	Ioxaglate[7]
Proprietary Names	[1]Renografin 76 Angiovist Hypaque [2]Isopaque [3]Conray	[4]Amipaque [5]Isovue [6]Omnipaque	[7]Hexabrix

Figure 15-11: Comparison of structure, iodine per particle, and side chain between standard and new contrast media. The number next to the proprietary name identifies the side chain it contains.

Filming Methods

Cineangiography uses intensification and amplification fluoroscopy and filming by a 35-mm movie camera as well as television monitoring and disk recording.[89] Perfection in image quality is achieved when each point in the object is recorded as a point on the film. In practice, this reproduction is hindered by the diffusion of light by intensifying screens interfering with sharpness and resolving power. Although the detail of the individual cine frame lacks the spatial resolution of the cut-film screen angiogram, the motion itself increases visual perception by noise averaging and use of the integrating (5 frames per second) or persistence ability of the eye (0.2 s). The circular image of the phosphor is usually overframed on relatively slow 35-mm film with an 18 × 24 mm useful film area. Meticulous attention to film processing and the film type is essential to obtain the desired contrast and image detail. Radiographic contrast, or the difference in density or grayness between areas, depends in part on the proper x-ray photon penetration of the subject, film contrast, and scatter radiation. The latter is minimized by a collimation of the x-ray beam. For

coronary angiography, short-scale, high-contrast, sharp white images on a dark gray background are desired; in the congenital heart patient, a long scale of shades of gray helps to define the entire cardiac anatomy. Biplane cineangiography is highly desirable in the study of complex congenital heart defects, especially in infancy. The total amount of contrast medium is significantly reduced, and chamber and great vessel relations are better defined.

To perform computer-enhanced digital angiography, the catheterization laboratory image intensifier and video camera are linked to an analogue-to-digital converter, computer system, and digital storage device. The analogue video signal is digitized into a series of discrete numerical values that represent continuous voltage fluctuation and can be stored on disks. The images are acquired in the standard cineradiographic mode and simultaneously are stored on film via the cine camera and digitized from the video image. The digital information is enhanced for display by a real-time image processor and is stored on a digital disk for further processing. In single-plane acquisition, exposure rates of 15, 30, and 60 frames per second in a 512 × 512 or 1024 × 1024 matrix are available. In simultaneous biplane acquisition, 7.5, 15, and 30 frames per second are possible. Enhanced images can be recalled and reviewed to allow selection of a freeze frame. The selected image can be stored and displayed on a separate monitor. A real-time image processor enhances and smooths the fluoroscopic image. For difficult projections, pulsed fluoroscopy is available on demand at approximately half the cine dose level, the last 5 s of which can be stored on digital disk for instant review. Varying degrees of enhancement, frame rates, and exposure times can be selected from a preprogrammed push-button module. Analytical programs include subtraction capabilities, ventricular ejection fraction, edge enhancement, and regional and global wall motion. An image mask is made electronically by reversing the polarity of the background image of bone and tissue. The mask is then superimposed on the angiographic image. The positive and negative images of the competing tissue background cancel, leaving the digital subtraction angiogram. Arterial stenosis quantification and 2× zoom magnification can be performed in postprocessing. A hand-held infrared control device permits image review and freeze-frame storage during the study. It can be placed in a sterile bag and operated by the cardiologist at tableside. Postcase review and additional image processing are accomplished via the view panel. Hard-copy images of selected frames, which are particularly useful for interventional procedures, can be recorded via video paper, x-ray film, or laser copier. In practice, the resolution of the digital arteriogram from the hard disk approaches that of cine film. Unacceptable image degradation occurs when the digital angiogram is transferred to videocassette tape. Thus, once a practical way of permanent digital image archiving is established and if a standard compatible system for exporting image data is developed, digital angiography is likely to replace film in the catheterization laboratory.[90] The compact disc-recordable (CD-R) format and a universal interchange standard set by users and makers, i.e., Digital Imaging and Communications in Medicine (DICOM), appears promising.

Positioning

Universal positioning capability of the x-ray and intensifier tubes by using stands of L-, U-, or C-arm configuration permits angled views of a supine patient. Two profile views of the curved ventricular septum are needed. They are made in degrees of axial obliquity and cranial angulation as follows: (1) The 40° left anterior oblique (LAO) and 30° cranial position (four-chamber view) outlines the posterior third of the ventricular septum, the valve plane in AV canal defects, and the four heart chambers without superimposition. (2) The 60° LAO and 30° cranial position (long-axial view) outlines the anterior two-thirds of the ventricular septum, the membranous ventricular septal defect, and the LV outflow tract (Fig. 15-12*A*, *B*). An elongated RAO view, which is useful for seeing the RV infundibulum and supracristal ventricular septal defect, is obtained by 30° axial RAO and 40° cranial angulation. The main pulmonary artery and its bifurcation are seen in the frontal position with 30° of cranial angulation; a steep LAO position with marked cranial angulation is also used.[91]

A successful procedure results when a rapid injection of the proper volume of contrast medium is made through an adequate-sized catheter, properly positioned, with detailed attention to radiologic technique and to the position of the x-ray tube or tubes. Complete opacification of the LV cavity without inducing ventricular ectopy defines a satisfactory LV angiogram.[92]

Uses of Angiography

Right atrial angiography is useful in defining the following: (1) the tricuspid valve in Ebstein's anomaly and tricuspid atresia or stenosis, (2) myxoma or thrombus, (3) juxtaposition of right atrial appendage in cyanotic congenital heart disease, (4) the right atrial border in pericardial effusion or tumor, and (5) atrial septal defect with right-to-left shunting or occasionally the site entrance of an anomalous pulmonary vein by reflux. In the lateral position, an RV injection is used to study the caliber and the level of obstruction to RV outflow and the relation of the great vessels to the right ventricle (Fig. 15-13). A pulmonary artery injection may be used to fill the left side of the heart to detect a left-to-right shunt and to detect the site of partial (Fig. 15-14) or total anomalous venous drainage of the pulmonary veins and to visualize the pulmonary artery and its branches (Fig. 15-15). An atrial septal defect is best defined by selectively injecting the right upper-lobe pulmonary vein rather than the left atrium itself. In patients with an endocardial cushion defect and an ostium primum atrial defect, selective LV angiography shows relative elongation (Swan's neck) of the LV outflow tract and shortening of the LV inflow tract due to deficiency of the upper part of the inlet ventricular septum (Fig. 15-16). To identify the pulmonary arteries in cases of pulmonary atresia with ventricular septal defect or to identify one pulmonary artery in cases where a shunt procedure has inadvertently produced discontinuity between right and left branches, a hand injection of contrast medium into an end-hole balloon catheter occluding a pulmonary vein or into a conventional catheter in the pulmonary vein wedge position frequently will opacify the ipsilateral pulmonary artery retrogradely back to its main confluence.[93] The size and origin of systemic artery-to-pulmonary artery collaterals arising from the descending aorta, the patent ductus, and the subclavian arteries should be defined in the patient with pulmonary atresia (Fig. 15-17).

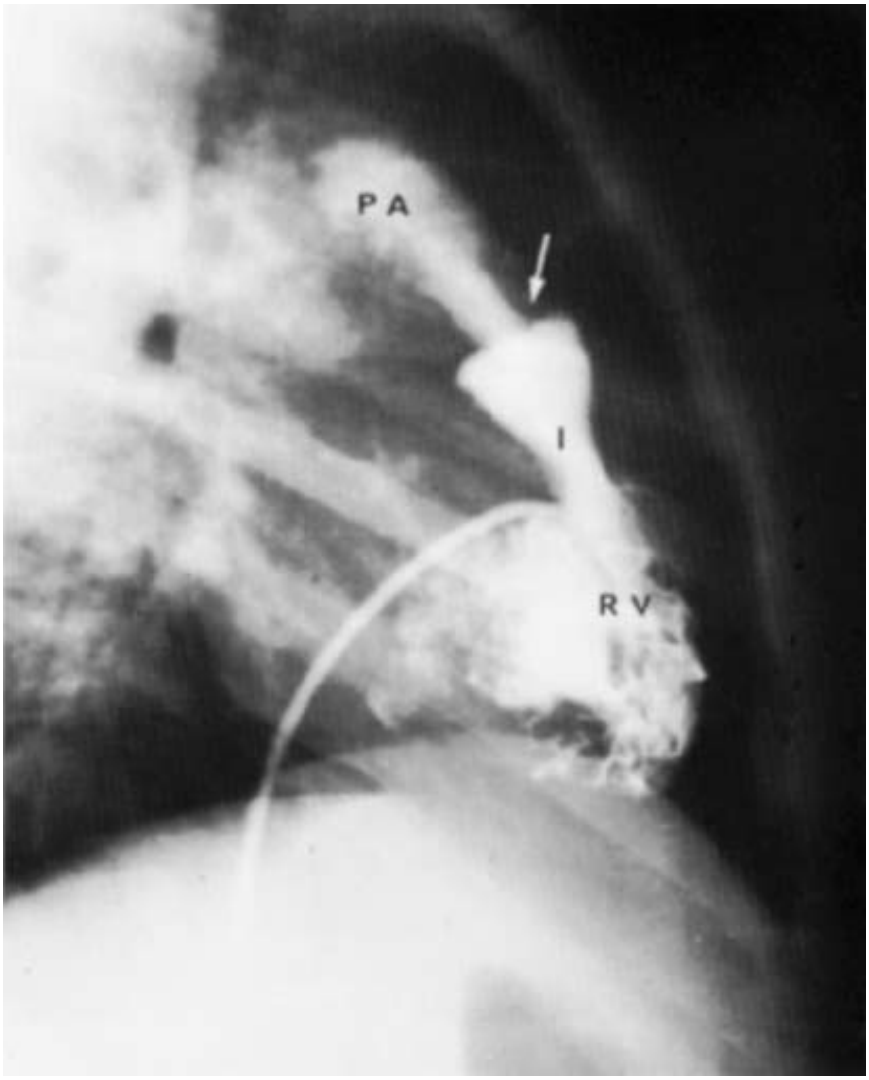

Figure 15-13: Valvular pulmonary stenosis (lateral view). Right ventricular injection of opaque medium. Contrast material exits through central orifice of pulmonary valve in form of a jet (*arrow*). RV, right ventricle; I, infundibulum of right ventricle; PA, pulmonary artery.

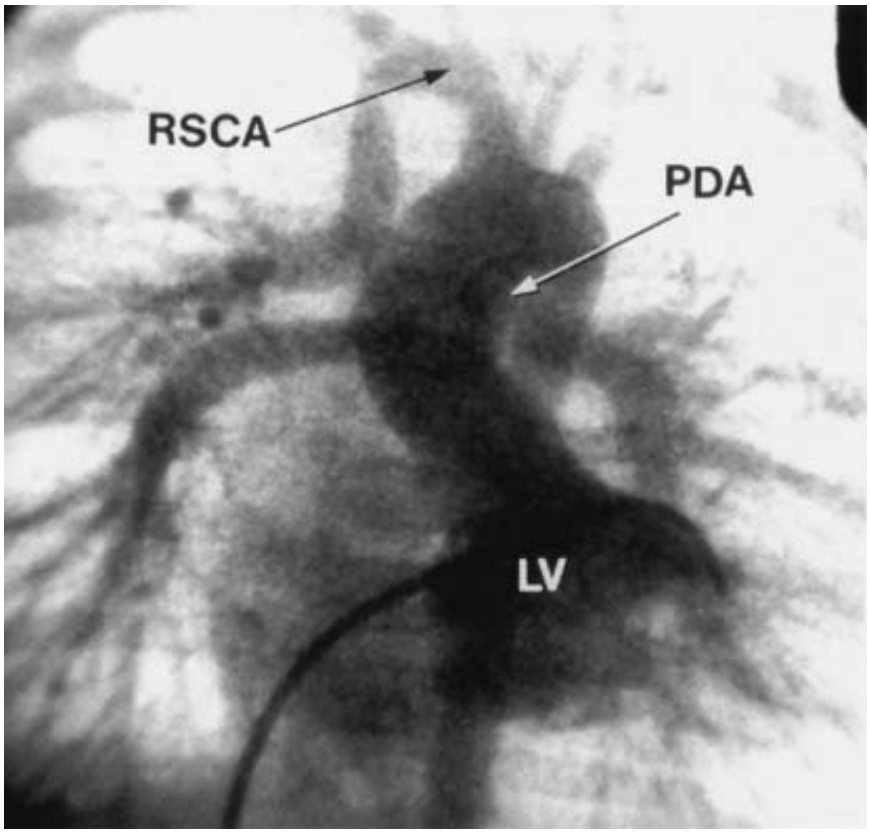

Figure 15-17: Selective LV angiogram in a patient with ventricular septal defect and pulmonary atresia, frontal view. The right and left pulmonary arteries are supplied by a patent ductus arteriosus (PDA). A branch from the right subclavian artery (RSCA) fills a separate right pulmonary artery supplying the right middle and upper lobe.

Valve Regurgitation

Injections made above the aortic valve serve to detect and qualitatively assess aortic regurgitation. In milder degrees of aortic regurgitation, a fine regurgitant jet or puff is noted; opacification is limited to the LV outflow tract, clearing with each systole (grade 1), or faint, persistent, incomplete opacification of the LV cavity (grade 2) occurs. In grades 3 and 4, no distinct jet is seen, and dense complete opacification of the left ventricle occurs either progressively or in one or two diastolic cycles, and LV density exceeds aortic density in the severe case. After an aortic injection, the size and mobility of a stenotic aortic valve may be visualized by negative-contrast washout of the opacified aorta with nonopaque ventricular blood. In the LAO view, the mouthlike opening of a bicuspid aortic valve is seen when fusion of the commissure between the right and the left aortic sinus leaflets occurs. An LV injection may display the level of subaortic obstruction to LV outflow. In patients with endocardial cushion defect, the frontal view may show a radiolucent notch in the anterior mitral valve leaflet or between the superior and inferior bridging leaflets of the AV valve.

LV injection in the RAO view is used to detect and grossly quantitate mitral regurgitation. Forty-five milliliters of contrast medium is delivered at 15 mL/s via a pigtail catheter positioned to avoid ventricular ectopy. The angiographic criteria for grading mitral regurgitation are somewhat subjective, so disagreement may arise between observers in assessing the degree of reflux. In grades 1 and 2 mitral regurgitation, a narrow- to moderate-width regurgitant jet of slight to moderate density is noted; minimum to moderate opacification of the left atrium clears quickly. In grades 3 and 4, a well-defined jet is absent, and left atrial opacification is intense, immediate, and lingering; thus the left atrium appears denser than the left ventricle or aorta in grade 4 mitral

regurgitation. In mitral valve prolapse, which is shown best in a lateral projection with slight cranial angulation, all or a portion of one or both leaflets balloons above the mitral annulus in systole, with or without associated mitral valve regurgitation. A normal mitral valve may leak if ectopic beating occurs. Unlike disk or ball valves, prosthetic tissue valves can be crossed with the catheter tip without interfering with valve function. Selective RV angiography in the RAO or lateral position via a pigtail catheter lying in the apex of the right ventricle gives adequate evaluation of tricuspid regurgitation.[94] Reflux into the SVC and IVC is associated with severe tricuspid regurgitation. A properly placed main pulmonary artery catheter will detect significant pulmonary regurgitation.

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Chapter 15: CARDIAC CATHETERIZATION, CORONARY ARTERIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

COMPLICATIONS OF CARDIAC CATHETERIZATIONAND ANGIOGRAPHY

An experienced operator can carry out catheterization of the right side of the heart without difficulty in practically all cases. Complications may include knotting of the catheter; breakage of the guidewire; perforation of the atrium, ventricle, or coronary vein; and pulmonary infarction or pulmonary artery rupture associated with balloon catheter inflation.[95] Complete heart block may be induced if left bundle-branch block is already present or if prolonged catheter manipulation is required in a cyanotic patient. Prolonged ventricular or atrial arrhythmia may occur.

In the catheterization of the left side of the heart, thrombosis or hematoma may occur at the percutaneous arterial puncture site, and blood may migrate into fascial and retroperitoneal planes.[96] Perforation may occur at a tortuous subclavian or pelvic arterial site. The most common vascular complication is femoral arterial pseudoaneurysm or pulsating hematoma, in part due to the increased use of heparin after catheterization (see Fig. 15-3). Pseudoaneurysm following catheterization may be detected by color Doppler flow imaging. In systole, a high-velocity flow signal moves into the sac of the pseudoaneurysm from the small puncture site in the superficial or common femoral artery; in diastole, there is a low flow velocity from the sac into the femoral artery retrogradely. In the presence of the femoral artery-to-femoral vein fistula, there is a constant-flow signal from the artery to the vein.[97,98] Ultrasound-guided compression obliteration of these communications has been helpful. Among approximately 23,000 patients (72 percent males) at Emory University Hospital who had coronary artery angiography via the percutaneous femoral approach using a no. 8 French multipurpose catheter, 14 patients (12 females and 2 males) required femoral artery thrombectomy. The smaller femoral artery of the female is more prone to thrombotic occlusion than is that of the male. Cerebral embolism results primarily from plaque material dislodgment in the ascending aorta and less often from a fibrin clot on catheters.[99] Isolated persistent diplopia or hemianopia may occur. In 30,000 coronary artery and LV catheterizations, 35 patients had central nervous system complications (carotid distribution in 15, vertebrobasilar in 20, and diffuse encephalopathy in 2). The deficit resolved in one-half of all patients and persisted in one-half. There were two deaths. Cholesterol crystal embolization shower syndrome may follow catheter manipulation in the aorta and can result in progressive renal failure. Transseptal puncture may result in inadvertent perforation of the aorta or the free wall of the atrium, with resulting cardiac tamponade.

Nausea with or without vomiting may develop immediately after the initial injection of contrast medium, probably related to direct stimulation of serotonin receptors in the brain. Adverse reactions also include sneezing, chills, low-grade fever, hives, itching, angioedema, bronchospasm, and shock. Since no anti-contrast medium immunoglobulin E (IgE) is found, these reactions are anaphylactoid rather than being true anaphylaxis. The mechanism may be related to activation of the kallikrein, classic or alternate complement, or intrinsic coagulation systems or to direct hyperosmolar or chemical cytotoxicity.[100] Rare reactions include parotitis (iodide mumps), glossitis, and pancreatic edema. A two-dose oral glucocorticoid regimen (methylprednisolone, 32 mg) given 12 and 2 h before standard contrast medium injection significantly reduces acute allergic reactions. Diphenhydramine hydrochloride, cimetidine hydrochloride, epinephrine, and hydrocortisone, singly or combined, have been added to a treatment protocol outlined in Table 15-2. Patients at high risk for contrast medium nephropathy usually have preexisting renal insufficiency and diabetes. An increase in serum creatinine levels of 0.5 to 1.0 mg/dL or a rise of

25 to 50 percent over baseline at 24 to 48 h after angiography is noted in 2 to 7 percent of an unselected population and is considered to reflect contrast medium-induced renal injury. Good hydration is essential in preventing or diminishing renal injury: 0.45% normal saline at a rate of 1 mL/kg per hour is begun 12 h before and is continued for 12 h after the procedure.[101] The mechanism of contrast nephrotoxicity is related in part to renal cortical vasoconstriction and to tubular cell toxicity[102,103] (Fig. 15-18). Renal insult in a high-risk-group subset in a randomized trial was diminished with the use of low-osmolality media. There is little difference in the rate in serum creatinine levels after angiography in low-risk groups whether ionic or nonionic contrast media are used.[104,105] Pulmonary edema following angiography may be caused by volume overload and a negative inotropic effect.

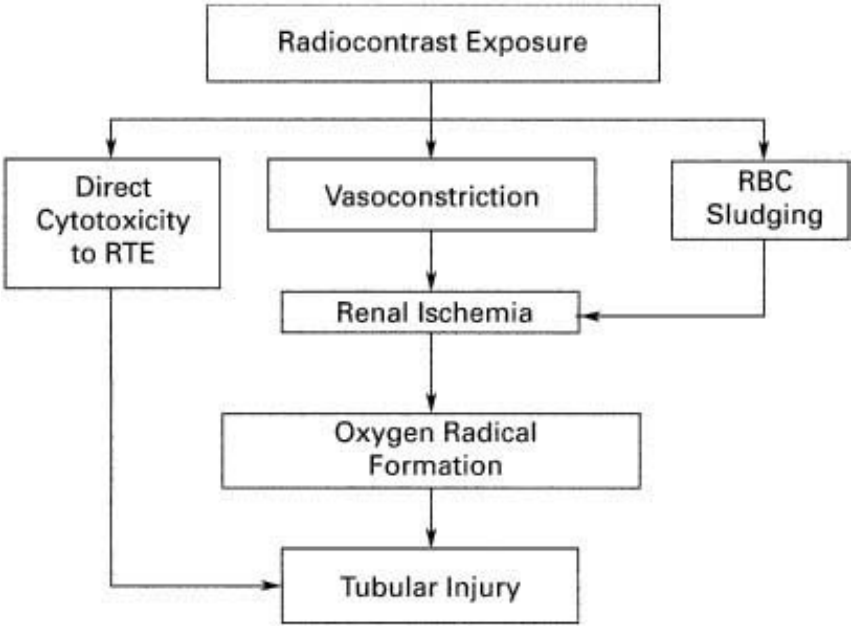


Figure 15-18: Proposed mechanisms of contrast media-induced acute renal injury. RBC, red blood cells; RTE, renal tubular epithelial cells. (From Rocher.[102] Reproduced with permission of the author and publisher.)

In desperately ill patients and in those with marked ventricular dysfunction or severe valvular obstruction, the desire for films that display the cardiac anatomy spectacularly should be tempered by the potential consequences of large doses of contrast medium in this setting.[106]

PREVIOUS | NEXT

Chapter 15: CARDIAC CATHETERIZATION, CORONARY ARTERIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

CORONARY ARTERIOGRAPHY AND LEFT VENTRICULOGRAPHY

Coronary arteriography remains the standard by which all methods of diagnosing coronary artery disease are measured. It is the primary method of defining coronary anatomy in living patients. To accomplish this in a safe, reliable, and reproducible manner, adherence to certain principles of performance and interpretation is required.[107-109]

Coronary arteriography provides not only an anatomic map of the coronary arteries, including the site, severity, and shape of stenotic lesions, but also the characteristics of distal vessels in terms of size, presence of atherosclerotic disease, mass of myocardium served, a rough index of differential coronary flow, identification of collateral vessels, and an estimate of their functional importance.[110-113] Intracoronary thrombi can be recognized, although it is clear from angioscopic studies that coronary arteriography is relatively insensitive in the detection of thrombi. In addition, the presence of coronary spasm can be ascertained by using provocative maneuvers.[114-116] The functional significance of a coronary stenosis can be assessed by measuring coronary flow directly, both at rest and during an intense coronary dilator stimulus. The difference between resting and maximal coronary flow is the coronary flow reserve capacity of the coronary bed. Coronary flow reserve can be measured in the coronary arteriography laboratory by using digital subtraction or intracoronary Doppler techniques.[117]

LV catheterization makes possible measurements of LV pressure at rest, with exercise, or after pharmacologic agents. Left ventriculography enables one to make a visual analysis of wall motion. Ventricular systolic and diastolic volume andejection fraction can be calculated. Careful correlation of the coronary arteriogram and left ventriculogram permits identification of stenotic and potentially bypassable arteries serving viable myocardium. LV wall motion can be further evaluated by the addition of stress such as atrial pacing, pharmacologic agents, or exercise. Augmenting LV contraction by the use of nitrates, catecholamines, or postextrasystolic beats may permit the identification of LV wall segments that have a potential for improved function after revascularization surgery.[118-120] The presence of associated valvular heart disease may be determined. In patients who have previously undergone surgery, patency of grafts and status of the native coronary arteries can be ascertained. In certain children with congenital heart disease, the location of the coronary arteries can be determined as an aid to planning surgical correction.[121]

Techniques of Coronary Arteriography

Sones ushered in the modern era of coronary arteriography in 1958 when he developed a safe and reliable method of selective coronary arteriography.[110] The Sones technique uses an antecubital incision over the brachial artery. The artery is exposed, and a woven Dacron catheter (Sones USCI) is passed into the brachial artery and maneuvered through the axillary and subclavian arteries into the ascending aorta. Manipulation techniques depend on deflecting the soft, tapered catheter tip off the aortic valve cusps up to the coronary orifices. The Sones technique has stood the test of time. The advantages are that it requires only one catheter, aortoiliac disease is avoided, and the operator is close to the aortic root and therefore has a good feel of the catheter tip. The disadvantages of antecubital dissection, arteriotomy, and arterial closure have been nearly entirely overcome by percutaneous entry of the brachial artery and, in recent years, the radial artery. Manipulation skills and precise knowledge of the aortic root anatomy are required. A detailed description of the Sones technique has been published.[122]

Percutaneous arterial catheterization, described in 1953 by Seldinger,[123] was first used to study the coronary arteries, as reported by Ricketts and Abrams in 1962.[124] Modification of catheters was made by Amplatz et al.[125] and by Judkins[126] in 1967. The Judkins technique requires three preformed catheters: one for each coronary artery and a pigtail catheter for the LV injection. The Judkins technique is much easier to

learn; paradoxically, this may be its major drawback. The femoral artery is punctured below the inguinal ligament, and a left coronary artery catheter is passed over the guidewire into the aorta. After the catheter is flushed and good pressure tracings are obtained from the tip, the catheter is advanced until it engages the left coronary orifice. The preformed shape of the catheter holds it against the inside of the aortic curve, enabling the tip to spring into the left coronary orifice. The tip is made in four lengths for use with different-sized aortic roots. After the left catheter is removed, the appropriate-sized right coronary catheter is inserted over a guidewire and positioned above the right coronary orifice, where it is rotated clockwise. The tip will descend and will be held against the outside curve of the aorta, causing it to spring into the right coronary orifice. LV studies are performed by replacing the coronary catheters with the pigtail catheter. A detailed description of the Judkins technique also has been published.[127]

This technique has the advantages of a percutaneous approach; the disadvantages are the requirement for multiple catheter exchanges and a potential increased risk of emboli to the coronary or cerebral circulation. Complications may arise from the ease of entry of the catheter tip into the coronary arteries. Some poorly trained angiographers have applied this technique without proper appreciation of the devastating consequences of catheter obstruction of the left main coronary artery. Methods of avoiding serious complications of catheter emboli, including systemic heparinization and catheter-debriding techniques, have reduced complications in active centers. In an attempt to combine the advantages of the Sones and Judkins techniques, the single-catheter percutaneous femoral approach was first applied by Schoonmaker in 1968, and use of this technique was reported by Schoonmaker and King.[128] This technique has been employed at Emory University Hospital in over 80,000 studies since 1972.

Performance of Coronary Arteriography

The description of our technique of coronary arteriography is brief; a more detailed description has been published.[129] It is our belief that one cannot become expert in performing coronary arteriography by reading. Only through training in an active laboratory and performing hundreds of coronary arteriograms under close supervision can the physician gain a proper appreciation of the potential hazards of coronary arteriography so that they can be avoided.[130] A close physician-patient relationship is essential to reduce fear of the examination. The patient is seen before the procedure, and a thorough history, physical examination, and description of the procedure are completed. Patients with mild or stable symptoms may undergo coronary arteriography as outpatients, unless noninvasive studies indicate the likely presence of severe anatomic problems such as left main coronary artery stenosis. In most laboratories, outpatient catheterization studies are performed with smaller-diameter catheters of a no. 5 or no. 6 French size. Cardiac medications are usually continued up to and through the procedure. An intravenous line is routinely started for administration of midazolam for conscious sedation. The intravenous line is also essential as a port for the administration of additional drugs during the procedure, as needed, if pain or hypotension occurs or if congestive failure is aggravated. Electrocardiographic and pulse oximetry monitoring is performed throughout the procedure. Atropine, lidocaine, propranolol, furosemide, glucocorticoids, an antihistamine, nitroglycerin, epinephrine and other vasopressors, and a narcotic should be readily available for intravenous administration. Heparin and antibiotics are not administered routinely in our laboratory. Patients with a history of anaphylactoid reactions to contrast media are pretreated with antihistamines and glucocorticoids.

A three-way stopcock manifold is connected to lines for pressure monitoring, contrast medium, and heparinized saline solution. A clear catheter is maintained by intermittent flushing with saline solution and contrast medium. The femoral artery is catheterized by the Seldinger technique, and a multipurpose polyurethane catheter is inserted into the descending aorta, where it is flushed before being advanced around the aortic arch without a guidewire. The catheter is advanced to the left ventricle, where, following pressure measurements and test injections to exclude catheter-tip entrapment, 10 to 20 mL of contrast medium is injected over 3 s. This slow injection allows adequate visualization without recoil of the end-hole and side-hole catheter. Filming is done routinely in the RAO view or in a biplane mode using RAO and LAO views.

Essential to any coronary arteriographic technique is a thorough knowledge of aortic root anatomy (Fig. 15-19). Usually the left coronary orifice arises from the left sinus of Valsalva, which is posterior and to the left. The right coronary artery usually arises from the right sinus of Valsalva, which is anterior. Because of extensive variation in the position, size, and number of orifices, considerable experience is required to

avoid failure to identify and study one of the arteries. Left coronary cannulation is performed in the following manner: The tip of the catheter is placed in the noncoronary cusp, which lies posterior and to the left (toward the spine in the RAO view). As the catheter is advanced with a slight clockwise rotation, the tip flips up into the left coronary ostium or into the left cusp. From the left coronary cusp, the catheter tip can be rotated posteriorly and advanced superiorly into the left coronary ostium (see Fig. 15-19). Right coronary artery catheterization is done by positioning the tip of the catheter above the left coronary cusp and rotating clockwise so that the tip sweeps along the anterior aortic root until it reaches the right coronary ostium (see Fig. 15-19). An alternative method is to advance the catheter tip in the right cusp; it curves into the right orifice. When the operator is unsuccessful in reaching one or the other coronary orifices, the catheter is removed and replaced by an appropriate Judkins or other preformed catheter.

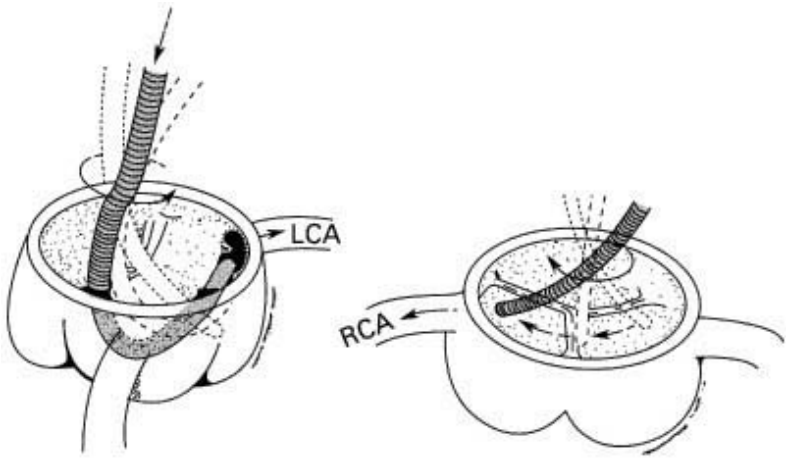


Figure 15-19: (*Left*) A 30° RAO view of the aortic root demonstrating the left coronary orifice. (*Right*) A 60° LAO view of the aortic root demonstrating location of the right coronary orifice. (From Schoonmaker and King.[128] Reproduced with permission from the American Heart Association, Inc., and the authors.)

All injections into the coronary arteries are preceded by aspiration of a small amount of contrast medium into the hand-held syringe (to exclude the possibility of air embolism) and are monitored visually until the contrast medium clears. Pressure monitoring is done after these injections. Hypotension following coronary injection usually clears spontaneously or with coughing, which transiently increases aortic pressure and enhances clearing of contrast medium. If hypotension lasting more than a few seconds occurs, especially in a patient with severe proximal coronary artery disease, a pressor agent in an adequate dose to obtain a quick response is started promptly. Adequate coronary perfusion pressure is essential. If congestive heart failure is aggravated by the effect of contrast medium, the first drug used is sublingual nitroglycerin; furosemide may be needed, however. When chest pain occurs, nitrates are given sublingually or intravenously, and the catheter is repositioned in the left ventricle to monitor LVEDP. If pain continues or ST-segment elevation occurs, coronary injection may reveal coronary spasm. Intracoronary nitroglycerin usually provides prompt relief. If severe elevation of end-diastolic pressure occurs, the patient may be propped up and given additional nitrates and oxygen. When tachycardia accompanied by adequate or elevated blood pressure develops during angina, 1-mg increments of propranolol or metroprolol may be given intravenously, producing dramatic relief. Narcotics are used for pain that is not relieved promptly by nitroglycerin and propranolol. Ventricular fibrillation, a rare occurrence, is corrected promptly with the defibrillator. All laboratory personnel must be thoroughly trained in cardiopulmonary resuscitation, since unstable patients may develop life-threatening arrhythmias before, during, and after angiography.[130] Minor anaphylactoid reactions are treated with antihistamines; more serious reactions are treated with the addition of epinephrine and glucocorticoids.[131] Maximal safety is obtained when an expert angiographer performs a brief but complete study, obtaining all clinically pertinent information with a minimal number of injections. Because of the osmotic diuresis induced by the contrast media, intravenous and oral fluid supplements are required after catheterization, and postural hypotension must be checked for when the patient is allowed up.

Interpretation of the Coronary Arteriogram

Once of interest to angiographers and surgeons only, the viewing and interpretation of coronary arteriograms should now be of vital interest to cardiologists if they are to make informed decisions about their patients. The coronary arteriogram should be viewed in a systematic fashion. Because coronary anatomy can be quite variable, one needs to view the films with an eye toward making sure the entire LV epicardial surface and septum are adequately supplied and that no gaps exist. If significant gaps are found, an occluded or anomalous artery is likely. The coronary arteries should be viewed one at a time, and some division of arterial segments such as the one suggested by the American Heart Association[132] should be made (Fig. 15-20). Areas of foreshortening and overlap should be examined in other views to convince the observer that there is not a hidden lesion. It is helpful for several observers to study the arteriogram. As each segment is viewed, a systematic scoring and recording system is mandatory if consistency is to be maintained and no segments are to be overlooked.

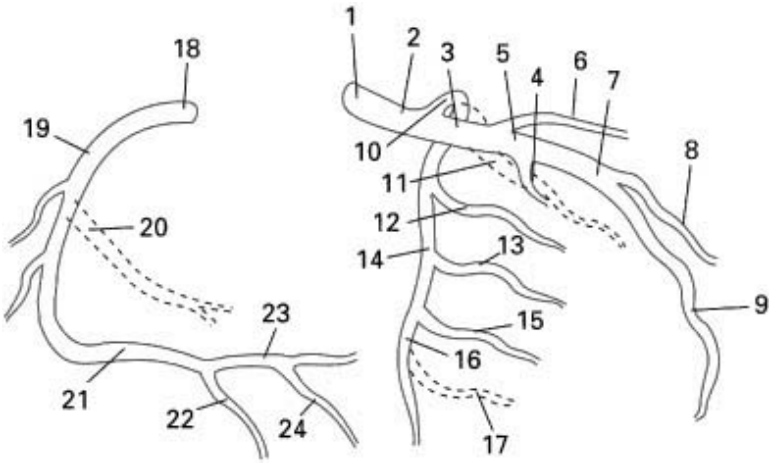


Figure 15-20: Diagram of the coronary circulation. Each arterial segment is evaluated carefully in all views and the degree of stenosis is determined. Left main coronary artery, 1, 2; left anterior descending coronary artery, 3, 5, 7, 9; diagonal branches, 6, 8; major septal perforating branch, 4; circumflex coronary artery in the atrioventricular groove, 10, 14, 16; ramus intermedius, 11; obtuse marginal branches, 12, 13, 15; posterior descending branch of the circumflex coronary artery, if present, 17; right coronary artery in the atrioventricular groove, 18, 19, 21, 23; large right ventricular branch of the right coronary artery, 20; posterior descending branch of the right coronary artery, 22; left ventricular branch of the right coronary artery, 24. (From King SB III, Douglas JS Jr. *Coronary Arteriography and Angioplasty*. New York: McGraw-Hill; 1985:363. Reproduced with permission from the publisher and authors.)

Angiographic Views

Filming is done in a number of projections so that all coronary arteries can be visualized throughout their lengths and significant disease can be detected and quantified. Multiple views in the transverse plane (Figs. 15-21, 15-22 and 15-23) were used until 1973, when Bunnell reported the advantages of obtaining views incorporating sagittal angulation of the x-ray beam along the long axis of the body (Fig. 15-24). Use of these views (Figs. 15-25 and 15-26) greatly enhances the ability to visualize the proximal left coronary artery, unmasking lesions that otherwise would be missed in up to 20 percent of patients and significantly improving diagnosis in an additional 30 to 40 percent.[133-135] The evolution of a new generation of x-ray equipment to obtain these views has revolutionized coronary arteriography. In most laboratories, standard views of the left coronary artery are the frontal view, 30° RAO, 45° LAO, 45° LAO with 30° of cranial angulation, 30° RAO with 30° of cranial angulation, and 30° RAO with 15° of caudal angulation. Other views may be needed to separate overlapping vessels or to focus on a particular problem area. The right coronary artery usually is visualized in the right and left oblique projections, and sagittally angulated views frequently are helpful in evaluating the proximal posterior descending artery (Figs. 15-27 and 15-28). The use of sagittally angulated views also provides for improved visualization of LV wall motion and mitral valve motion and for evaluation of the LV outflow tract.[136]

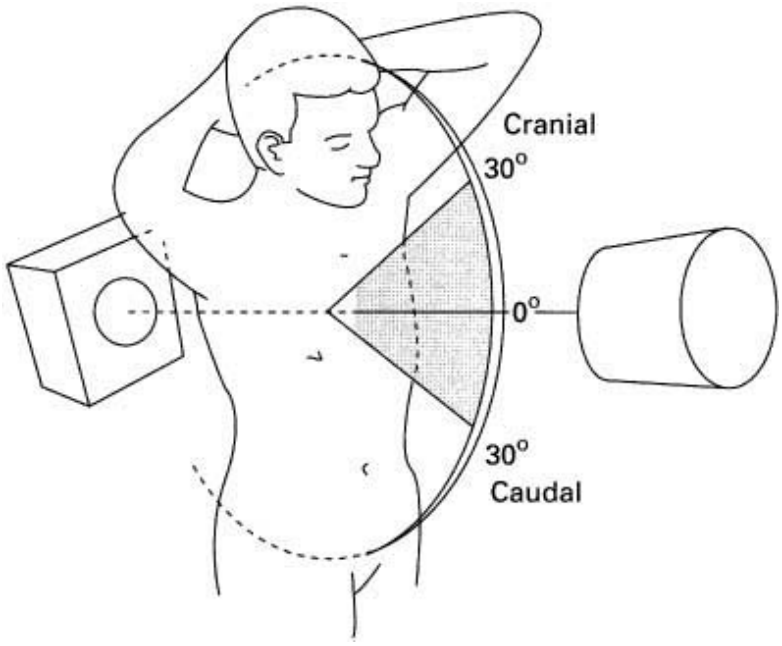
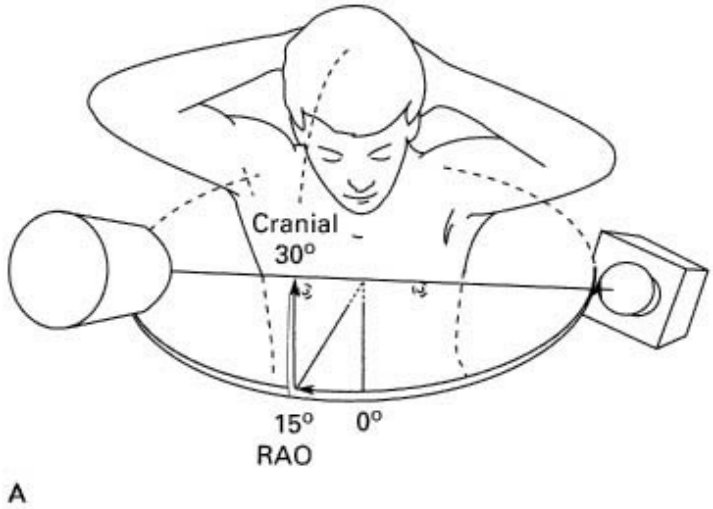


Figure 15-24: Illustration of sagittal angulation of x-ray beam in coronary arteriography. (From King et al.[136] Reproduced with permission from the publisher, editor, and authors.)



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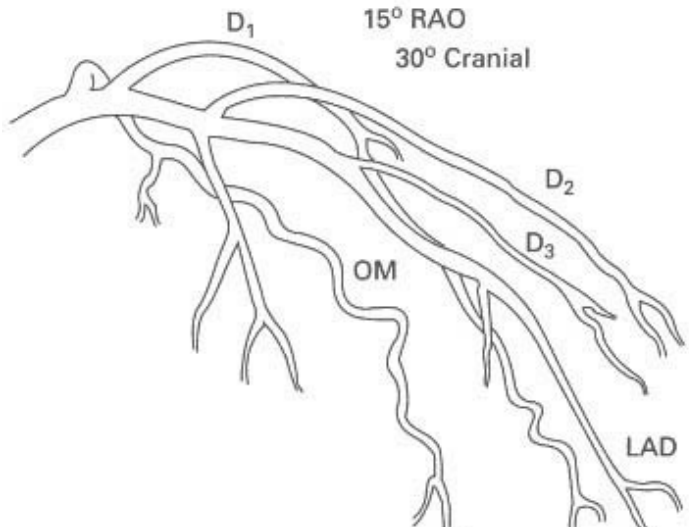

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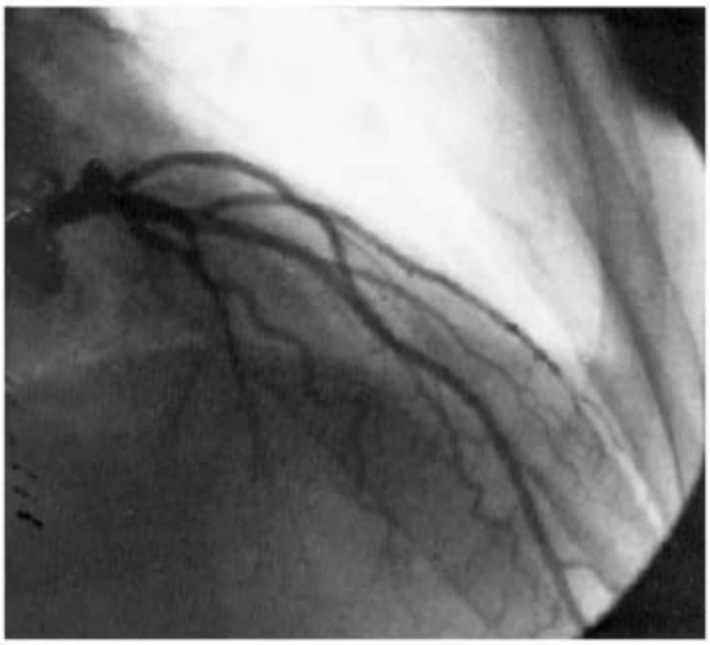

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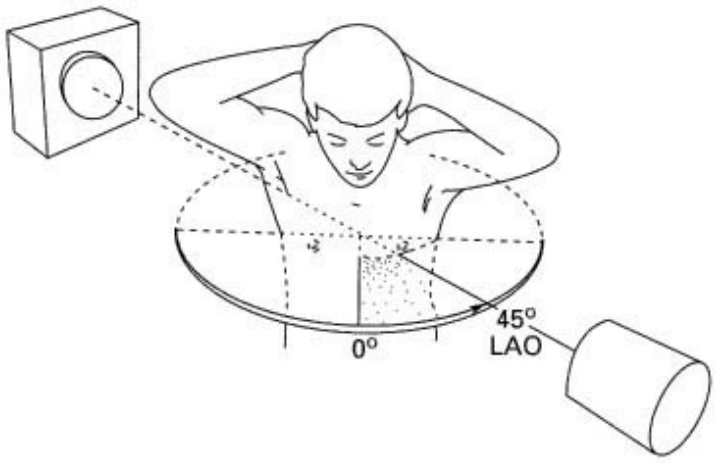
Figure 15-26: Diagrammatic illustration of the direction of the x-ray beam and the left coronary angiogram in the 15° RAO with 30° of cranial angulation. This view is particularly helpful in analyzing the mid-left anterior descending artery and the diagonal branch points. Overlap with diagonal branches is usually avoided. The origin of the circumflex artery may be well seen, as in this illustration. (From King et al.[136] Reproduced with permission from the publisher, editor, and authors.)



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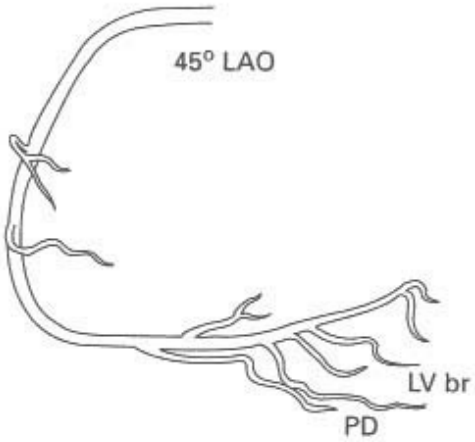

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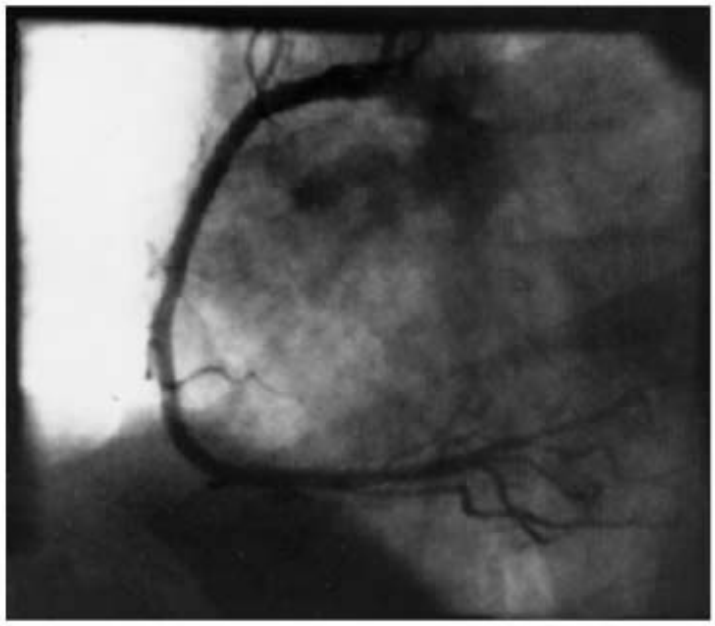

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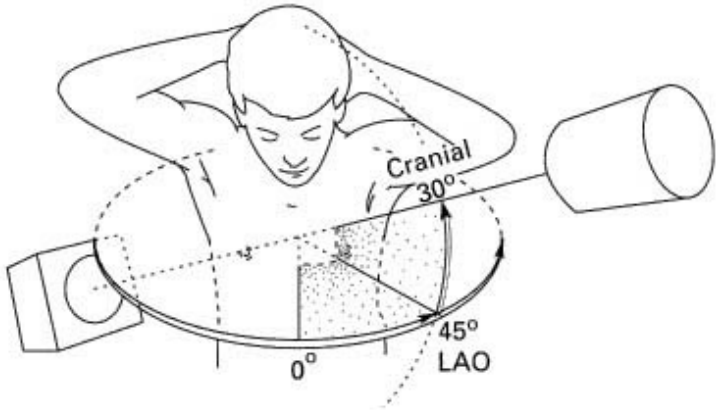
Figure 15-27: Diagrammatic illustration of the direction of the x-ray beam and the right coronary artery in the 45° LAO projection. This view is excellent for visualizing the proximal mid and distal right coronary artery in the AV groove since the direction of the x-ray beam is perpendicular to these arterial segments. Ostial lesions of the right coronary artery are now well visualized if the proximal right coronary artery takes an anterior direction from the aorta and therefore originates in a direction parallel to the x-ray beam. This usually can be overcome by turning to a more severe left oblique projection. The posterior descending and LV branches of the right coronary artery, which pass down the posterior aspect of the heart toward the

apex, are severely foreshortened because the long axis of these vessels is in the same direction as the x-ray beam. The proximal posterior descending branches can be visualized by cranial angulation of the overhead intensifier (see Fig. 15-28) or from a right oblique view. The image intensifier is in the standard LAO position. (From King et al.[136] Reproduced with permission from the publisher, editor, and authors.)



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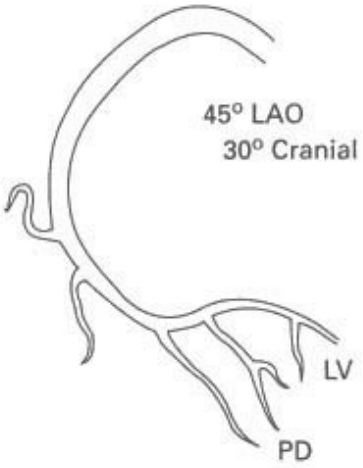

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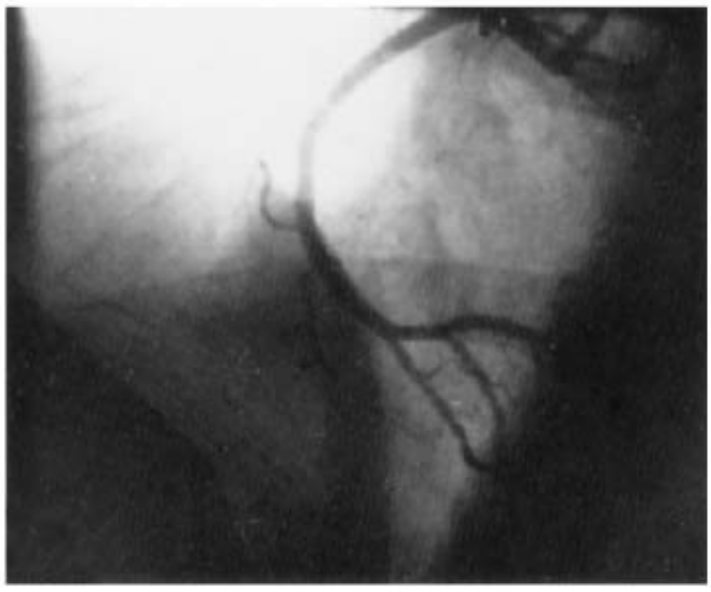

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Figure 15-28: Diagrammatic illustration of the direction of the x-ray beam and the right coronary artery in 30° LAO with 30° of cranial angulation. Cranial angulation of the image intensifier overcomes the problem of foreshortening of the posterior descending and left ventricular branches observed in Fig. 15-27. Lesions in the posterior descending or LV branches can be well visualized. When the right coronary artery originates anteriorly from the aorta, the proximal portion of the vessel is frequently well seen in this projection. With anomalous origin of the left anterior descending artery from the right coronary artery, this view is helpful because the standard LAO view produces considerable foreshortening of the anomalous artery. The direction of the x-ray beam is the same as in Fig. 15-25. (From King et al.[136] Reproduced with permission from the publisher, editor, and authors.)

THE LEFT CORONARY ARTERY

The ostium of the left coronary artery originates from the left sinus of Valsalva near the sinotubular ridge. The main left coronary artery usually courses to the left and slightly anterior. After a quite variable length, it gives rise at near right angles to the circumflex artery and continues in a straight line as the anterior descending artery (Figs. 15-29 and 15-30). The left orifice and the left main coronary artery are best seen in a direct frontal view or in a shallow LAO or RAO projection or a shallow LAO with 30° of cranial angulation. The diagonal artery may arise between the circumflex and anterior descending arteries as a trifurcation of the left main coronary artery, or the diagonal branch may originate from the anterior descending artery and course over the anterolateral free wall of the left ventricle. The diagonal branches are seen on the side in the RAO view; however, the origin is obscured by overlap with the anterior descending artery (see Figs. 15-29 and 15-30). The LAO view separates the anterior descending artery and diagonals somewhat; however, because of the frequent horizontal orientation of these arteries, there may be considerable foreshortening. Cranial angulation of the overhead intensifier with shallow LAO or RAO rotation is most helpful in separating the proximal anterior descending artery and its diagonal branches (see Figs. 15-25 and 15-26). The anterior descending artery continues in the interventricular groove toward the apex, giving rise at nearly right angles to the septal perforating arteries that go deep into the muscular septum. The first septal perforator may arise before or after the first diagonal and is usually the largest septal artery. The septal vessels differ from the epicardial arteries in that they are straighter and move little with cardiac action, in contrast to the buckling of epicardial arteries that frequently occurs with systole. The left anterior descending artery usually continues around the apex but may end short of the apex in association with an unusually long posterior descending artery. The anterior descending artery is usually best visualized in the RAO view and in a cranially angulated shallow oblique view unless the orientation of the anterior descending artery is unusually superior, in which case a caudally angulated LAO view or a straight lateral view may be helpful.

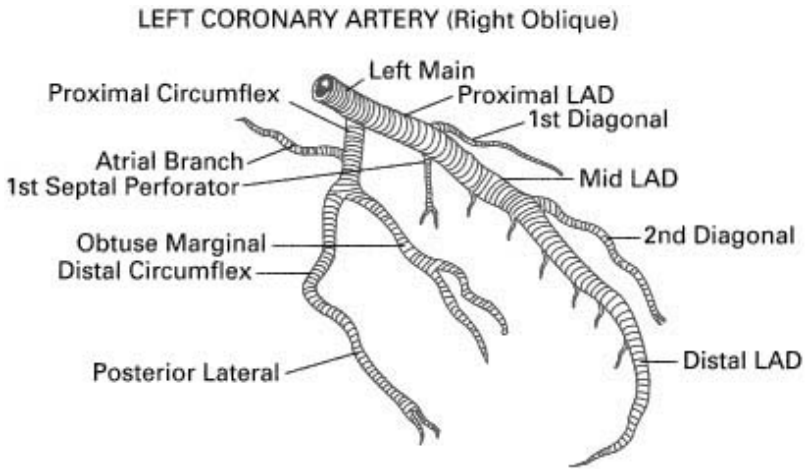


Figure 15-29: Anatomy of the left coronary tree in the right oblique view.

The circumflex coronary artery, after its right-angle origin from the left anterior descending artery, travels in the AV groove. Its course is quite variable. The artery may terminate in one or more large, obtuse marginal branches that course over the lateral to posterolateral LV free wall, or it may continue as a large artery in the interventricular groove and, in 10 to 15 percent of cases, give rise to a posterior descending artery, which more often arises from the right coronary artery (Fig. 15-31). When the circumflex artery supplies the major posterior descending artery, it is commonly referred to as a *dominant* circumflex artery. The circumflex artery in the AV groove is best seen in the LAO view, but surgically more important marginal branches are visualized best in the RAO view. Occasionally, proximal stenoses in the circumflex artery are best viewed in an RAO view with 15° of caudal angulation, which produces a view as though looking from the superior aspect of the liver toward the left shoulder.

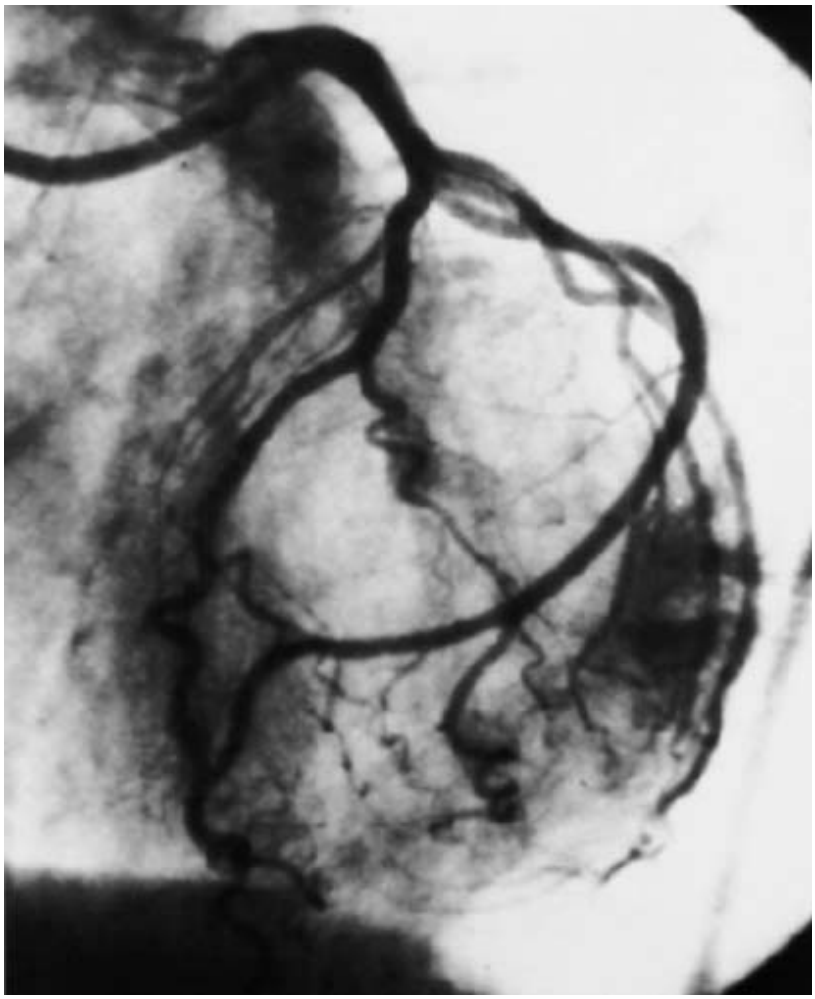


Figure 15-31: LAO view of the left coronary artery demonstrating dominant circumflex coronary artery giving rise to the posterior descending artery.

THE RIGHT CORONARY ARTERY

The right coronary artery orifice normally is located in the right sinus of Valsalva. It may be high near the sinotubular ridge or above it, in the midsinus, or occasionally low near the aortic valve. The artery commonly courses upward from the plane of the aortic valve and then travels in the right AV groove as a conduit to reach the posterior LV wall (Figs. 15-32 and 15-33). Along the way, several vessels arise. The conus branch and sinus node branches arise first, followed by small RV branches. At the acute margin of the heart, there is usually a large branch that courses over the right ventricle. In some cases this may supply the apical portion of the interventricular septum and therefore be of greater importance. The posterior descending artery usually arises before the right coronary artery reaches the crux of the heart (junction of the interventricular and interatrial septa). The posterior descending artery arises from the right coronary

artery at right angles and travels in the posterior interventricular groove, supplying the perforating branches to the basal and posterior one-third of the septum. A right coronary artery that supplies the major posterior descending branch has been referred to as a *dominant* right coronary artery. The posterior descending artery usually stops before reaching the apex, but it may curl around the apex in association with a short anterior descending artery to form the loop previously described. After giving rise to the posterior descending artery, the right coronary artery becomes intramyocardial at the crux, gives rise to the AV node artery, and subsequently returns to the surface, making an inverted U curve (see Fig. 15-33). The LV branches of the right coronary artery are variable and cover the same area as the posterolateral branches of a large circumflex system. The proximal conduit portion of the right coronary artery is well seen in standard RAO and LAO views. Because of its horizontal orientation, however, the origin of the posterior descending artery is well seen in the RAO view but foreshortened in the LAO view; to overcome this, cranial angulation of the intensifier is necessary. Pathologic studies indicate that lesions at the takeoff of the posterior descending artery frequently are overlooked if standard oblique views in the transverse plane are used.

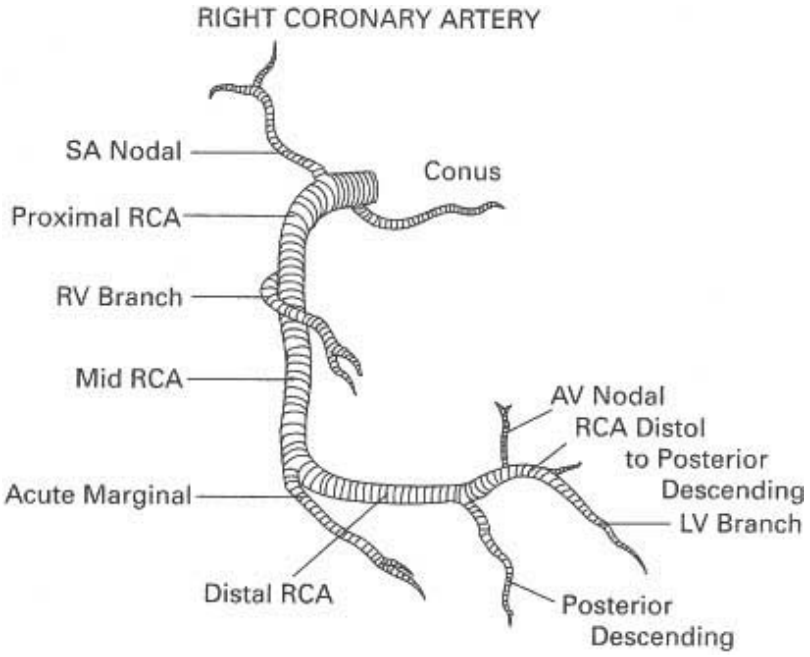


Figure 15-32: Anatomy of the right coronary tree.

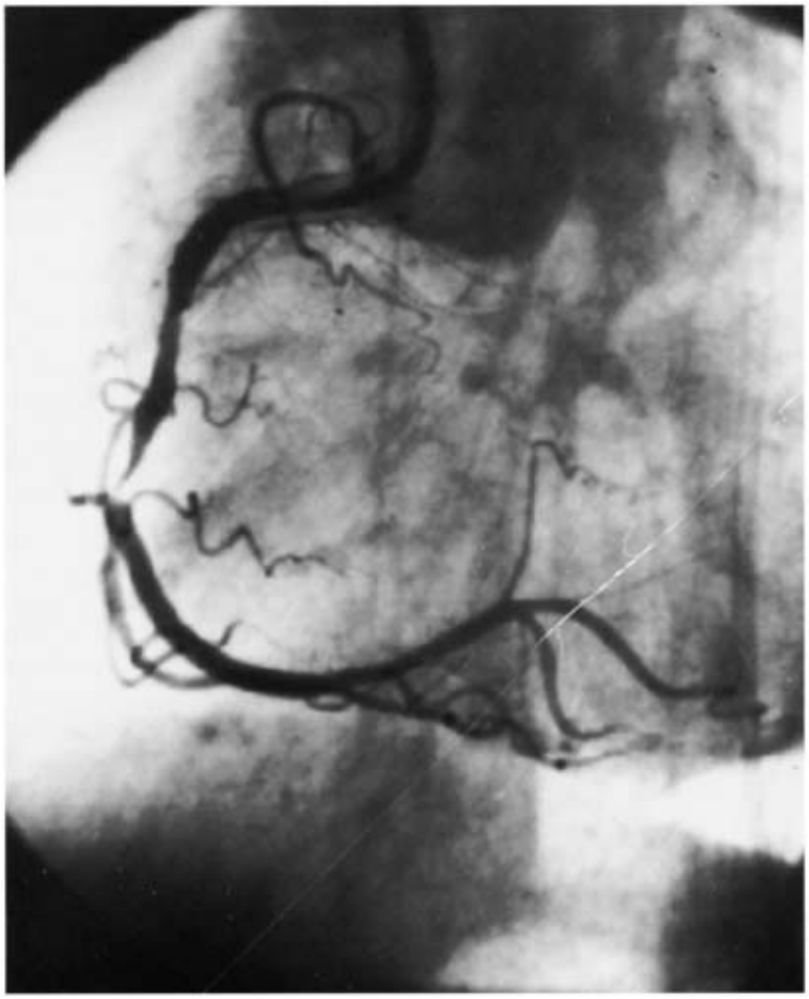


Figure 15-33: LAO view of the right coronary artery (RCA) with high-grade lesion in its midportion.

Grading Stenoses

Visual inspection of the coronary arteriogram traditionally has been used to assess the severity of coronary artery stenosis. In our laboratory, a system of analyzing each arterial segment has been used, and the degree of stenosis is recorded as a reduction in lumen diameter expressed as a percentage, with total occlusion being 100 percent. Measurement of cineangiograms has been done with a programmable digital caliper system. In each available projection, the frame showing the most severe stenosis in end-diastole is chosen for measurement. The percentage of diameter stenosis recorded is a mean value of the measurements from two or three available projections. This method has been shown to reduce observer variability. Although cross-sectional area reduction is the measurement of greatest physiologic importance, use of diameter stenosis is in keeping with the American Heart Association recommendation that the diameter method be adopted for grading coronary artery stenoses.[132] A 50 percent reduction in diameter is equivalent to a 75 percent reduction in cross-sectional area, and a 75 percent reduction in diameter is equal to a 90 percent reduction in cross-sectional area. It is of great importance to identify which method of expressing stenosis is being used. From the standpoint of surgically significant lesions, it has been our practice to consider stenoses with greater than 50 percent diameter reduction, or greater than 75 percent cross-sectional area reduction, as lesions that may produce myocardial ischemia. Lesions in series and long stenoses are of added importance. Quantitative computerized methods for calculating coronary artery stenosis are used for clinical investigations and are also increasingly used for routine clinical coronary arteriography.[137] Techniques employing edge-detection algorithms are often applied clinically.

Pitfalls in Coronary Arteriography

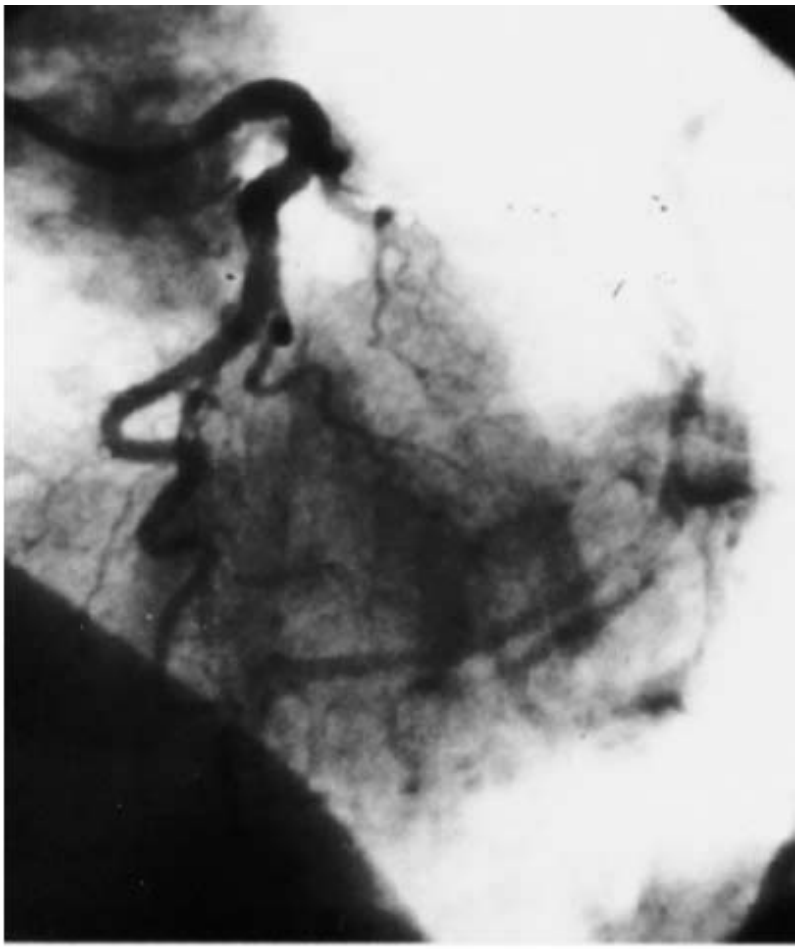
There are a number of pitfalls in coronary arteriography that should be looked for and avoided.

1. *Short left main or double left coronary orifices*. When the left main orifice is very short or absent, selective injection of the anterior descending or circumflex arteries may be done (Fig. 15-34). If, on viewing an arteriogram, no circumflex or anterior descending artery is seen filling either primarily or through collaterals from the right coronary artery, the possibility that the artery was missed by subselective injection must be entertained.
2. *Orifice lesions*. The left and right coronary artery orifices need to be seen on a tangent with the aortic sinuses. Some backflow from the orifices is needed if the catheter is lying within the left main or proximal right coronary artery to avoid missing an orifice lesion.
3. *Myocardial bridges*. The anterior descending, diagonal, and marginal branches not uncommonly dip intramyocardially, and the overlying myocardium may act to compress the artery during systole (Fig. 15-35). If the coronary artery is not viewed carefully in diastole, this bridging may give the appearance of an area of stenosis.[138]
4. *Foreshortening*. When possible, avoid reading lesions in segments that are seen only coming toward or away from the image intensifier. Dense opacification of segments seen end-on may produce the appearance of a lesion in an intervening segment.
5. *Coronary spasm*. Catheter-induced spasm may give the appearance of a lesion (Fig. 15-36). When spasm is suspected (usually at the catheter tip in the right coronary artery), nitrates should be given, and the injection should be repeated in 5 to 10 min. Spontaneous coronary artery spasm is a separate problem, and when this is suspected, nitrates and atropine are avoided because the atropine may play a role in blocking coronary artery spasm. Provocation with ergot derivatives will identify most patients with spontaneous coronary artery spasm.[114-116]
6. *Anomalous coronary arteries.* Coronary arteries may arise from ectopic locations, or a single coronary artery may be present.[139] Only by ensuring that the entire epicardial surface has an adequate arterial supply can one be confident that all branches have been visualized.
7. *Totally occluded arteries or vein grafts*. Absence of vascularity in a portion of the heart may indicate total occlusion of its arterial supply. Usually, however, collateral channels permit visualization of the distal occluded artery unless it is an acute occlusion. Vessels filled solely by collaterals have very little pressure supporting their walls and may appear smaller than their actual lumen size, giving a false sense of pessimism about the possibilities for surgical anastomosis.

Limitations of Coronary Arteriography

Despite significant improvements in the quality of coronary arteriographic studies as a result of improved x-ray imaging systems, there remain a number of limitations of the method. Film interpretation is subjective. Different angiographers may interpret the same film differently, and the same angiographer may render a different interpretation at a time remote from the first reading.[140,141] It has been reported that the average standard deviation of estimation of any segmental stenosis by experienced angiographers may be as high as 20 percent and that disagreement about the number of major vessels with 70 percent stenosis may occur 30 percent of the time.[142] These reported studies, however, used only views in the transverse plane, imposing greater interpretive burdens than are encountered when sagittally angulated views are obtained. Further studies using sagittally angulated views would be expected to show less variability in interpreting coronary arteriograms. Inter- and intraobserver variability in interpreting coronary arteriograms is not unlike interpretive differences in chest x-rays or other diagnostic studies involving human error and judgment. Routine use of several readers has been shown to reduce interpretive error.[141] Although correlation of angiography with postmortem findings has been acceptable in most studies,[142-148] certain coronary pathologic-anatomic factors may favor angiographic underestimation of the degree of stenosis present in any arterial segment. In large part, this is due to the tendency for diffuse atheromatous narrowing of the coronary arteries to occur. In attempting to grade stenosis of an obviously narrow segment, one may not have a normal segment for comparison or may choose for comparison an apparently normal segment that in fact has diffuse tubular narrowing.[145-147] This leads to underestimation of the degree of stenosis present. Pathologic studies currently available probably overestimate the frequency of this problem, since the pathologic material available for study represents the severest end of the spectrum of the disease. Eccentric atherosclerotic plaques also may be underestimated unless the minor axis of the stenotic lumen is visualized. Sagittally angulated views are particularly valuable in this regard. Very discrete membrane-like lesions, which fortunately are rare, may be missed unless they are visualized directly in the plane of the lesion. Pathologic studies have shown poor correlation between left main coronary stenosis at autopsy and that at angiography, especially in the presence of a short left main coronary artery, and point out the importance of sufficient angiographic views and excellent interpretive skills in evaluating this critical

portion of the coronary circulation.[148] Quantitative computer techniques have shown excellent correlation between the cross-sectional luminal area of stenotic lesions at arteriography and direct planimetered measurements of distended postmortem specimens.[149] Dynamic phenomena that are not active at the time of the study may be important. "Hit and run" events such as coronary embolization or thrombosis with subsequent resolution, coronary artery spasm, and even primary coronary artery dissection may leave LV scars but not result in coronary angiographic findings.



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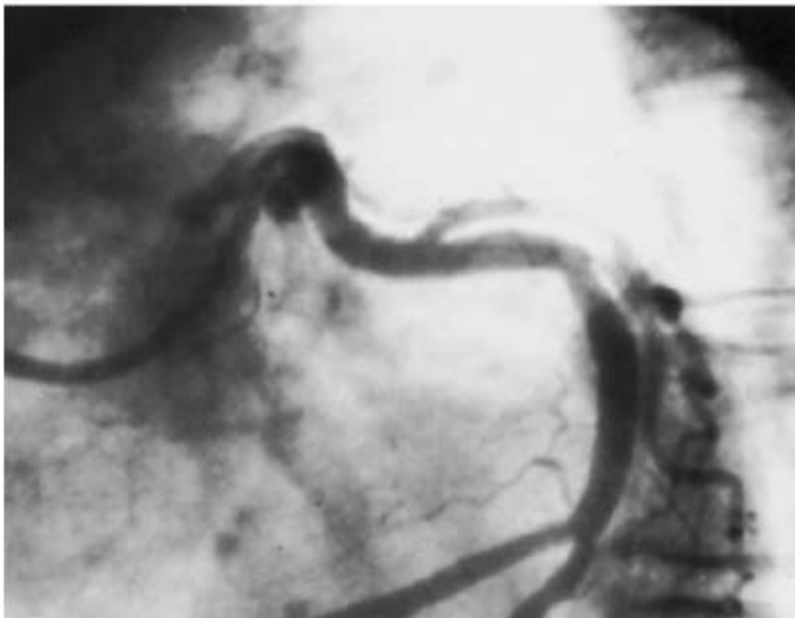

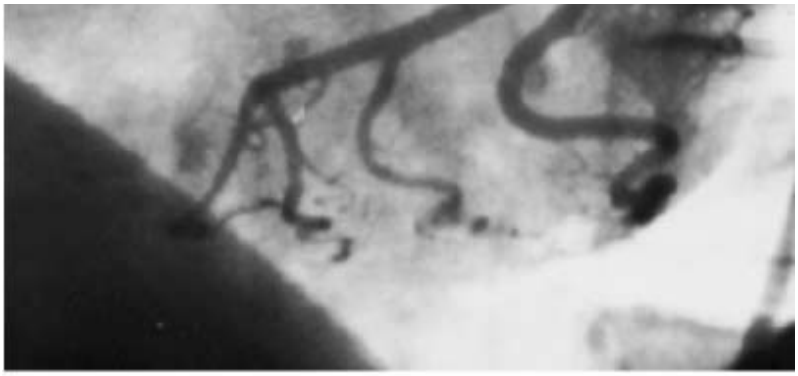

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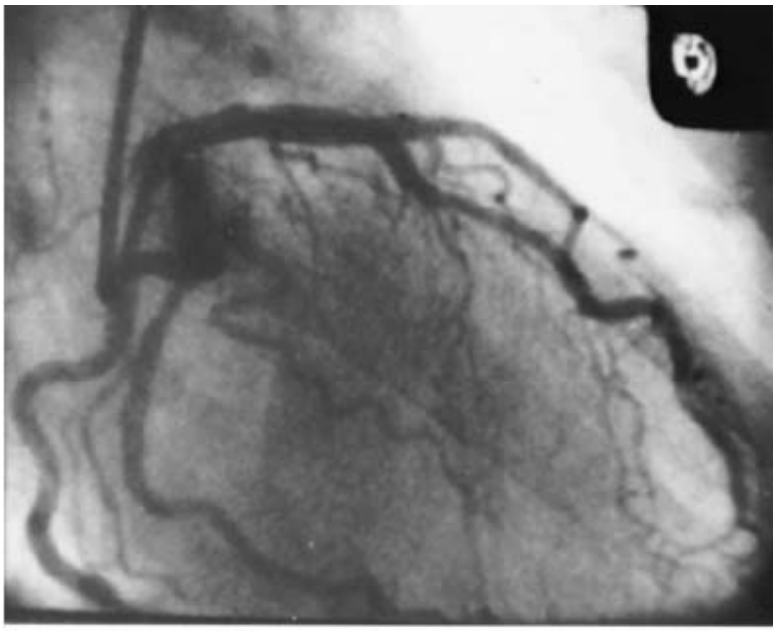
Figure 15-34: *A.* LAO view of selective injection into left anterior descending (LAD) artery. *B.* LAO view of selective injection into circumflex artery.



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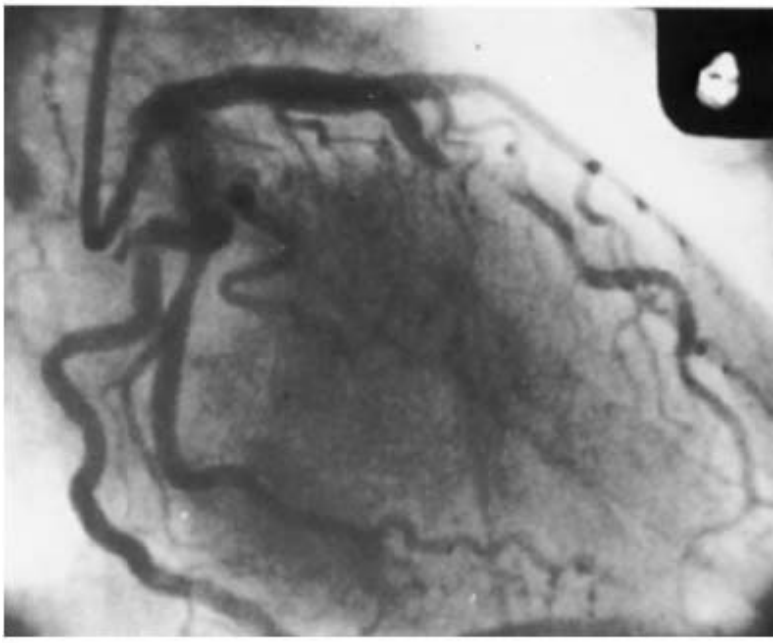
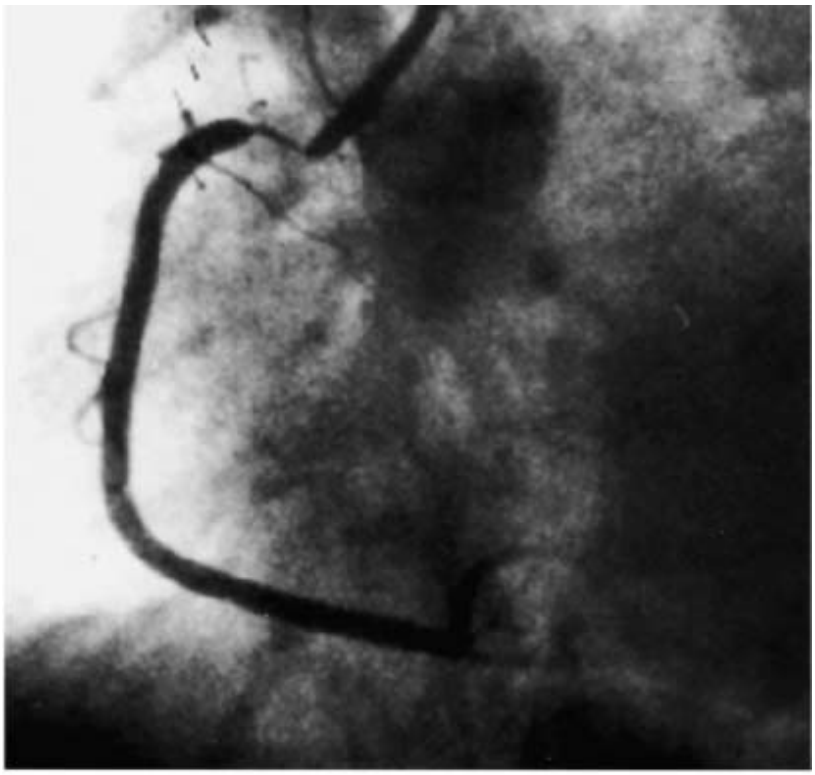


B

B

Figure 15-35: RAO view of left coronary artery system. *A.* Diastolic appearance of anterior descending artery showing smooth lumen. *B.* Systolic appearance showing obliteration of the lumen by an overriding muscular bridge.



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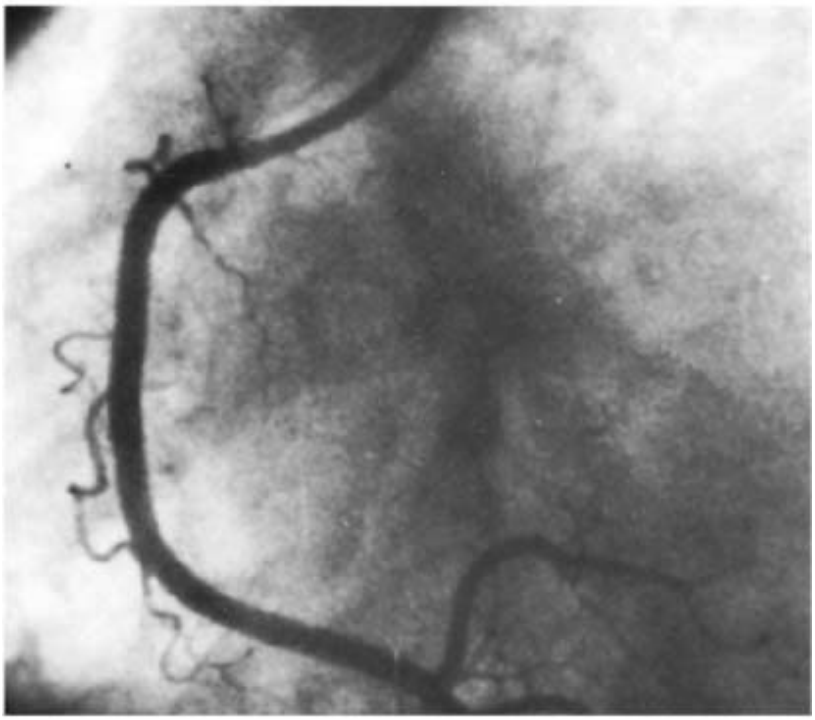

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Figure 15-36: *A.* LAO view of right coronary injection showing pericatheter spasm. *B.* Same view following nitroglycerin, showing relief of spasm.

Risk of Coronary Arteriography

As with any invasive procedure, there is a finite risk to patients undergoing coronary arteriography. The magnitude of the risk is influenced by certain factors definable prior to the procedure (e.g., skill of the angiographer and instability of clinical symp toms) but primarily by the extent of the disease found at coronary arteriography and left ventriculography.[111,128,150-156] Physicians referring patients for coronary arteriograms must be aware of the complication rate in a given laboratory and, when practical, should achieve stability of clinical symptoms prior to study. This is not to say that unstable patients should not be studied, but the physician must balance the risk of the procedure and potential benefit against the risk of not doing the procedure. The frequency of major complications has decreased in active centers (Table 15-3).

Table 15-3: Complications of Coronary Arteriography

	CASS[a]		
	1979[151]	1983[154]	SCAI ,[b] 1990-1995[155]
Death	0.0020	0.0007	0.001 each year
Myocardial infarction	0.0025	0.0027	<0.001 each year
Cerebral emboli	0.0003	0.0007	<0.001 each year
Arterial complications	0.0080	0.0082	-
Ventricular fibrillation	0.0063	0.0038	0.003 (0.002 in 1995)

[a]Coronary Artery Surgery Study.[b]Society for Coronary Angiography and Interventions.

Major complications are of two types: Local arterial complications consist of arterial occlusion or stenosis, hematoma formation, false aneurysm, and infection; the other and more lethal group of complications relates to thromboembolic events or depression of myocardial function due to infarction or acute ischemia. Thromboemboli are more commonly due to multiple catheter and guidewire exchanges, during which thrombus material is stripped from the catheter surface at the puncture site only to be deposited on a subsequent catheter. The addition of systemic heparinization was felt to have reduced thromboembolic complications in some laboratories. The early CASS report[151] and that by Abrams and Adams,[150] however, found that the use of heparin did not influence complication rates. Of equal or greater importance may be the routine use of catheter debriding techniques, with vigorous aspiration and flushing of the catheter in the abdominal aorta to dislodge any retained thrombus material. Minor allergic reactions to contrast media in the form of urticaria occur commonly, but anaphylactic and pyrogenic reactions are exceedingly rare. Radiation exposure to the patient, estimated as 20 to 45 rem, has little risk unless multiple restudies are needed.

Reported mortality rates related to coronary arteriography range from 0.05 to 4 percent, and virtually all deaths occur in patients with severe, multivessel coronary disease or left main coronary artery stenosis.[126,150-153] Of 30 patients whose deaths were related to diagnostic cardiac catheterization at the Toronto hospital, 18 (60 percent) had left main coronary disease. In 89 percent (16 of 18) of left main disease patients and in 50 percent (4 of 8) of coronary disease patients without apparent left main disease, death was related to catheter-induced left main trauma. A widely quoted acceptable mortality rate for coronary arteriography is 0.1 percent. Patient selection, however, may play an important role in determining mortality. Studies in predominantly stable patients will result in a very low mortality rate. On the other hand, if a broad spectrum of patients is studied-including those with preinfarction angina, acute myocardial infarction, and complications of myocardial infarction such as heart failure, cardiogenic shock, ruptured interventricular septum, and ruptured papillary muscle-complication rates will be higher, depending on the frequency with which sicker patients are studied. The overall mortality rate in the CASS and Society for

Cardiac Angiography and Interventions reports was 0.07 to 0.1 percent. It was 0.05 percent for single-vessel disease, 0.07 percent for double-vessel disease, 0.12 percent for triple-vessel disease, and 0.8 percent in patients with left main coronary artery stenosis.[151,154] The point to be made is that laboratory and surgical teams must be prepared to act in the best interest of severely ill patients and not be overly concerned with an arbitrary mortality figure.

Left Ventriculography

Left ventriculography is the standard method for evaluating LV performance in the coronary angiography laboratory. The normal pattern of LV contraction is a uniform and almost concentric inward movement of all points along the endocardial surface during systole. Harrison introduced the term *asynergy,* which has been used to indicate a disturbance of the normal contraction pattern. The Ad Hoc Committee for Grading of Coronary Artery Disease of the American Heart Association[132] has recommended that five RAO segments and two LAO left ventricular segments be defined and characterized as to wall motion (Fig. 15-37). Herman and coworkers classified LV asynergy according to the severity of the contractile abnormality, and a similar classification of LV wall motion was recommended by the Ad Hoc Committee:

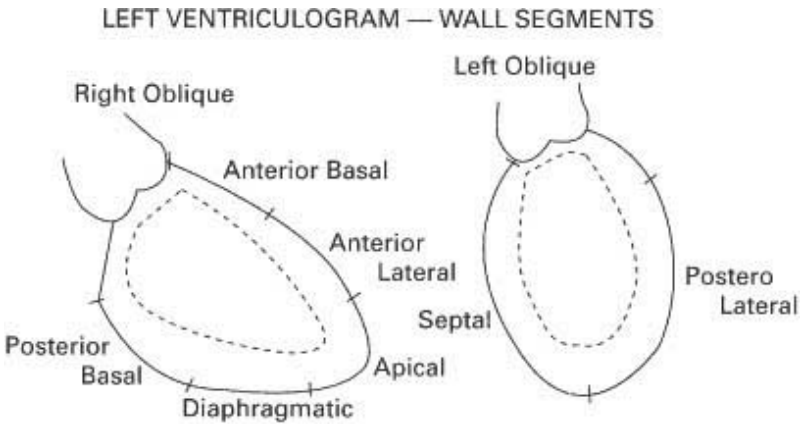

Figure 15-37: LV wall silhouette in RAO and LAO views.

- *Normal:* Normal wall motion of the indicated ventricular segment
- *Reduced:* Reduced velocity and/or amplitude of indicated wall segment
- *None:* Absence of appropriate wall motion of indicated ventricular segment
- *Dyskinetic:* Paradoxical wall motion of the indicated segment
- *Aneurysmal:* Bulging during systole and diastole with sharply defined margins of indicated ventricular segment
- *Undefined*

Many angiographers use the term *akinesis* when no wall motion is present and the term *hypokinesis* when wall motion is reduced.

The ability of the left ventricle to function as a pump is best analyzed by LV volume determinations. Single-plane and biplane volume determinations may differ significantly in patients with coronary artery disease and nonhomogeneous contraction patterns. In particular, the single-plane RAO or lateral left ventriculogram frequently underestimates overall LV contraction because it selectively visualizes the anterior and inferior free walls of the left ventricle, which are most commonly involved in myocardial infarction. Vogel et al.[157] found that the single-plane RAO left ventriculogram underestimated ejection fraction in 70 percent of patients with coronary artery disease. For this reason, biplane left ventriculography frequently is desirable in evaluating patients with coronary artery disease.

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Chapter 15: CARDIAC CATHETERIZATION, CORONARY ARTERIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

MEASUREMENTS OF CORONARY BLOOD FLOW AND PRESSURE

Coronary artery disease affects the vessel wall with a highly variable influence on the configuration of the lumen and subsequent resistance to blood flow. The functional characterization of a coronary stenosis identified on angiography remains a well-recognized limitation,[158-160] repeatedly documented by intravascular ultrasound (IVUS) imaging and ischemic testing. Measurements of coronary flow and pressure can be obtained directly using Doppler and pressure sensor angioplasty guidewires.[161]

Coronary Physiology

Coronary blood flow increases from a resting level to a maximum depending on myocardial oxygen demand and other hyperemic stimuli. Normally, epicardial resistance to flow is trivial, with flow normally controlled by the precapillary arteriolar resistance vessels. Coronary blood flow in a normal artery supplying normal myocardium can increase more than threefold in adults. However, some patients may have conditions affecting the microcirculation (LV hypertrophy, myocardial ischemia, diabetes, or other conditions impairing the microcirculatory responses) that can blunt the normal increase in coronary flow.

When a significant atherosclerotic stenosis produces epicardial conduit resistance, the distal vascular bed dilates to maintain satisfactory basal flow appropriate for myocardial oxygen demand. Friction and turbulence at the site of the stenosis produce energy loss and reduced pressure distal to the stenosis,thus resulting in a pressure gradient between proximal (aortic pressure) and distal coronary artery segments. As coronary flow increases across the stenosis, the distal pressure decreases along a curvilinear pressure-flow relationship of coronary stenosis resistance as described by Gould et al.[162,163] From this relationship, both coronary flow reserve (CFR) and pressure-derived fractional flow reserve (see below) can be elucidated and applied for coronary lesion assessment (Fig. 15-38). Because of the strong association of coronary flow with indirect ischemia testing,[164-167] directly measured coronary physiologic data can be used to determine coronary lesion significance and provide objective evidence of ischemia.

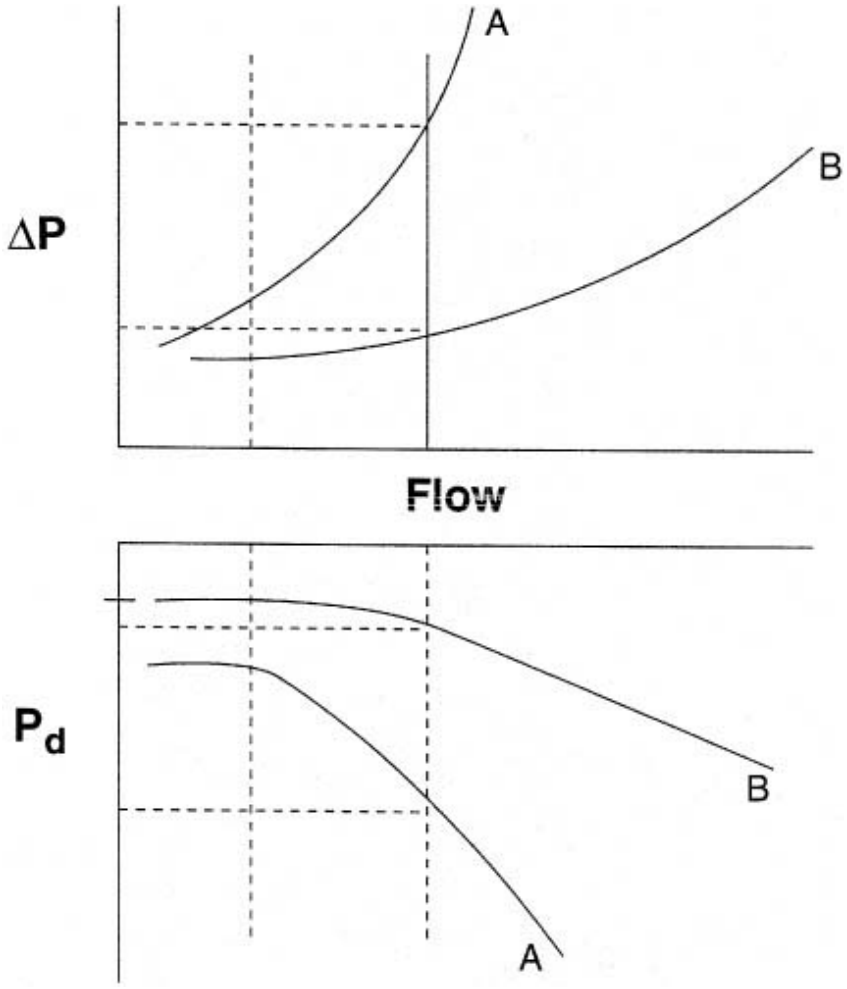

Figure 15-38: Coronary pressure-flow relationships for two stenoses of the same angiographic severity. (*Top*) P_a = aortic P = pressure gradient (aortic-distal coronary pressure, P_d) versus coronary flow. (*Bottom*) Absolute P_d versus flow. Increasing flow produces marked loss of P_d as well as an increase in P_d = distal coronary P. The loss of P_d in absolute terms determines myocardial perfusion pressure (P_d - venous pressure) and the potential for inducible ischemia.

Fundamental Concepts: Doppler Flow

A change in sound frequency occurs as a transmitter moves to or away from a receiver. The change in the sound frequency is proportional to the speed of the target or transmitter, a phenomenon called the *Doppler effect.* In practice, a piezoelectric crystal that both emits and receives high-frequency sounds is mounted on the tip of an intravascular device. The velocity of red blood cells flowing past the device through an artery can be determined from the *frequency shift,* defined as the difference between the transmitted and returning frequency, where

$$\text{AVA (in cm}^2) = \frac{F}{C \times 44.5\sqrt{P_1 - P_2}}$$

$$= \frac{\text{aortic valve flow (mL/s of systole)}}{1 \times 44.5\sqrt{\text{LVS} - \text{ASP}}}$$

Volumetric flow can be determined as the product of vessel area (cm^2) and flow velocity (cm/s), yielding a value in cubic centimeters per second. Absolute Doppler flow velocities represent changes in volumetric coronary flow when the vessel cross-sectional area remains constant over the measurement period. The Doppler guidewire velocity and volumetric relationship has been validated during intravascular measurement by Doucette et al.[168] and Labovitz et al.[169]

Fundamental Concepts: Fractional Flow Reserve

Pressure gradients (aortic-coronary mean pressure) at rest do not accurately characterize the ischemic potential of a stenosis.[170,171] Resting translesional pressure gradients measured during the early years of angioplasty were not accepted because of inadequate devices (nos. 3-4 French catheters) used under inappropriate circumstances (i.e., not during maximal hyperemia). The translesional gradient was incompletely interpreted (i.e., resting gradients rather than hyperemia-induced fractional flow reserve). A new concept based on the pressure-derived measurement of coronary perfusion, called *fractional flow reserve* (FFR),[170,171] is a measure of the fraction of maximal coronary blood flow that traverses the stenotic vessel as a percentage of blood flow through the same artery in the theoretical absence of the stenosis. This measurement is derived from the mean pressure distal to the stenosis divided by the mean pressure proximal to the stenosis at maximal hyperemia. The FFR reflects the true reduction in myocardial perfusion resulting from a stenosis rather than merely a stenosis pressure gradient. During maximal hyperemia, resistance is minimal across both the epicardial and microvascular beds. Because the ratio of the absolute distal coronary to aortic pressures is measured when myocardial resistance is minimal, the status of the microcirculation does not, in theory, affect the FFR. Unlike CFR, FFR is independent of hemodynamic and microcirculatory factors.[172,173] The normal value for FFR is 1.0 for each patient, coronary artery, myocardial distribution, and microcirculatory status (Figs. 15-39 and 15-40).

Pharmacologic Hyperemic Stimuli

Stenosis severity always should be assessed using flow measurements during maximal hyperemia. The most widely used maximal vasodilator agents are adenosine, papaverine, and dipyridamole. [174-176] The hyperosmolar ionic and low-osmolar nonionic contrast media do not produce maximal vasodilatation.

Intracoronary and intravenous adenosine produces hyperemia equivalent to papaverine[18] but has a much shorter half-life (Fig. 15-41). Intravenous adenosine produces similar hyperemia equal to that of intracoronary adenosine but in a sustained fashion. Both intracoronary and intravenous adenosine has an extremely high safety profile in low doses and has become the pharmacologic stimulus of choice in the catheterization laboratory.

Intracoronary adenosine should be injected through catheters without side holes because of inadequate delivery of adenosine for maximal hyperemia. Side hole guiding catheters require an approximate doubling of the intracoronary adenosine dose due to loss of drug during injection.[177]

Absolute and Relative Coronary and Fractional Flow Reserve

Absolute CFR is the ratio of maximal hyperemic to basal mean flow velocity in the target vessel (Fig. 15-42). This ratio is equivalent to a volumetric blood flow reserve if the cross-sectional area is unchanged during the measurements. CFR may underestimate the volumetric flow reserve in some vessels that may have intact endothelial function and flow-mediated vasodilatation. CFR is the summed response of flow through the conduit and the myocardial bed; thus an abnormal CFR does not separate a significant stenosis from an abnormal microcirculation (Fig. 15-43). Measurement of CFR in an angiographically normal vessel can serve as a reference value against which to compare the results in a target vessel. The relative CFR (rCFR), the ratio of CFR_{target} to $CFR_{reference}$, in theory, should identify whether an impaired target CFR is the result of a flow-limiting stenosis or microvascular abnormalities (Fig. 15-44). The normal absolute CFR is 2.7 ± 0.6[178] in adults in the cardiac catheterization laboratory with chest pain syndromes. Absolute CFR appears reproducible among angiographically normal vessels within a 10 percent variance. The average CFR measured using the flow-velocity technique in patients with normal coronary arteries undergoing cardiac catheterization differs little between patients who have had cardiac transplantation and those who have chest pain syndromes and angiographically normal arteries, with approximately 12 percent of patients having a CFR of less than 2.0. rCFR relies on the assumption that the microvascular circulatory response is uniformly distributed among the myocardial beds. The normal range for rCFR is 0.8 to 1.0.[179,180] The major limitations of rCFR include patients with three-vessel coronary disease who have no suitable reference vessel, patients in whom the target vessel supplies an area of

myocardial infarction with LV regional dysfunction, or patients in whom the microcirculatory responses are heterogeneous.

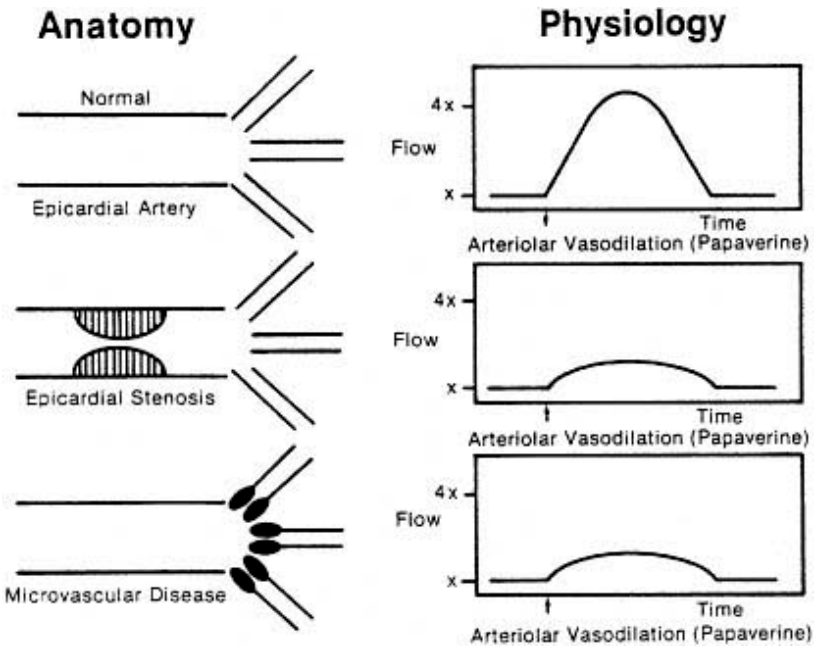

Figure 15-43: Comparison of coronary flow reserve (CFR) in arteries with normal (*top*) epicardial stenosis (*middle*) and abnormal microcirculation (*bottom*).

rCFR and FFR are more specific for flow limitations due to a stenosis than CFR. FFR, rCFR, and CFR were determined in 21 patients in 24 target vessels for stenosis severity ranging from 40 to 95 percent, with an average of 74 ± 15 percent.[179] Absolute CFR did not correlate with percentage area stenosis or FFR. FFR, as well as rCFR, showed a curvilinear relationship with percentage area stenosis ($r = 0.89$ and $r = 0.79$; $p < 0.0001$), with a close linear relationship between FFR and rCFR (0.91; $p < 0.0001$). rCFR closely correlated with FFR and percentage area stenosis. Absolute CFR, as expected, varied due to the influence of microvascular flow status (Table 15-4).

Table 15-4: Comparison of Absolute and Relative CFR and FFR

	Hemodynamic Independence	Independent of Microcirculation Abnormalities	Unequivocal Normal Values	Use in Multivessel CAD
CFR	-	-	Range > 2.0	+
rCFR	+	+	1.0	-
FFR	+	+	1.0	+

Intracoronary Blood Flow Measurements and Ischemia Testing

Several single-center studies[164-166,181-183] and one multicenter trial[167] have reported strong correlations with myocardial stress perfusion imaging and post-stenotic coronary flow velocity reserve. An abnormal distal hyperemic flow velocity reserve (<2.0) corresponded with reversible myocardial perfusion imaging defects with high sensitivity (86-92 percent), specificity (89-100 percent), predictive accuracy (89-96

percent), and positive and negative predictive values (94-100 and 77-95 percent), respectively.

The sensitivity of FFR for reversible ischemia (FFR < 0.75) was 88 percent, specificity 100 percent, positive and negative predictive values 100 and 88 percent, respectively, with a predictive accuracy of 93 percent (Table 15-5).

Table 15-5: Stress Testing and Directly Measured Coronary Hemodynamics

Author	Ref	*n*	Ischemic Test	CFR	Sensitivity	Specificity	PV+	PV-	Accuracy
POSTSTENOTIC CORONARY FLOW VELOCITY RESERVE (CFR)									
Miller	7	33	Adeno/dipy MIBI	<2.0	82	100	100	77	89
Joye	10	30	Exercise thallium	<2.0	94	95	94	95	94
Deychak	9	17	Exercise thallium	<1.8	94	94	100	91	96
Heller	8	100	Exercise thallium	<1.8	89	92	96	89	92
Danzi	25	30	Dipy echo	<2.0	91	84	-	-	87
Schulman	26	35	Exercise ECG	<2.0	95	71	-	-	86
FRACTIONAL FLOW RESERVE, MYOCARDIUM									
Pijls	14	45	Four-test standard	<0.75	88	100	100	88	93
de Bruyne	15	60	Exercise ECG	<0.72	100	87	-	-	-
Bartunek	24	37	Dobu/exercise echo	<0.68	95	90	-	-	-

NOTE: Adeno/dipy MIBI, adenosine or dipyridamole sestamibi scan; CFR, coronary vasodilatory reserve; Dobu, dobutamine; PV +/PV-, prepactive value positive/negative.

Other Lesion-Specific Flow-Velocity Measurements

There are four lesion-specific physiologic measurements: (1) the rCFR ratio ($CFR_{target}/CFR_{normal}$), (2) the translesional pressure gradient at hyperemia (FFR_{myo}), (3) the proximal-to-distal velocity ratio, and (4) the diastolic/systolic velocity ratio (DSVR). The most accurate and practical measurements are the rCFR and FFR, as discussed earlier.

The proximal-to-distal flow velocity ratio depends on coronary arterial branching, which results in decremental volumetric flow and cross-sectional vessel area from the proximal to the distal myocardial regions. Because both volume and cross-sectional area diminish along the course of the vessel, velocity

remains relatively constant (usually within 10 to 15 percent of the proximal velocity in vessel segments of more than 2 mm diameter). Maintenance of the flow velocity (but not volume) from the proximal to the distal part of the artery (i.e., the ratio of proximal-to-distal flow) can be used as a marker of lesion-specific disease within the artery. In normal arteries, the proximal-to-distal flow velocity ratio should be 1.0.[184] A strong correlation exists between translesional pressure gradients and the ratios of the proximal-to-distal total flow velocity integrals ($r = 0.8$, $p < 0.001$), with a weaker relationship between pressure gradients and QCA ($r = 0.6$, $p < 0.001$).[184] In angiographically intermediate stenoses (50-70 percent), angiography was a poor predictor of translesional gradients ($r = 0.2$, p = ns), whereas the flow velocity ratios continued to have a strong correlation with such gradients ($r = 0.8$, $p < 0.0001$). The proximal-to-distal flow velocity ratio demonstrated highly significant differences between patients with and without significant stenoses. A proximal-to-distal flow velocity integral ratio of less than 1.7 was associated with a gradient of less than 30 mmHg in more than 85 percent of patients. However, the proximal-to-distal ratio will be valid in arteries without branches or in those with ostial stenoses. The proximal-to-distal flow ratio index is sensitive but not lesion-specific.

Similarly, the phasic pattern of coronary flow (DSVR) reflects stenosis resistance. As a stenosis becomes more severe, diastolic flow is impaired first; then, as the stenosis increases, systolic flow is diminished. The normal DSVR is less than 1.8, 1.5, and 1.2 for the left anterior descending, circumflex, and proximal right coronary arteries, respectively.[185] A reduction in the normal DSVR generally indicates an important stenosis but is only a weak index for lesion-specific flow impairment. The relationship between DSVR and lesion severity requires a normally contracting myocardium in the region of the target stenosis to be accurate.

Case Example: Physiologic Assessment of Critical Circumflex Lesion

A 78-year-old woman presented with unstable angina. Coronary arteriography revealed a nondominant right coronary artery, a 90 percent midcircumflex lesion, and a mildly and diffusely diseased left anterior descending coronary artery (Fig. 15-45*A*, top left). CFR and translesional pressure were measured to demonstrate the effect of angioplasty on the coronary physiologic parameters and use these variables as an end point. Coronary angioplasty was performed using a Doppler flow wire. Before angioplasty, circumflex CFR was 1.1, left anterior descending CFR was 2.0, and rCFR was 0.5 (see Fig. 15-45*A*, top right and bottom). The FFR was measured before angioplasty using a pressure guidewire (see Fig. 15-45*A*, bottom). The FFR was 0.33. A pressure transducer pullback to verify gradient location is shown at the far right of the tracing (see Fig. 15-8*A*, far right). After angioplasty (see Fig. 15-45*B*, left), the angiographic result appears satisfactory; however, the CFR in the circumflex (CFR_{CFX}) is still impaired at 1.5 (see Fig. 15-45*B*, right). After stent placement for the impaired CFR_{CFX}, the angiogram is somewhat improved with a 0 percent residual stenosis, but the CFR_{CFX} is now 2.0, rCFR is 1.0, and FFR is 1.0 (see Fig. 15-45*C*, top right and bottom right), indicating a highly successful and correlative physiologic result for this angioplasty.

Summary

Coronary pressure and flow describe coronary lesion resistance. The strong correlation of directly measured coronary flow and pressure to indirect ischemia testing can facilitate clinical in-lab decisions. Use of in-lab physiology strongly complements coronary lumenology and continues to have important clinical and economic implications for and research into the coronary circulation of patients.

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Figure 15-9: Dimensions of the left ventricular (LV) cavity in end-diastole used for the calculation of the ventricular volume by the area-length method, biplane technique. A-P, anteroposterior plane; A_a, A_l, area, A-P and area lateral plane (planimetry); L_a, L_l, length or long axis of the left ventricle (measured); D_a, D_l, diameter of short axis, A-P lateral plane (derived; L_m, maximum length or long axis whether from the lateral A-P or lateral plane; h, wall thickness, LV. See text for formulas. (Left and middle portion of figures from Sandler and Dodge.[66] Right portion of figure from Dodge HT. Hemodynamic aspects of cardiac failure. *Hosp Pract* 1971; January:91. Illustration by B. Tagawa and A. Miller. Reproduced with permission from the publishers and authors.)

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Figure 15-39: Schematic drawing illustrating the rationale of comparing relative and fractional myocardial flow reserve in this particular group of patients. The relative flow reserve (RFR) is the ratio of hyperemic flow in the anterior region (depending on the stenotic left anterior descending coronary artery) to the hyperemic flow in the normal region (depending on the left circumflex coronary artery). The myocardial fractional flow reserve (FFR) is the ratio of hyperemic flow in the anterior region (depending on the stenotic left anterior descending coronary artery) to hyperemic flow in that same region in the hypothetical case of a normal left anterior descending coronary artery (*faint lines*). These measurements are derived from the mean pressure distal to the stenosis divided by the mean pressure proximal to the stenosis at maximal hyperemia. In the case of a similar decrease of myocardial resistance during hyperemia in the left anterior descending area and the left circumflex area, the value of both the relative and the fractional myocardial flow reserves should be identical. n, the hypothetical normal left anterior descending coronary artery; n', normal left circumflex coronary artery; s, stenotic left anterior descending coronary artery. (Reproduced with permission from de Bruyne B, Banohuin T, Melin J, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation* 1994; 89:1013-1022.)

Figure 15-40: Hemodynamic and coronary flow velocity tracings demonstrating coronary flow reserve (CFR) and fractional flow reserve (FFR) data collection. Aortic (P_a) and distal coronary pressure (P_d) at baseline and during adenosine hyperemia (*at vertical line*). Coronary velocity shows a 2.2-fold increase with adenosine. FFR = 0.78.

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Figure 15-42: (*Left*) Coronary flow velocity signals obtained in a normal circumflex artery (CFX) of a patient undergoing angioplasty of the right coronary artery. The top half represents continuous flow-velocity signals in real time. The electrocardiogram, aortic pressure, and spectral flow signals are provided from top to bottom. The scale is 0-120 cm/s. S and D, systolic and diastolic periods demarcated by the electrocardiogram, respectively. (*Right*) The trend plot of the continuous flow velocity measurement (average peak velocity, APV) is shown in the right-hand panel on the lower tracing. After intracoronary adenosine administration, APV increased from 11 to 29 cm/s, producing a coronary flow ratio (CFR) of 2.6. The duration of hyperemia is 45 s. The trend velocity scale is 0 to 40 cm/s. The time base is 90 s. (Reproduced with permission from Kern MJ, de Bruyne B, Pijls NHJ, et al. From Research to clinical practice: Current role of physiologically based decision making in the catheterization laboratory. *J Am Coll Cardiol* 1997; 30:613-620.)

Figure 15-43: Comparison of coronary flow reserve (CFR) in arteries with normal (*top*) epicardial stenosis (*middle*) and abnormal microcirculation (*bottom*).

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Customer Privacy Policy

Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 16:

NUCLEAR CARDIOLOGY

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OVERVIEW

During the last three decades, a number of noninvasive testing modalities have become widely available in clinical cardiology. Since the early 1970s, there has been a sustained growth of nearly 15 percent per year in the field of nuclear cardiology. Today, state-of-the-art nuclear cardiology allows for the measurement of both myocardial function and relative regional perfusion at rest and stress, providing accurate risk assessment in a wide variety of patient subsets. This chapter provides a synopsis of published evidence on the role of nuclear cardiology procedures in diagnosis and risk assessment with a view to effective clinical management of patients with suspected or known coronary artery disease (CAD). Positron emission tomography (PET) is discussed in Chap. 19.

Major Advances in Clinical Cardiology

Important experimental and clinical research has led to a substantial reduction in the risk of coronary artery disease events in westernized countries.[1] Current evidence from randomized trials notes a 35 to 50 percent reduction in mortality associated with ischemic heart disease and stroke.[2] A comparison of mortality statistics from 1973 to 1993 reveals a decrease in the total number of deaths, mostly affecting the young and middle-aged population (see Chap. 38). Improved outcomes were the result of improved diagnosis and effective risk-reducing therapies.[3,4] New therapies aimed at reducing blood pressure and cholesterol levels are effective strategies for the prevention of cardiovascular disease.[5] In the case of cholesterol lowering, a linear relationship between serum levels and CAD risk has been established, a 10 percent reduction in cholesterol levels being associated with a 30 percent reduction in disease incidence; and the widespread availability of effective, low-risk drugs has made major cholesterol reduction feasible.[6] An overview of randomized trials for coronary artery bypass surgery (CABS) indicates that the appropriate surgical treatment has resulted in an overall mortality reduction as compared with medical treatment.[7] These effective therapies have increased the importance of accurate risk assessment, ideally more accurately and quantitatively based than is feasible from historical information alone or nonimaging treadmill stress testing.

Despite the abundance of high-quality evidence on the effectiveness of medical and surgical management of patients, the body of evidence on the effectiveness of noninvasive testing in guiding management decisions is less well established. Nonetheless, evidence-based medicine is now the standard serving for the evaluation of new technologies and their assimilation into daily clinical practice. Nuclear cardiology is a well-established modality with large observational series available to provide the basis for effective medical management of patients with suspected or known CAD.

Era of Cost Containment in Medical Practice

Declining reimbursement levels coupled with an ever-increasing emphasis on cost containment

has led many to advocate development of a body of evidence to justify use of any medical procedure. For a nonivasive test, justification may be defined as assessing its economic and clinical incremental value as compared with other modalities. A synthesis of evidence reviewed in the recent ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina revealed an abundance of data on the clinical incremental value of nuclear cardiology procedures.[8] Selected reports are also available on economic data for nuclear cardiology procedures as compared with other noninvasive tests used in cardiology.[9]

Historical Perspectives in Nuclear Cardiology

Continuous growth in the field of nuclear cardiology over the last three decades has been facilitated by the development of improved perfusion tracers, enhancements in scintillation cameras, and dramatic improvements in computer technology and specialized computer hardware and software, allowing for rapid assessment of patient data. In 1999, nearly 5 million myocardial perfusion studies were performed in the United States, a rate nearly threefold higher than other stress imaging tests. Major growth in procedure use has occurred in the outpatient setting, with an ever-increasing proportion of tests being performed in nonhospital facilities. The Anger scintillation camera, the imaging device used today for virtually all of nuclear cardiology except PET, became clinically available in the late 1960s. In the 1990s, the principal advances were the wide use of dual and triple detector cameras that improved image quality and shortened acquisition time as well as dramatic increases in the speed of computer systems that decreased processing time and made gated single-photon emission tomography (SPECT) clinically feasible. In 1973, Liebowitz et al. introduced thallium 201 (^{201}Tl) for medical use.[10] Following its commercial availability, ^{201}Tl quickly became the myocardial perfusion imaging agent of choice, a position it maintained until the technetium 99m (^{99m}Tc) perfusion agents became widely accepted. In 1990, ^{99m}Tc sestamibi was approved for use in the United States. Owing to its more favorable physical properties and better image quality, this agent has become the most frequently used radiopharmaceutical in the United States. Another ^{99m}Tc-based agent, tetrofosmin, was approved in the United States in 1997 and has also demonstrated widespread growth. By 1998, some 72 percent of nuclear cardiology tests used a ^{99m}Tc myocardial perfusion imaging agent.

State-of-the-Art Nuclear Cardiology

With the recent widespread availability of powerful computer systems as well as multidetector SPECT systems, gated myocardial perfusion scintigraphy has become routine; it was performed in 66 percent of myocardial perfusion SPECT studies in the United States in 1999, providing objective assessments of global and regional myocardial function in addition to traditional perfusion assessment. The increasing acceptance of the gated myocardial perfusion SPECT technique is a consequence of its becoming a powerful clinical tool to address a variety of clinical questions arising in the assessment of patients with known or suspected CAD. Although radionuclide angiography played a prominent role in noninvasive testing in decades past, in the 1990s the use of this modality became largely replaced by echocardiography and gated perfusion SPECT. Some important clinical applications of this modality remain, however, and are discussed in the latter portion of this chapter.

NEXT

Chapter 16: NUCLEAR CARDIOLOGY

MYOCARDIAL PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

A large number of acquisition protocols and techniques are used in nuclear cardiology today. Most of them are based on the Anger scintillation camera or a variation of it. The Anger scintillation camera (or gamma camera) consists of one or more scintillation detectors, typically made of high-density materials such as NaI, sodium iodide. Myocardial perfusion scintigraphy can be performed with either planar or SPECT approaches. With the planar technique, generally three two-dimensional (2D) images are obtained, usually 10 to 15 min each. Myocardial perfusion SPECT consists of imaging the 3D distribution of a radioactive perfusion agent in the myocardium. For SPECT acquisition, the camera detectors rotate around the patient in a circular or elliptical fashion, collecting a "projection image" at every few degrees. The 3D distribution of radioactivity is then mathematically "reconstructed" from the 2D projection images, usually using a process called "filtered-backprojection" and incorporating a variety of filters that enhance the images.

Multidetector cameras have come to be more commonly purchased than single-detector systems, and their increasing diffusion is an important factor supporting the increasing utilization of gated SPECT. Dual-detector cameras with the two detectors positioned at 90 degrees allow completion of 180-degree SPECT acquisitions in half the time taken by a single detector system for the same count level, or collection of twice the counts in the same time, and are therefore highly efficient for gated cardiac SPECT for imaging perfusion and function. A gated SPECT acquisition is similar to a standard SPECT acquisition, since in both cases the camera detector(s) rotates around the long axis of the patient, acquiring a number of planar ("projection") images at regular angular intervals (Fig. 16-1). What distinguishes the gated from the nongated technique is that, in the former, a number (8 or 16) of projection images is acquired at each projection angle, with each image (also called an interval or frame) corresponding to a specific portion of the cardiac cycle. A gated SPECT acquisition results in a standard SPECT data set ("summed" gated SPECT), from which perfusion is assessed, and a larger gated SPECT data set, from which function is evaluated. Gated SPECT has become the most commonly performed perfusion SPECT protocol as a direct consequence of the ease and modest expense with which perfusion assessment is "upgraded" to perfusion/function assessment and of the documentation of incremental information by the combined measurements.

As long as adequate count statistics are achieved, there is no limitation as to the specific perfusion agent that can be imaged with the gated SPECT technique. The quality of the gated SPECT study is directly related to the number of counts in its individual frames. Count statistics are influenced by numerous factors, including injected dose, acquisition time, patient size, number of detectors, collimation, number of frames, and count acceptance criteria.

Radiopharmaceuticals

THALLIUM 201

A cyclotron-generated radionuclide with a half-life of 73 h, ^{201}Tl emits gamma rays from 68 to 80 kev (94 percent abundant) and at 167 kev (10 percent abundant). Owing to its relatively long half-life, the absorbed radiation dose is such that recommended injected doses are limited to 2 to 4

mCi. ^{201}Tl has excellent physiologic properties for myocardial perfusion imaging. Importantly for stress myocardial perfusion scintigraphy, a linear relationship between blood flow to viable myocardium and ^{201}Tl uptake is maintained during exercise[11] up to very high levels of flow (e.g., vasodilator stress, >3 mL/min/g), where a "roll-off" in uptake occurs.[12] After intravenous injection, thallium is rapidly extracted throughout the body roughly in proportion to the distribution of cardiac output.[13] As an unbound potassium analog, ^{201}Tl redistributes over time. At equilibrium its distribution of ^{201}Tl is proportional to the regional potassium pool, reflecting the amount of viable myocardium. Thus, following intravenous injection and initial myocardial uptake, approximately half of the ^{201}Tl washes out of the normal myocardium over 5 to 8 h.[14] Differential washout rates between hypoperfused but viable myocardium and normal zones and washin to initially hypoperfused zones are the fundamental mechanisms of ^{201}Tl redistribution.

A factor governing the washout rate of ^{201}Tl is the concentration gradient between the myocardial cell and the blood. There is slower blood clearance of ^{201}Tl following resting or low-level exercise injection. Diffuse slow washout rates, mimicking diffuse ischemia, may be observed in normal patients who do not achieve adequate levels of stress. Hyperinsulinemic states slow redistribution, leading to an underestimation of viable myocardium; thus, fasting is recommended prior to and for 4 h following ^{201}Tl injection.[15]

An inverse relationship between the degree of coronary stenosis and subsequent redistribution of ^{201}Tl (i.e., late redistribution) has been reported.[16] Redistribution may occur early in areas with minor stenoses (where hyperemia postexercise would be expected), and late in regions with critical stenoses (in which poststress hyperemia is unlikely and resting hypoperfusion slows the delivery of thallium to the region).[17]

^{99m}Tc SESTAMIBI AND TETROFOSMIN

^{99m}Tc is produced from a molybdenum-99m generator, has a half-life of 6 h, and emits monoenergetic gamma rays at 140 kev. The whole-body radiation dose is estimated to be 16 mrad/mCi, in contrast to 240 mrad/mCi associated with ^{201}Tl. Owing to this more favorable dosimetry, larger doses of ^{99m}Tc myocardial perfusion imaging agents are used than with ^{201}Tl, usually in the range of 30 mCi. ^{99m}Tc sestamibi belongs to a class of compounds called *isonitriles* and is a complex organic compound that behaves physiologically as a monovalent cation. Following its extraction from the blood, ^{99m}Tc sestamibi is bound by mitochondria, and only a limited amount of myocardial washout (or washin) occurs over time.[18,19] As with ^{201}Tl, the initial uptake of ^{99m}Tc sestamibi is a function of myocardial perfusion to viable tissue. In general, ^{201}Tl has a higher myocardial uptake (as measured by the percent injected dose per gram of myocardium) throughout the range of flow, secondary to a higher extraction fraction than ^{99m}Tc sestamibi (approximately 85 percent compared with 65 percent).[20,21] At very low levels of flow, extraction of these tracers appears to increase, affecting ^{99m}Tc sestamibi more than ^{201}Tl.[22]

^{99m}Tc tetrofosmin is extracted by the myocardium and bound in mitochondria, like sestamibi. The extraction fraction of this agent is slightly lower than that of sestamibi.[23] There is less hepatic uptake with this tracer than with ^{99m}Tc sestamibi, resulting in more favorable heart/liver ratios early following resting injection.[24,25]

OTHER ^{99m}Tc MYOCARDIAL PERFUSION AGENTS

^{99m}Tc teboroxime belongs to another class of ^{99m}Tc myocardial perfusion agents, which are neutral lipophilic complexes of boronic acid called BATO compounds. ^{99m}Tc teboroxine appears to have a higher extraction fraction than ^{201}Tl. The high extraction fraction with this agent plateaus at a higher flow rate than any other agent.[26,27] These highly desirable extraction characteristics of

teboroxime are counterbalanced by a rapid washout from the myocardium.[28] Thus, the kinetic properties of ^{99m}Tc teboroxime require that initial imaging be completed within the first few minutes after tracer injection in order to reflect blood-flow distribution at the time of injection. This limits its use to multiple-detector systems.[29] Due to the requirement for very rapid imaging, ^{99m}Tc teboroxime is the most technically demanding of the available myocardial perfusion tracers.

^{99m}Tc NOET is a neutral lipophilic myocardial perfusion imaging agent based on a Tc-nitrido core.[30] Although an extraction fraction as high as 76 percent with this tracer has been reported under hyperemic conditions,[31] there are other reports of much lower extraction than that associated with ^{201}Tl.[32] There appears to be redistribution over time of this tracer, related in part to the absence of intracellular binding and in part to higher circulating blood levels of radioactivity with this tracer as compared with ^{99m}Tc sestamibi.[31] ^{99m}Tc NOET overall may have kinetic and imaging properties very similar to those of ^{201}Tl, with the advantage of the higher photon flux associated with the higher injected dose that is possible with a ^{99m}Tc agent.[33] The redistribution of ^{99m}Tc NOET appears to be almost complete after 90 min of reflow, potentially shortening the clinical protocols applicable for assessment of myocardial viability with this tracer. A disadvantage of this tracer, like that of ^{201}Tl, is the lack of flexibility in the timing of postexercise imaging and the ability to repeat imaging.

^{99m}Tc furifosmin appears to be very similar to ^{99m}Tc tetrofosmin,[34,35] with an extraction fraction lower than that of ^{99m}Tc sestamibi. Neither ^{99m}Tc NOET nor ^{99m}Tc furifosmin have been approved for clinical use in the United States at this time.

Imaging Protocols and Image Interpretation

^{201}Tl PROTOCOLS

With ^{201}Tl, a variety of SPECT acquisition protocols are available (Fig. 16-2). When ^{201}Tl alone is employed as the radiopharmaceutical, the usual acquisition protocol uses some combination of stress with redistribution and/or reinjection imaging. The latter, as initially described, involved obtaining an additional image in patients with nonreversible ("fixed") perfusion defects following reinjection of one-half of the dose used at stress, with imaging performed immediately thereafter[36] (Fig. 16-2*A*). This protocol improves detection of viable myocardium over standard-stress 4-h redistribution imaging.[37] Since it requires three image acquisitions and a decision as to whether the reinjection is needed, a two-acquisition sequence with stress and redistribution/reinjection imaging is commonly performed. If no fixed defects are noted, with this approach further imaging is not required. If, on the other hand, following the 4-h reinjection/redistribution image, fixed defects are present, 24-h imaging results in a small but significant improvement in detection of viable myocardium[16,37] (Fig. 16-2*B*). An alternate protocol that appears to be gaining popularity is to give sublingual nitroglycerin prior to the reinjection of ^{201}Tl. With this approach, the frequency of further improvement at 24-h imaging may be substantially reduced; i.e., we consider it likely that a stress- and nitrate-augmented early reinjection protocol will reduce the benefit of, and thus the need for, 24-h imaging.[38] The other form of thallium imaging in frequent use is the rest/redistribution protocol, considered to be the most effective ^{201}Tl protocol for the assessment of viable myocardium[39,40] (Fig. 16-2*C*).

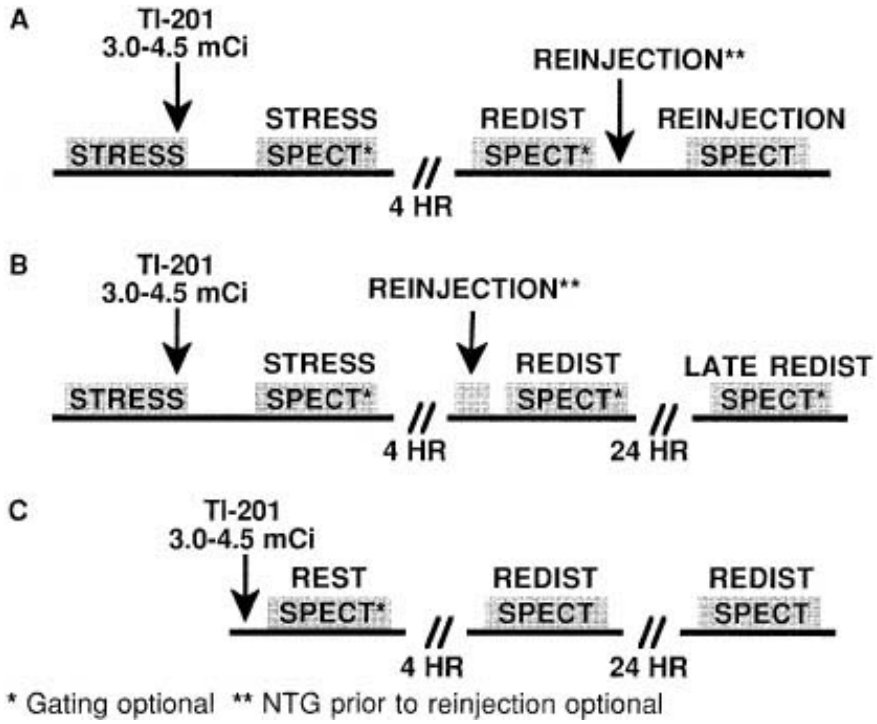

Figure 16-2: 201Tl protocols. *A.* Stress/redistribution (redist), reinjection. *B.* Stress/reinjection/late redistribution. *C.* Rest/redistribution.

With a ^{201}Tl SPECT protocol, most investigators utilize all-purpose rather than high-resolution collimators,[41] although some prefer high-resolution collimators.[42,43] If high-resolution collimators are used, lengthening of the time of acquisition for ^{201}Tl SPECT should be considered-compared with ^{99m}Tc-based SPECT protocol-to provide adequate SPECT count statistics. This is particularly relevant for late redistribution imaging, because of the lower count rate due to radioactive decay. The timing of the initial poststress acquisition is particularly important with thallium, since excessive delay could result in decreased sensitivity for detection of coronary artery disease, owing to early redistribution of the radiopharmaceutical. However, SPECT acquisition of either the ^{201}Tl or the ^{99m}Tc myocardial perfusion agent should begin ≥10 min following exercise injection because of the frequent observation of an artifactual perfusion defect due to "upward creep of the heart."[44] This phenomenon is related to the increased depth of respiration very early postexercise, which is associated with an average lower position of the diaphragm in the chest compared with the normal ventilatory state. This causes the heart to gradually move cephalad during the early portion of SPECT acquisition, resulting in a form of motion artifact after reconstruction. By delaying acquisition until 10 to 15 min after exercise stress, this "upward creep" artifact is avoided. Although initially described with ^{99m}Tc sestamibi, gated SPECT can also be performed with ^{201}Tl, particularly with multidetector system. LVEF measurement with gated ^{201}Tl SPECT correlates highly with that of ^{99m}Tc sestamibi SPECT.[45]

^{99m}Tc SESTAMIBI OR TETROFOSMIN PROTOCOLS

Owing to the absence of clinically significant redistribution, separate rest and stress injections are standard with ^{99m}Tc sestamibi or tetrofosmin SPECT (Fig. 16-3).[46,47] A benefit of the absence of redistribution is that image acquisition can be repeated if imaging artifact is suspected. In this regard, imaging in the prone position, as well as in the supine position, increases the specificity of myocardial perfusion SPECT with ^{99m}Tc sestamibi or tetrofosmin.[47] A variety of protocols can be used with these agents, including 2-day stress/rest, same-day rest/stress, same-day stress/rest, and dual isotope. From the standpoint of defect contrast and optimal image quality, the 2-day

stress/rest protocol is ideal (Fig. 16-3*A*). With the 2-day stress/rest protocol, both the stress and the rest study are obtained following the injection of high doses of ^{99m}Tc sestamibi or tetrofosmin, allowing the acquisition of high-quality, high-count images for the accurate assessment of perfusion and function. The principal drawback of this protocol is its requirement for two imaging days, resulting in a delay in the delivery of final information to be used in patient management. The same-day low-dose rest/high-dose stress protocol[48] (Fig. 16-3*B*) has the disadvantage of causing a reduction in stress defect contrast, as approximately 15 percent of the radioactivity observed at the time of stress imaging comes from the preexisting resting myocardial distribution. The same-day low-dose stress/high-dose rest sequence[49,50] (Fig. 16-3*C*), on the other hand, has the advantage of requiring image acquisition times essentially identical to those used for ^{201}Tl imaging, making it easy for a laboratory to alternate between the two protocols. The principal drawback of this approach is that less than ideal count rates are associated with the most important stress image set, and it is difficult to assess defect reversibility accurately.[51] With respect to the assessment of myocardial viability, all stress/rest or rest/stress ^{99m}Tc sestamibi or tetrofosmin imaging protocols have theoretical limitations in distinguishing severely hibernating myocardium from infarction. These constraints do not apply to ^{201}Tl because of its redistribution properties.[52,53] Viability assessment with ^{99m}Tc sestamibi or tetrofosmin may be improved by the administration of nitroglycerin prior to the rest-injection study.[54,55]

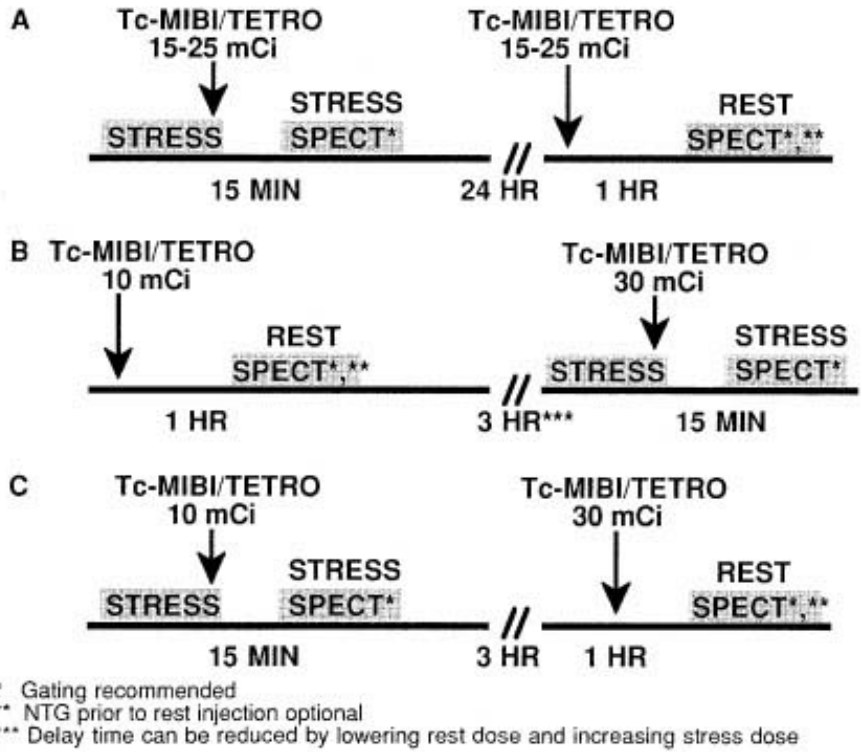

Figure 16-3: Two day (*A*), same-day rest-stress (*B*), and same-day stress-rest (*C*), 99mTc sestamibi or tetrofosmin protocols. Tc = 99mTc; MIBI = sestamibi; Tetro = tetrofosmin.

A common alternative to the standard ^{99m}Tc sestamibi or tetrofosmin protocols is a rest ^{201}Tl/stress ^{99m}Tc sestamibi dual-isotope SPECT (Fig. 16-4).[56] Dual isotope imaging takes advantage of the Anger camera's ability to collect data in different energy windows and can be performed with simultaneous or separate rest/stress acquisitions. The separate acquisition approach using rest ^{201}Tl/stress ^{99m}Tc sestamibi or tetrofosmin does not require correction for cross-contamination between the two radioisotopes,[56] whereas this correction is likely to be required with the simultaneous dual-isotope approach.[57] Of note, with this protocol, if defects are

present on the rest ^{201}Tl study, redistribution ^{201}Tl SPECT can be performed before or 24 h after the ^{99m}Tc sestamibi or tetrofosmin injection.[58]

ATTENUATION CORRECTION

Several camera manufacturers have recently provided hardware and software implementation of attenuation correction protocols, and these have undergone preliminary validation.[59,60] In general, these attenuation corrections are imperfect, reducing but not eliminating apparent perfusion defects due to soft tissue attenuation in normal patients. At times, true perfusion defects might be obscured or eliminated by the application of these approaches. The artifactual elimination of perfusion defects is usually due to filtering or to scatter from adjacent organs, which becomes more apparent after attenuation correction. It is prudent to visualize attenuation-corrected tomographic data sets simultaneously with noncorrected datasets.

20-SEGMENT VISUAL ANALYSIS

The use of a semiquantitative scoring system in which each of 20 segments is scored according to a 5-point scheme provides an approach to interpretation that is more systematic and reproducible than simple qualitative evaluation. The 20-segment scoring system is based on three short axis slices [distal (apical), mid-, and basal] to represent the entire LV, with the apex represented by two segments visualized in a midvertical long-axis image. Each of the 20 segments has a distinct name and number, as indicated in Fig. 16-5. Each segment is scored as follows: 0 = normal, 1 = slight reduction of uptake (equivocal), 2 = moderate reduction of uptake (usually implies a significant abnormality), 3 = severe reduction of uptake, 4 = absence of radioactive uptake.[61] Perfusion defects with scores of three or four can be reported as consistent with a critical (≥90 percent) coronary stenosis.[62,63]

The 20-segment scoring system standardizes the visual interpretation of scans, reduces the likelihood of overlooking significant defects, and provides an important semiquantitative global index that can be used for overall assessment of extent and severity of abnormality. Each segment roughly corresponds to 5 percent of the LV. Recently a 17-segment scoring system has been proposed in which the smaller size of the apical short-axis slice is accounted for by dividing the slice into four segments, while the apex is considered a single segment.[64]

SUMMED SCORES

The 20-segment, 5-point scoring system lends itself to the derivation of summed scores (i.e., global indices of perfusion) (Table 16-1).[65] The summed stress score (SSS) is defined as the sum of the stress scores for the 20 segments. The summed rest score (SRS) is defined as the sum of the rest scores or redistribution scores, and the summed differences score (SDS), measuring the degree of reversibility, is defined as the difference between the summed stress score and the summed rest score. It is essential to consider the normal regional variation of count distribution typical of myocardial perfusion scintigraphy before assigning a perfusion score. For example, the basal interventricular septum (membranous septum) has reduced blood flow, and (because of its depth) is subject to greater attenuation than other portions of the myocardium. This "normal septal dropout," frequently observed as an apparent defect on the basal septal slices, should be assigned a score of 0 rather than a score suggesting the presence of abnormality. Risk groups may be defined using the SSS,[66,67] where a score <4 is considered normal or nearly normal, scores of 4 to 8 are mildly abnormal, scores of 9 to 13 moderately abnormal, and summed stress scores >13 severely abnormal.

The 20 myocardial segments can be ascribed to individual coronary territories.[56,68] The inferior and basal septal segments are ascribed to the PDA (posterior descending artery), the lateral

segments to the left circumflex coronary artery, and the mid- and distal septal as well as all anterior slices to the left anterior descending coronary artery. Although isolated apical abnormalities are usually associated with left anterior descending disease, the left circumflex or right coronary artery can also supply the apex. If only anterior wall segments are abnormal, sparing the apex and the septum, the abnormalities are usually considered to represent disease of the diagonal branch of the left anterior descending coronary artery. The coronary assignment is altered for regions at the border between specific vessels territories, depending on the pattern of perfusion defect abnormality in the adjacent segments. At times, a dominant perfusion defect in a specific vascular territory will "tail" into a contiguous territory of another vessel. In these circumstances, the defect would generally be attributed to the vessel associated with the dominant defect. This pertains most commonly to the inferoseptal and inferolateral walls, but also to the anterolateral wall. Regarding the septum, if an inferoseptal defect is present (excluding the basal inferoseptal segment, which is generally a right coronary artery territory), the septal abnormalities would be assigned to the left anterior descending or right coronary artery, depending on which of these vessels had a perfusion defect. Similarly, if an inferolateral or anterolateral defect but not both were present in patients with adjacent defects in either the anterior or inferior wall, the lateral wall defect would be assigned to the vessel attributed to the neighboring defect. In general, isolated septal defects (without anterior wall or inferior wall involvement) are rare; isolated lateral wall defects (in the absence of anterior wall or inferior wall defects) would be attributed to the left circumflex coronary artery.[56]

GATED SPECT

Gated perfusion SPECT can be used to quantify a variety of global function parameters, including LVEF, end-diastolic volumes, and end-systolic volumes. Diastolic function assessment is generally not performed with gated SPECT, since it requires too large a number of gating intervals.[69] Regional parameters of function that can be quantitated from gated perfusion SPECT images include LV myocardial wall motion and thickening. Quantitation of gated perfusion SPECT images can be performed by employing algorithms adapted from other imaging modalities, including methods resembling equilibrium radionuclide angiography data processing[70,71] and biplane Simpson's rule analogs or by fully 3D algorithms. The most common algorithms are fully 3D and are based on the automatic detection of endocardial and epicardial surface points.[72-76]

In validation studies of gated perfusion SPECT LVEF published to date,[77] it is apparent that the agreement between gated SPECT and gold standard measurements of LVEF is generally very good to excellent. Indeed, it has been pointed out that 2D "gold standards" may be intrinsically less accurate than gated SPECT algorithms operating in the 3D space because of geometric assumptions required by the former.[72] The normal threshold for the global LVEF measured from gated SPECT images is slightly lower than that measured using other imaging modalities, or approximately 45 percent, due to an approximate 3-4 point underestimation of true LVEF associated with the use of only eight gating intervals.[77] Normal limits for eight-frame LVEF and LV volumes have been recently reported.[78-80] LVEFs can be slightly overestimated in analyzing gated SPECT images of small hearts.[81] Figure 16-6 illustrates an example of perfusion SPECT quantitative perfusion analysis (including the 20-segment scores) and quantitative gated SPECT from a patient with severe disease of the left anterior descending coronary artery.

ASSESSMENT OF MYOCARDIAL VIABILITY

The presence of myocardial viability is implied with the myocardial perfusion tracers if the degree of uptake at rest, redistribution, or following nitrate-augmented rest injection[82-86] is normal. If a region has severely reduced or absent uptake of radioactivity in these settings, it is considered to

be nonviable. Areas with moderate reduction of counts in these conditions (score 2 at redistribution or nitrate-augmented rest) are usually partially viable, and patients in this group have a variable response in terms of postoperative improvement. Some have utilized a cutoff percentage of maximal counts in the myocardium for predicting viability in a region in question[87,88]; others use the number of standard deviations below normal. An example of rest-redistribution imaging of myocardial viability is illustrated in Fig. 16-7 for a patient with poor LVEF (<35 percent) evaluated for CABS.

OTHER ABNORMALITIES

In addition to perfusion defects, several nonperfusion abnormalities can be observed with myocardial perfusion SPECT including size of the LV, transient ischemic dilation (TID) of the LV,[89,90] RV myocardial uptake pattern, RV size, and abnormalities of lung uptake or other abnormal extracardiac activity.

Transient Ischemic Dilation of the Left Ventricle

TID is considered present when the LV cavity appears to be significantly larger in the poststress images than at rest (Fig. 16-6)[89,90] and may actually be an apparent cavity dilation secondary to diffuse subendocardial ischemia (obscuring the endocardial border). This explains why TID may be seen for several hours following stress, when true cavity dilation is probably no longer present.[91] The correlation between TID of LV and lung uptake is weak, suggesting that there may be different pathophysiologic mechanisms for each; their measurements may be complementary in assessing the extent and severity of CAD for risk stratification.[92] TID was initially reported to be moderately sensitive and highly specific for critical stenosis (greater than 90 percent narrowing) in vessels supplying a large portion of the myocardium (i.e., proximal left anterior descending or multivessel 90 percent lesions).[89,90] Dipyridamole-induced TID has similar implications as those associated with exercise.[91] TID can easily be measured by slight modifications of the quantitative gated SPECT algorithms. The upper limits of normal for the TID ratio in dual-isotope imaging has been reported to be 1.22. Patients who have TID of the LV (TID > 1.22) are likely to have severe and extensive CAD (>90 percent stenosis of the proximal left anterior descending coronary artery, or of multiple vessels).[90]

Increased Lung Uptake of Radioactivity

Increased lung uptake of ^{201}Tl was first described by Boucher et al., as noted on the anterior view of planar thallium images.[93] It is generally accepted that increased pulmonary uptake of thallium reflects increased pulmonary capillary wedge pressure. When noted at rest, it reflects increased pulmonary capillary wedge pressure at rest,[94] and when noted with stress (either exercise or pharmacologic), it indicates the presence of increased pulmonary capillary wedge pressure during stress.[95] Nonischemic causes of increased pulmonary capillary wedge pressure, such as mitral regurgitation, mitral stenosis, etc., are also associated with increased pulmonary thallium uptake. Increased thallium lung uptake after exercise has been shown to have incremental prognostic information over myocardial perfusion defect assessment.[96] Only a few studies have examined the implications of increased pulmonary uptake of ^{99m}Tc sestamibi, with differing results.[95,97-99] It is possible that the differences among these reports are largely explained by the frequent greater delay in imaging of ^{99m}Tc sestamibi following stress than is associated with imaging of ^{201}Tl. The impact of the starting time of poststress acquisition of ^{99m}Tc sestamibi studies on lung uptake has been confirmed by Hurwitz et al.,[98] who found a good correlation between lung-heart ratio and angiographic findings on immediate images (4 min after stress), whereas no such correlation was found on the late images. By delaying 1 to 2 h following stress, increased pulmonary uptake that would have been present initially might no longer be present at the time of imaging. The

prognostic implications of increased exercise sestamibi lung uptake as well as the findings of increased uptake in pharmacologic stress with this tracer have not yet been explored.

EXERCISE PROTOCOLS

Exercise stress is the most commonly performed form of stress for myocardial perfusion SPECT. Exercise stress allows assessment of exercise capacity and symptoms as well as ST-segment response, providing additional clinical information that can be useful in daily clinical decision making (see Chap. 14). For exercise nuclear imaging, (1) an indwelling intravenous line for injection of the tracer at peak exercise is inserted, (2) injection of the tracer is performed at maximal stress, and (3) exercise is continued for an additional minute to allow optimal myocardial tracer concentration.

PHARMACOLOGIC STRESS PROTOCOLS

For patients who cannot achieve an adequate level of stress, pharmacologic stress testing is generally performed.[100-104] Generally, if the patient cannot perform ≥5 METs or more of exertional stress or fails to achieve ≥85 percent of maximal predicted heart rate a pharmacologic stress protocol should be encouraged. The preferred form of pharmacologic stress for myocardial perfusion SPECT is the use of coronary vasodilators-dipyridamole or adenosine, providing a three- to fivefold increase in coronary flow. Dipyridamole blocks the cellular reuptake of adenosine, increasing the extracellular adenosine concentration. Increased extracellular adenosine, either with adenosine infusion or dipyridamole, causes coronary vasodilation. The comparative effects of the vasodilators, exercise, and dobutamine are illustrated in Fig. 16-8. In general, the diagnostic accuracy of myocardial perfusion scintigraphy using pharmacologic stress is equivalent to that of exercise, despite the differences in flow rates.[100]

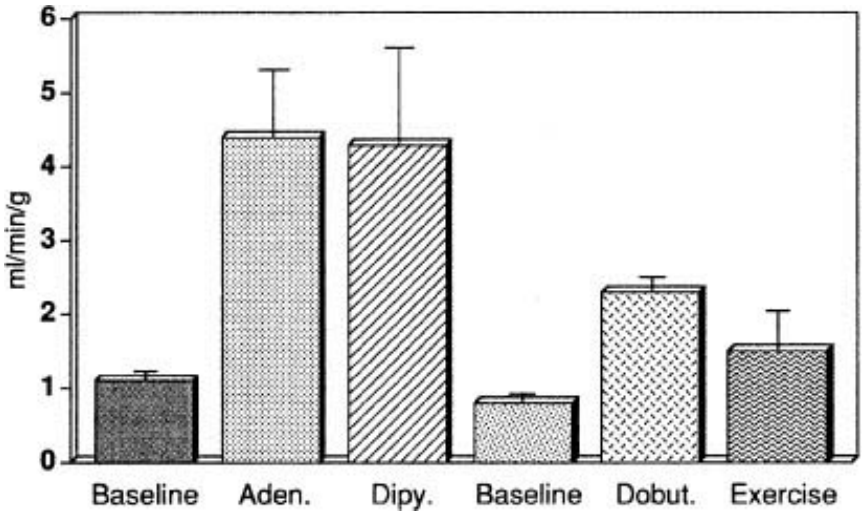

Figure 16-8: Coronary blood flow at baseline, exercise, dobutamine (Dobut.), adenosine (Aden.), and dipyridamole (Dipy.) stress measured with 13*N*-labeled ammonia. Baseline results are listed twice because of slight differences in absolute results. (Reproduced with permission from Iskandrian et al.[111])

Importantly, methylxanthines, such as theophylline or caffeine, block adenosine binding and can eliminate the effects of dipyridamole or adenosine on coronary vasodilation. Since the half-life of caffeine is variable[105] with either dipyridamole or adenosine, it has been recommended that patients be off caffeine-containing compounds for 24 h prior to imaging. There is no currently

available means of identifying patients in whom the pharmacologic effects of adenosine or dipyridamole have been blocked by caffeine; in contrast to exercise, the heart rate or blood pressure does not provide accurate information regarding response.[106]

Dipyridamole is usually infused at 0.142 mg/kg/min for 4 min, although some investigators have recommended increasing the dose by 50 percent.[100,101] The maximal effect occurs approximately 3 to 4 min after termination of the infusion. Side effects are common and transient, including nonspecific chest pain, shortness of breath, dizziness, and flushing. Severe side effects are rare, being noted that in only 1 of 10,000 in the largest study to date.[102] The side effects can usually be reversed by intravenous administration of aminophylline, usually 75 to 125 mg, although additional administration of nitroglycerin may occasionally be needed. Due to the potential side effect of severe bronchospasm, dipyridamole is contraindicated for patients with asthma. Adenosine is infused intravenously, usually at a dose of 140 mg/kg/min over 6 min, with administration of the radiopharmaceutical at the midpoint of the infusion.[107] Minor and transient side effects occur more frequently with adenosine, than with dipyridamole.[107] With adenosine, there is an increased incidence of advanced atrioventricular (AV) block. As the half-life of adenosine is very short (several seconds), side effects usually remit quickly within termination of the infusion. Adenosine is considered contraindicated for patients with equal to or greater than first-degree AV block, sick sinus syndrome, or bronchospasm.

COMBINED PHARMACOLOGIC AND EXERCISE TESTING

It has become increasingly common to combine vasodilator stress with low-level exercise. This is generally accomplished by beginning exercise at the end of the dipyridamole infusion. With adenosine stress, exercise is initiated during the adenosine infusion.[108]

DOBUTAMINE STRESS

An alternative to vasodilator stress is inotropic stress, usually performed with dobutamine.[109,110] At the present time, dobutamine stress is usually reserved for patients with asthma or those who have recently ingested caffeine. Dobutamine stress is associated with a lower rate pressure product and a lower degree of hyperemia in the myocardial bed than with exercise[111,112] or vasodilator stress (Fig. 16-8). Side effects are more common than with the vasodilator stress, including, more commonly, premature ventricular contractions serious side effects are rare.[113] Thus, dobutamine is not considered the agent of first choice for myocardial perfusion scintigraphy. Arbutamine, another inotropic agent, is not currently available in the United States.[114,115]

LEFT BUNDLE-BRANCH BLOCK

Patients with LBBB may frequently demonstrate reversible defects in the interventricular septum in the absence of CAD.[116] The mechanism has been postulated to be a true septal ischemia that occurs in LBBB in the presence of marked tachycardia. This perfusion defect may indicate a decrease in flow resulting from an increase in early diastolic compressive resistance, in turn caused by delayed ventricular relaxation.[117] In view of this pathophysiology, stress techniques that do not increase heart rate as markedly as exercise are preferred in LBBB; i.e., adenosine or dipyridamole testing without walking is generally considered preferable in LBBB patients.[118,119]

Nonperfusion Myocardial SPECT

Radionuclide imaging has an inherent advantage over other cardiac imaging techniques for assessment of myocardial metabolic and biochemical processes. Two nonperfusion myocardial scintigraphic applications in common use in other countries are fatty-acid imaging and imaging of myocardial innervation. The most commonly used radionuclide for these purposes is iodine 123

(^{123}I). From a biochemical standpoint, ^{123}I is an excellent metabolic imaging tracer, since it is easily incorporated into a wide variety of compounds by a halogen exchange reaction in which the iodine replaces a methyl group. Unfortunately, none of the ^{123}I-labeled compounds is currently commercially available for routine use in the United States.

FATTY ACID IMAGING

A comprehensive review of this subject has recently been provided by Tamaki.[120] Two principal types of fatty acid compounds have been described for myocardial imaging. Straight-chain fatty acid imaging has been most commnly performed with ^{123}I iodophenyl pentadecanoic acid (IPPA). With this tracer, initial uptake allows assessment of myocardial perfusion at rest or exercise.[121] The washout of ^{123}I IPPA appears to be related to fatty-acid metabolism (primarily beta oxidation) and can provide information about myocardial ischemia and myocardial viability. In ischemic but viable myocardium, IPPA washout is slower than normal but faster than in infarcted tissue.[122] This intermediate range of IPPA washout has been shown to be predictive of improvement in LV function after revascularization. Iskandrian et al.[123] have suggested that defect reversibility was more commonly seen with IPPA SPECT than with rest/redistribution ^{201}Tl SPECT. Despite these promising features for assessment of myocardial perfusion and viability through sequential SPECT acquisitions, this radiopharmaceutical has not yet become commercially available in the United States.

The other major class of fatty-acid compounds for SPECT are modified branched-chain fatty acids. These agents provide superior imaging quality with the Anger scintillation camera, since the washout of the modified branched-chain fatty acid is slower than that of the straight-chain agents due to partial metabolic trapping in the myocardium. Betamethyl iodophenylpentadecanoic acid (BMIPP), first introduced by Knapp et al.,[124] has become widely used in Japan and Europe. This tracer appears to uncover an "ischemic memory" and may have unique capability for the assessment of previously severely ischemic myocardium. Discordant radiopharmaceutical uptake, with less BMIPP uptake than with ^{201}Tl, has been described in patients with unstable angina and those with acute myocardial infarction who were acutely revascularized.[125] This finding likely represents a persistent metabolic abnormality out of proportion to the perfusion abnormality at the time of injection. Furutani et al.[126] have suggested that this finding allows assessment of the amount of myocardium at risk in the subacute phase of the myocardial infarction (MI). For patients revascularized during acute MI, the size of the BMIPP defect 1 week after revascularization reflects the area of risk measured by ^{99m}Tc perfusion imaging before revascularization.[126a] In 50 consecutive patients with MI receiving BMIPP and thallium scans (average follow-up 23 months), discordant BMIPP uptake compared with ^{201}Tl was the best predictor of future cardiac events, followed by the number of coronary stenoses. In unstable angina, a decrease in BMIPP has been reported under resting conditions, even after chest pain has resolved.[127]

IMAGING OF MYOCARDIAL INNERVATION

Imaging of myocardial innervation is another application of the tracer technique to cardiac imaging recently reveiwed by Dae.[128] The sympathetic nerves of the myocardium take up exogenously administered catecholamines with high affinity.[129] An analog of a false nerve transmitter is meta-^{125}I-iodobenzylguanidine (MIBG). MIBG is taken up in myocardial sympathetic nerve endings in a manner similar to norepinephrine,[130] but it is not metabolized. In regionally denervated myocardium, MIBG uptake is decreased while perfusion is unchanged.[131] In the setting of ischemic heart disease, it is generally held that ischemia must be severe enough to cause myocardial necrosis before regional denervation (and subsequent decreased MIBG uptake)

occurs.[132] In "syndrome X," abnormal cardiac MIBG uptake has been reported in 75 percent of patients, with the abnormality out of proportion to perfusion defects supporting the cardiac origin of chest pain in this syndrome.[133] Furthermore, in diabetic patients, assessment of myocardial MIBG uptake may be useful in defining autonomic dysfunction early in the course of type I disease.[134] Asymmetric uptake of MIBG has been shown for patients with ventricular tachycardia and no CAD.[135,136] Regional decreases of MIBG uptake in the basal left ventricle have also been demonstrated in a high proportion of patients with arrhythmogenic RV cardiomyopathy,[137] and abnormal MIBG uptake has been reported in idiopathic ventricular tachycardia and ventricular fibrillation.[138]

In nonischemic cardiomyopathy, abnormality of MIBG distribution and washout has been reported.[139] Generally, in congestive heart failure, excessive stimulation of the cardiac nervous system is believed to lead to further depression of cardiac function and may play a role in sudden death.[140] Recent studies have suggested that impaired cardiac sympathetic innervation in heart failure patients can be assessed by MIBG.[141] The late myocardial-to-mediastinal MIBG uptake 4 h after injection was shown to be the most powerful predictor of cardiac death, providing incremental information over clinical variables in a large clinical study. Furthermore, MIBG imaging may be useful in predicting the effectiveness of beta-blocker therapy for patients with dilated myocardial myopathies.[142,143] The pattern of a low heart-to-mediastinal ratio on 4-h delayed MIBG images appears to be predictive of a poor response to beta-blocker therapy.[128]

INFARCT-AVID IMAGING

Hot-spot (infarct-avid) imaging methods for detecting acute MI are among the oldest techniques in nuclear cardiology. These techniques have included ^{99m}Tc pyrophosphate myocardial scintigraphy,[144-148] indium 111 (^{111}In) antimyosin antibody scintigraphy,[149] and ^{99m}Tc glucarate imaging.[150] Although these methods have been documented to be sensitive and specific for the detection of myocardial necrosis, they are not widely utilized owing to the needed delay between injection and imaging. Antimyosin antibody, not available in the United States, is highly specific for myocardial necrosis and has been shown to be useful in the assessment of myocarditis[151] and the necrosis associated with cardiac transplant rejection.[151a] A new agent, ^{99m}Tc glucarate, a small molecule similar to glucose with rapid blood pool clearance, is taken up acutely in the necrotic myocardium[150,152] and becomes positive in the very early hours after onset of necrosis.

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Chapter 16: NUCLEAR CARDIOLOGY

RADIONUCLIDE ANGIOGRAPHY (RNA)

Among the first applications of nuclear techniques in cardiology was the assessment of cardiac function using RNA or radionuclide ventriculography (RNV). The techniques of RNA can be performed by either equilibrium or first-pass methods. With the equilibrium approach, a blood-pool tracer (usually ^{99m}Tc-labeled red blood cells) images using a large number of cardiac beats after equilibration is attained within the intravascular compartment. With the first-pass approach, imaging is performed only during the initial transit of radioactivity through the central circulation. With both methods, assessments can be made of LVEF, RVEF, LV regional wall motion, and LV volumes.

The first-pass technique is a type of dynamic acquisition that uses rapid temporal sampling (20 to 100 frames per second) to look at the initial transit of a radionuclide bolus through the central circulation. This form of imaging is limited to the planar approach. The perfusion agents ^{99m}Tc sestamibi and ^{99m}Tc tetrofosmin can be used with success in first-pass studies.[153] Acquisition is completed in less than 1 min and can be performed in any desired view; in practice, however, these studies are usually limited to a single acquisition and are most commonly performed in either the anterior or right anterior oblique view.

Equilibrium RNA uses ECG-gated acquisitions, in which each frame corresponds to a specific portion (interval or gate) of the cardiac cycle, identified relative to the R wave on the patient's ECG. Because of the use of a multiple-gated acquisition, the term *MUGA scan* has also been applied to this technique. The cardiac cycle is divided in as many as 8 to 64 intervals and data from multiple cardiac cycles are averaged to ensure adequate count statistics. For equilibrium-gated RNA, the imaged radiopharmaceutical must stay within the vascular compartment during the imaging period. Although labeled proteins such as ^{99m}Tc albumin could be employed for blood pool imaging, labeled red blood cells are most commonly employed, labeled either through in vivo or in vitro methods. The latter provides the highest target-to-background ratio. Acquisition typically takes 5 to 10 min per view and multiple planar views are obtained. For exercise RNA, image acquisition can be as brief as 2 min.

Because of the ability to image the blood pool radiopharmaceuticals for a substantial time period, SPECT acquisition is also practical with equilibrium radionuclide angiography.[154,155] It has recently been shown that equilibrium blood pool SPECT acquisition and processing are essentially the same as for myocardial perfusion SPECT, and thus can be easily adopted in the laboratory where myocardial perfusion SPECT is being performed. Methods for automatically assessing LVEF from gated blood pool SPECT have been developed and validated.[156] Since the SPECT approach avoids the overlap of cardiac chambers inherent in planar imaging, it enhances assessment of regional function and may well become the method of choice for radionuclide angiography.

For exercise RNA, again either equilibrium or first-pass techniques can be employed. With the first-pass technique for exercise radionuclide angiography, a multicrystal camera has been most commonly used.[157] The advantage of first-pass over equilibrium RNA is that ventricular function assessments at the true peak of exercise can be obtained, since the procedure is accomplished in less than 30 s. For this purpose, patients can use either bicycle[157] or treadmill[158,159] exercise. At

the peak of exercise, the patient's chest is placed against the surface of the scintillation camera and a bolus injection is made, usually with 15 to 30 mCi of ^{99m}Tc radiopharmaceutical; most commonly, a 40-frames-per-second acquisition is used for the 30 s. Subsequently LVEF is computed, most commonly in a semiautomatic fashion using a count-based technique applied to motion-corrected, background-corrected scintigraphic data. LVEF is computed from the portion of the first pass of radionuclide through the central circulation that corresponds to the left ventricular filling and emptying phase. In a similar fashion, the first-pass scintigraphic data can be used to evaluate RVEF by processing the data acquired during the RV phase of the first pass.

For the equilibrium RNA, EFs of the LV[160-162] or RV[163] can be measured. The preferred method for measurement of EF from equilibrium RNA is referred to as the "area-counts" technique. This method takes advantage of the proportionality between the volume of a cardiac chamber and the number of counts emitted from that chamber following injection of a blood-pool radiopharmaceutical. Thus, a background-corrected curve of ventricular activity versus time is a curve of relative volume versus time of the corresponding ventricle. From this curve, EF can be measured as a function of the peak (relative end-diastolic) and the nadir (relative end-systolic) volume by the formula EDC - ESC/EDC, where EDC and ESC represent background-corrected counts in the end-diastolic and end-systolic frames, respectively. It is generally accepted that for most accurate measurement of LVEF, 16 frames or more per cardiac cycle are required. For measurement of RVEF, it has been demonstrated that carefully placed regions of interest over the RV at end-diastole and end-systole, using a left periventricular background region of interest, provide an effective method for assessment of RVEF. Very high degrees of correlation have been reported between LVEF and contrast ventriculography. Good correlation has been demonstrated between RVEF measurements using equilibrium RNA and RV first pass measurements.[163] RNA is considered one of the "gold standards" for assessing LVEF on the basis of its accuracy and reproducibility.[164,165]

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Chapter 16: NUCLEAR CARDIOLOGY

CLINICAL APPLICATIONS OF NUCLEAR CARDIOLOGY

The principles of diagnostic and prognostic accuracy outlined below are followed by a review of the evidence for the most common indications for nuclear cardiology procedures in the outpatient and inpatient cardiology settings.

Selecting the Appropriate Test Candidates

BAYESIAN THEORY: INTEGRATION OF PRETEST PROBABILITY ASSESSMENT INTO TEST INTERPRETATION

The central premise underlying patient selection for nuclear imaging is the ability to determine clinically an individual patient's likelihood of CAD or risk of important cardiac outcomes. The accurate evaluation of pretest clinical risk allows for the appropriate selection of patients who would most likely benefit from referral to nuclear imaging. The clinical pretest risk assessment may be estimated using published nomograms or from available computerized programs (see Chaps. 14, 38, and 40). Integrated predictive models based on clinical history and physical examination parameters have been developed from large patient registries and are published in the form of a nomogram for estimating the likelihood of CAD as well as cardiac survival. A review of models indicating the likelihood of clinical disease, aimed for use in varying populations, is presented in Chap. 38. For patient populations, several models have been developed with a large proportion of symptomatic patients designed to predict significant and extensive CAD as well as cardiac survival.[166-171] One of these approaches uses a validated computer algorithm to determine CAD likelihood based on age, sex, symptom classification, and conventional cardiac risk factors (resting systolic blood pressure, smoking history, glucose intolerance, resting ECG ST-segment abnormalities, and family history of early CAD).[171]

The rationale for selection of patients for noninvasive diagnostic and prognostic testing is based upon Bayesian theory (Chaps. 14 and 40), by which the posttest probability is a function of the patient's pretest clinical risk and the sensitivity and specificity of the test. The ability to shift posttest probabilities is directly related to pretest probability of disease or event risk. The greatest shift in posttest probabilities of disease occurs in those patients with an intermediate pretest probability of CAD.

Diagnostic Accuracy

Detection of CAD is one of the most common indications for performing myocardial perfusion SPECT. This referral is most appropriate in patients who are at intermediate risk of CAD, often including those with an abnormal rest electrocardiogram (ECG) where interpretation of exertional ST-segment changes is problematic.

A clinical algorithm for the purpose of simple detection of CAD based on these concepts, including the known sensitivity and specificity of treadmill ECG testing, is illustrated in Fig. 16-9.[172] Patients with a low probability (<0.15) of having angiographically significant (>50 percent stenosis) CAD can be identified even before standard exercise tolerance test (ETT) is performed. Patients with a low pre-ETT likelihood of CAD do not require further diagnostic testing, although continued medical follow-up or a "watchful waiting" approach is recommended. Patients with a low-intermediate pre-ETT likelihood of CAD (0.15 to 0.50) would undergo standard ETT as the next diagnostic step. Those who continue to have an intermediate likelihood of CAD after ETT (or those with an indeterminate ETT, as with LBBB, LVH, perfusion, ejection, etc.) and those whose pre-ETT likelihood of CAD is in the 0.50 to 0.85 range (in these patients even a negative ETT would not result in a low likelihood of CAD) will benefit from stress nuclear

testing. Patients with a high pre-ETT likelihood of CAD (>0.85) are generally considered to have an established diagnosis of CAD and would not need nuclear stress testing for diagnostic purposes. A variation of this approach was recently published in the "ACC/AHA/ACP-ASIM Guidelines for Management of Patients with Chronic Stable Angina."[8] The application of nuclear testing for diagnosis and the intermediate likelihood of CAD has been given a class I indication (condition for which there is general agreement that a given procedure is useful and effective).[8]

Table 16-2 presents uncorrected sensitivities and specificities of myocardial perfusion SPECT for the detection of angiographically significant (≥50 to 70 percent stenosis) CAD. From the ACC/AHA/ACP-ASIM stable angina guidelines (Chaps. 14 and 40), in populations referred to nuclear SPECT (i.e., a large proportion with uninterpretable ST segments), there is an improved predictive accuracy-defined as [(true positives + true negatives)/total]-by nuclear testing over pretest information and ECG stress testing.[8,173] Despite the differences in the extraction characteristics of the various nuclear tracers, there have been few reports that reveal marked differences in test sensitivity. Owing principally to a reduction in soft tissue artifact, there is an increase in test specificity with ^{99m}Tc-based agents as compared with ^{201}Tl imaging in women.[174] SPECT acquisition can be repeated with ^{99m}Tc-based agents when either attenuation or motion artifact is suspected further increasing specificity. A major limitation to the use of test statistics such as sensitivity and specificity for CAD is that they require referral to cardiac catheterization for calculation. In estimating the true sensitivity and specificity of noninvasive testing, referral or workup bias must be taken into account.[47,175] Sensitivity is the proportion of patients with disease who are correctly detected as abnormal by the test, and specificity is the proportion of patients without disease who are correctly detected as normal by the test. As routine patient workup results in preferential catheterization of patients with abnormal test results, the resulting observed test sensitivity is enhanced and the specificity is decreased. In general, referral bias leads to an overestimation in test sensitivity and a lowering in test specificity.[176] Once the test becomes used as a "gatekeeper" to catheterization, sensitivity and specificity can no longer be accurately measured. Thus, due to referral bias, test specificity becomes a poor measure of the ability of a test to exclude disease.

Table 16-2: Sensitivity and Specificity of Stress Myocardial Perfusion SPECT for Detecting CAD (≥50% stenosis), Without Correction for Referral Bias Results from the ACC/AHA/ACP/ASIM Guidelines for Chronic Stable Angina*

	Publication Years	No. of Studies	Sensitivity†	Specificity†
Exercise SPECT	1984-1997	16	0.88	0.72
Adenosine SPECT	1991-1997	9	0.89	0.81

*From Ref. [8]. †Average of reported sensitivities and specificities.

The normalcy rate has been advocated as an improved measure for this purpose.[47] This has been defined as the percentage of patients with normal test results in a population with a low likelihood of disease. A synthesis of data on nuclear SPECT normalcy rates has been reported to be in the range of 80 to 90 percent with ^{201}Tl testing and generally greater than 90 percent with ^{99m}Tc sestamibi SPECT; it would be expected to be similar to the latter for ^{99m}Tc tetrofosmin SPECT (Table 16-3).

Table 16-3: Normalcy Rate of Stress SPECT in Patients with a Low Likelihood of CAD (<5 to 10%)

Year	Author	Reference	Stress	Isotope	Normalcy Rate	%
1989	Maddahi	(176A)	exercise	Tl	24/28	86
1989	Iskandrian	(176B)	exercise	Tl	123/131	94
1990	Kiat	(176C)	exercise	MIBI	7/8	88
1990	Van Train	(176D)	exercise	Tl	62/76	82
1992	Kiat	(176E)	exercise	Tl	49/55	89
1993	Berman	(56)	exercise	Tl/MIBI	102/107	95
1994	Heo	(176F)	exercise or adenosine	Tl/MIBI	33/34	97
1994	Van Train	(176G)	exercise	MIBI	30/37	81
1995	Zaret	(176H)	exercise	Tetrofosmin	56/58	97
1995	Kiat	(176I)	arbutamine	Tl	52/58	90
1996	Hendel	(35)	exercise	Furifosmin	39/39	100
1996	Amanullah	(176J)	adenosine	MIBI	66/71	93
1997	Heo	(176K)	exercise	MIBI	58/61	95
Total					**701/763**	92

ABBREVIATIONS: CAD = coronary artery disease; MIBI = ^{99m}Tc-sestamibi; Tl = Tl-201; tetrofosmin = ^{99m}Tc -tetrofosmin; furifosmin = ^{99m}Tc -furifosmin.

Principles of the Use of Nuclear Cardiology for Risk Stratification/Patient Management

The most rapidly growing area of application of myocardial perfusion SPECT is risk stratification based on increased acceptance of a new paradigm in patient management. A risk-based approach to patients with suspected CAD appears better suited to the modern environment of cost containment and dramatic improvements in medical therapy than the approach focusing on simple diagnosis, in which the patient with suspected disease undergoes coronary angiography and then is frequently revascularized. With the risk-based approach, the focus is not on predicting who has CAD but on identifying and separating patients at risk for cardiac death, patients at risk for nonfatal myocardial infarction, and patients at low risk for either event.

The basic concept in the use of nuclear tests for risk stratification is that they are best applied to patients with an intermediate risk of a subsequent cardiac event, analogous to the optimal diagnostic application of nuclear testing of patients with an intermediate likelihood of having CAD. For prognostic testing, patients known to be at high or low risk for event would not be appropriate patients for cost-effective risk stratification with nuclear imaging since they are already stratified in the era of cost containment, the intensity of management and the effectiveness of therapy is tailored to patient risk. For low-risk patients, minimal further diagnostic testing results in the avoidance of excessive downstream costs. In contrast, high-risk patients are appropriately aggressively managed and usually undergo coronary angiography with consideration of revascularization. In chronic CAD, it has been suggested that a greater than 3 percent per year mortality rate can be used to identify patients with minimal symptoms whose mortality rate can be improved by coronary artery bypass grafting.[7] For purposes of risk assessment, it has been proposed that low risk be defined as a less than 1 percent cardiac mortality rate per year. Thus, intermediate-risk could be defined by patients in whom the cardiac mortality is in the range of 1 to 3 percent per year.[8] Since the

mortality risk for patients undergoing either coronary artery bypass grafting or angioplasty is greater than 1 percent per year,[177] mildly symptomatic patients with a less than 1 percent mortality rate would not be candidates for revascularization to improve survival and would be appropriately classified by this rate as at a low risk of death. Note that while, for diagnostic testing, nuclear imaging would be most appropriate in patients with an intermediate likelihood of CAD, for risk stratification this appropriateness extends to the groups of patients with a high likelihood of CAD.

PHYSIOLOGIC BASIS FOR RISK ASSESSMENT IN MYOCARDIAL PERFUSION SPECT

The basis for the power of nuclear testing for risk stratification is found in the fact that the major determinants of prognosis in CAD can be assessed by measurements of stress-induced perfusion or function. These measurements include the amount of infarcted myocardium, the amount of jeopardized myocardium (supplied by vessels with hemodynamically significant stenosis), and the degree of jeopardy (severity of the individual coronary artery stenosis). An additional important factor in prognostic assessment is the stability (or instability) of the CAD process. This last consideration may help to interpret what appears to be a paradox: nuclear tests, which in general are expected to be positive only in the presence of hemodynamically significant stenosis, are associated with a very low risk of either cardiac death of nonfatal MI when normal; in contrast, it has been observed that most MIs occur in regions with pre-MI lesions causing less than 50 percent stenosis.[178,179] It has been postulated that this paradox may be explained by the different response to stress of mild stenoses associated with stable and unstable plaque. Thus, beyond the ability to define anatomic stenosis, nuclear tests (by virtue of their physiologic assessments) may be able to discern abnormalities of endothelial function associated with high risk, even in the absence of significant stenosis.

To maximally extract the information regarding these prognostic determinants in CAD, it is necessary to consider the full extent and severity of abnormality, either quantitatively[180,181] or semiquantitatively,[56] rather than simply determining that the nuclear study is normal or abnormal. Furthermore, there appears to be incremental value in measuring both perfusion and function for the purposes of risk stratification, thus leading to increased prognostic utility of gated cardiac SPECT over standard myocardial perfusion SPECT.

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Chapter 16: NUCLEAR CARDIOLOGY

ASSESSMENT OF STABLE OUTPATIENT POPULATIONS

Suspected Chronic Coronary Artery Disease

The most frequent reason for referral to the nuclear laboratory is the evaluation of known or suspected CAD. In outpatient populations, this often includes the evaluation of the presence and extent of cardiac ischemia. Stress nuclear imaging is an integral part of the evaluation of symptomatic patients for CAD. An imaging modality is commonly used in intermediate-risk patients or those with resting ECG abnormalities that preclude evaluation with the routine treadmill test. In this patient population, nuclear imaging most commonly includes myocardial perfusion SPECT performed to evaluate stress-induced defects and, more recently, gated SPECT to also allow assessment of ventricular function. If the ECG could not be interpreted for purposes of stress testing (e.g., LBBB, LV hypertrophy, digoxin therapy, Wolff-Parkinson-White syndrome), direct nuclear testing is highly effective in prognostic stratification (Chap. 14).

A synthesis of available data reveals that a normal scan is uniformly associated with a <1% annual risk of cardiac death or MI.[8,67,182183-183a] Abnormal scans are associated with an increased risk of cardiac events.[8,67,182] Characteristics of low-, intermediate-, and high-risk scans are listed in Table 40-4.

Normal Perfusion Scan

The event rate associated with a normal or low-risk perfusion scan has been shown by numerous investigators to be <1 percent per year of follow-up and to be isotope-independent-similar to the data from exercise and pharmacologic stress SPECT.[65-67,182] A recent meta-analysis of the prognostic value of a normal stress perfusion scan reveals that the annual risk of MI or cardiac death after a normal perfusion scan is 0.7 percent (95 percent CI 0.5 to 0.9 percent).[183] This uniformly low event rate is critical when applying nuclear test information to risk stratification. In the absence of limiting symptoms in patients who are at low risk of major cardiac events with normal perfusion scans, a conservative approach to posttest patient management would be appropriate. This conservative approach includes medical follow-up for signs of clinical worsening and treatment of cardiac risk factors and related cardiac symptoms (see Chap. 40).

Mild-Risk Perfusion Scans

Multiple randomized trials have demonstrated that revascularization can reduce the risk of cardiac death in selected high-risk subsets. However, since the annual mortality rate of patients undergoing revascularization is at least 1 percent,[177] patients predicted to have a rate of cardiac death of less than 1 percent per year do not warrant revascularization for purposes of improving survival. Recently, Hachamovitch et al. analyzed 5183 patients undergoing stress perfusion SPECT testing.[67] A total of 158 nonfatal MIs and 119 cardiac deaths were observed during follow-up of 646 ± 226 days. The nonfatal MI and cardiac death rates as a function of the summed stress perfusion scores are illustrated in Fig. 16-10. Patients with moderately and severely abnormal scans were at intermediate risk for both cardiac death and MI. Importantly, however, patients with mildly abnormal summed stress scores were at intermediate risk for MI (2.7 percent risk of MI per year of follow-up), but at low risk for subsequent mortality (0.8 percent annual cardiac death rate). Based on the results of this study, patients with a mildly abnormal scan (summed stress score between 4 and 8) could be considered as having "flow-limiting" CAD and intermediate risk of MI but to be at low risk of cardiac death. These patients would be candidates for aggressive risk-factor modification using secondary prevention guidelines. Medical therapy known to reduce a patient's risk of acute ischemic syndromes or cardiac hospitalizations [e.g., statins, acetylsalicylic acid, angiotensin converting enzyme (ACE) inhibitors, etc.] would then be indicated.[184-193]

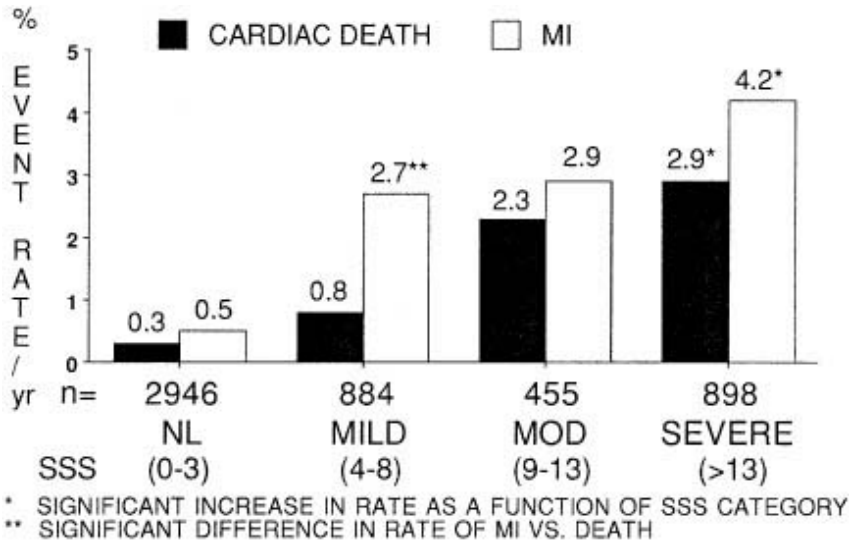

Figure 16-10: Rates of cardiac death (*solid bars*) and myocardial infarction (*open bars*) per year as a function of scan result. The numbers of patients within each scan category are shown underneath each pair of columns. *Statistically significant increase as a function of scan result. **Statistically significant increase in rate of MI versus cardiac death with scan category. NL = normal, MILD = mildly abnormal, MOD = moderately abnormal, SEVERE = severely abnormal. (Reproduced with permission from Hachamovitch et al.[67])

Moderately to Severely Abnormal Perfusion Scans

The relationship of varying extent and severity of perfusion abnormalities with cardiac outcomes has been reported in a variety of patient subsets.[66,67] Although both reversible and fixed stress perfusion defects are predictors of prognosis, those at highest risk of cardiac events include patients with extensive multizone abnormalities. Prognosis is also dependent on both the severity of perfusion defects (a correlate of the magnitude of stenosis) and their extent (a correlate of the amount of myocardium supplied by vessels with significant disease).[67] The combination of both of these factors is predictive of cardiac event rates. That is, as the severity and extent of defects worsens, there is an increase in the rate of major cardiac outcomes (Fig. 16-9). Annual cardiac event rates have been reported to range from 0.3 to 4.2 percent for patients with a normal, mild, moderate, and severely abnormal perfusion scans.[67]

Evidence Supporting Nuclear Imaging for Patients with an Intermediate/Indeterminate Treadmill Test

Several recent reports support nuclear testing in patients with uninterpretable or intermediate exercise ECG response.[66,195] An initial report from Cedars-Sinai (Fig. 16-11) demonstrated that myocardial perfusion SPECT was most effective in risk stratification and governing management of patients with intermediate treadmill test result (i.e., Duke treadmill score, a composite score integrating ST-segment changes, chest pain, and exercise time).[66] Patients with a low Duke treadmill score had a hard event rate of less than 1 percent, perhaps not needing nuclear testing.[194] Those with a high Duke treadmill score (representing less than 5 percent of the population) overall had a high event rate of 7.7 percent over the 18-month follow-up, and could have been directly catheterized. The majority of the patients in the study, however, fell into the category of an intermediate Duke treadmill score with an intermediate event rate of 2.5 percent. Within this category, those patients with a normal scan had a very low event rate and were infrequently catheterized; those with moderately abnormal scans had intermediate event rates and an intermediate rate of catheterization; and those with moderately to severely abnormal scans had higher event rates with higher rates of catheterization. Thus, the nuclear tests were able to stratify patients who could not be differentiated according to risk by Duke treadmill score alone. Similar results were shown by Shaw et al. in a large multicenter publication reporting event rates in 2498 patients with intermediate Duke treadmill scores undergoing stress myocardial perfusion SPECT (Fig. 16-12).[195]

Guidelines for Management of Patients with Stable Chest Pain by SPECT Results

Thus, patients with mildly abnormal scans (summed stress score between 4 and 8) could be considered as having CAD and intermediate risk of MI, but low risk of cardiac death[67] (Fig. 16-13). In the absence of refractory symptoms, these patients would be candidates for aggressive risk-factor modification without catheterization, using secondary prevention guidelines. Unlike the case with revascularization, a variety of medical therapies have been shown by randomized trials to reduce the risk of MI.[184-193] For patients with very abnormal summed stress scores, early revascularization resulted in a favorable survival benefit when compared with medical therapy from a recent observational assessment.[67] O'Keefe et al. reported similar results with medical versus invasive strategy.[196] As noted below, these recommendations for guiding patient management may now be further influenced by combining perfusion and poststress ventricular function variables from gated SPECT (LVEF and systolic volume). It is noteworthy that the above-described application of nuclear testing for risk stratification and prognosis in patients with an intermediate or high probability of CAD has been given class I recommendations in the ACC/AHA/ACP-ASIM guidelines.[8]

It appears that for patients who are appropriately referred to testing in the first place (patients with intermediate to high likelihood of CAD), a normal scan result is associated with a very low risk for approximately 2 years. After that time the risk rises, suggesting that repeat testing after 2 years should be considered in most patients for prognostic purposes.[197]

Current Data May Underestimate the True Prognostic Value of SPECT

The foregoing information provides compelling evidence that ^{99m}Tc sestamibi or ^{201}Tl myocardial perfusion SPECT is effective in the prognostic stratification of patients. Preliminary data have also been reported suggesting that ^{99m}Tc tetrofosmin is effective in risk stratification in chronic CAD.[198] It would appear, however, that current data on risk stratification by myocardial perfusion SPECT may actually underestimate the strength of this modality. In all the data quoted above, patients referred for early revascularization following nuclear testing were excluded (censored) from consideration in the prognostic studies. Although there is a reason for this censorship-namely, that the event rate may have been altered by the revascularization procedure-the exclusion results in the published data's inability to reflect the prognostic information derived from scans performed in the highest risk patient subset. A similar effect occurs to the extent that physicians and patients alter therapy and modify risk factors on the basis of the scan information, thereby probably reducing the event rate that might be observed for a given abnormal scan pattern in a natural history study. In other words, if patients with high-risk abnormalities are treated medically, they are likely to be treated aggressively in a manner that would lower their observed event rates.

Additionally, recent technical advances in the field of myocardial perfusion SPECT have typically not been included in the prognostic assessments. For example, the impact of quantitative analysis on prognosis has not been studied in any detail, although it has been reported to be equal to that of semiquantitative analysis, potentially improving the ability to generalize the findings to less experienced laboratories.[199]

ADDED VALUE OF GATED SPECT

The potent information contained in the ejection fraction assessed from gated SPECT is likely to enhance the prognostic content of myocardial perfusion SPECT. Since gated SPECT has become routine only recently, there are few reports of its incremental value over perfusion in assessing prognosis. Evidence that gated SPECT is likely to add to prognostic assessment is provided by prior ejection fraction data. LV ejection fraction has been shown to risk-stratify suspected disease patients according to their risk of subsequent cardiac death. In a series of reports from the Duke databank using rest and exercise first-pass radionuclide angiography, patients with suspected disease could be risk-stratified using a diagnostic threshold of 50 percent EF.[200-205]

In a preliminary communication, Hachamovitch et al. demonstrated that after risk adjustment for pretest likelihood of CAD and results of perfusion SPECT, EF provided significant incremental value in prediction

of cardiac death or nonfatal myocardial infarction in patients with known or suspected chronic CAD.[206] Sharir et al.,[207] studying 1680 patients, demonstrated that poststress LVEF, as measured by gated SPECT, provided significant information over the extent and severity of perfusion defect as measured by the summed stress score (Fig. 16-14). Furthermore, these authors demonstrated that LV end-systolic volume provided added information over poststress LVEF in prediction of cardiac death (Fig. 16-15). The relatively low cardiac death rate in patients with abnormal perfusion and normal LV function in this study is probably explained by a referral bias in which patients with greatest ischemia by SSS were preferentially sent for early revascularization and thus censored from assessment of the prognostic value of the test. In a subsequent preliminary report of 2600 patients, Sharir et al. have shown that while poststress EF provides incremental information over prescan and perfusion variables in prediction of cardiac death, the perfusion variables are stronger predictors of nonfatal MI. Once prescan and perfusion variables were known, poststress EF did not provide incremental information with respect to the risk of nonfatal MI.[208]

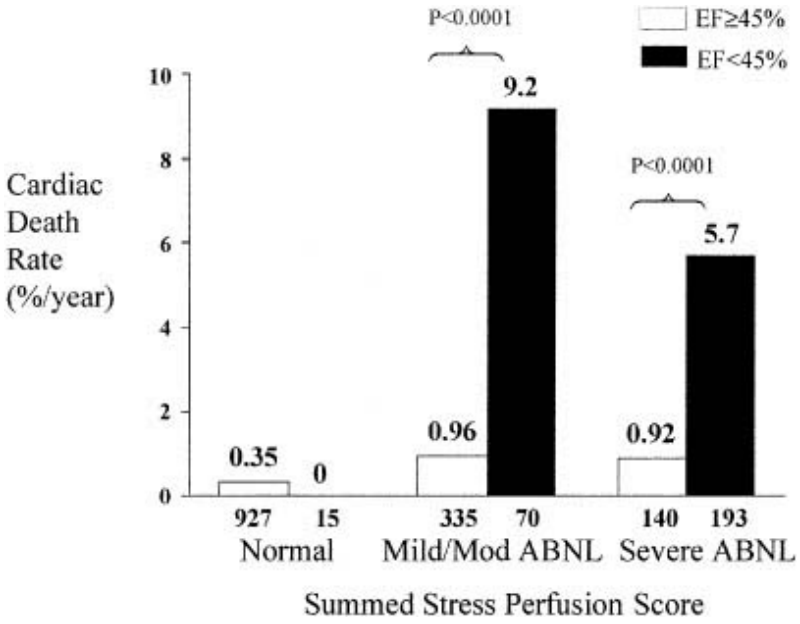

Figure 16-14: Cardiac death (percent per year) as a function of perfusion abnormality and poststress EF by gated SPECT. The number of patients within each category is indicated below ech column. MOD = moderate; ABNL = abnormality. The categories for summed stress score are normal (0-3), mild/moderate (4-13), severe (greater than 13). (Adapted with permission from Sharir et al.[207])

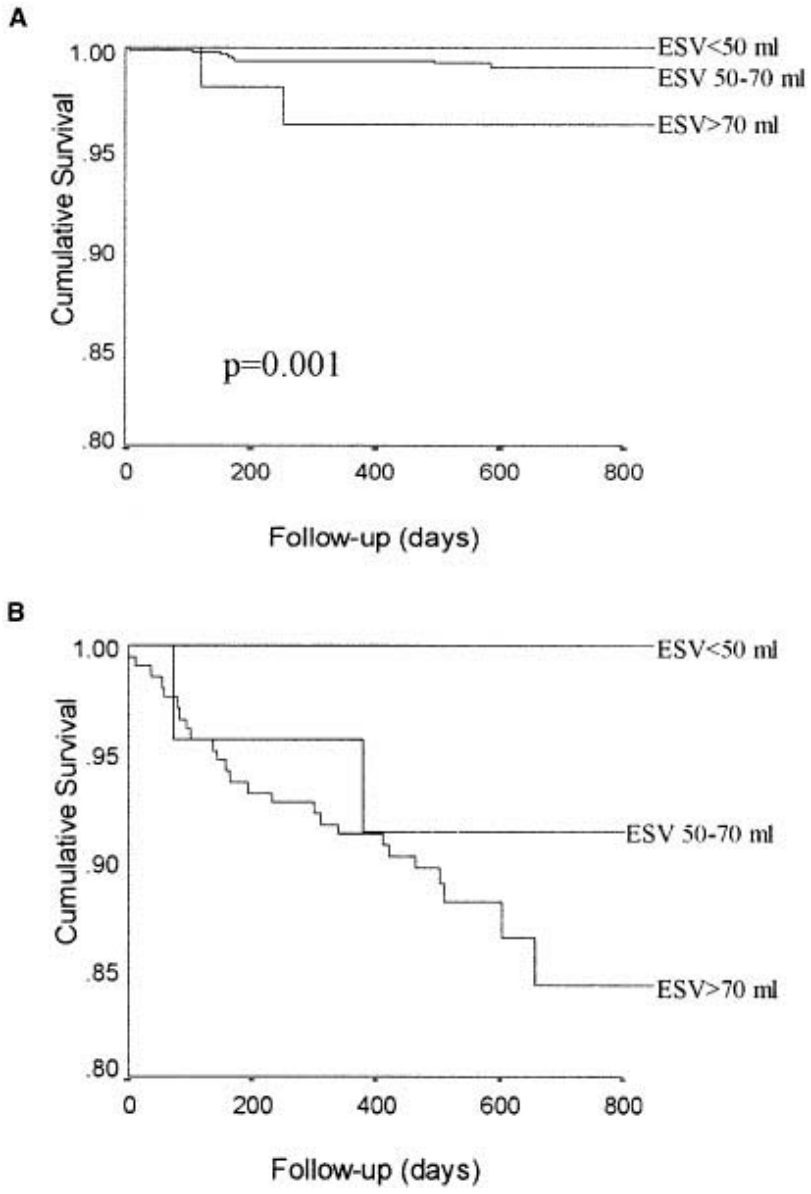

Figure 16-15: Cumulative survival of patients with poststress EF by quantitative gated SPECT greater than or equal to 45 percent (*left*) and less than 45 percent (*right*) stratified by end-systolic volume (ESV), also measured by gated SPECT. (Adapted with permission from Sharir et al.[207])

In the future, complex algorithms will need to be developed that incorporate all of the information from gated SPECT for purposes of guiding patient management. In this regard, it is likely that poststress EF (related predominately to the size of MI) and summed difference score (an expression of the amount of stress-induced ischemia) will provide the greatest complementary information. As an initial approach, Sharir et al. have reported the combination of the ejection fraction and reversible ischemia in the prediction of cardiac events. If poststress EF is less than 30 percent, cardiac death or nonfatal MI rates appear to be high regardless of the amount of ischemia as assessed by the summed difference score. In patients with poststress EF from 30 to 50 percent, mild amounts of ischemia were associated with relatively high cardiac event rates. In patients with ejection fractions of greater than 50 percent, only patients with moderately extensive ischemia were at high risk of cardiac events.

Other important information that can be derived from myocardial perfusion scintigraphy and may be related to risk has not been widely included in the prognostic assessment. Such information includes the assessment of poststress wall motion abnormalities on gated SPECT, a sign of exercise-induced stunning and a marker of severe CAD.[209,210] Additionally, transient ischemic dilation of the LV[89,90] and pulmonary uptake of radioactivity as determined by the measurement of lung/heart ratios of radioactivity[95,211,212] have been shown to be of prognostic importance[96,212,213] but are not yet part of most analyses of myocardial

perfusion SPECT for purposes of risk stratification. Extensive resting defect reversibility rest ^{201}Tl/stress ^{99m}Tc sestamibi, evaluated by 24-h ^{201}Tl imaging, has been shown to be predictive of a higher mortality rate than would be predicted by rest or stress perfusion defect abnormalities alone.[213]

NUCLEAR TESTING AS THE GATEKEEPER TO CARDIAC CATHETERIZATION

The major clinical decisions after nuclear testing include the decision to initiate new medical therapy, to refer a patient to cardiac catheterization, or to provide a conservative, watchful waiting approach to care. Among patients with normal scans, only a small proportion will require cardiac catheterization as a result of clinical symptomatology.[65] In a population of 2203 patients[66] (follow-up, 18 months), by multivariate analysis, the nuclear result was the dominant factor determining the referral to catheterization. This relationship between the results of myocardial perfusion SPECT and catheterization rates have also been reported by Bateman et al.[214] and Nallamothu et al.[215] (Fig. 16-16). Hachamovitch et al.[67] reported that when catheterization was limited to patients with moderate to severe perfusion abnormalities (i.e., summed stress score >8), significant cost savings (17 percent reduction in cardiac catheterization rate) could be achieved for 5183 patients undergoing dual isotope stress SPECT imaging.

In the era of cost containment, it becomes increasingly important to determine whether noninvasive testing can result in substantial cost savings in the diagnosis of CAD. Shaw et al.[216] evaluated a total of 11,249 consecutive stable angina patients, including our own, in a large multicenter study. In a matched cohort study of patients with chronic stable angina comparing direct catherization to myocardial perfusion SPECT with selective catheterization, there was a substantial reduction (31 to 50 percent) in costs for all levels of pretest clinical risk using the myocardial perfusion SPECT plus selective catheterization approach. This cost reduction was seen in both the diagnostic (early) and follow-up (late) costs, which included costs of revascularization (Fig. 16-17). The rates of subsequent nonfatal MI and cardiac death were virtually identical in comparisons of direct catheterization and myocardial perfusion imaging with selective catheterization approaches in all patient risk subsets of stable chestpain patients (Fig. 16-18). What was significantly different was the rate of revascularization, which was reduced by nearly 50 percent in the cohort receiving myocardial perfusion imaging with selective catheterization. In fact, patients with normal perfusion results had a reduced rate of cardiac catheterization as well as a reduced frequency of normal coronary angiographic findings at the time of catheterization.

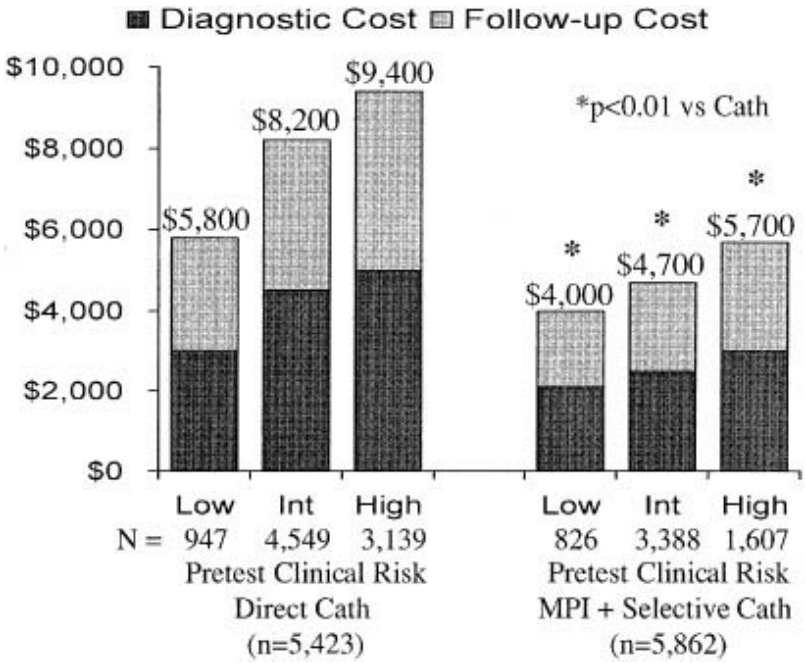

Figure 16-17: Comparative cost between screening strategies employing direct catheterization (Cath) and myocardial perfusion imaging (MPI) with selective Cath. Low, Int, and High represent low-, intermediate-,

and high-risk subsets of the patients with stable angina. Shown are the initial diagnostic costs (*solid bars*) and follow-up costs including costs of revascularization (*gray bars*). A 30 to 41 percent reduction in costs was noted in each category. (Adapted with permission from Shaw et al.[216])

The Role of RNA in Chronic CAD

In chronic CAD, the principal applications of RNA at the present time are at rest. Resting RNA using either equilibrium or first-pass techniques can be effective in defining the presence of a reduced LVEF, and thereby a patient population for whom ACE inhibitors can be effective. Following initial observations in patients with MI,[217] subsequent randomized trials in patients with chronic CAD demonstrated that patients who have reduced LVEF obtain a distinct beneficial effect from the long-term administration of ACE inhibitors. Thus, the available evidence would suggest that patients with suspected acute or chronic CAD are candidates for ACE inhibitor therapy if LVEF is low.[5,8,218,219] The other manner in which patients with CAD can benefit from RNA is with serial assessment of ventricular function. This is important in assessing the efficacy of treatments such as ACE inhibitor therapy and has been used in many trials of a variety of approaches to patients with severe reductions of LVEF. Commonly, a measurement of LVEF by equilibrium RNA is required as a method of documenting severe reduction of LVEF prior to admission into heart failure trials.

For the detection of CAD and management of patients with this condition, exercise RNA continues to play a role in some centers. The most commonly utilized measurement derived from RNA for these decisions is the peak exercise LVEF, whether from first-pass or equilibrium techniques. Many studies have reported the prognostic power of exercise EF as measured by the first-pass technique for subsequent cardiovascular death or nonfatal MI.[200-205,220] Similar reports have emerged from equilibrium RNA.[221-226] In a recent report by Shaw et al., the prognostic value of LV function during exercise was examined in 863 consecutive patients undergoing exercise gated equilibrium RNA within 90 days of catheterization who were followed up for subsequent events, with 99 percent of survivors completing five years of follow-up.[222] In a multivariable analysis, the resting or exercise EF contained significant predictive information ($p < 0.0001$). The rest or exercise EF contained similarly predictive information (exercise EF provided 63 percent of the information of the exercise model and resting EF provided 60 percent). When considering the addtion of the presence and extent of CAD observed at catheterization rest and exercise RNA data still provided significant improvement in the prediction of cardiac death.[222] There was aninverse relationship between peak exercise LVEF and survival.[219,222]

Bonow et al., using equilibrium RNA, documented the complementary role of exercise RNA and coronary angiography.[224] In this study, patients with triple-vessel disease and preserved LVEF at rest could be divided into a group in which mortality was negligible when exercise ejection fraction was normal and a high-risk group with an annual mortality of 7 percent when exercise ejection fraction was <50 percent.[224] Similarly, among patients with one- or two-vessel disease and reduced resting LVEF, those with normal EF responses did not exhibit any mortality over a 5-year follow-up, whereas 26 percent of patients with an abnormal EF response at exercise died in this time frame. Recently, Supino et al.[228] reported a 9-year follow-up of 167 stable patients with triple-vessel disease who had undergone rest and exercise RNA. Change in the LVEF from rest to exercise was the strongest predictor of major cardiac events and also predicted which patients would benefit from CABS. Patients whose LV ejection fraction decreased 8 percent or more with exercise had survival-prolonging benefit from bypass surgery performed less than 1 month after testing. Thus, data from several studies indicate that patients with chronic CAD can be accurately assessed with respect to prognosis by exercise RNA and that such assessment contains information that is complementary to that provided by standard clinical assessment as well as by coronary angiography.

Postcatheterization Patients

Although coronary angiography provides detail of coronary anatomy, the functional implications of coronary stenoses are not always evident from the angiographic data. High-grade stenoses in the absence of collaterals are appropriately considered lesions of clinical significance; frequently, however, lesions of

lesser grade are observed, or the implications of higher-grade lesions may be unclear due to presence of excellent collateral vessels. In these cases, the application of stress nuclear testing can supplement risk assessment for patients on the basis of the extent of stress-induced ischemia. Legrand et al. used exercise planar nuclear procedures to demonstrate that coronary flow reserve was normal in patients with 0 to 25 percent lesions and abnormal in patients with stenoses greater than 75 percent.[229] For patients in those extreme ranges, the data from nuclear testing were concordant with the angiographic results, supporting the concept that when angiographic results are clear, nuclear testing is not needed for functional assessment. In the range of 25 to 75 percent stenosis, however, there was an intermediate coronary flow reserve, unpredictable on the basis of coronary stenosis alone. In those patients, nuclear tests effectively separated the patients with low coronary flow reserve from those with normal coronary flow reserve. Therefore, the data on these patients with intermediate stenoses support the concept that nuclear testing can be useful with respect to functional significance in further assessment of such lesions. Similar data have been observed using sestamibi by Miller et al.[230]

Assessment of Therapy

With the broadening of the application of aggressive medical therapy (as an alternative to revascularization) to various subgroups of patients with CAD, methods for evaluation of the efficacy of medical therapy become of increasing importance. In this regard, it is likely that nuclear cardiology techniques will find an additional area of growth in serial patient assessment. After a patient is defined as being an appropriate candidate for medical therapy, nuclear techniques can be effectively employed to determine whether therapy has been successful or whether the patient's risk status has worsened, thereby requiring a change in therapeutic regimen. A requirement for serial applications is that the nuclear techniques being utilized be highly reproducible and that the degree of change in the assessed variables associated with measurement error be known. In an initial report on 16 patients with stable CAD and reversible perfusion defects, evaluated with quantitative ^{201}Tl myocardial perfusion SPECT following exercise performed on two separate occasions, the quantitative extent of stress perfusion defect showed a concordance coefficient of 0.94 and a mean absolute deviation of 5.1 percent.[231] Very similar findings were reported with serial exercise ^{201}Tl SPECT by Mahmarian et al.,[232] also using a quantitative analysis approach. These investigators demonstrated that a 10 percent change in total perfusion defect size in an individual patient defined the 95 percent confidence interval for exceeding the variability of the method. Although the statistical analyses were different between these studies, the results are very similar. More recently, high repeatability of exercise ^{99m}Tc sestamibi SPECT has been demonstrated using quantitative analysis approaches.[233] The summed stress score has also been shown to be highly reproducible.[233] These data provide the initial validation for the clinical application of nuclear methods for sequential assessment of therapy. In this regard, Mahmarian et al. had previously documented that transdermal nitroglycerin patch therapy reduces the extent of exercise-induced myocardial ischemia.[234] Lewin et al. have demonstrated that a sustained improvement in myocardial perfusion can be achieved with isosorbide mononitrate.[235] Most recently, Dakik and associates have demonstrated that SPECT imaging can be utilized to demonstrate a reduction in perfusion defect size in patients undergoing intensive medical therapy versus coronary angioplasty following acute MI.[236] Sequential assessment of perfusion and function with gated SPECT is also being applied in large randomized trials comparing medical therapy with angioplasty (COURAGE: *C*linical *O*utcomes *U*tilizing *R*evascularization and *A*ggressive *D*rug *E*valuation, see Chap. 10) and in evaluating the response of stress myocardial perfusion to therapy with vascular endothelial growth factor.[237]

Evidence Supporting Nuclear Testing for Patients after Percutaneous Coronary Intervention (PCI)

Nuclear testing is useful following PCI owing to the frequent occurrence of significant restenosis. Although recurrent symptoms often herald the presence of restenosis, clinically significant restenosis is frequently silent.[238] Exercise ^{201}Tl SPECT data obtained by Hecht et al.[239] have demonstrated that nuclear testing is accurate in defining the presence of restenosis. Subsequent work by Hecht et al. demonstrated this accurate detection of restenosis in asymptomatic as well as symptomatic patients.[240] Recent data suggest that nuclear testing remains effective in detecting restenosis for patients undergoing angioplasty with coronary stenting.[241,242] Pfisterer et al., using planar ^{201}Tl scintigraphy, demonstrated that silent and symptomatic ischemia in patients undergoing exercise scintigraphy 6 months following PCI, predicted an increased risk

of recurrent ischemic events.[238] In the angioplasty compared to medical therapy study (ACME), exercise planar ^{201}Tl scintigraphy was performed before and 6 months after randomization to medical therapy or PCI.[243] There was a significantly lower mortality rate in patients with either therapy in whom exercise-induced ischemia by scintigraphy was no longer present in the 6-month study (6 versus 18 percent, normalizing versus those nonnormalizing, $p = 0.02$). A preliminary report by Lewin et al. from our institution[244] has demonstrated that event rates are strongly related to the summed stress score following PCI, with a pattern very similar to that observed in patients with no known CAD; i.e., patients with mildly abnormal scans appeared to have increased rates of nonfatal MI but low rates of cardiac death, whereas the rates of both of these events were in the intermediate to high range in patients with more abnormal scans. This preliminary report also documented that there was an appropriate use of nuclear scan in guiding decisions for catheterization, with low early catheterization rates following nuclear scanning in patients with little evidence of ischemia.[244] A review of the use of nuclear testing after PCI has been published.[245,246]

The general recommended approach of nuclear testing in the post-PCI patient would therefore be as follows: in patients with single vessel CAD and angina or interpretable ST segment depression pre-PCI, post-PCI assessment could be performed on a clinical or standard exercise testing basis. In other patients, when symptoms develop, nuclear testing can be helpful in defining the culprit vessel and assessing the extent of ischemic abnormality. For patients with no symptoms, nuclear testing between 3 and 6 months after angioplasty has been recommended. Whenever moderate to severe ischemia is found by nuclear testing, consideration should be given to repeat catheterization.

Evidence Supporting Nuclear Testing after Coronary Bypass Surgery

Nuclear testing has become central in the assessment of the post-CABS patient. It is known that 75 percent of vein grafts can be expected to be occluded or severely stenosed by 10 years after surgery, particularly in patients undergoing saphenous vein CABS.[247,248] Due to an increased incidence of graft closure, a 5-year cutoff point to evaluate the postbypass patient may be considered appropriate.[246,249-251] Kaplan-Meier survival and MI-free survival for post-CABS patients undergoing exercise ^{201}Tl imaging from a recent study is depicted in Fig. 16-19.[250] This study also demonstrated that exercise ^{201}Tl SPECT is predictive of hard cardiac events even in the asymptomatic postbypass patient.[250] Moreover, we have reported findings using ^{99m}Tc sestamibi, illustrating that nuclear stress testing is effective in predicting subsequent events and determining need for catheterization in the post-CABS population.[251] In general, the recommendations for the post-CABS patient are that when symptoms develop, SPECT imaging is useful in determining the presence and extent of CAD. In the asymptomatic patient, SPECT perfusion imaging should be considered in the 5 to 7 years postoperative time frame. Whenever moderate to severe ischemia is present, consideration of repeat catheterization arises.[246,251]

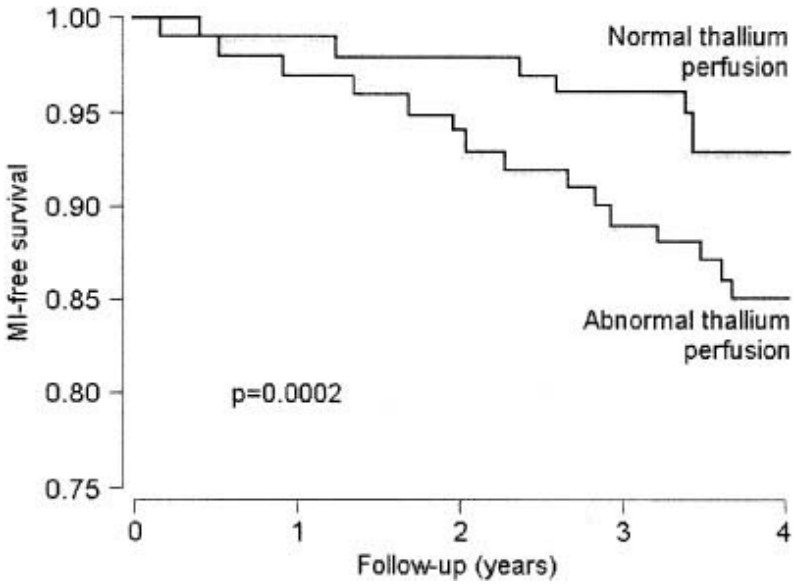

Figure 16-19: Kaplan-Meier plot for post-CABS patients associates reversible thallium defects with MI-free survival. Patients with reversible thallium perfusion defects had higher event rates. (From Lauer et al.,[250] with permission.)

Nuclear Testing for Risk Stratification in Special Populations

One of the principal strengths of nuclear cardiology is that a very large database has been accumulated, far larger than for any other noninvasive modality, documenting clear effectiveness of myocardial perfusion SPECT in risk stratification of appropriately selected patients with suspected chronic CAD. These large databases have now made it possible to evaluate risk in subsets of chronic CAD. Several of these applications are separately described below.

DIABETES

Myocardial perfusion SPECT has now been reported to be highly effective in risk stratification of patients with diabetes.[252,253] For example, in a study of 1271 patients with diabetes and 5862 without, Kang et al. demonstrated that a normal scan was similarly predictive of low cardiac event rates in both groups. Risk-adjusted event-free survival in patients with mildly and moderately abnormal scans, as defined by the SSS, was worse in patients with diabetes than in those without[252] (Fig. 16-20). A recent multicenter series reported that the extent of perfusion deficits and cardiac symptoms is more predictive of cardiac mortality in diabetics.[254] In a preliminary report, Lewin et al. have shown that in patients without diabetes, those with a moderately abnormal SSS had a cardiac mortality rate similar to that of patients with a mildly abnormal or normal SSS, whereas diabetics with moderately abnormal SSS had increased mortality rates. These findings suggest that in nondiabetic patients with known or suspected chronic CAD, the group with relatively low risk for cardiac death may be extended beyond that observed in general populations, potentially increasing the group of patients appropriately defined for noninvasive strategies (see also Chap. 78).[253]

LEFT BUNDLE-BRANCH BLOCK

Myocardial perfusion SPECT is highly useful for risk stratification in patients with LBBB. In a long-term follow-up of 245 patients with LBBB, Wagdy et al.[255] demonstrated that myocardial perfusion SPECT with vasodilator stress was an excellent predictor of cardiac events, with high risk being defined by a large, severe, fixed defect, a large reversible defect, cardiac enlargement and increased pulmonary uptake, or low resting EF. The 3-year survival was 57 percent in the high-risk group, versus 87 percent in the low-risk group ($p < 0.0001$). Similar findings have been reported by Nallamothu et al. in 293 medically treated patients with LBBB followed for 33 months.[256]

GENDER-BASED DIFFERENCES IN THE PROGNOSTIC VALUE OF PERFUSION IMAGING

For women, CAD incidence lags 10 years behind that of men. With the onset of menopause, the prevalence of CAD increases, achieving equivalence in disease prevalence at age 70 years.[257] In nondiabetic women before the age of 45 years, the likelihood of CAD is exceedingly low. In addition to differences in disease prevalence, a number of studies of small series of female patients have reported technical limitations and diminished accuracy in exercise treadmill testing, ^{201}Tl imaging, and in echocardiography.[174,258,259] With a perception on the part of clinicians of diminished accuracy of test results, reports have described sex-related bias in referral to cardiac catheterization after noninvasive testing.[260,261] When ^{201}Tl is used as the radiopharmaceutical in women, false-positive test results may be due to soft-tissue (breast) attenuation in the anterior and anterolateral segments.[174,262] In a small randomized trial comparing the diagnostic accuracy of ^{201}Tl with that of ^{99m}Tc sestamibi, test specificity was 67 versus 92 percent, respectively,[174] suggesting that gated SPECT with a ^{99m}Tc perfusion agent may be the preferred form of SPECT in women. Reports from large female populations indicate that for both ^{99m}Tc sestamibi (rest and exercise) and dual-isotope myocardial perfusion SPECT, there is an added incremental prognostic value of myocardial perfusion data as compared to clinical and exercise variables in women.[66,263,264] From a recent multicenter registry of 3402 women with stable chest pain symptoms, risk stratification was similar by gender (84 percent underwent ^{99m}Tc sestamibi SPECT).[264] By the number of vascular territories with ischemia, 3-year survival ranged from 98.5 to 85 percent for none to three vascular territories abnormal by SPECT.[264] Amanullah and colleagues reported on 130 women undergoing adenosine ^{99m}Tc sestamibi SPECT, revealing that a moderately to severely abnormal perfusion scan (i.e., SSS >8) was associated with a sensitivity and specificity of 91 and 70 percent for the detection of multivessel CAD.[265]

PROGNOSTIC VALUE OF PERFUSION IMAGING IN THE ELDERLY

Patients over age 65 years have a higher disease prevalence and risk of major cardiac events as well as more frequent comorbid diseases. Exercise duration, heart rate, and total workload decrease with increasing age of our screened population. The prognostic value of perfusion scintigraphy has been reported in several recent series.[266,267] In an ambulatory population over age 70 years, abnormal exercise thallium imaging was accurate in identifying a high-risk population.[266] In a consecutive series of elderly patients, those with evidence of reversibility and a fixed defect were at highest risk of 3-year cardiac death or MI.[266] Cardiac death or MI at 2 years after testing occurred in almost half of elderly patients with a high-risk perfusion scan. Similarly, Hachamovitch et al. found that exercise dual-isotope SPECT was able to risk-stratify patients aged 65 and older successfully-patients with normal scans had less than a 1 percent event rate over the first year of follow-up.[266a] In addition, the perfusion scan added incremental prognostic information over nonnuclear variables, and the addition of myocardial perfusion imaging to test strategies reduced the overall cost of testing per patient. In an elderly cohort of patients 80 years of age and older, Amanullah et al. found that dual-isotope adenosine myocardial perfusion SPECT was able to risk-stratify patients and yield incremental prognostic value over clinical variables.[267] In general, for the elderly as well as for those patients with functional limitations, similar risk assessment is possible with exercise and pharmacologic stress SPECT.[267a] Owing to the higher mortality rate of the general population in this age group, upward adjustment of the "intermediate-risk" group to levels higher than the 1 to 3 percent used for general populations may be appropriate. In this regard, Hayes et al. evaluated 1848 consecutive patients ≥80 years of age undergoing rest ^{201}Tl/stress ^{99m}Tc sestamibi dual isotope myocardial perfusion SPECT. Annualized cardiac death rates ranged from 1.9 percent in 722 patients with normal summed stress score to 9.3 percent in 401 patients with severely abnormal summed stress score (SSS ≥13).[267b]

PREOPERATIVE RISK ASSESSMENT IN NONCARDIAC SURGERY PATIENTS

Preoperative risk assessment is a common reason for cardiology consultation. Although clinical history, physical examination, and the resting ECG are highly useful, in many clinical settings these tools are inadequate. In contrast, assessment of LV function and/or jeopardized myocardium provides an accurate method to complement clinical assessment. Patients with peripheral vascular disease are at increased risk of having CAD. A large coronary angiographic study of asymptomatic patients revealed that 44 percent of patients undergoing peripheral vascular surgery have angiographically significant CAD.[268] It has furthermore been shown that peripheral vascular surgery, with its associated marked hemodynamic stresses,

carries at least a moderate risk of perioperative events for patients with known CAD. Since these patients frequently cannot exercise, they are ideal candidates for the utilization of vasodilator stress in conjunction with myocardial perfusion imaging, and a large body of literature exists documenting the effectiveness of nuclear stress testing in this context. Although some have advocated the routine application of stress nuclear testing in this patient group, recent guidelines have been developed suggesting that nuclear testing is best reserved for patients with an intermediate risk of a cardiac event at the time of the procedure. Data supporting this approach were first presented by Eagle et al.[269] and then expanded in 1996 to include 3368 operations.[270] A metanalysis of the comparative value of the vasodilator myocardial perfusion scintigraphy and dobutamine echocardiography in risk stratification before vascular surgery has been published.[271] Together with other data sets, these data led to the guidelines for perioperative cardiovascular evaluation, published by the ACC/AHA task force (see Chap. 74). From these guidelines, candidates for vasodilator myocardial perfusion SPECT (or dobutamine echo) include patients with two of three high-risk factors (Table 16-4). In general, this includes patients who are at intermediate risk for cardiac events.

Table 16-4: Shortcut to Noninvasive Testing Based on Guidelines*†

- Intermediate clinical predictors are present (Canadian class 1 or 2 angina, prior myocardial infarction based on history or pathologic Q waves, compensated or prior CHF, or diabetes)
- Poor functional capacity (<4 METS)
- High surgical risk procedure (emergency major operations; aortic repair or peripheral vascular; prolonged surgical procedures with large fluid shifts and or blood loss)

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*Based on Leppo JA, American Society of Nuclear Cardiology, Tutorial in Nuclear Cardiology, Sept. 30-Oct. 3, Washington, D.C., 1999.†Noninvasive testing is useful in preoperative patients if any two factors are present.

Assessment of Myocardial Viability

Mortality associated with LV dysfunction in the setting of severe CAD is quite high.[272-275] Patients with LV dysfunction who undergo CABS receive a greater proportional risk reduction compared to patients with preserved function.[8] The clinical setting in which viability assessment is most commonly used is the evaluation of patients with poor LV function, when the likelihood of improvement after revascularization is being considered. This information can be useful in determining the appropriateness of medical management, revascularization, or cardiac transplantation. Excellent reviews of radionuclide techniques for assessment of myocardial viability have recently been provided by Bonow[272,273] and Dilsizian.[274]

As early as 1989, positron emission tomographic (PET) imaging was studied to examine the differential benefit of identifying viable from nonviable myocardium (see Chap. 19). Improved regional function postsurgery would occur more often in the setting of some modicum of myocardial viability. In addition to PET imaging, various protocols utilizing combinations of rest, redistribution, and reinjection thallium imaging have been devised, validated, and compared to assess the presence of hibernating myocardium optimally. When reversibility of defects is noted on stress/rest or stress/redistribution studies, the likelihood of postrevascularization improvement of regions with abnormal ventricular function is high. The likelihood of improvement is also high for patients in whom reversibility is noted on rest/redistribution myocardial perfusion scintigraphy. Improvement would also be expected in patients with very severe angiographic CAD (virtually certain to cause severe flow restriction with stress) if normal, mildly reduced, or even moderately reduced tracer uptake is noted on rest or redistribution scintigraphy, since it could be predicted that such patients would show clear reversibility if stress-rest or stress-redistribution imaging were feasible. This inference is commonly made for patients with known coronary anatomy, unstable angina, and physician reluctance to perform stress imaging. When severe reduction in uptake of radioactivity is noted on redistribution ^{201}Tl imaging, the likelihood of improvement in regional ventricular function is low.

When a moderate defect is noted at rest (or redistribution), the likelihood of improvement is intermediate.

Many studies have demonstrated thallium protocols using either rest-redistribution or stress-redistribution-reinjection to be nearly as accurate as PET in assessing myocardial viability.[274] Recent studies have also examined the predictive value of ^{99m}Tc sestamibi for functional recovery post-CABS. Summary data of the positive and negative predictive value of ^{201}Tl and ^{99m}Tc sestamibi in estimating functional recovery following CABS (using 2- to 3-month post-RNA or echocardiographic imaging) have shown that the positive predictive value (either weighted average or pooled) ranged from 69 to 79 percent and was similar by radioisotope. The negative predictive value (either by pooled or weighted average) ranged from 72 to 85 percent and was also similar by radioisotope. These accuracy statistics are dependent upon underlying risk (with higher predictive values noted for higher-risk populations); average patient samples were 25 to 30 for ^{201}Tl and ^{99m}Tc sestamibi.[272-275]

Currently there is controversy as to whether resting myocardial perfusion scintigraphy with ^{99m}Tc sestamibi (particularly if augmented by preinjection administration of nitroglycerin)[85,86] is as effective as redistribution ^{201}Tl scintigraphy in assessing myocardial viability. Without nitroglycerin, however, in principle it would be expected that rest/redistribution ^{201}Tl myocardial perfusion scintigraphy would be a more accurate approach than ^{99m}Tc sestamibi imaging for detection of viability in patients with severe hibernation (severe reduction in resting blood flood, downregulation of ventricular function, but preservation of the ability to improve ventricular function with restoration of blood flow).[277,278] Of note, it has been suggested for both ^{99m}Tc sestamibi[88] and ^{99m}Tc tetrofosmin[24] that an increase in extraction fraction at low flow may make the resting study with the ^{99m}Tc agent more like a redistribution thallium than a resting thallium study, potentially explaining the observed excellent ability of these tracers, even without nitroglycerin administration, to predict postrevascularization improvement in ventricular function.

Several technical improvements could improve the use of myocardial perfusion SPECT in the assessment of myocardial viability. As mentioned above for ^{99m}Tc sestamibi and tetrofosmin, the possibility of further enhancing the viability information of reinjection ^{201}Tl through the administration of nitroglycerin has been described.[38,276] Furthermore, in many of the studies assessing viability, a single cutoff point for myocardial counts in the region in question compared to the maximal observed value is employed: e.g., 50 or 60 percent of the maximal counts.[87,88] Of note, however, is the fact that the inferior wall in non-attenuation-corrected SPECT studies has far fewer counts than the other myocardial regions. This observation would suggest that the ability to predict viability for myocardial perfusion SPECT would be enhanced by approaches that take into account the number of standard deviations below normal in a given region rather than a single percentage of maximal count uptake. Finally, the use of combined rest-redistributioned ^{201}Tl/stress ^{99m}Tc sestamibi or tetrofosmin dual isotope SPECT may be particularly effective in assessing myocardial viability, since the protocol can combine what may be the optimal rest SPECT protocol (rest and redistribution ^{201}Tl) with a stress imaging assessment.[56,213]

Table 16-5 illustrates conceptually the relationship between several different myocardial states associated with chronic CAD and the patterns that might be observed on myocardial perfusion SPECT. In the presence of myocardial hibernation, resting blood flow would be expected to be mildly to even severely reduced, with corresponding reductions in resting ^{201}Tl or ^{99m}Tc perfusion agent uptake.[277,278] With ^{201}Tl, the equilibrium uptake of radioactivity would also be expected to be normal or potentially slightly reduced if true equilibrium was not achieved or if prolonged hibernation had resulted in cellular degeneration.[278] Thus these patients often demonstrate resting reversibility of perfusion defects.[213] For the ^{99m}Tc agents, resting perfusion (and thus viability assessment) can be enhanced by nitroglycerin administration prior to the resting injection of the tracer.[85,86] If patients with hibernation are subjected to stress, an even greater degree of reduction in flow would be expected, causing a greater degree of defect reversibility in most cases. The likelihood of improvement with revascularization is great in these patients.

Table 16-5: Scintigraphic and Clinical Characteristics of Hypocontractile Regions According to Their Viability Status

Viability Status	Rest	Redistribution (Tl-201)	Rest Reversibility	Stress/Rest/RI Reversibility	Likelihood of Improvement with Revasc
Q MI	↓↓↓	↓↓↓	-	-	-
Non Q MI	↓-↓↓	↓-↓↓	-	±*	±*
Hibernation	↓ to ↓↓↓	→ to ↓	+	+++	+++
Stunning (with exercise)	→	→	→	+++	+++
Remodeled	→	→	→	→	→
Nonischemic CM with incidental CAD	→	→	→	→	→

*Depends on stenosis of IRA.
ABBREVIATIONS: Q = Q wave; MI = myocardial infarction; CM = cardiomyopathy; RI = reinjection; Revasc = revascularization.

Stunning occurs in the setting of a prolonged episode of severe ischemia[279] with subsequent restoration of flow. It is usually associated with acute CAD and is most often seen in the setting of aborted MI (either by thrombolytic therapy, direct revascularization, or spontaneous thrombolysis). Stunning can also occur in the setting of chronic CAD, such as following prolonged exercise in patients with high-grade coronary lesions.[209,280] In these circumstances, resting myocardial perfusion scintigraphy is generally normal or minimally reduced, reflecting the return of normal or nearly normal perfusion. Equilibrium ^{201}Tl concentration would be normal, and there would be no evidence of resting reversibility. However, patients with exercise-induced stunning would be expected to demonstrate marked perfusion defects on the stress study.[209] In these patients, the likelihood of improvement in exercise flow and function, as well as postexercise function following revascularization, would be high. It should be noted that stunning observed in conjunction with stress is not generally associated with an abnormality of true resting ventricular function but is discovered as a consequence of measuring ventricular function early after using stress testing.[209,280] For this type of stunning abnormality to improve, revascularization is usually necessary; in contrast, improvement in ventricular function occurs spontaneously over time with the stunning associated with an aborted acute coronary syndrome.

A great deal of attention has recently been placed on the remodeled LV, usually occurring as a consequence of extensive prior MI.[281,282] In this circumstance, LV function can become diffusely abnormal, even in areas remote from the infarct zone. The area of abnormal contraction associated with remodeling in these patients would be expected to have normal resting ^{99m}Tc perfusion tracer or ^{201}Tl uptake, normal equilibrium ^{201}Tl uptake, no evidence of reversibility on either stress or rest imaging, and little likelihood of improvement following revascularization. Patients with remodeled LVs may have very profoundly reduced ventricular function. Given the differential response to revascularization of the remodeled LV and the hibernating LV, this ability of nuclear scanning to differentiate between them becomes important.

Nuclear Cardiology Applications Unique to RNA

ASSESSMENT OF ANTHRACYCLINE CARDIOTOXICITY

RNA, using either the equilibrium or first-pass approach has become the method of choice for evaluating the effects of doxorubicin and other anthracyclines on LV function in patients with suspected

cardiotoxicity. In an early report, Alexander and colleagues demonstrated that patients with normal LVEF that had not fallen by more than 15 points did not develop cardiotoxicity with continued doxorubicin therapy; however, once EF fell below 45 percent or by more than 15 percent, continued doxorubicin therapy was commonly associated with irreversible cardiac failure.[283] In a subsequent report of a large high-risk population from the same group, guidelines were established for the use of continued doxorubicin therapy.[284] These recommendations are summarized in Table 16-6. In a group of 70 high-risk patients in whom these guidelines were strictly followed, 2.9 percent developed subsequent congestive heart failure (CHF) that responded to therapy. Of 212 high-risk patients in whom the recommendations were not closely followed, 21 percent developed CHF ($p < .001$ versus the strict-guideline group). The CHF in the majority of these patients was considered moderate to severe. Similar findings have been reported by other groups.[285,286]

Table 16-6: Guidelines for Monitoring Patients Receiving Doxorubicin*

Perform baseline radionuclide angiocardiography at rest for calculation of left ventricular ejection fraction (LVEF) prior to administration of 100 mg/m^2 doxorubicin. Subsequent studies are performed at least three weeks after the indicated total cumulative doses have been given, before consideration of the next dose.
PATIENTS WITH NORMAL BASELINE LVEF (≥50%)
Perform the second study after 250 to 300 mg/m^2
Repeat study after 400 mg/m^2 in patients with known heart disease, radiation exposure, abnormal electrocardiographic results, or cyclophosphamide therapy; or after 450 mg/m^2 in the absence of any of these risk factors.
Perform sequential studies thereafter prior to each dose.
Discontinue doxorubicin therapy once functional criteria for cardiotoxicity develop, i.e., absolute decrease in LVEF ≥10% (EF units)
PATIENTS WITH ABNORMAL BASELINE LVEF (≤50%)
Doxorubicin therapy should not be initiated with baseline LVEF ≤30%.
In patients with LVEF >30% and <50%, sequential studies should be obtained prior to each dose.
Discontinue doxorubicin with cardiotoxicity: absolute decrease in LVEF ≥10% (EF units) and/or final LVEF ≥30%.

*From Ref. [284].

DETERMINING THE TIME FOR VALVE REPLACEMENT IN AORTIC REGURGITATION

It has been demonstrated that resting LVEF, as measured by equilibrium RVA, provides an excellent method for the sequential follow-up of asymptomatic patients with aortic regurgitation. For patients with chronic aortic regurgitation, a fall in LVEF has been shown to be strongly predictive of the development of subsequent progressive severe deterioration in LV function.[287,288] These investigators have suggested that asymptomatic patients with severe aortic regurgitation whose EFs at rest fall below normal should be considered for elective valve replacement. Using a combination of rest/exercise RNA and rest/echo, a recent study by Borer et al.[289] demonstrated in asymptomatic patients with severe aortic insufficiency that if a change in LVEF from rest to exercise, normalized for the change in end-systolic stress from rest to exercise, is abnormal, even patients with normal resting LVEF and no symptoms were likely to develop future complications. Cheitlin[290] suggested, however, that the more commonly available, less complex periodic assessment of rest LVEF or end-systolic volume may be as good an approach for determining the time for operative intervention in this condition.

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Chapter 16: NUCLEAR CARDIOLOGY

ACUTE CORONARY ISCHEMIC SYNDROMES

Acute coronary ischemic syndromes have been categorized as acute transmural (Q) MI, nontransmural (non-Q) MI, and unstable angina pectoris. More recently, unstable angina and non-ST-segment elevation MI have been linked since flow preservation strategies and treatment are similar in these conditions (see Chap. 41). In general, all of these syndromes have the underlying pathophysiology of the presence of severe obstruction or closure of a coronary artery secondary to acute thrombus formation or spasm in a segment of an artery. Because of this relationship to closure of a vessel, myocardial perfusion/function scintigraphy is an effective means of detecting patients with acute ischemic syndromes. Acute coronary syndromes represent a wide array of clinical presentations from worsening chest pain in patients seen in the outpatient clinic to acute MI. Annually, there are a total of 1.5 million admissions to coronary care units in the United States, with half of these patients ruling in for ischemia or MI (Chaps. 41 and 42). A number of guidelines have described the advantages of postinfarction stratification afforded by nuclear testing.[218,219,291] While less dramatic than with chronic CAD, there has been continued growth in the application of nuclear cardiology to the assessment of patients with acute ischemic syndromes.

Evaluation of Acute Chest Pain

Although the diagnosis of acute MI is frequently straightforward, in many patients it is not. For example, the ECG is diagnostic in only two-thirds of patients with MI at the time of their initial presentation to the emergency department (ED). In non-Q-wave MI, and particularly in left circumflex MI, the ECG is frequently normal.[292,293] Furthermore, the ECG is frequently nondiagnostic even when abnormal (e.g., with LBBB, nonspecific ST- or T-wave changes, pacemakers).[294] From the emergency physician's standpoint, the problem of missed MIs in the ED is of particular importance. It is has been estimated that up to 50,000 patients per year in the United States have MIs that are missed, representing approximately 4 percent of all patients with MIs who present to the ED.[218,219,291,295] Approximately 25 to 40 percent of malpractice claims against emergency physicians arise from patients with missed MI.[295] It has also been demonstrated that patients discharged from the ED with missed MIs have a substantially higher mortality rate than patients in whom MI is appropriately detected and results in admission.[294,296] Therefore, with respect to patients with normal or nondiagnostic initial ECGs on presentation to the ED, an important clinical problem is how to distinguish those with acute coronary syndromes, who may benefit from early intervention, from those who may require less intensive care, can be discharged, or undergo immediate stress testing (see Chaps. 41 and 42).

For patients without ST-segment elevation, clinical management is not defined. The reasons are multifold, including the fact that only a small portion of patients presenting with an acute onset of chest pain symptoms are eligible for thrombolysis (i.e., 9 to 39 percent).[218,291] Of the remaining cohort of chest pain patients presenting to the ED, the outcome of patients with only minor ST-T-wave changes is variable. Evidence from the recent GUSTO IIa trial revealed that the outcome of patients with presenting ST-segment depression was 6.8 percent for 30-day mortality and 12.4 percent for death or MI at 1 year. Of the non-ST-segment elevation candidates, 28 percent have three-vessel CAD and half have an MI during the index hospitalization. As such, in nonthrombolytic candidates the risk of CAD and major cardiac complications varies and may be

high in a large proportion of patients.[297]

Because many of these patients are subsequently ruled out for MI, chest pain units have been instituted for the acute evaluation of chest pain patients presenting to the ED.[298,299] The chest pain units provide an integrated approach to the diagnosis and treatment of patients at risk for CAD. This includes laboratory tests, cardiac imaging, and early and aggressive treatment vis-à-vis a dedicated staff of nurses and physicians. A number of reports have documented the economic savings that have been realized by the introduction of these dedicated facilities.[298,299] The ROMIO study randomized 100 low-risk patients to an ED-based rapid-rule-out protocol or to routine hospital care.[299] The results revealed that the hospital stay was shorter and charges were lower with the rapid protocol than with routine care ($p = 0.001$). Among patients in whom ischemia was ruled out, those assigned to the rapid protocol had a shorter hospital stay (median 11.9 versus 22.8 h, $p = 0.0001$) and lower initial ($893 versus $1349, $p = 0.0001$) and 30-day ($898 versus $1522, $p = 0.0001$) hospital charges than did patients given routine care.

^{99m}Tc sestamibi or tetrofosmin SPECT, with injection during chest pain, provides an excellent opportunity to reduce clinical indecision in the acute evaluation of chest pain[300-302] (Fig. 16-21). Investigations have demonstrated a role for myocardial perfusion imaging in the initial evaluation of these patients. Hilton and colleagues performed acute sestamibi imaging for patients presenting to their ED with typical angina and normal or nondiagnostic ECGS.[300] Only one patient of 70 in this cohort with a normal scan experienced a subsequent cardiac event on follow-up (cardiac death, MI, PCI, CABS, thrombolysis). Patients with equivocal or abnormal scans had event rates of 13 and 71 percent, respectively. The nuclear scan provided incremental risk stratification over clinical and ECG data. Based on these data, nuclear imaging can be used to assist in the risk stratification of patients with ongoing symptoms whose diagnosis cannot be clearly determined in an ED setting. In patients with ongoing symptoms, a normal perfusion scan can identify patients who can either be discharged early or admitted to non-intensive-care beds.

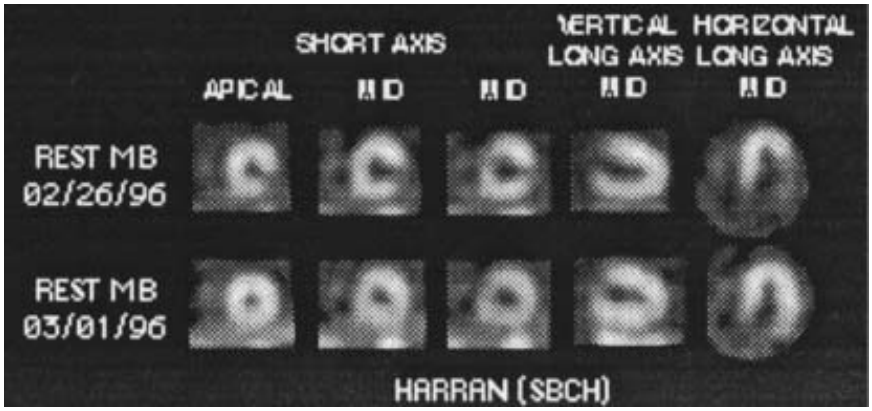

Figure 16-21: Resting sestamibi (MB) injected during chest pain in emergency department (*top*) and 3 days post-PCI of the left circumflex coronary artery (LCX) (*bottom*) in patient with no EGG or enzyme abnormalities. Clear evidence of extensive myocardial salvage in LCX territory is shown.

A number of larger series have been reported.[303-307] Tatum et al.[303] developed a triage evaluation strategy in which patients with a very high, high, or very low probability of an acute ischemic syndrome did not undergo nuclear testing, but those with a moderate to low probability of an acute ischemic syndrome did. It was found that 338 of 438 patients had normal studies and 100 patients had abnormal studies. Subsequent deaths and MIs over the following year were found to

occur only in the patients with abnormal ^{99m}Tc sestamibi studies, while none of the 338 patients with normal ^{99m}Tc sestamibi studies developed subsequent MI (these studies included assessment of perfusion as well as myocardial function using gated SPECT). This group subsequently demonstrated, in a study of 620 patients with acute chest pain, that early myocardial perfusion SPECT and serial cardiac troponin I measurements have comparable sensitivies for identifying MI. This study also demonstrated that the two tests provide complementary information for identifying patients at risk for acute coronary syndromes.[304] In another report of 218 patients, this group demonstrated that myocardial perfusion scintigraphy is useful in assessing chest pain associated with cocaine use, with abnormal studies being very infrequent in this population.[305] A multicenter series employing ^{99m}Tc tetrofosmin of 357 patients presenting to six centers with symptoms suggestive of myocardial ischemia was recently published.[306] This study examined the predictive value of rest ^{99m}Tc tetrofosmin SPECT at the time of ED admission for patients with a nondiagnostic ECG upon presentation. Of this study cohort, 20 patients had an acute MI, with a test sensitivity of 90 percent and a specificity of 60 percent. Most of the missed MIs were small inferior wall MIs mistaken as attenuation artifacts. The slightly lower sensitivity for acute MI in this series might be attributed to not using gated SPECT, which helps distinguish true resting perfusion defect from attentuation artifacts in these patients. In the analysis of these authors, using a normal SPECT image to decide not to admit a patient to the hospital would result in a 57 percent reduction in hospital admissions with a mean cost savings per patient of $4258.

A synthesis of published reports on acute use of myocardial perfusion imaging reveals an average sensitivity and specificity of 98 and 69 percent, respectively, for patients who are admitted with an abnormal perfusion scan.[302,303,306-308] A predictive model of index MI or revascularization based on multivariable risk-adjusted logistic regression has been reported in a cohort of 532 patients with acute chest pain revealed the following predictors: abnormal ^{99m}Tc sestamibi scan [odds ratio (OR) = 14-fold], diabetes (OR = 2.8-fold), typical angina (OR = 2.1-fold), and male gender (OR = twofold).[307] A very recent randomized clinical trial in 2300 patients tested the incremental value of historical, ECG, and sestamibi parameters in the decision to admit a patient presenting with acute chest pain (multicenter trial sponsored by the Agency for Healthcare Policy Research).[309] This trial randomized patients without a prior CAD history but with symptoms suggestive of acute ischemia, and a nondiagnostic ECG, to a nuclear scan versus no scan strategy. This study compared the ability of the scan to correctly classify patients who should be admitted as well as the costs associated with each comparative management strategy and demonstrated a 20 percent reduction in hospital admissions of patients subsequently shown not to have acute ischemic syndromes, no change in admission rates of patients with acute ischemic syndromes, and modest cost savings associated with nuclear scanning. Among 2127 patients whose final confirmed diagnosis was not acute cardiac ischemia, 52 percent of the patients randomized to the usual-care strategy were admitted to hospital or observation in what could be classified in retrospect as unnecessary admissions. Among the patients randomized to have a sestamibi scan as part of their evaluation strategy, however, the unnecessary admission rate was reduced to 42 percent. These data suggest that incorporating perfusion imaging into an ED strategy for patients with chest pain and a nondiagnostic ECG can improve the effectiveness of ED triage. Furthermore, projecting data on total direct costs from one site to the entire trial, we estimate that the added cost of the perfusion scan was more than overridden by the savings accrued from the reduction in unnecessary admissions in patients without acute ischemia.

Guidelines for SPECT Imaging in the ED

Several considerations are important for the most effective application of acute nuclear imaging. If the patient has had prior MI, the studies are generally not useful. The principal exception to this rule occurs in patients who had previously undergone myocardial perfusion scintigraphy, the results of which are immediately available to compare with the results of the new study performed

during acute chest pain. Also, combined assessment of perfusion and function should be routinely performed in order to minimize the false negative rate. Of note, ^{99m}Tc-based myocardial perfusion imaging agents (^{99m}Tc sestamibi or tetrofosmin) are preferable in this acute ischemic syndrome application, since they may be injected during chest pain in the emergency department and imaged 30 min to 4 h later. Thus, the absence of redistribution with these myocardial perfusion imaging agents provides an advantage for acute imaging applications.

The accuracy of this approach for detecting an acute ischemic syndrome is probably related to the timing of injection with respect to the patient's chest pain. Ideally, the agent would be administered during chest pain or the first hour after chest pain; however, the importance of this timing has not been widely studied. In this regard, patients with unstable angina could conceivably have intermittent coronary occlusion, with normalization of myocardial perfusion at the time the vessel is open.

Because of this consideration, a protocol suggested by Ziffer et al.[310] is recommended for the assessment of those patients in whom chest pain has been relieved prior to injection (Fig. 16-22). In this protocol, patients with ongoing chest pain and resolved chest pain are managed differently. The former are injected with ^{99m}Tc sestamibi, as noted above; a normal study in this cohort may result in either discharge or referral for immediate stress testing, depending on the clinical likelihood of an acute ischemic syndrome. On the other hand, patients with abnormal initial studies are admitted with a presumptive acute ischemic syndrome.

Unique to the protocol described by Ziffer is the handling of a patient with resolved chest pain in the ED. In this case, a resting ^{201}Tl injection would be performed instead of resting ^{99m}Tc sestamibi or ^{99m}Tc tetrofosmin. If the resting ^{201}Tl SPECT is abnormal, the patient would be admitted and therapy for an acute ischemic syndrome begun, including consideration of early coronary angiography. Redistribution imaging may be useful for the assessment of myocardial viability. If the resting ^{201}Tl study is normal, the patient would not be discharged, since the possibility of resolved chest pain secondary to unstable angina would not yet have been evaluated. The patient would instead be submitted to a stress ^{99m}Tc sestamibi study (after a series of negative enzyme studies) employing the resting ^{201}Tl/stress ^{99m}Tc sestamibi protocol described at the beginning of Chap. 56. Based on these combined assessments, patient management would range from discharge (with a normal scan or mildly abnormal scan) to admission (with a clearly abnormal scan). In this latter case, the presumptive diagnosis would be that unstable angina caused the resting chest pain that had led to the emergency room presentation.

Ziffer et al. have recently published preliminary data on 2737 patients undergoing this protocol.[310] In 32 percent of the patients only resting imaging was performed, while in the remaining 68 percent rest and subsequent stress imaging were performed. Overall, 77 percent of all patients imaged were discharged without admission, and 23 percent were admitted. When the success of this protocol was evaluated, two aspects were of particular importance. The investigators compared the event rates for patients who were discharged from the hospital following imaging to the event rates that had previously been observed for patients discharged from the emergency room before the myocardial perfusion imaging protocol had been instituted. With the chest pain center and the myocardial perfusion imaging protocol, the annualized event rate for patients discharged from the emergency room was 0.17 percent. In the patients discharged in the period immediately prior to the opening of the chest pain center, the annualized cardiac event rate was 2.7 percent. Thus, use of myocardial perfusion scintigraphy in the chest pain center was associated with a 16-fold reduction in the event rate (death or nonfatal MI) for patients discharged. In a subsequent preliminary communication, Ziffer et al. demonstrated clear cost savings by applying myocardial perfusion scintigraphy to appropriately selected patients.[311] Application of this modified protocol to patients in whom acute chest pain has resolved is illustrated in Fig. 16-23, in which a patient with unstable angina was correctly classified by the combination of rest and stress

scintigraphy but would have been misclassified by the use of resting scintigraphy alone.

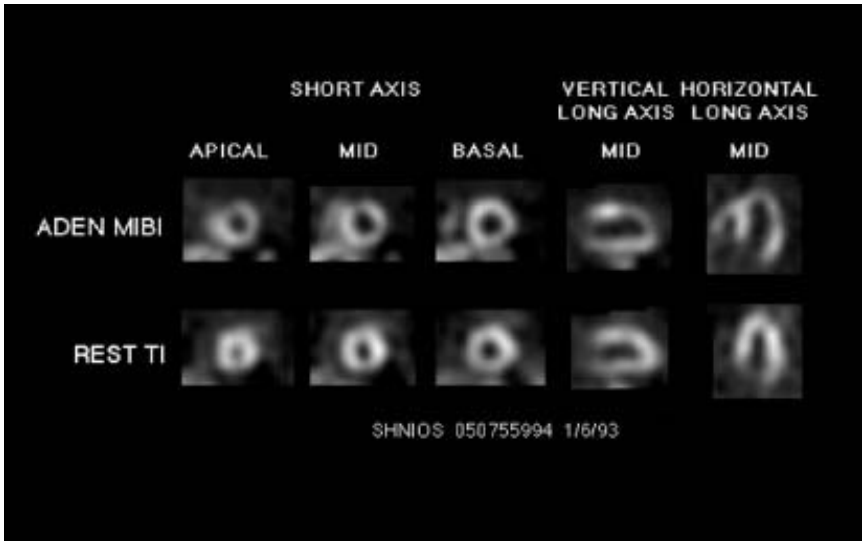

Figure 16-23: Normal rest 201Tl SPECT (*bottom*) followed by adenosine 99mTc sestamibi (ADEN MIBI) (*top*) in a patient with intermittent chest pain which had resolved prior to injection with 201Tl at rest. Reversible defects are seen in the left arterior descending and left circumflex territories. Angiography revealed 50 percent left main, 100 percent left anterior descending, 90 percent left circumflex, and 50 percent right coronary artery stenoses.

Assessment during Early Hospitalization for Acute Coronary Syndromes

Early (i.e., within 24 h) risk assessment has included perfusion or ventricular function imaging. Miller et al.[312] have documented that there is a strong relationship between the size of a very early myocardial perfusion defect (an indicator of infarct size) and subsequent mortality in the setting of acute MI. Overall a 3 percent mortality rate was observed in patients following acute MI. However, 7 percent of patients with myocardial perfusion defects (infarct size) greater than 12 percent of the myocardium had died at the end of a 2-year follow-up, compared to zero percent of the patients with infarct size less than 12 percent.[312] Christian et al.[313] have shown that rest myocardial perfusion SPECT, when combined with resting LV function, can provide information on myocardial stunning. In patients with acute MI, when there was a mismatch (with LVEF lower than would be expected from admission myocardial perfusion SPECT defect size), late improvement in LV function could be predicted.[313]

Radionuclide angiography has also been applied in the coronary care unit setting for assessing prognosis in patients with acute MI,[314,315] establishing the diagnosis of RV infarction,[314,315] and differentiating causes of cardiogenic shock.[314,315] A strong inverse relationship between resting EF and 1-year cardiac mortality has been demonstrated in large multicenter trials[316] (Fig. 16-24). At the other end of the clinical spectrum, resting RNA can aid in the assessment of the cause of low cardiac output in the acute setting. The approach can accurately distinguish patients with LV dysfunction, RV dysfunction, mitral regurgitation, cardiac tamponade, and ventricular septal defect. Those with LV dysfunction would have substantially reduced LVEF and concomitant severe wall motion abnormalities. The syndrome with predominant RV dysfunction is easily recognized by RV enlargement and a greater reduction in RVEF than LVEF.[314,315] Mitral regurgitation severe enough to allow low cardiac output in the setting of acute MI would be detectable through the LV/RV stroke-count ratio which can be derived from the regions of interest utilized to calculate RVEF and LVEF. Similarly, if a pericardial effusion, with or without

bleeding, is large enough to cause hemodynamic compromise, it would easily be detected by equilibrium RNA as a halo surrounding the left cardiac chambers. Furthermore, in the postoperative setting, RNA allows identification of pericardial bleeding.[317,318] By combining a first-pass and equilibrium acquisition (with acquisition of one to two frames per cardiac cycle), one can also assess the presence of a ventricular septal defect through analyzing the pulmonary time-activity curve.

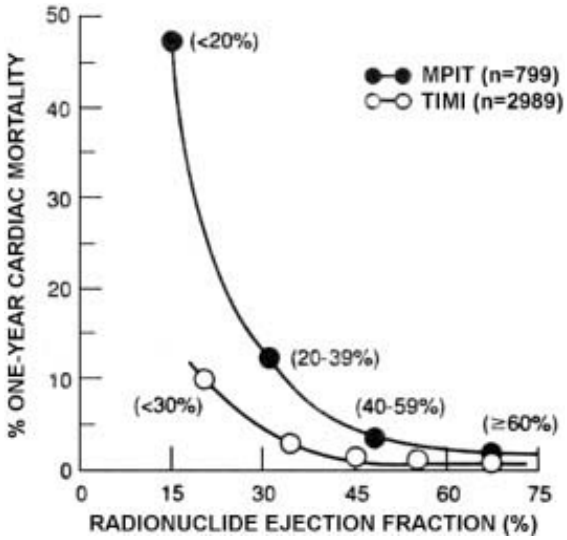

Figure 16-24: One-year mortality rates after acute myocardial infarction as function of left ventricular ejection fraction at rest. Data are shown from Multicenter Postinfarction Trial (MPIT) a decade ago and compared with more recent Thrombolysis in Myocardial Infarction (TIMI) II Trial. (From the Multicenter Postinfarction Research Group,[316] with permission.)

SELECTION OF INITIAL THERAPY

An important application of myocardial perfusion scintigraphy in acute ischemic syndromes is the selection of the appropriate therapy for patients with a known ischemic syndrome. For example, in patients presenting late (greater than 12 h) after onset of symptoms and acute MI, Christian et al. have suggested that not all patients will benefit from reperfusion therapy but that the benefit might be predictable based on the myocardial perfusion imaging pattern at the time of admission.[318] In this regard, thrombolytic therapy or angioplasty may not be beneficial in patients with severely reduced or absent myocardial perfusion late following symptoms, but these therapies may be successful for patients with preserved myocardial perfusion (and therefore preserved myocardial viability).

It has been suggested that considerations as to whether thrombolytic therapy or PCI should be performed can be elucidated by resting myocardial perfusion scintigraphy in the following conditions: (1) patients presenting late after chest pain, as noted above, (2) patients with ST-segment depression in whom injection can be made during chest pain (those with severe reduction in flow would be candidates for thrombolytic therapy or PCI, whereas those without decrease in flow would not be good candidates). Additionally, (3) patients with LBBB, in whom thrombolytic therapy or PCI are generally recommended, could most likely be better classified for therapy on the basis of resting myocardial perfusion scintigraphy rather than through the use of clinical criteria alone. None of these applications have been well studied by randomized trials, but they remain interesting potential clinical applications.

EVALUATION OF THERAPY

It has by now been well demonstrated that myocardial perfusion scintigraphy is useful in the assessment of therapeutic efficacy for patients undergoing thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA). Maddahi et al. first demonstrated this application using ^{201}Tl planar scintigraphy in the early 1980s.[319,320] Subsequently, Gibbons et al.[321] reported similar findings using ^{99m}Tc sestamibi. On the basis of extensive work by that group of investigators, myocardial perfusion scintigraphy can be used in patients with acute MI before and after therapy (or even simply after therapy) and represents an efficient, less expensive endpoint for examining the efficacy of a variety of therapies compared to conventional mortality endpoints.

ASSESSMENT OF MYOCARDIAL VIABILITY

In the setting of acute MI, at times it becomes clinically important to assess the viability of abnormally contracting segments. In this regard, it has become important to recognize the high frequency of myocardial stunning that occurs in the setting of an aborted acute MI. Since the earliest thrombolytic trials, it has been clear that severe and extensive wall motion abnormalities and severe reduction of LV function can be associated with the stunned myocardium when thrombolytic therapy or PTCA is applied early enough to abort the development of myocardial necrosis. Although the return of ventricular function may be delayed by up to several months, the degree of improvement in ventricular function can be dramatic. In this regard, the finding of normal or nearly normal perfusion after initial therapy (thrombolytic therapy or PTCA) can be used to accurately predict the return of ventricular function in a patient with an acute ischemic syndrome, whereas ongoing resting ischemia might indicate the need for urgent revascularization.[321a]

Discharge Planning Post-Unstable Angina

Guidelines developed under the sponsorship of the Agency for Health Care Policy Research (AHCPR) have indicated a clear role for the use of nuclear testing in patients admitted with unstable angina.[291] Although at the present time most patients admitted with unstable angina are referred to catheterization, the guidelines suggest that a significant number of these patients should be medically treated after appropriate risk stratification. This strategy is applicable to patients who respond quickly to medical therapy, particularly in the presence of concomitant conditions that increase the risk of or decrease the likelihood of using an invasive strategy (e.g., very advanced age or debilitation). In these medically stabilized patients, either exercise or pharmacologic stress testing with perfusion imaging can effectively stratify patients into low- and high-risk subsets, as demonstrated by a number of studies.[291] Failure of medical treatment to control ischemia or the presence of hemodynamic instability would result in referral to catheterization. Hemodynamically stable patients with medically controlled ischemia would be candidates for a noninvasive management approach. Within this approach, those patients at low risk by clinical factors (patients who probably did not have unstable angina initially) can be managed as outpatients and referred to stress testing within 72 h of initial admission. Patients at intermediate to high risk who have been pain-free for 48 h and have no recurrent angina, LV dysfunction, or significant ventricular dysrhythmias are also candidates for in-hospital noninvasive risk stratification. The initial test on these patients could be treadmill ECG testing in those individuals with normal resting ECGs who are not on digoxin and are able to perform exercise. Patients with abnormal rest ECGs or on digoxin would undergo exercise or pharmacologic stress imaging; those patients unable to exercise would undergo pharmacological stress imaging. Either of these latter two groups are also potential candidates for stress echocardiographic studies. The decision between stress echocardiography and stress perfusion imaging would be guided by test availability and local expertise. For hospitalized patients with acute unstable angina, the 1994 AHCPR guidelines reported annual rates of cardiac death or MI of

3 percent for patients with normal test results as compared with 18 percent event rates for patients with high-risk nuclear scan results.[291]

Discharge Planning after Uncomplicated Acute MI

Practice guidelines in the United States have indicated that stress testing (with or without imaging) can be effective in risk stratification and guiding subsequent management of hospitalized patients without acute MI in whom the clinical indications of high risk are not present.[291] This suggestion is based on the results of several clinical trials. For example, in the TIMI-IIB study of 1681 patients assigned to early catheterization and 1658 patients assigned to "watchful waiting" strategies following acute MI with thrombolysis, there was no significant difference with respect to cardiac death, MI, or anginal status. Of importance, these excellent outcomes with "watchful waiting" were obtained without any standardized approach to the use of noninvasive testing.[218] Recently, the results of the Veterans Affairs non Q-Wave Infarction Strategies in Hospital (VANQWISH) trial provided similar data for patients with non Q-wave MI.[322] Common clinical thought had been that patients with non-Q-wave MIs were more likely to have a subsequent acute event and should require more aggressive management when compared to patients with Q-wave MIs. Nonetheless, this supposition was not borne out by the VANQWISH study. A total of 920 patients were randomly assigned to "invasive" (462 patients) versus "conservative" (458 patients) management. The invasive management included early catheterization performed a median of 2 days following MI (see Chap. 41). The conservative management included the use of RNA and predischarge symptom-limited exercise ^{201}Tl study or dipyridamole ^{201}Tl study. Catheterization was recommended if recurrent angina developed with ECG changes (>2-mm ST-segment depression on exercise testing), if there were two or more reversible defects on the ^{201}Tl study, or if increased ^{201}Tl uptake was observed.[355] The probability of event-free survival was higher in patients undergoing conservative therapy than in patients undergoing the invasive therapy approach.

Despite these findings, there is discordance between the practice guidelines and the actual practice in the United States. Mark et al. reported that 72 percent of patients following acute MI underwent early catheterization in the United States, compared to only 25 percent of patients in Canada. Interestingly, there was no significant difference in 1-year mortality rates between the two countries.[323] Topol et al. have noted that only 9 percent of patients undergoing PTCA after a recent MI had stress testing prior to their angioplasty.[324a]

Both exercise[324a] and pharmacologic stress testing postmyocardial infarction has also shown to effectively identify patients at low and high risk of subsequent events.[325,326] With respect to perfusion scintigraphy, it should be noted here that the post-MI application is one in which the use of pharmacologic stress over low-level nuclear stress testing may be particularly advantageous. Although either type of stress would be recommended by the guidelines, our preference is to use pharmacologic stress. The reasons are as follows: (1) pharmacologic stress does not require that the patient be able to exercise; (2) it can be easily and safely employed as early as 2 days following MI[327,328]; (3) it lowers rather than raises blood pressure, avoiding the potential problem of myocardial rupture; and (4) it produces a maximal hyperemic stimulus, thereby obviating the need for maximal stress testing after recovery.

In studies performed in the postthrombolytic era by Mahmarian and colleagues suggested that adenosine thallium SPECT is effective in stratifying patients in the post-MI period.[325,329] In the most recent study, they also showed that there is incremental value in knowing the LVEF as well as the extent of jeopardized myocardium, as determined by equilibrium radionuclide angiography and adenosine ^{201}Tl myocardial perfusion SPECT.[329] These same investigators have demonstrated the value of adding LVEF to exercise myocardial perfusion SPECT.[325] As

described above, these assessments can now be made with a single study using gated myocardial perfusion SPECT. Assessment of increased lung uptake of radioactivity during myocardial perfusion scintigraphy has also been shown to be of prognostic significance in patients with acute syndromes of unstable angina and non-Q-wave MI.[330] Overall, myocardial perfusion test results which have been demonstrated to indicate high risk (and thus the need for angiography) in the predischarge patient include reversible defects in the MI zone, a multivessel defect pattern, large nonreversible defects, transient left ventricular dilation, increased lung uptake, and reduced left ventricular ejection fraction.[330a]

A recent landmark multicenter randomized trial has been reported comparing submaximal ^{99m}Tc sestamibi SPECT at discharge to early dipyridamole ^{99m}Tc sestamibi SPECT performed 2 to 4 days after acute MI.[331] A total of 451 patients presenting with first acute MI were randomized in a 3:1 ratio to either (1) an early (days 2 to 4) dipyridamole ^{99m}Tc sestamibi SPECT and a predischarge (days 6 to 12) submaximal exercise ^{99m}Tc sestamibi SPECT or (2) only the predischarge study. The very early use of dipyridamole testing was associated with no adverse events, indicating the safety of this approach in appropriately selected post-MI patients. Multivariate predictors of in-hospital events included the summed stress score and summed reversibility scores, derived using a 17-segment model with the same 0-to-4 scale described above,[56,66] as well as peak creatine kinase levels. For postdischarge cardiac events, the multivariate predictors in patients undergoing dipyridamole sestamibi SPECT were the SSS, the summed reversibility score, the summed rest score, and anterior MI. Dipyridamole sestamibi imaging showed better risk stratification than submaximal exercise myocardial perfusion imaging (Fig. 16-25). Importantly, the submaximal exercise ECG had no significant predictive value for cardiac events. Interestingly, the ability to separate low- and high-risk subsets by use the of the SSS in early dipyridamole sestamibi SPECT was significantly better for patients who received thrombolysis than for those who did not (Fig. 16-26).

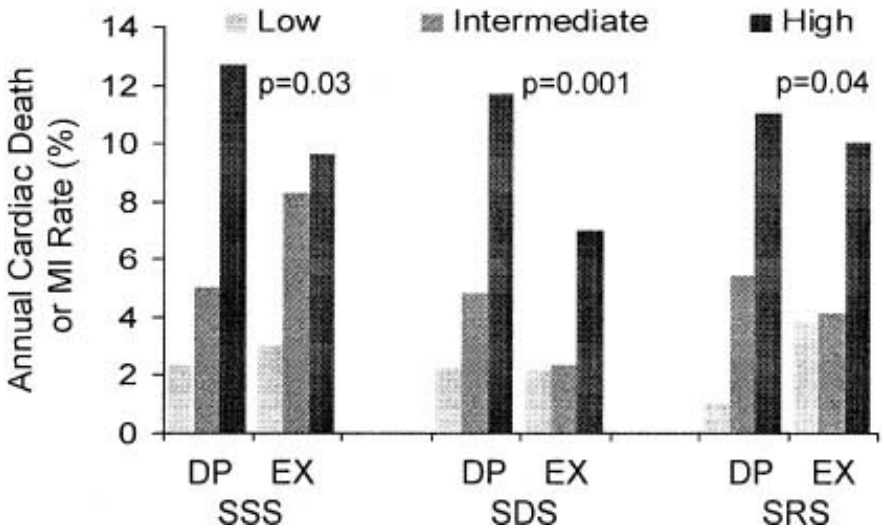

Figure 16-25: Annual cardiac death rate or recurrent MI rate as a function of SSS, SDS, and SRS for dipyridamole (DP) and submaximal exercise (EX) 99mTc sestamibi SPECT imaging. Event rate increased as scores increased. The ability to predict cardiac events was better for dipyridamole studies than for exercise studies for each summed score (*p* value depicted). All event rates are derived from risk-adjusted Cox survival curves. Intermed indicates intermediate. (From Brown et al.,[321] with permission.)

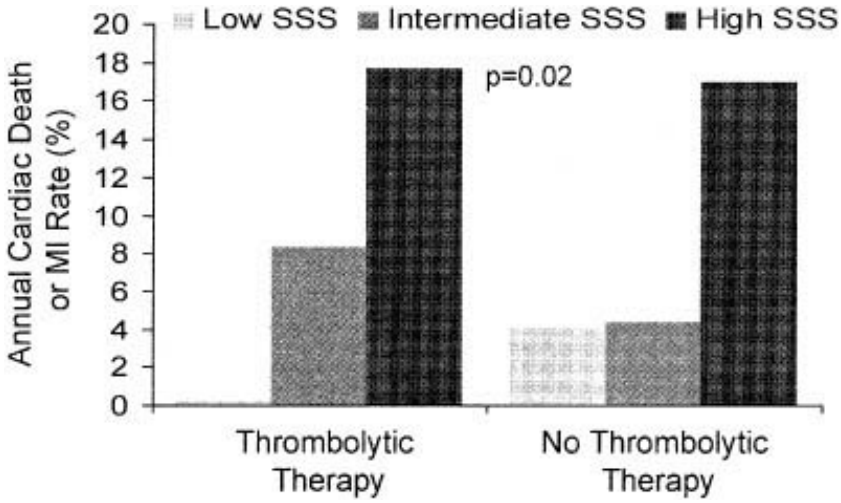

Figure 16-26: Annual cardiac death or MI rate as a function of SSS and thrombolytic therapy. The predictive value of SSS was greater for patients receiving thrombolysis (p = 0.02). (From Brown et al.,[331] with permission.)

The investigators found a significant interaction between the degree of reversibility on dipyridamole sestamibi imaging (SDS) and the overall stress perfusion defect size (SSS) (Fig. 16-27). In the low and intermediate summed stress score groups, the annual cardiac death or nonfatal infarction rate was low when the SDS was low (0 to 2). The event rate in patients with intermediate SSS (5 to 8) increased to 6 percent in patients with intermediate SDS (3 to 7) and to 17 percent in patients with high SDS (greater than 7). In patients with high SSS (greater than 8), the cardiac event rate was high regardless of the extent of defect reversibility by SDS. The authors concluded that the dipyridamole sestamibi scanning very early after MI predicts early and late cardiac events, with superior prognostic value compared with submaximal exercise testing. They suggested that the technique can allow management decisions to be made earlier in patients with acute MI, with potentially significant cost implications associated with earlier discharge of low-risk patients.[331]

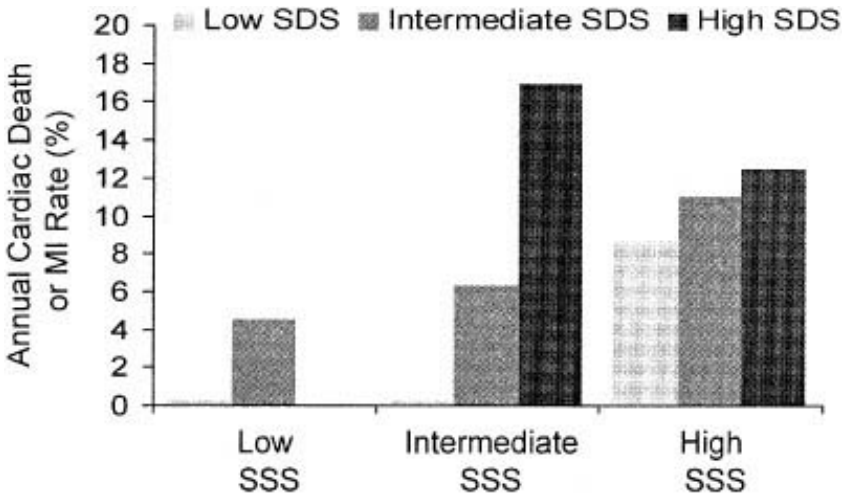

Figure 16-27: Annual cardiac death or MI rate as a function of SDS for a given SSS. For each SSS subgroup, cardiac event risk increased as SDS increased. The effect of SDS was greatest in the intermediate (intermed) SSS group. (From Brown et al.,[331] with permission.)

The potential of this early hospital discharge summary was discussed in an accompanying editorial.[332] The editorial points out that intervenous adenosine may be preferable to dipyramole in the very early post-MI patient owing to its very brief half-life; it also suggests that if a management strategy based on the results of this study were widely adopted, substantial cost savings could be realized in appropriate patients populations. Recent work of Dakik et al.[236] suggests that the approach to medical therapy might safely be extended to patients considered to be at moderate to even high risk following acute MI, with serial nuclear studies providing the basis for initial selection of therapy as well as for subsequent assessment of its effectiveness and consideration for therapeutic change.

It is anticipated that these results will be integrated into the future guidelines for the management of patients with acute MI.

One of the major dilemmas in post-MI patient management is the timing and use of cardiac catheterization. Conceptually, a conservative patient management approach of "watchful waiting" for provocative ischemia or recurrent symptoms could result in worse outcomes, while at the same time an aggressive approach to care (i.e., early and direct catheterization) might result in more expensive care without an improvement in outcomes.[218] In fact, the challenge for clinicians caring for acute MI patients is to identify the balance between extra clinical benefits and extra costs. Currently, routine catheterization is performed in the vast majority of patients with acute MI.[218] An alternate strategy that has been advocated in several recent national guidelines is to refer to catheterization (with consideration of early revascularization) only when clinically necessary and to use noninvasive testing to selectively identify patients for catheterization.[219] From the recent American College of Physicians (ACP) guidelines for risk stratification after MI, a 3 to 5 day assessment of ventricular function for patients with an uncomplicated hospital course is recommended.[219] For patients with preserved systolic function, a vasodilator stress myocardial perfusion SPECT early (i.e., days 2 to 4)[331] in the course of care of the uncomplicated MI patient may provide important information regarding residual risk as well as reassurance to the patient and family regarding their risk of cardiac events during the year following discharge.[219] This approach may also allow for the early discharge of appropriate low-risk patients with acute myocardial infarction, potentially as early as three to five days following admission (Fig. 16-28).

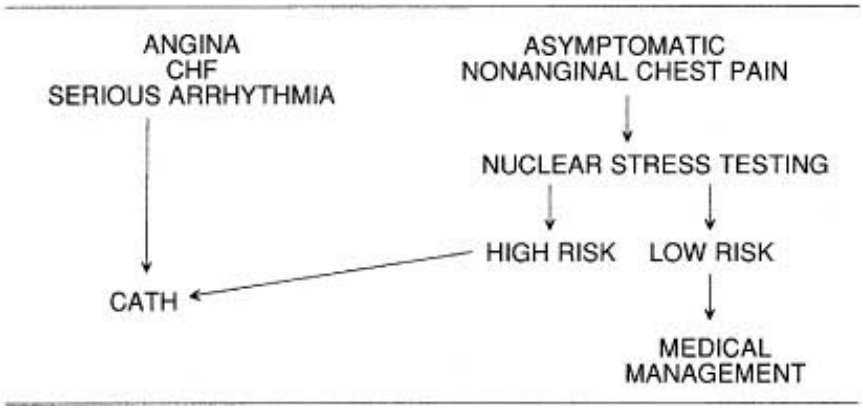

Figure 16-28: Management strategy for the use of nuclear stress testing in patients recovering from acute MI. Cath = catheterization; CHF = congestive heart failure.

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Chapter 16: NUCLEAR CARDIOLOGY

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 17:

COMPUTED TOMOGRAPHY OF THE HEART

Author: John J. Mahmarian

Computed tomography has emerged as a technique that can fully evaluate both cardiac structure and function. Recent advances in imaging speed have allowed for more complete evaluation of relatively stationary structures, such as the thoracic aorta, and rapidly moving structures, such as the myocardium. When combined with electrocardiographic (ECG) gating, literally "freeze frame" images of the heart can be obtained, obviating most of the blur caused by motion artifact during systole and diastole. This is particularly important when obtaining contrast-enhanced images of the coronary arteries or quantifying coronary artery calcium.

Two types of computed tomographic (CT) scanners are currently available for performing cardiac evaluations. Continuously rotating spiral CT scanners can acquire images within 500 ms, whereas exposure times have been markedly reduced to 50 ms with the advent of electron-beam computed tomography (EBCT).

TECHNICAL CONSIDERATIONS

Spiral Computed Tomography

Traditional CT scanners produce images by rotating an x-ray tube around a circular gantry through which the patient passes on a table. With spiral CT scanners, the x-ray tube rotates continuously as the table moves through the gantry without the need for incremental stops. The x-ray tube can make one revolution around the patient in less than 1 s, and the table can advance through the gantry to acquire up to two slices per second. Further improvements in spiral CT technology have increased the number of images that can be obtained through each revolution of the x-ray beam, thus shortening total acquisition times at any given slice thickness.

The actual rotation of the x-ray tube is limited, however, by its mechanical movement around the patient. Therefore, imaging time is still currently limited to at best 500 ms. When imaging the constantly moving myocardium and coronary arteries, faster acquisition times are required to avoid image blur, even when ECG gating is employed.

EBCT

EBCT uses an electron beam of 130 kV that is deflected via a magnetic coil and focused to strike a series of four tungsten targets located beneath the patient (Fig. 17-1). The electron beam is magnetically swept along the tungsten targets at a 210° arc. Each target ring is separated by a distance of 4 mm. The resulting x-rays generated beneath the patient are then attenuated as they pass through the thorax and recorded by a series of two twin fixed detector arrays arranged in a semicircle above the patient. Imaging is complete within 50 ms, which is the time required for the electron beam to sweep along the tungsten targets. With a 100-ms acquisition time, a "freeze frame" image of the myocardium and coronary arteries in end-diastole can be achieved with little, if any, motion blur.

EBCT is commonly operated using three different acquisition modes. The *cine mode* creates real-time cross-sectional views of the beating heart and is commonly used to assess both global and regional right ventricular (RV) and left ventricular (LV) function (Fig. 17-2). The *volume mode* allows acquisition of a single image with each preselected movement of the patient couch. Up to 40 continuous slices can be obtained scanning 12 to 32 cm of anatomy (Fig. 17-3). This imaging mode is commonly gated to the electrocardiogram to obtain high-resolution static images for detailed evaluation of cardiovascular anatomy, such as coronary artery calcification (see also Chap. 40). The *triggered (flow) mode* is used to assess blood flow through specific cardiac chambers and the myocardium itself. This mode allows acquisition of some 20 to 40 consecutive scans, where imaging occurs at a designated time during each cardiac cycle. From these consecutive scans, time-density curves can be constructed that can estimate blood flow through specific cardiac chambers and within the myocardium.

NEXT

Chapter 17: COMPUTED TOMOGRAPHY OF THE HEART

EVALUATION OF MYOCARDIAL STRUCTURE AND FUNCTION

Both the left and right ventricles are well visualized by spiral computed tomography and EBCT, allowing excellent spatial separation between the two structures. Delineation of the epicardial and endocardial surfaces allows accurate and reproducible measurement of LV and RV wall thickness and myocardial mass.[1-3] LV hypertrophy can be quantified and serially assessed. RV dysplasia is accurately diagnosed based on the characteristic EBCT findings of an enlarged right ventricle with a scalloped appearance, trabeculations with low attenuation characteristics, and abundant epicardial adipose tissue.[4]

EBCT can assess LV and RV hemodynamics[5] as well as regional myocardial wall motion and thickening.[6-8] The cine mode is used to acquire multiple gated images of the right and left ventricles during maximal contrast enhancement of the cavities.[7,8] This affords accurate and reproducible quantification of LV and RV end-diastolic and end-systolic volumes and ejection fraction.[5,7] EBCT is comparable with first-pass radionuclide angiography for calculation of left ventricular ejection fraction (LVEF) in patients with myocardial infarction[9] (Fig. 17-4). Serial changes in RV and LV volumes and diastolic parameters are well defined in patients following acute myocardial infarction.[10-12] Ventricular remodeling can be assessed by using EBCT in a similar fashion to gated blood pool radionuclide angiography[13,14] and echocardiography.[15] Cine EBCT can identify wall thinning and impaired LV thickening in an area of previous myocardial infarction[16] and delineate the presence of anterior and posterior LV aneurysms and associated mural thrombus[17,18] (Fig. 17-5).

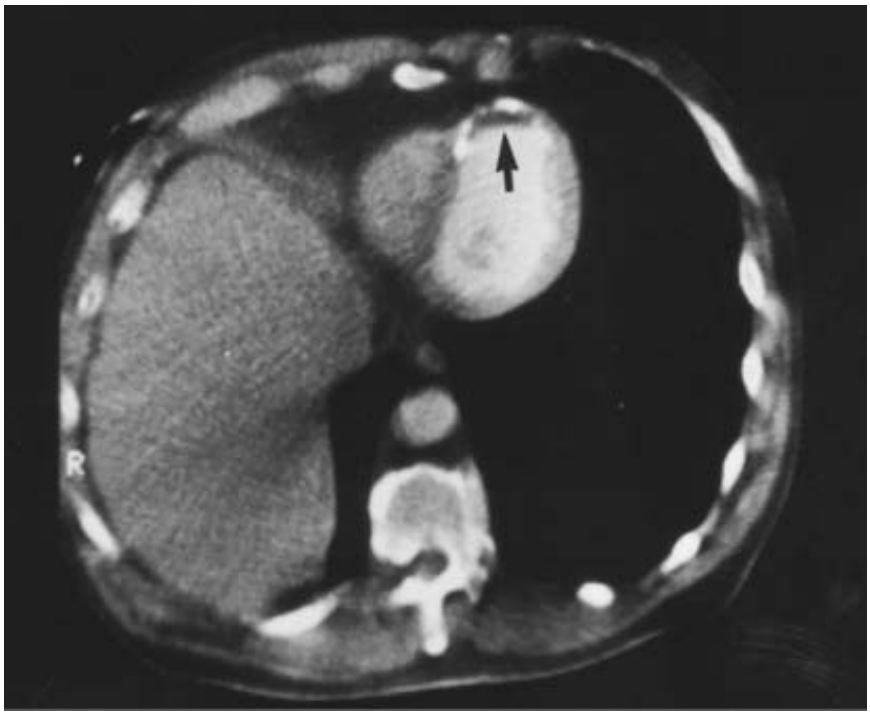

Figure 17-5: A single frame from a contrast-enhanced cine CT scan demonstrates thrombus in a LV aneurysm. Also note that the wall of the aneurysm is calcified.

Stress-rest EBCT imaging has been used to detect underlying ischemic heart disease based on changes in global LVEF and regional wall motion. One *small* study compared semisupine bicycle exercise contrast-enhanced EBCT with ^{99m}Tc myocardial perfusion single-photon-emission computed tomography (SPECT) in patients with suspected coronary artery disease (CAD), all of whom underwent angiography.[7] An abnormal EBCT study was defined as a less than 5 percent increase in LVEF during exercise. The sensitivity and specificity of exercise EBCT for detecting CAD were 81 and 76 percent, respectively, when using the global LVEF criteria for abnormalcy but improved to 88 and 100 percent when regional wall motion abnormalities were considered. EBCT was as accurate as ^{99m}Tc SPECT in the diagnosis of CAD.

Although echocardiography generally is used to assess valvular heart disease, EBCT is an alternative modality in patients with poor acoustic windows. In patients with mitral or aortic regurgitation, EBCT can accurately determine LV and RV stroke volumes and thereby calculate valvular regurgitant fractions.[5,19] When contemplating possible need for valvular surgery, EBCT can delineate the important parameters of LV chamber size, wall thickness, and LVEF. As with gated blood pool radionuclide angiography, EBCT cannot distinguish mitral from aortic regurgitation and cannot calculate the regurgitant fraction if significant right-sided valvular regurgitation is present. One of the complications of mitral valve disease is the development of left atrial thrombi. *One study* showed greater accuracy of EBCT as compared with transthoracic echocardiography in demonstrating left atrial thrombi.[20] Whether EBCT can detect thrombi as well as transesophageal echocardiography remains to be determined.

PREVIOUS | NEXT

Chapter 17: COMPUTED TOMOGRAPHY OF THE HEART

EVALUATION OF CAD

Detection of Coronary Artery Calcification

For the detection of coronary artery calcium with EBCT, typically 40 consecutive 3-mm-thick images are acquired at a rate of 100 ms per image from the base of the heart to just below the carina. Images are obtained at end-inspiration with ECG triggering at 80 percent of the RR interval (end-diastole). A calcified lesion generally is defined as either two or three adjacent pixels (0.68-1.02 mm^2 for a 512^2 reconstruction matrix and a camera field size of 30 cm) of greater than 130 Hounsfield units (HU). Each calcified lesion is multiplied by a density factor as follows: 1 for lesions with a maximal density between 130 and 199 HU, 2 for lesions between 200 and 299 HU, 3 for lesions between 300 and 399 HU, and 4 for lesions greater than 400 HU. The total coronary artery calcium score (CACS) is calculated as the sum of each calcified lesion in the four main coronary arteries over all the consecutive tomographic slices (Fig. 17-6).

With spiral computed tomography, consecutive 3-mm-thick images are acquired at a rate of two contiguous 2.5-mm slices per second. ECG gating generally is not employed. Calcified lesions are defined as those with a tomographic density greater than 90 HU (2 standard deviations above blood density) with an area greater than 0.5 mm^2. A modified density factor is used: 1 for lesions of 90 to 199 HU, 2 for lesions of 200 to 299 HU, 3 for lesions of 300 to 399 HU, and 4 for lesions greater than 400 HU. As with EBCT scoring, the total CACS is calculated as the sum of each calcified plaque over all the tomographic slices.

To date, only 1 small study has directly compared EBCT with conventional CT scanning in patients referred for coronary angiography.[21] Thirty-seven of 42 patients had significant (>50 percent) stenosis in at least one coronary artery. A close linear correlation was observed between the CACS derived from EBCT versus conventional CT scanning ($r = 0.98$; $p < 0.0001$). There are no other published studies comparing EBCT with either conventional or spiral CT. The EBCT-derived CACS correlates with calcified areas found in individual coronary arteries as determined by histomorphometric measurements[22] (Fig. 17-7). No such data are available using conventional or spiral CT.

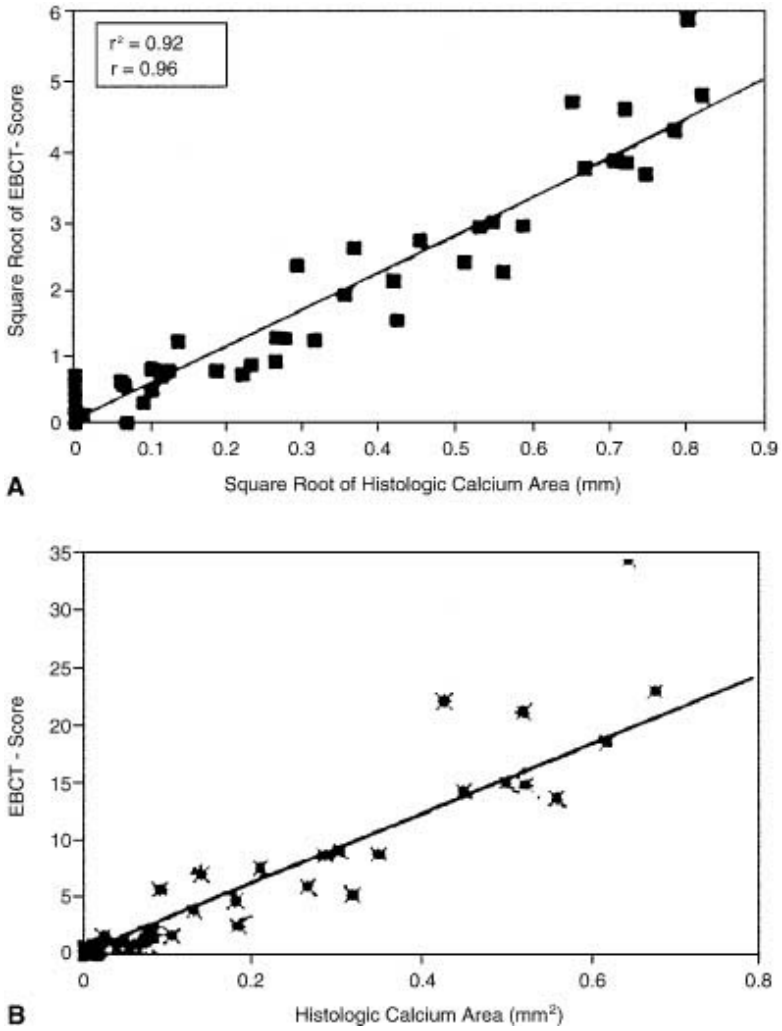

Figure 17-7: Linear regression comparing the EBCT CACS [square root transformation (*A*) and actual data (*B*)] versus the calcium area measured at histomorphometric examination. There is an apparent high positive correlation between the EBCT calcium score and histomorphometric calcium area ($r2 = 0.92$, $r = 0.96$; $p < 0.0001$). (From Mautner et al.[22] Reproduced with permission from the publisher and authors.)

Coronary Artery Calcification and Atherosclerotic Plaque Burden

The presence of coronary artery calcification is clearly indicative of coronary atherosclerosis.[23,24] Furthermore, the CACS severity, as assessed by EBCT, is directly related to the total atherosclerotic plaque burden present in the epicardial coronary arteries.[23,24] Coronary calcification begins early in life but progresses more rapidly in older individuals who have further advanced atherosclerotic lesions.[25] Calcification is an active, organized, and regulated process occurring during atherosclerotic plaque development, where calcium phosphate in the form of hydroxyapatite precipitates in atherosclerotic coronary arteries in a similar fashion as observed in bone mineralization.[26-28] Although lack of calcification does not categorically exclude the presence of atherosclerotic plaque, calcification occurs exclusively in atherosclerotic arteries and is not found in normal coronary arteries. However, it does not necessarily correlate with the presence or extent of coronary artery luminal stenosis (Chap. 40).

The presence and extent of histologically determined plaque area have been compared with the total calcium area as assessed by EBCT in individual coronary arteries derived from autopsied hearts.[23] A strong linear correlation exists between total coronary artery plaque area and the extent of coronary artery calcification as found in individual hearts ($r = 0.93$; $p < 0.001$) and in individual coronary arteries ($r = 0.90$; $p < 0.001$) (Fig. 17-8). However, the total calcium area underestimates total plaque area, with approximately five times as many noncalcified as calcified plaques.[23]

Coronary Artery Calcification and Stenosis Severity

Significant (>50 percent) coronary artery stenosis by angiography is associated with the presence of coronary artery calcium as assessed by EBCT. *Stenosis severity is not directly related to the total CACS, however*. A recent study compared calcium extent with coronary artery luminal diameter stenosis determined by morphologic examination of 723 coronary artery segments.[24] Although coronary stenosis severity increased with increasing coronary artery calcification, this relationship was poor and could not be used to estimate angiographic stenosis severity on a segment-by-segment basis (Fig. 17-9). One explanation is that coronary artery diameter increases with increasing plaque burden so as to maintain luminal patency.[29,30] Noncalcified plaques are usually associated with less than 50 percent diameter stenosis and typically less than 20 percent stenosis.[24] These data indicate that lack of coronary calcification predicts a very low likelihood of obstructive CAD.

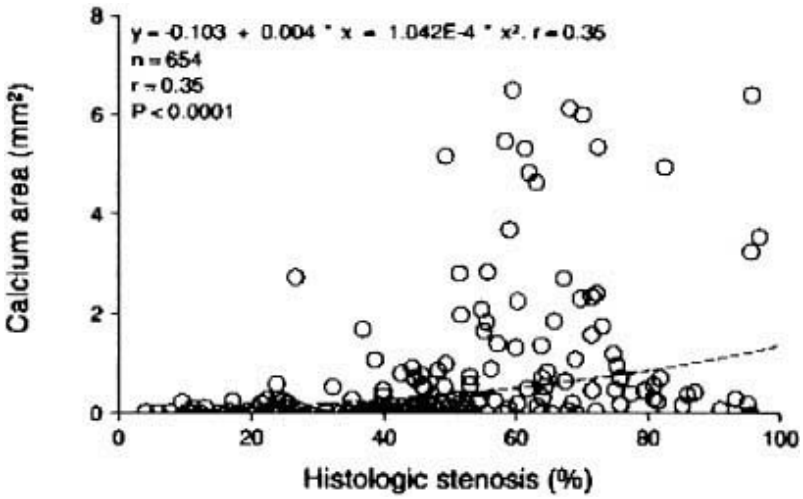

Figure 17-9: Graph showing the polynomial regression analysis of coronary calcium area (mm2) versus percent histologic stenosis for 654 coronary artery segments with calcium greater than 0 mm2. (From Sangiorgi et al.[24] Reproduced with permission from the publisher and authors.)

Clinical angiographic trials confirm the relationship between CACS severity and the presence of significant (≥50 percent) CAD.[31-42] Although the diagnostic accuracy of EBCT improves with age, most younger patients (<50 years) with obstructive CAD also have coronary calcification (85 percent).[37,39] To date, there are 12 studies evaluating EBCT with coronary angiography where obstructive CAD was defined as greater than 50 percent luminal diameter stenosis[31-42] (Table 17-1). In these studies, the overall sensitivity and specificity for detecting obstructive CAD are 95 and 43 percent, respectively. *The poor specificity* of EBCT can be reconciled by the fact that the presence of coronary artery calcification confirms the presence of atherosclerotic plaque that may not necessarily be obstructive in nature. The CACS severity may be a better barometer of obstructive CAD than the mere presence of calcium. Budoff et al.[37] observed that specificity increased with the number of calcified coronary arteries (i.e., high calcium scores). Two separate reports in patients referred for coronary angiography found that a CACS of more than 100 best predicted obstructive CAD with an equally high sensitivity and specificity of 80 percent.[43,44] There appears to be a threshold CACS above which most patients will have significant coronary artery stenosis. However, despite the relationship between obstructive CAD and CACS severity, *the latter is still too imprecise in itself to be used as a definitive criterion for proceeding directly to coronary angiography*. The current ACC/AHA guidelines on coronary angiography do not recommend coronary angiography on the basis of a positive EBCT.

Table 17-1: Accuracy of EBCT Coronary Artery Calcification in Detecting Significant (>50%) Coronary Artery Stenosis as Defined by Angiography

Study	*N*	Sensitivity (%)	Specificity (%)	Positive PA	Negative PA
Agatston, 1990[31]	584	96	51	31	98
Breen, 1992[32]	100	100	47	63	100
Bielak, 1994[33]	160	96	45	57	93
Kaufman, 1995[34]	160	93	67	81	86
Rumberger, 1995[35]	139	98	39	59	97
Braun, 1996[36]	102	93	73	93	73
Budoff, 1996[37]	710	95	44	72	84
Detrano, 1996[38]	491	95	31	51	89
Fallavollita, 1996[39]	106	85	45	66	70
Baumgart, 1997[40]	57	97	21	56	86
Kennedy, 1998[42]	368	96	31	51	90
Schmermund, 1997[41]	118	95	88	99	58
TOTAL	3095	95	43	60	90

ABBREVIATIONS: PA = predictive accuracy.

Distinguishing Ischemic from Nonischemic Conditions with Computed Tomography

The presence or absence of coronary artery calcification by EBCT may help to distinguish patients with ischemic versus nonischemic dilated cardiomyopathy.[45,46] In one study, 44 of 53 patients without significant (>50 percent stenosis) CAD (83 percent) had a CACS of 0, whereas 71 of 72 (99 percent) with CAD had an abnormal EBCT study. Importantly, 44 of 45 patients with a normal EBCT had nonischemic dilated cardiomyopathy (98 percent negative predictive value). The total CACS increased with the extent and severity of underlying CAD (Fig. 17-10). Differentiating ischemic from non-ischemic dilated cardiomyopathy also has been demonstrated with spiral computed tomography.[46]

EBCT may be able to distinguish ischemic versus nonischemic chest pain in patients presenting to the emergency room with nondiagnostic electrocardiograms.[47] In one series, none of 47 patients with a normal EBCT had a subsequent cardiac event over a 1-month period. Conversely, 7 of 86 patients (8 percent) who had coronary calcification had a subsequent myocardial infarction ($n = 4$) or revascularization procedure ($n = 3$). The high negative predictive value of EBCT, despite its low positive predictive value, may improve triage of patients with questionable ischemic symptoms.

In two recent reports, most asymptomatic patients who had a subsequent first acute myocardial infarction had coronary calcification by EBCT (96 percent).[41,48] Since many acute myocardial infarctions occur following rupture of nonobstructive plaques, it is not surprising that the CACS will be mild (<100) in a large percentage (34 percent) of patients and severe (>400) in relatively few (27 percent).[48] In one study evaluating survivors of a first myocardial infarction with spiral CT, 19 percent lacked coronary artery calcification.[49] This higher percentage of normal studies may reflect the lower sensitivity of spiral CT as compared to EBCT for detecting calcium. Patients without calcium generally are younger in age and tend to be active smokers.[48,50] With the exception of young smokers, a normal EBCT defines a population at low

likelihood for significant CAD and subsequent acute cardiac events. *Larger prospective trials in patients with acute coronary syndromes are needed to further delineate the role of EBCT in this population*.

Coronary Artery Calcification: Prognostic Implications

The likelihood of plaque rupture and the development of acute cardiovascular events is related to the total atherosclerotic plaque burden.[51,52] Since there is a direct relationship between the CACS severity and the extent of atherosclerotic plaque, the calcium score should predict risk for subsequent cardiovascular events among otherwise heterogeneous patient populations with cardiac risk factors even though most plaques vulnerable to erosion or fissure resulting in plaque rupture contain minimal calcium.[52a] In a study by He et al.,[53] the CACS severity identified a high-risk group of asymptomatic subjects who had silent myocardial ischemia. In fact, the total CACS was the best single predictor of an abnormal stress SPECT study. Many studies have now demonstrated an increased risk for cardiac events in asymptomatic patients who have extensive silent myocardial ischemia.[54-58] Since the total CACS severity predicts the presence of significant anatomic CAD and myocardial ischemia, it could be useful for risk assessment of asymptomatic individuals and potentially guide therapeutics.

Several recent trials have studied whether the extent of coronary artery calcification as assessed by EBCT can predict subsequent patient outcome. In an early series by Secci et al.,[59] 324 initially asymptomatic subjects were followed for 32 ± 4 months. Eleven patients died or had a nonfatal myocardial infarction (3.3 percent), and an additional 12 patients (3.7 percent) underwent coronary revascularization. A threefold higher event rate was observed in patients in the highest quartile of CACS (>506). In another report from the same group, 1196 asymptomatic patients were followed for 41 ± 5 months after undergoing EBCT.[60] Subjects with a CACS of greater than 44 (median value in this trial) were 2.3 times more likely to suffer myocardial infarction or cardiovascular death as compared with subjects with lower scores. Patients were enrolled only if they had greater than 10 percent risk for developing cardiovascular events over an 8-year period, as determined by the Framingham risk model. In this group at relatively high pretest clinical risk for cardiovascular events, the CACS results did not add to the Framingham risk model for predicting patient outcome.

Arad et al.[61] followed 1173 asymptomatic patients for 19 months after an initial screening EBCT. During follow-up, 18 patients (1.53 percent) had 26 cardiac events, including *1 death, 7 nonfatal myocardial infarctions,* and 17 coronary revascularization procedures. No events occurred in patients with a normal study, and the negative predictive value was 99.8 percent in patients with a CACS of less than 100. The positive predictive accuracy for cardiac events increased as the CACS increased from greater than 100 (5.5 percent) to 160 (7.1 percent) to greater than 680 (14 percent). Callister et al.[48] also reported similar data on 632 asymptomatic patients who were *referred* for a screening EBCT and then followed for 32 ± 7 months. In this study, both the absolute CACS and the age- and gender-adjusted relative CACS percentiles predicted subsequent hard cardiac events of death and nonfatal myocardial infarction. Hard cardiac events occurred in only 0.3 percent of subjects with a normal EBCT, but this increased to 13 percent in those with a CACS of greater than 400. Likewise, in patients in the lower 50th percentile for CACS severity based on age and gender, the total cardiac event rate was only 1.1 percent compared with 8.2 percent for patients with a CACS greater than the 50th percentile (Table 17-2). In the studies of both Arad et al. and Callister et al., there were no adjusted estimates of outcome.[52,61a]

Table 17-2: Cardiac Event Rates in Asymptomatic Subjects Based on Absolute and Relative Coronary Artery Calcium Scores

Absolute Calcium Score	Event Rate, Death/NFMI
0	0.3% (1/292)
1-99	5.5% (12/219)
100-400	10.8% (8/74)
>400	12.8% (6/47)
Calcium Score Percentile	
<50th	1.1% (4/351)
>50th	8.2% (23/281)
>75th	10.5% (19/181)
>90th	11.8% (11/93)

ABBREVIATIONS: NFMI = nonfatal myocardial infarction.
SOURCE: From Callister et al.[48] Adapted with permission of the publisher and authors.

The exceedingly low cardiac event rate in subjects with a CACS of less than 100 is consistent with angiographic studies indicating a comparably low likelihood of significant CAD and an extremely low incidence of stress-induced myocardial ischemia (1.5 percent) in such individuals.[53] The increasing number of cardiac events with an ever-increasing CACS is also consistent with the dramatic increase in the incidence of stress-induced myocardial ischemia when scores are greater than 100 and particularly greater than 400.[53] All these data in asymptomatic patients indicate a potential role of EBCT in screening subjects for subclinical CAD. However, enrollment in prognostic studies primarily has been limited to Caucasian men. Whether the CACS severity has similar prognostic value in other patient populations remains unclear.[62] Since cardiac event rates are known to be very low in asymptomatic individuals with cardiac risk factors[57,61,63-66] (Table 17-3), large prospective trials in patients of greater ethnic diversity, followed for a longer period of time, will be needed to further clarify the value of EBCT in risk stratification.[67]

Table 17-3: Cardiac Event Rates in Asymptomatic Patients

Study	*N*	% Men	Age (yrs)	F/U	Total Deaths/yr	CV Deaths/yr	Nonfatal MIs/yr	Angina Pectoris/yr
Arad et al.[61]	1173	71%	53 ± 11	1.6 yrs	-	0.05%	0.37%	2.3%
Shepherd et al.[66]	6595	100%	55 ± 5 (45-64)	5 yrs	0.73%	0.27%	1.0%	-
Detrano et al.[63]	1462	88%	63 ± 8 (≥45)	1 yr	-	0.40%	0.7%	2.5%
Ekelund et al.[57]	3806	100%	48 (35-59)	7.4 yrs	0.49%	0.24%	1.0%	-
MRFIT[65]	12,866	100%	46 (35-57)	7.0 yrs	0.58%	0.31%	0.7%	1.6%
Gordon et al.[66]	3640	100%	(30-70)	8.5 yrs	0.58%	0.27%	-	-
TOTAL	29,541	98%	-		0.60%	0.28%	0.8%	1.74%

ABBREVIATIONS: CV = cardiovascular; MI = myocardial infarction

Screening for CAD Using EBCT

One of the most novel applications of EBCT may be as a screening test for identifying subjects with subclinical CAD based on the presence and severity of coronary artery calcification (for contrary view see Chap. 40). This is particularly true in view of recent primary prevention trials demonstrating that aggressive risk factor modification, including treatment of hyperlipidemia, reduces the incidence of subsequent cardiac events.[64,68]

RISK FACTOR ANALYSIS

Traditional risk factor analysis is commonly used to identify individuals who are at increased risk for developing cardiovascular disease based on standard clinical criteria.[69,70] Implicit to this risk model is the assumption that a certain combination of risk factors will promote atherosclerosis, which, in turn, will result in cardiovascular events. However, among individuals with a similar risk factor profile, the presence and severity of atherosclerosis will vary enormously; thereby overestimating risk in certain subjects and underestimating risk in others. This discrepancy will be most apparent among individuals with several risk factors who are members of a more heterogeneous population at risk compared with those without risk factors (a more uniformly low-risk group) or those with multiple risk factors (a more uniformly high-risk group). The imprecision of risk factor analysis for identifying patients with significant atherosclerosis is probably related to the fact that traditional risk factor analysis fails to incorporate presently unknown biochemical, environmental, and genetic factors that promote the development of CAD.

Since the development of symptomatic cardiovascular disease occurs almost exclusively in patients with atherosclerosis, it would seem advantageous in risk assessment to use a technique that directly measures the presence and severity of atherosclerotic burden rather than estimate its presence through indirect measures. For example, although there is a clear relationship between the number of cardiac risk factors and the

presence of coronary artery calcification by EBCT, in one recent series, 40 percent of men and 30 percent of women without risk factors had coronary artery calcification, whereas 26 percent of men and 36 percent of women with greater than three traditional risk factors did not.[71] Similarly, in the Healthy Women Study, risk factor analysis was imprecise at predicting coronary calcification in postmenopausal women.[72] Although the combination of a high low-density lipoprotein (LDL) cholesterol level, a low high-density lipoprotein (HDL) cholesterol level, and a history of cigarette smoking was a strong predictor of coronary artery calcification, this risk factor profile was observed in only 6 percent of all women studied. Furthermore, only 6 of 21 women with the highest calcium scores (>101) had this risk factor profile. Conversely, 20 percent of women in the lowest risk profile (i.e., nonsmokers, LDL cholesterol < 130 mg/dL, and HDL cholesterol > 60 mg/dL) had calcium by EBCT. The incorporation of EBCT calcium results into traditional risk factor analysis may improve accuracy for identifying significant obstructive CAD in symptomatic patients[44,73] and also may be helpful in excluding extensive three-vessel or left main CAD in others.[74]

SUBCLINICAL CAD DETECTION AND STRESS TESTING

Noninvasive techniques, such as exercise treadmill testing and myocardial perfusion imaging, can identify patients with coronary atherosclerosis. However, unlike EBCT, which can detect coronary atherosclerosis at its earliest stages, these techniques can only identify patients with advanced CAD who manifest myocardial ischemia. Although the presence and extent of ischemia can accurately identify asymptomatic individuals at high risk for cardiac events[55-57] (Fig. 17-11), the very low prevalence of a positive test result (<5 percent) precludes their use as primary screening tests for the early detection and treatment of CAD. In fact, both exercise treadmill testing and myocardial perfusion imaging have received a class III indication (no justification for their use) for screening asymptomatic individuals (see Chap. 40).[75,76]

EBCT AND MYOCARDIAL PERFUSION IMAGING

A recent trial explored the complementary role of EBCT and myocardial perfusion SPECT for identifying both subclinical CAD and silent myocardial ischemia in a generally asymptomatic population who had risk factors for CAD development.[53] The purpose of this study was to identify (1) patients with subclinical CAD who might benefit from aggressive risk factor modification and (2) those who are at relatively higher short-term risk for cardiac events based on the presence of silent myocardial ischemia. Among the 3895 subjects who had EBCT, 411 also underwent stress SPECT within a close temporal period (median 17 days). The mean CACS was significantly higher in the 81 subjects (20 percent) who had an abnormal (1065 ± 983) as compared with a normal (286 ± 394; $p < 0.00001$) SPECT. The likelihood of an abnormal SPECT increased dramatically with the total CACS. Whereas only 1 percent of subjects with a total CACS of less than 100 had an abnormal SPECT, this was observed in 46 percent of those with scores of 400 or higher. Only 10 percent of all 3895 subjects scanned with EBCT had a CACS of 400 or higher. Large ischemic perfusion defects were virtually confined to subjects who had a CACS of 400 or higher. Patients with large ischemic perfusion defects by SPECT are known to be at high risk for subsequent cardiac events, whereas patients with small perfusion defects or those with normal scans have an exceedingly low cardiac event rate.[55,56,77-79] Although a similar percentage of subjects had an abnormal SPECT (16.1 percent) or stress electrocardiogram (17.5 percent; p = NS), only the former was related to the total CACS (Fig. 17-12), further illustrating the poor predictive accuracy of treadmill testing for detecting CAD in asymptomatic subjects (see also Chap. 14).

In the author's opinion, the results of this study support the role of EBCT as an initial screening test for identifying subjects with varying degrees of coronary atherosclerosis and emphasize the effectiveness of selectively combining SPECT with EBCT in the anticipated small percentage of subjects who will have a high (>400) CACS so as to specifically identify those with silent myocardial ischemia (Fig. 17-13). *These results need further confirmation.* Although the cost-effectiveness of using EBCT as a screening test requires further clinical investigation, it has been proposed that the CACS may be used to guide therapeutics and recommend the need for additional diagnostic testing.[80] This approach has not been sanctioned by the ACC/AHA expert consensus document on EBCT for the diagnosis and prognosis of

CAD[81] or by the AHA Prevention V Conference[82] (see Chap. 40).

Tracking Changes in Coronary Artery Calcification

Sequential testing with EBCT may be useful in determining the rate of progression of coronary atherosclerosis[83] or in identifying treatment effects based on regression of coronary artery calcification.[84] In order for sequential testing to have any clinical relevance, the biologic changes being studied need to be greater than the intrinsic variability of the test result. Thus, if a CACS increased from 300 to 400, only by knowing the variability inherent to the test result could one determine whether this was a true patient change.

EBCT REPRODUCIBILITY

The reproducibility of EBCT has been evaluated using both the traditional Agatston scoring system[33,85-87] and a more recent volumetric calcium scoring system.[88] With the Agatston method, good inter- and intraobserver reproducibility is reported for recalculating the CACS on a single scan.[31,86] However, significant variability exists when comparing the results of two separate studies on the same patient. Devries et al.[85] studied 91 subjects who had two EBCT scans performed 24 h apart using an identical acquisition protocol. The variability in CACS observed in the 42 subjects who were abnormal on both scans was 49 ± 45 percent. Variability was inversely related to the absolute value of the CACS, being particularly great when the initial score was less than 10 (72 ± 54 percent). In a report by Bielak et al.,[33] 256 patients had two EBCT studies performed minutes apart. The mean CACS was 73 ± 233 (scan 1) versus 75 ± 242 (scan 2). Linear regression analysis showed that the two scores were highly correlated ($r = 0.962$; $p = 0.0001$). However, CACS variability was greatest particularly in patients with low scores. These studies indicate that large changes in initial CACS may be needed to be confident that a real change has occurred beyond chance alone. If one considers that the rate of progression of CACS in patients with known CAD may be less than the observed variability of the test,[83] EBCT assessments using the Agatston scoring system may not be able to track changes in atherosclerotic plaque burden.

The volumetric calcium scoring method proposed by Callister et al.[88] calculates the volume of calcified plaque area rather than generating a CACS based on an arbitrary plaque attenuation coefficient (i.e., Agatston method). This method has been shown in one study to be more reproducible than the Agatston method, with an approximately 40 percent reduction in overall variability.[88]

TRACKING CALCIUM PROGRESSION/REGRESSION

If the reproducibility of EBCT using the volumetric method is adequate, an important question is whether EBCT can be used to track the effects of pharmacologic therapy on plaque progression.[84] In a recent *retrospective* analysis with all of its limitations, Callister et al.[84] studied 149 asymptomatic hyperlipidemic patients who had no history of prior CAD or treatment of hyperlipidemia and who underwent a baseline screening EBCT. Following EBCT, treatment with a statin drug was begun at the discretion of the referring physician. Serial measurements of LDL cholesterol were obtained and correlated with the change in calcified plaque volume. Sixty-five treated patients achieved an LDL cholesterol level of less than 120 mg/dL (mean 100 ± 17 mg/dL), whereas 40 did not (mean 139 ± 18 mg/dL). In the 44 untreated patients, the mean LDL cholesterol level was 147 ± 22 mg/dL. Importantly, in the 44 untreated patients and in the 40 treated patients with an LDL cholesterol level of greater than 120 mg/dL, the calcium score increased by 52 ± 36 and 25 ± 22 percent, respectively. However, in the treated patients who achieved an LDL cholesterol level of less than 120 mg/dL, the calcium score decreased by 7 ± 23 percent. Sixty-three percent of the patients in this group had a net decrease in their calcium volume score, whereas none of the other patients had a reduction in calcium score.

These data suggest that aggressive treatment with cholesterol-lowering medication can reduce *calcified plaque burden* as assessed by EBCT. The reduction in calcified plaque burden presumably indicates a reduction in total atherosclerotic plaque, which is consistent with prior angiographic studies showing a

small, albeit significant, reduction in coronary artery stenosis severity with long-term statin therapy.[89,90]

Contrast Angiography of Bypass Grafts and Native Coronary Arteries

BYPASS GRAFTS

Contrast-enhanced EBCT can visualize both coronary artery bypass grafts[91-93] and native coronary arteries.[94-97] Initial studies using conventional CT angiography reported a sensitivity and specificity of 93 and 95 percent, respectively, for detecting graft patency when compared with coronary angiography.[98] More recently, spiral CT also has been studied for identifying bypass graft patency.[99] The sensitivity, specificity, and diagnostic accuracy for detecting graft patency were 92, 97, and 93 percent, respectively.[99] Positive predictive accuracy for graft closure was 78 percent, and the negative predictive accuracy for graft patency was 99 percent. The accurate detection of internal mammary artery grafts was somewhat lower than that for vein grafts, as was the detection of distal anastomotic sites. Studies using EBCT have likewise reported high sensitivity (89 percent), specificity (93 percent), and overall diagnostic accuracy (92 percent) for detecting bypass graft patency.[91] However, as with spiral computed tomography, EBCT cannot distinguish partially obstructive versus nonobstructed grafts, and the accuracy for assessing graft patency is worse for the right and circumflex arteries as compared with the left anterior descending coronary artery.

NATIVE CORONARY ARTERIES

EBCT also has been established as a noninvasive method for visualizing the epicardial coronary arteries.[94-97] The imaging technique is similar to that used for scanning for coronary artery calcification but requires intravenous contrast material injection. A scout scan is first performed to localize the position of the heart in the chest. The time from contrast material injection to peak contrast enhancement of the aortic root is then determined. The amount of dye administered is based on the heart rate and the number of slices desired. Forty contrast-enhanced cross-sectional images of the heart of 3-mm thickness are then obtained during full inspiration at an acquisition rate of 100 ms per image (one image per cardiac cycle). Image acquisition is gated to the electrocardiogram in a standard fashion. Using the preceding parameters and depending on the heart rate, the total imaging time is between 30 and 50 s (Fig. 17-14).

Several small series have compared EBCT with standard coronary angiography for detecting CAD[94-97] (Table 17-4). The overall sensitivity of EBCT for detecting significant (>50 percent) stenosis is 83 percent and increases to 92 percent for detecting high-grade (>75 percent) stenosis (Fig. 17-15). Specificity is also comparably high at 92 percent.

Table 17-4: Diagnostic Accuracy of Contrast Enhanced EBCT as Defined by Coronary Angiography

Study	No. of Pts	CAD Definition	ARI	Sensitivity	Specificity	Positive PA	Negative PA	Overall Accuracy
Achenbach et al.[94]	125	>75%	376/500 (75%)	69/75 (92%)	282/301 (94%)	69/88 (78%)	282/288 (98%)	351/376 (93%)
Schmermund et al.[95]	28	>50%	237/330* (72%)	31/38 (82%)	176/199 (88%)	31/54 (57%)	176/183 (96%)	207/237 (87%)
Rensing et al.[96]	37	>50%	211/259* (81%)	25/33 (76%)	168/178 (94%)	25/35 (71%)	168/176 (95%)	193/211 (91%)

Budoff et al.[97]	52	>50%	185/208 (89%)	43/55 (78%)	118/130 (91%)	43/55 (78%)	118/130 (91%)	161/185 (87%)
TOTAL	242		1009/1297 (78%)	168/201 (83%)	744/808 (92%)	168/232 (72%)	741/777 (96%)	912/1009 (90%)

ABBREVIATIONS: ARI = arteries (segments*) interpretable by EBCT; PA = predictive accuracy.

EBCT can detect high-grade restenosis after previous coronary artery angioplasty with high sensitivity (94 percent) and specificity (82 percent).[100] Most patients (96 percent) without restenosis by EBCT have comparable normal angiographic findings (Fig. 17-16).

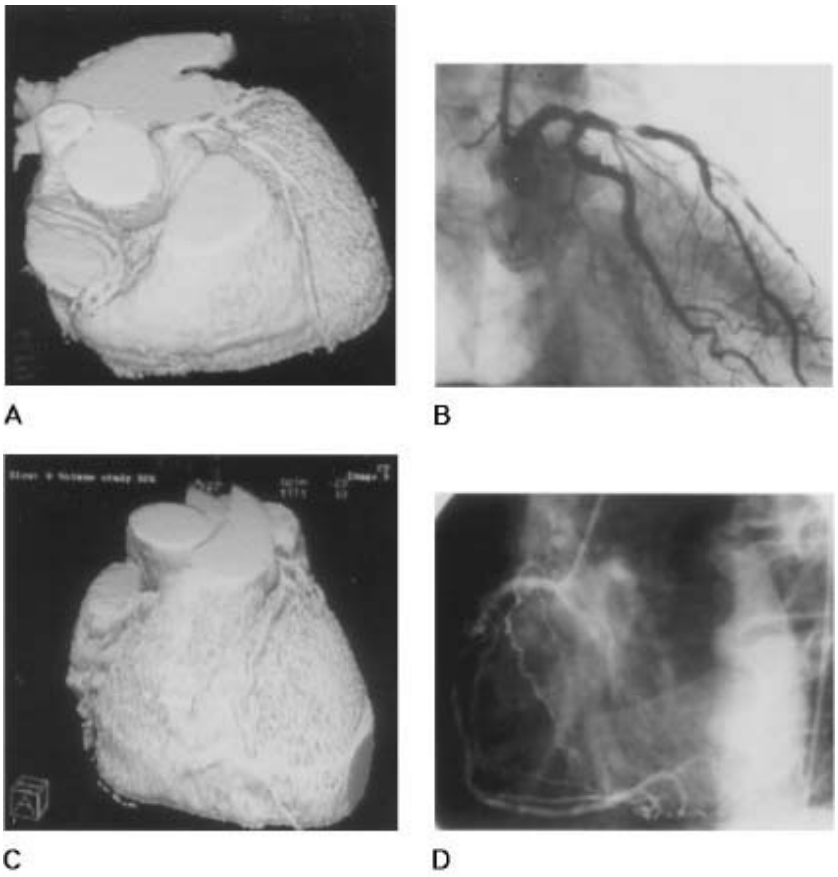

Figure 17-16: Three-dimensional EBCT reconstruction and coronary angiography depicting high-grade restenosis after coronary angioplasty of the proximal left anterior descending coronary artery (*A*, *B*) and right coronary artery (*C*, *D*). (From Achenbach et al.[100] Reproduced with permission from the publisher and authors.)

These reports are encouraging, but several points must be emphasized. EBCT *cannot* assess approximately 20 to 25 percent of all coronary arteries due to technical factors, such as respiration artifact, the presence of severe coronary calcification, and motion artifacts. Respiration artifacts can be avoided by instructing patients about proper breath-holding techniques. *Motion artifacts* are observed most commonly with the right and circumflex coronary arteries because they lie in close proximity to the atria, which contract at end-diastole. The right and circumflex arteries also lie perpendicular to the imaging plane, limiting spatial resolution. Imaging at a different time in diastole (to avoid atrial contraction), shortening acquisition time,

and imaging in different cardiac planes may obviate these problems.

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EVALUATION OF PERICARDIAL DISEASE

Computed tomography provides excellent visualization of the pericardium and associated mediastinal structures[101-104] (Fig. 17-17). Although echocardiography remains the primary diagnostic technique for assessing pericardial abnormalities, CT scanning can be useful, particularly when visualization of the pericardium is suboptimal with echocardiography. CT scanning can readily detect pericardial effusion and can help determine the characteristics of the fluid based on CT density.[105]

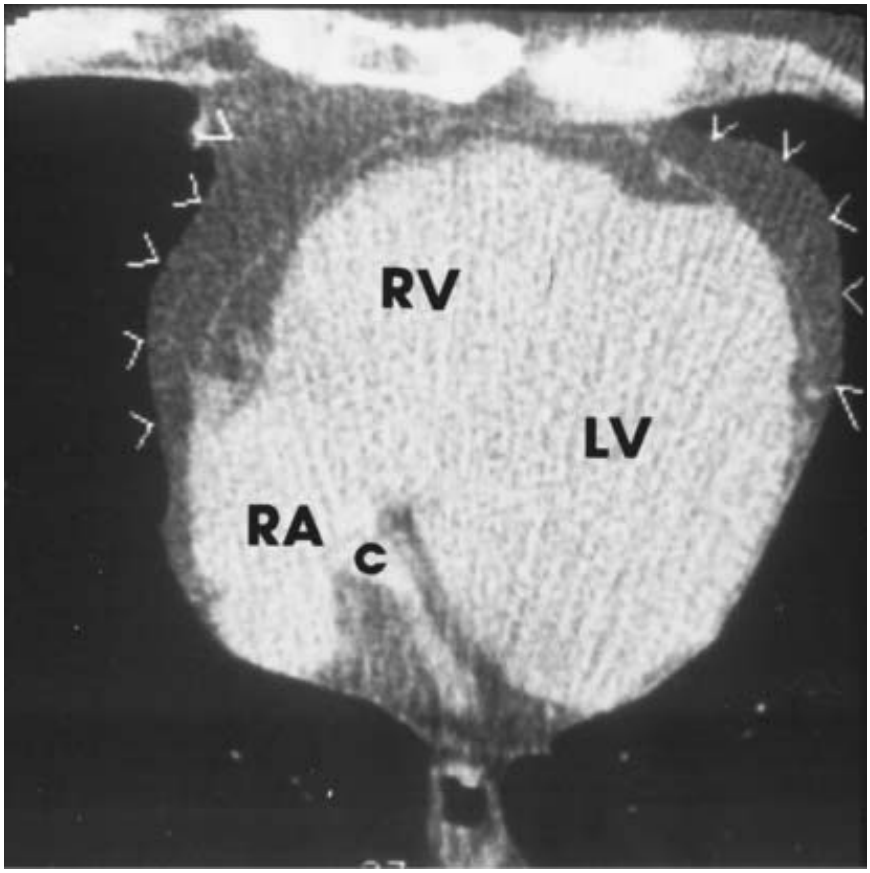

Figure 17-17: The fat that resides both inside and outside (*arrowheads*) the pericardium provides sufficient contrast to outline the normal pericardium, which is only 1- to 2-mm thick. Contrast enhancement with iodine agents is unnecessary. C, coronary sinus; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Brundage BH, Mao SS. In: Schlant RC et al., eds. *Diagnostic Atlas of the Heart*. New York: McGraw-Hill; 1996:243. Reproduced with permission from the publisher and authors.)

CT scanning is useful in accurately diagnosing constrictive pericarditis and distinguishing it from similar conditions, such as restrictive myopathy.[102] Based on the presence of pericardial thickening (Fig. 17-18) or calcification (Fig. 17-19), cine EBCT can assess both the

anatomic and functional abnormalities associated with pericardial constriction.[103] A pericardial thickness of more than 4 mm in a patient with typical abnormal rapid early LV diastolic filling is diagnostic of pericardial constriction.

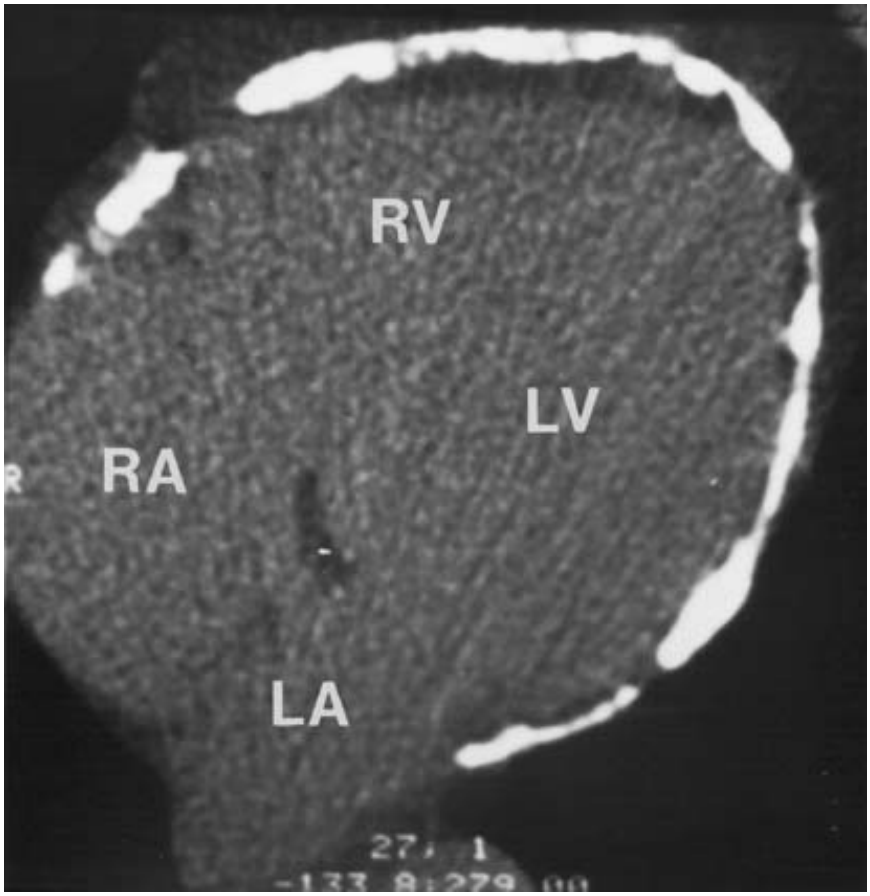

Figure 17-19: Densely calcified pericardium is easily identified in this scan of the midheart. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Brundage BH, Mao SS. In: Schlant RC et al., eds. *Diagnostic Atlas of the Heart*. New York: McGraw-Hill; 1996:243. Reproduced with permission from the publisher and authors.)

CT scanning can assess congenital abnormalities such as absence of the pericardium[106] or pericardial cyst.[107] CT scanning is currently one of the best techniques for defining the location and extent of mediastinal tumors and in diagnosing metastatic involvement of the pericardium.[107,108]

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Chapter 17: COMPUTED TOMOGRAPHY OF THE HEART

EVALUATION OF CONGENITAL HEART DISEASE

Standard CT scanning and EBCT are both useful techniques in the evaluation of patients with congenital heart disease. Anomalies of the aortic arch, septal defects, tetralogy of Fallot, Ebstein's anomaly, and abnormal arteriovenous connections can all be carefully evaluated with CT techniques[109,110] (Fig. 17-20). EBCT, due to its high spatial resolution, also can evaluate the atrioventricular valves in conditions such as tricuspid and mitral valve atresia,[111,112] and detect congenital abnormalities of the coronary arteries.[113] Beyond identifying structural abnormalities, EBCT can be used to accurately quantify intracardiac shunts,[114,115] assess RV and LV function,[5,7] measure myocardial mass,[1-3] and evaluate valvular function. Despite the applications of CT scanning in evaluating congenital heart disease, magnetic resonance imaging is the modality of choice because it does not require x-ray exposure or the need for intravenous contrast material for both structural and functional delineation.

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EVALUATION OF CARDIAC TUMORS

The presence and extent of intracardiac tumors (Chap. 77) can be well defined with either conventional CT scanning or EBCT. CT scanning also can delineate metastatic tumor within the myocardial wall. Intracardiac tumors are readily detected by noninvasive two-dimensional echocardiography. Tumors such as myxomas, however, are also well visualized by EBCT, particularly when imaging is performed following intravenous contrast enhancement[116] (Fig. 17-21).

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DISEASES OF THE GREAT VESSELS

Conventional CT scanning is widely used for diagnosing thoracic aortic aneurysms and dissections.[117-119] With the introduction of spiral CT scanners, up to 60 images of approximately 2- to 3-mm thickness can be acquired within a single 30-s breathhold. A complete study of the thoracic aorta can be completed in only several minutes. Following scan acquisition, three-dimensional reconstructions are readily produced that can be rotated and viewed from multiple angulations to facilitate diagnosis. EBCT also can acquire rapid CT images with elimination of aortic pulsation as a cause for potential artifact.[120]

Aortic dissection is readily diagnosed with CT angiography with greater than 90 percent accuracy. In a recent study comparing spiral computed tomography, magnetic resonance imaging, and two-dimensional echocardiography, CT and magnetic resonance imaging were shown to be superior to echocardiography in their diagnostic accuracy.[119] Similar comparisons with EBCT are not available, but the increased imaging speed with EBCT over spiral CT would appear to be an advantage. Excellent definition of the intimal flap, false and true lumens, and the amount of intraaneurysmal thrombus can be determined.

CT scanning is also an effective method for diagnosing aortic aneurysm, defining its maximal diameter, and monitoring its expansion over time[120] (Fig. 17-22). CT scanning can diagnose traumatic aneurysms of the thoracic aorta,[118] sinus of Valsalva aneurysms, and coarctation of the aorta (Fig. 17-23). In patients undergoing redo coronary artery bypass surgery, CT scanning may guide the surgical approach by defining the position of the sternum to the right ventricle and aorta and thereby avoid unnecessary bleeding.[121]

Both spiral CT[122,123] and EBCT[124] can diagnose acute and chronic pulmonary thromboembolism (Fig. 17-24). CT scanning may be particularly useful in confirming the diagnosis of acute pulmonary embolism in patients with an intermediate nuclear ventilation-perfusion scan.[123]

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Figure 17-13: EBCT (*A*) and SPECT (*B*) images of asymptomatic subject who had a high-risk CACS of 937. Circles define regions of coronary calcification. The treadmill test was terminated at 9.0 min due to patient fatigue. SPECT demonstrated a large, reversible 48 percent perfusion defect within the distribution of all 3 major coronary arteries (COMP-SC) (*B*). This patient had severe 3-vessel disease on angiography and underwent CABG. PDS indicates perfusion defect size. (From He et al.[53] Reproduced with permission from the publisher and authors.)

Figure 17-14: EBCT images of the heart. *A*. A cross section of the heart at the level of the aortic root depicts the origin of the left main (LM), proximal left anterior descending (LAD) (*arrow*), and left circumflex (*arrowhead*) coronary arteries. *B*. A contrast-enhanced three-dimensional reconstruction of the entire heart. *C*. The main stem of the pulmonary artery and the atrial appendages have been removed to show the LM, LAD, and right (RCA) coronary arteries. (From Achenbach et al.[94] Reproduced with permission from the publisher and authors.)

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Figure 17-16: Three-dimensional EBCT reconstruction and coronary angiography depicting high-grade restenosis after coronary angioplasty of the proximal left anterior descending coronary artery (*A, B*) and right coronary artery (*C, D*). (From Achenbach et al.[100] Reproduced with permission from the publisher and authors.)

Figure 17-17: The fat that resides both inside and outside (*arrowheads*) the pericardium provides sufficient contrast to outline the normal pericardium, which is only 1- to 2-mm thick. Contrast enhancement with iodine agents is unnecessary. C, coronary sinus; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Brundage BH, Mao SS. In: Schlant RC et al., eds. *Diagnostic Atlas of the Heart*. New York: McGraw-Hill; 1996:243. Reproduced with permission from the publisher and authors.)

Figure 17-18: Diffuse pericardial thickening surrounding the entire heart in a patient with pericardial constriction.

Figure 17-19: Densely calcified pericardium is easily identified in this scan of the midheart. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Brundage BH, Mao SS. In: Schlant RC et al., eds. *Diagnostic Atlas of the Heart*. New York: McGraw-Hill; 1996:243. Reproduced with permission from the publisher and authors.)

Figure 17-20: Postoperative EBCT study of a patient operated for tetralogy of Fallot demonstrates (*A*) RV dilatation and aneurysm (*open arrows*) with paradoxical diastolic flattening of the interventricular septum due to severe tricuspid regurgitation. The same study (*B*) revealed residual stenosis of the right pulmonary artery (RPA). Aao, ascending aorta; Dao, descending aorta; LV, left ventricle; MPA, main pulmonary artery; RA, right atrium; SVC, superior vena cava.

Figure 17-21: A single diastolic frame from a contrast-enhanced cine CT scan defines the left atrial septal attachment of a myxoma (M). The frondlike excrescences are characteristic of this tumor. LV, left ventricle; O, left ventricular outflow tract; RV, right ventricle; S, superior vena cava. (From Brundage BH, Mao SS. In: Schlant RC et al., eds. *Diagnostic Atlas of the Heart*. New York: McGraw-Hill; 1996:244. Reproduced with permission from the publisher and authors.)

Figure 17-22: A large thrombus (t)-filled aneurysm of the aortic arch occupies most of the upper left thoracic cavity. The innominate vein (i) courses anterior to the innominate and left common carotid artery.

Figure 17-23: Three-dimensional EBCT reconstructions of aortic arch, innominate vein (IV), main (MPA), left (LPA), and right (RPA) pulmonary arteries in a patient with recurrent coarctation of the aorta. The upper panel (*A*) shows a possible web along the upper surface of the aortic isthmus (AoI) (*arrow*) with aneurysmal dilatation of the descending aorta (DAo) below the coarctation site. The lower panel (*B*) shows a well-defined web (*arrow*). The corresponding aortogram (*C*) (*right*) shows a discrete web below AoI with a DAo aneurysm. Aao, ascending aorta; IA, innominate artery; SVC, superior vena cava; VA, vertebral artery. (From Pitlick PT, Anthony CL, Moore P, et al. Three-dimensional visualization of recurrent coarctation of the aorta by electron-beam tomography and MRI. *Circulation* 1999; 99:3086-3087. Reproduced with permission from the publisher and authors.)

Figure 17-24: Large left pulmonary artery (LPA) chronic thrombus (*arrows*) is outlined by contrast medium on this high-resolution ultrafast CT scan. Aao, ascending aorta; Dao, descending aorta; MPA, main pulmonary artery.

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Customer Privacy Policy

Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 18A:

MAGNETIC RESONANCE IMAGING OF THE HEART

Authors: Mark Doyle, Gerald M. Pohost

INTRODUCTION

The phenomenon of nuclear magnetic resonance (NMR) was discovered more than 60 years ago, and NMR spectroscopic methods were initially applied by physicists and chemists to explore molecular structure and composition.[1,2] Although NMR spectroscopy has proved invaluable in providing metabolic information in a variety of different myocardial physiologic and pathologic states, it is still used primarily as a research tool. The concept of using NMR to obtain images was propounded by Lauterbur[3] and was introduced independently by Mansfield in the early 1970s, when it was discovered that an inhomogeneous magnetic field can localize nuclei in space and thus produce an image. Advances in computer technology and superconducting magnets now allow routine clinical NMR imaging. Images are obtained with exquisite morphologic detail, in any tomographic orientation, in a nondestructive and noninvasive manner. As NMR entered mainstream clinical practice, the potential for public concern about "nuclear"technology was avoided by using the less descriptive term *magnetic resonance imaging* (MRI). It is important to note that there are types of magnetic resonance in addition to NMR, including electron spin resonance and Mossbauer spectroscopy.

Physicians and patients have become aware of the great versatility of MRI, and that knowledge has allowed the modality to become the "gold standard" of noninvasive imaging for many diagnostic and management areas in noncardiac diseases. Similarly, MRI has the potential to become an invaluable tool for evaluating cardiovascular morphology, function, perfusion, and viability. Even diagnostic imaging of the coronary arteries promises to become a reality in the near future. In addition, investigations of the clinical characteristics of plaque promise an exciting future in this area of MRI.

This chapter focuses on the basic principles and practices of applying MRI for the evaluation of normal cardiovascular structures and the diagnosis of diseases that affect the heart.

NEXT

Last modified: September 27, 2001 .

Chapter 18A: MAGNETIC RESONANCE IMAGING OF THE HEART

PRINCIPLES OF NMR

Magnetism and Vectors

To fully understand NMR, one must have extensive knowledge of quantum and nuclear physics; fortunately, the basic theory of NMR can be explained by using concepts drawn mostly from classical physics. An intrinsic property of atomic nuclei is that of *spin*. The combination of nuclear spin and electric charge is analogous to an electric current circulating in a small wire loop, producing a small magnetic field (Fig. 18A-1). The strength of the magnetic field produced by the nucleus is expressed in terms of a magnetic moment.

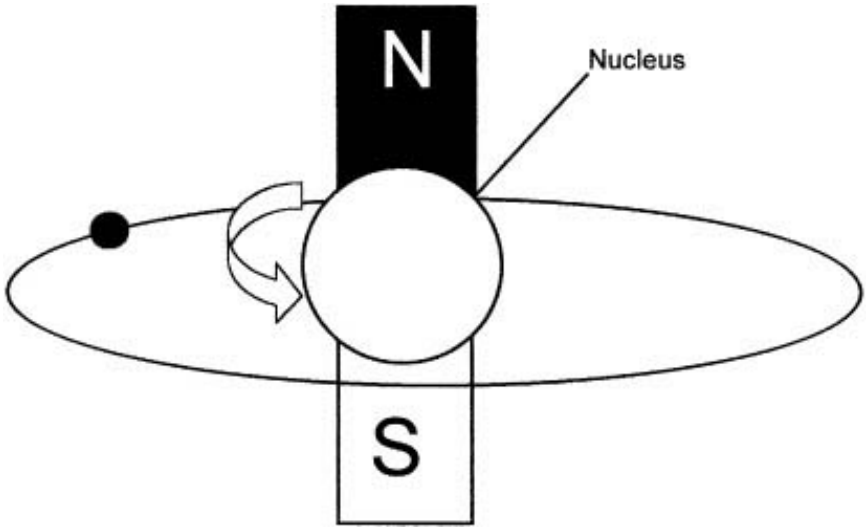


Figure 18a-1: The positively charged nucleus of a hydrogen atom spins and creates a magnetic field.

Within the body, nuclei orient randomly in space and do not produce any net magnetization; however, positioning the body within a strong magnetic field produces a net magnetic moment within the body. Intuitively, one might expect all nuclei to align parallel to the magnetic field (B_0), however, two energy states are created: parallel and antiparallel to B_0. Since the parallel alignment is at a lower energy level, slightly more nuclei become aligned parallel to B_0, causing the body to become weakly magnetized (Fig. 18A-2). The strength of the magnetization vector is proportional to the strength of B_0, the energy difference between spin states, and temperature. The fractional excess in the lower-energy state is extremely small [i.e., about 3 per million for hydrogen nuclei in at a field of strength 1.5 tesla (T) at body temperature].

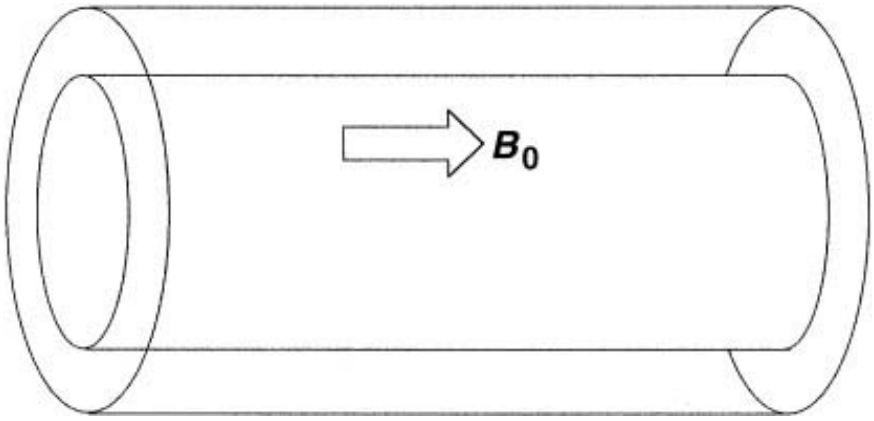


Figure 18a-2: The nuclei of the hydrogen atoms within the body (represented by the black and white bar magnets) align with the magnetic field (B_0), both parallel and antiparallel. Slightly more nuclei align parallel to the B_0, creating a net magnetization vector (*open arrow*).

In equilibrium, the magnetic moment does not yield a detectable signal. Signal can be generated by perturbing the system, causing its net magnetization to deviate from alignment with B_0. When tilted from alignment, the magnetization vector experiences a torque that causes it to precess. The phenomenon of nuclear precession is analogous to the precession exhibited by a spinning gyroscope tilted from alignment with the earth's gravitational field. Importantly, the precession frequency (ω_0) is much lower than the spinning frequency and is proportional to the field strength B_0. The frequency ω_0 is related to B_0 by a constant (γ) termed the *gyromagnetic ratio*, and these valves are related by the Larmor equation: $\omega_0 = \gamma B_0$ The gyromagnetic ratio (γ) is unique for each nuclear isotope.

The Resonance Phenomenon

To displace spins from alignment with B_0, a magnetic field of much lower strength (B_1) is applied so that B_1 rotates in a plane perpendicular to B_0. If the B_1 field rotates at the Larmor frequency, it will maximally affect the net magnetization of the body by virtue of being on resonance (Fig. 18A-3). The resonance frequency of the B_1 field is in the radiofrequency (RF) range and contributes the term *resonance* to NMR and MRI. The angle (θ) of rotation from B_0 is proportional to the time *(t)* of application of the rotating field and the strength, $|B_1|$: $\theta = \gamma |B_1| t$ When B_1 is turned off, the spins are free to precess under the influence of the extrinsic static magnetic field. It is during this time of free precession that the spins give off a detectable electromagnetic signal, again in the RF frequency range. The spin signal decays over a matter of tens of milliseconds and is known as *a free induction decay* (FID) (Fig. 18A-4).

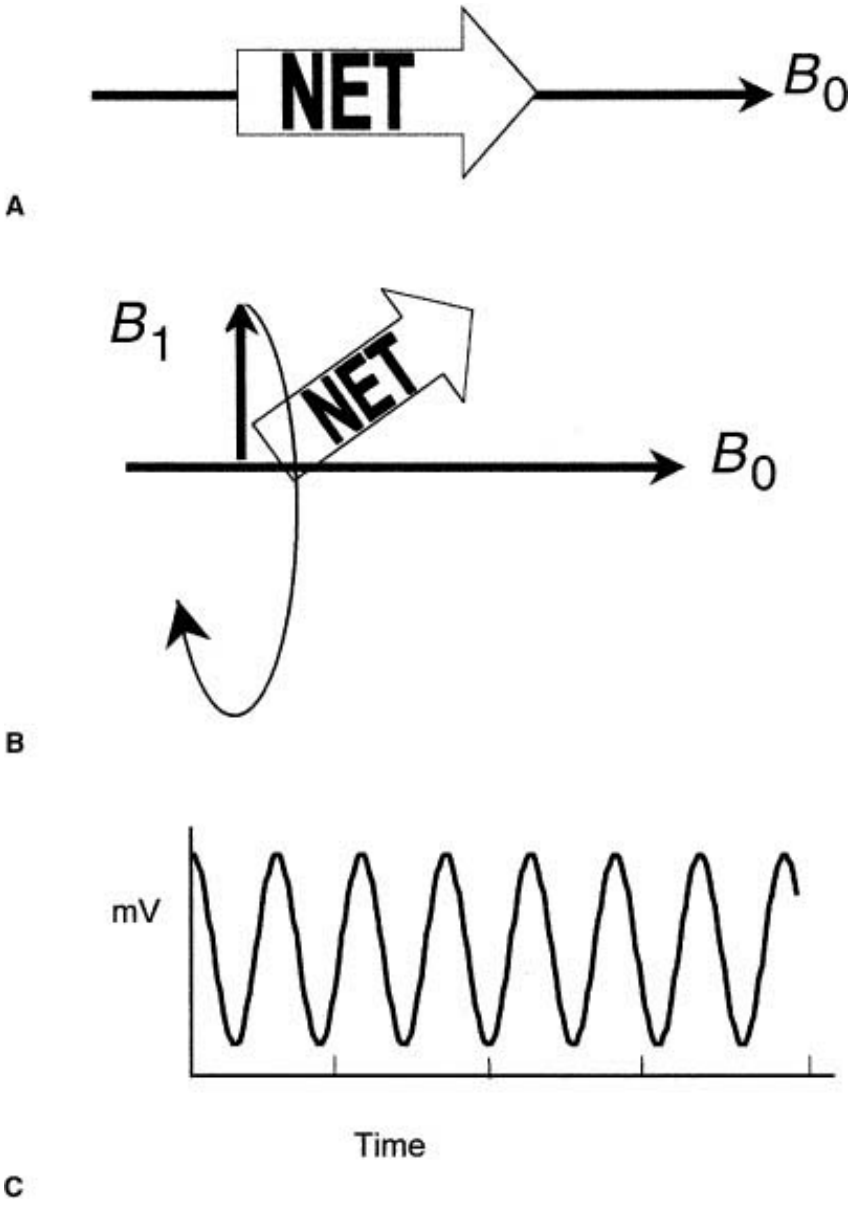


Figure 18a-3: The net magnetization vector (NET) aligns with B_0 (*A*). A rotating magnetic field (B_1) applied as a radiofrequency (RF) pulse causes the vector to precess out of B_0 alignment (*B*). The RF pulse is then discontinued, and the vector precesses, producing a signal (*C*) with a characteristic frequency, which depends on the field strength (B_0) of the magnet and the atomic species producing the signal (usually hydrogen).

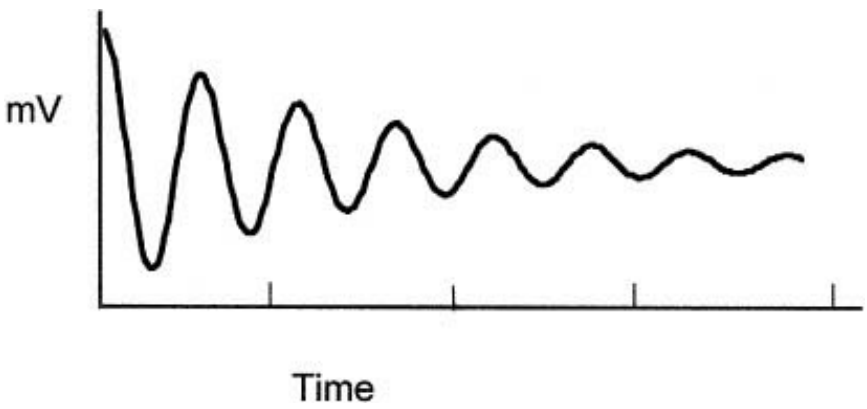


Figure 18a-4: The signal detected from the freely precessing nuclei decay, typically in a matter of milliseconds.

Relaxation

The spin signal gradually decays as a result of "relaxation" phenomena, that is, the gradual return of nuclei to their equilibrium energy states. Two distinct relaxation parameters are used frequently: T1 and T2; these parameters can be exploited to enhance image contrast.

T1 RELAXATION

Nuclei in the body are surrounded by a network of structures collectively known as the *lattice*. The lattice and the spin system constantly exchange energy; hence, nuclei lose the energy initially imparted by the RF pulse, resulting in a decrease in the net magnetic moment as spins realign along the B_0 axis. The realignment occurs in an exponential manner, and T1 relates to the time constant of this exponential decay. The time constant, T1, for a particular sample is the time needed for 63 percent of the nuclei to return to their equilibrium value. T1 frequently is referred to as the spin-lattice relaxation time. After a perturbation of the spin system, a time period of 5 T1 is regarded as necessary for the spins to return to equilibrium. Since spin-lattice relaxation requires an exchange of energy, the process is field-strength-dependent. The T1 of myocardium is approximately 900 ms at a field strength of 1.5 T and is less at lower fields.

T2 RELAXATION

Aside from the lattice, the interaction of neighboring spins contributes to the relaxation process. These interactions are referred to as *spin-spin relaxation* or *T2 relaxation*. Spin-spin relaxation occurs in the so-called transverse plane, i.e., the plane orthogonal to the B_0 direction in which the spins precess. The spin-spin interaction does not require any net energy exchange but instead can be envisioned as a loss of coherence of the precessing spins. As the spins gradually lose phase coherence, their net signal diminishes exponentially. The T2 for a sample is the time interval for the transverse magnetization to decay to 37 percent of its initial value. Additionally, in practice, B_0 fields are not perfectly homogeneous. Thus, nuclei within a sample are exposed to slightly different magnetic fields and, as a result, precess at slightly different frequencies. The free induction decay in such a field occurs more rapidly than is indicated by purely T2 considerations. This more rapid rate of decay is termed $T2^*$ ("T2 star"). The T2 process does not involve an exchange of energy with the lattice and is essentially independent of field strength. The T2 of myocardium is approximately 80 ms.

Each type of tissue has characteristic T1 and T2 relaxation properties that are influenced by a variety of conditions, including the proximity and mobility of molecules in the surrounding environment, the hydrogen concentration of the tissue, and exposure to the local magnetic fields at the molecular level. MR image contrast can be made sensitive to these conditions through the use of specialized pulse sequences that can be implemented by using the computer in the MR system. Image contrast generally is described in terms of the level of T1 or T2 "weighting" (described later in this chapter). Additionally, image contrast can be sensitive to motion of either the blood or the myocardium. These different contrast mechanisms can be understood in terms of the image-forming process of MRI techniques used clinically to image cardiovascular structures

Magnetic Resonance Image Formation

MRI is the most complex of all the medical imaging modalities, and it is important in regard to optimal image interpretation to have an understanding of the technical aspects of image formation. While scanner technology is constantly improving, certain basic system features remain constant.

The following paragraphs describe the basic elements of an MR system.

A general misconception exists that clinical MR systems, which are used commonly for brain and musculoskeletal imaging, cannot perform cardiovascular imaging and thus a dedicated cardiovascular system is needed. In fact, specialized software can produce a means for cardiovascular imaging in most clinical systems. Typically, the only additional hardware requirements are cardiac and respiratory gating devices, which are available for most systems. However, optimal cardiovascular magnetic resonance (CMR) requires a specialized system dedicated to cardiovascular applications. Clinical MR systems use superconducting magnets with field strengths typically ranging from 0.5 to 1.5 T. A tesla is the equivalent of 10,000 gauss (G). To put this into perspective, the earth's magnetic field is between 0.3 and 0.7 G, and a household magnet is about 100 G (0.01 T). Higher-field-strength magnets result in an increased signal-to-noise ratio and, as a consequence, clearer images; however, these higher field strengths often exaggerate artifacts because of cardiac, respiratory, and blood flow motion. Most clinical systems operate at 1.5 T, but clinical magnets with field strengths as high as 8 T are being used for research.

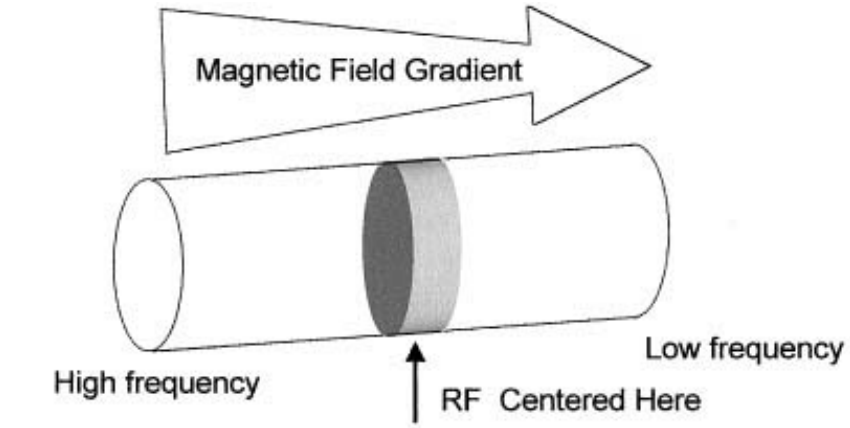
Systems tailored for cardiac applications generally acquire data rapidly to "freeze" cardiac motion and produce images with minimal blur. In an attempt to decrease scan times, the signal-to-noise ratio generally is reduced. Thus, of particular importance to cardiac systems is the requirement to obtain data with a high signal-to-noise ratio. Thus, cardiac systems typically are supplied with specialized receiver coils. Signal reception is optimal when the coil is closest to the heart. Typically, a cardiac coil comes in two parts: one positioned posteriorly and one positioned anteriorly over the heart. These coils are usually of the efficient phased-array design.[4]

As a result of its lesser regularity, respiratory motion is more difficult to compensate for than is normal cardiac motion. Cardiac motion is accommodated by synchronizing the acquisitions with the electrocardiogram. However, for general cardiac imaging, simultaneous triggering with the respiratory cycle is generally time-prohibitive. To accommodate the requirements for respiratory compensation, a number of rapid cardiac scan approaches have been developed that can be applied in combination with respiratory compensation. One method of respiratory compensation is to have the patient voluntarily suspend breathing temporarily (typically for 15 to 30 s). During this interval, the scan is performed. Other methods involve tracking the respiratory excursion of the heart by means of a belt and bellows apparatus secured around the patient's waist. Alternatively, an MRI-derived "navigator" signal (analogous to an M-mode echocardiogram) can be used to track the position of the diaphragm and allow synchronization with the respiratory cycle.[5,6]

GRADIENTS

To produce an image, spatial discrimination must be encoded in the NMR signal. Within a homogeneous B_0 field, all nuclei resonate at the same frequency; thus, after the application of an RF pulse, a single frequency signal is produced with no spatial information. To generate an image, the magnetic field must vary over the field of interest. This is best accomplished by applying a linear magnetic field gradient over the sample. Three orthogonal gradients are incorporated into the scanner system: in the craniocaudal direction (z), in the right-to-left direction (x), and in the anterior-posterior direction (y). These gradients are controlled by the scanner's computer system. The first step in spatial resolution is to select a slice at a specified location. Slice selection is accomplished by the application of a linear gradient orthogonal to the desired slice direction. This gradient generates a range of resonant frequencies along the direction of the gradient. When the B_1 RF pulse is applied at a specific frequency (corresponding to the resonance frequency of the desired slice position), only spins in a narrow frequency range experience the effect of the RF pulse (Fig. 18A-5*A*). In this way, a slice can be selected with programmable orientation and thickness. To generate an image of the slice, it is necessary to apply gradients in two dimensions. Unfortunately, the application of two such gradients simultaneously results in a single gradient

vector. Hence, image generation in two dimensions requires that the two gradients be applied at separate times. This feature is responsible for the relatively long acquisition times associated with cardiovascular MRI. It is important to realize that the MRI signal does not directly relate to an image. Instead, an image is formed by the mathematical process known as a Fourier transform (Fig. 18A-5*B*). The MRI signal is acquired and assembled into a matrix that is termed k-space, and an image is produced when the Fourier transform is applied. In Fig. 18A-5*C*, the process of acquiring lines in k-space is illustrated. The data are read in the presence of one imaging gradient termed the *frequency encoding* or *measurement* gradient. To step between lines of k-space, a "phase-encoding" gradient is applied as indicated in Fig. 18A-5*C*.



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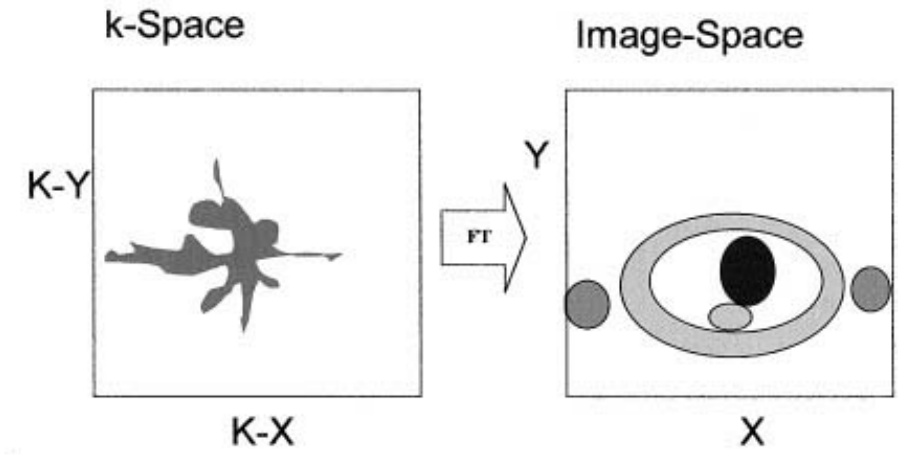

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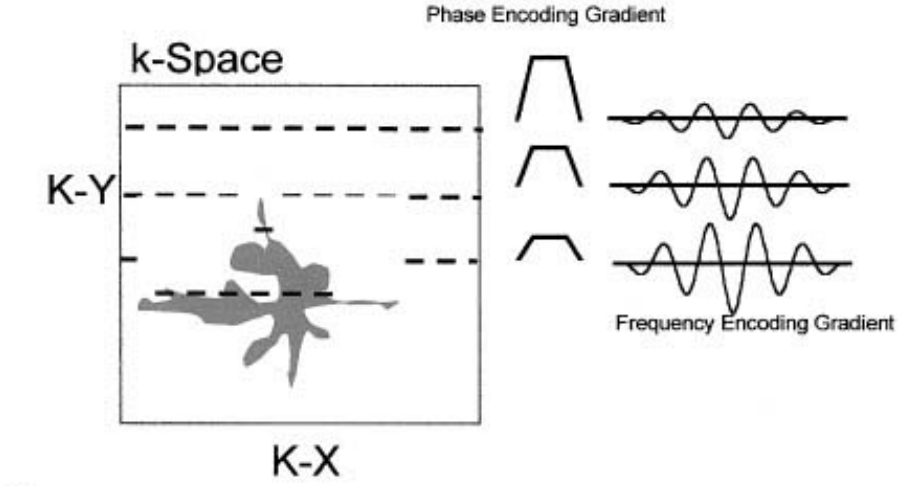

C

C

Figure 18a-5: A combination of gradient and RF energy is used to select a slice in the sample (*A*). The gradient imposes a range of frequencies over the sample, and the B_1 field is applied at the frequency needed to select the slice. The data sampled by MRI are in the so-called k-space of the frequency domain (*B*). Images in this domain are converted into images in the spatial domain by performing a Fourier transform (FT). Each line of k-space is sampled by application of a "frequency-encoding" gradient (typically for 2-3 ms) (*C*). To step between each line of k-space, a "phase-encoding" gradient is applied (typically in 1 ms).

PULSE SEQUENCES

A pulse sequence is a set of RF and gradient waveforms that are required for image generation. Different pulse sequences highlight different features in an MR image.

Gated Spin Echo

On slice selection using the gradient and RF pulse combination, the signal is maximal immediately at the end of the RF pulse. However, relatively few sequences can use the signal at this time, since the signal generally requires some form of preparation before it can be useful. However, as time from the RF pulse elapses, the signal loses coherence because of the combined effects of T2 and magnet inhomogeneities.

The application of a second pulse of 180° causes the spins to reverse direction and realign (or refocus), resulting in a so-called spin echo. This refocused echo signal is corrected for the effects of field inhomogeneity (but not for the effects of T2 relaxation). The time from the RF pulse to the maximal signal is called the *echo time* (TE). The time interval between each "phase-encoding" step in the image-generating process is called the *repetition time* (TR). The imaging computer can vary TE and TR to affect the degree of T1 and T2 "weighting" in the images; i.e., for a short TE and TR the image becomes T1-weighted, and for a long TE and TR the image becomes T2-weighted. However, much of the contrast in such spin-echo images occurs as a result of rapidly flowing blood. Since blood moves between applications of the two RF pulses, the signal emanating from the region with flowing blood is related to the blood flow. In the presence of rapid blood flow that is directed out of the imaging plane, there is no signal, since the blood does not experience the refocusing pulse. As blood flow decreases, its signal increases. Thus, within vascular lumens and cardiac chambers, signal voids generally are seen in spin-echo images (also termed dark blood images). This sequence highlights cardiovascular wall morphology (Fig. 18A-6).

Gated Gradient Echo

Another widely used method for generating clinical images involves applying a magnetic gradient to recall a signal echo. After the RF pulse used in slice selection, an additional gradient is applied and then reversed after several milliseconds. This refocuses the spins into an echo. The major difference between this "gradient-echo" approach and the "spin-echo" approach is that with gradient-echo approach, only one RF pulse is applied. Thus, gradient-echo images can be made sensitive to flowing blood (since even moving blood experiences the signal-refocusing properties of the gradient echo sequence). This method typically uses rapidly repeated RF pulses and causes partial "saturation" (i.e., heavy T1 weighting) of spins. Thus, decreased signal from static tissues results from the rapid repetition rates of the RF pulse. However, blood flowing into the imaging plane will not have been exposed to the slice-selective train of RF pulses and thus will not be "saturated," resulting in an intense blood signal relative to the static tissue signal with low intensity (Fig. 18A-6). Consequently, flowing blood appears bright. Thus, the gradient-echo-

type sequence also is known as the *bright blood sequence*. This imaging approach is quite useful, since the resultant images may be displayed in a cine/movie to allow visualization of cardiac and blood pool motion. One should note that turbulent flow causes dephasing of spins as a result of chaotic motion, resulting in signal loss. Therefore, this technique is useful for visualizing regurgitant, stenotic, and shunt lesions.

Rapid Imaging

Of particular importance to cardiovascular imaging are rapid imaging sequences, since the gated approaches result in a prolongation of the basic scan time. A two-dimensional (2D) image of a stationary object can be generated in a matter of seconds (e.g., with a TR of 7 ms, an image with 128 lines can be generated in less than 1 s). With the requirement of cardiac triggering, the scan time will be extended to the time of 128 cardiac cycles. Thus, methods for producing cardiac images in shorter times have been an active area of research.[7-9] One such rapid sequence is echo-planar imaging (EPI).[10-13] EPI is based on the gradient-echo approach, but instead of just one echo being recalled, a number of echoes are recalled, speeding up the sequence. The main disadvantage of the EPI approach is that the echo train can be quite long (i.e., greater than 50 ms) and thus the images are heavily T2-weighted. An approach that avoids the T2 weighting of EPI is the segmented or turbo imaging approach. This involves the acquisition of a series of single gradient echoes that are acquired rapidly in a group and assigned to one cardiac phase.[14-17] Further modification and variants continue to be developed to allow the production of cardiac images in ever shorter scan times.

One rapid technique that merits special mention is spiral imaging. This approach does not encode data in an orthogonal matrix (as is done in the techniques described above) but acquires data in a curved matrix. This approach exploits the fact that it is physically easier to drive the imaging gradients by using a waveform with gradually increasing amplitude as opposed to abruptly switching the polarity of the gradients (as is required for the gradient-echo and spin-echo approaches). Spiral approaches have been used to produce high-resolution images of the coronary arteries. The disadvantage of this technique is that high system performance is required.[18]

SPECIALIZED PULSE SEQUENCES

An imaging sequence that can be used in conjunction with many of the approaches described above is that of tagging[19-22] (Fig. 18A-7). Typically, tagging involves applying a set of parallel lines or a grid of orthogonal lines at the time of the electrocardiogram (ECG)R wave. Once they are applied, these lines or grids then move with the heart to highlight motion. Naturally, since the lines or grids are composed of tagged signal regions, they cannot interfere with cardiac function. Such RF tagging allows quantification of cardiac function on a regional basis.

Specialized sequence known as phase-velocity mapping (PVM) is used to determine blood flow and myocardial motion. PVM uses NMR signal phase (as opposed to signal amplitude) that is made sensitive to motion.[23-27] With PVM, two image sets are required to generate a velocity map, and this doubles the scan time compared with conventional MRI. However, the advantage of generating such "phase-velocity maps" is that the velocity in any selectable direction can be encoded.

It can be appreciated that many creative pulse sequences can be used to highlight morphology, function, blood flow, perfusion, and even diffusion. These include techniques applied to MR angiography (MRA), quantification of cardiac function, quantification and visualization of blood flow velocity, and cardiac perfusion imaging. Clinical application of these techniques will be discussed in detail later in this chapter.

Patient Considerations

PATIENT COMFORT

Most patients tolerate the MRI procedure without the need for sedation. However, claustrophobia limits scan completion in approximately 5 percent of patients. Although rarely necessary, gentle sedation may be required so that the patient can relax and then remain motionless during the scan acquisition. Methods more commonly used to decrease anxiety include removing the patient from the magnet bore between scans and allowing a friend or family member to be positioned at the head of the bore to talk to the patient during scanning. Earphones are placed on the patient to minimize the acoustic noise, allowing many patients to sleep during the scan. However, for protocols that require the patient to perform breath holds, it is necessary for the patient to remain conscious throughout the examination. For these scans, some systems allow the patient to view movies through special MRI-compatible virtual reality systems. Newer magnets are shorter and may reduce the incidence of claustrophobia. Scan preparation and imaging time vary with the complexity of the clinical question to be answered. For example, if only ventricular function is assessed, the study can be performed in approximately 20 min; however, if the patient is being assessed for complex congenital heart disease, imaging times of 1 h or more may be required. As scanner technology and software have improved, imaging times have decreased. However, as the capabilities of MRI have increased, the amount of clinical data that can be acquired during an MRI session has increased. Thus, typically an MRI scan session can last 30 to 45 min. However, during this time a great deal of clinical information can be acquired.

PATIENT SAFETY

As with any diagnostic medical technique, safety is a critical issue, and safety procedures and rules should be familiar to the physicians ordering the scan and the technicians performing the scan. MR techniques can be contraindicated in a patient because of (1) the potential of the magnetic field to move or dislodge an object or device, (2) the possibility that the RF field will heat a conductor such as a pacemaker electrode, (3) the potential for inducing electric currents in a conductor such as a pacing electrode, and (4) the generation of artifacts by metallic objects that can confound diagnoses. The most common implanted devices that exclude a patient from having an MRI study are pacemakers (permanent or temporary) and automated implantable cardiovascular defibrillators. At least six deaths have occurred in patients with pacemakers, and those deaths were thought to be related to an MRI procedure.[28] Prosthetic heart valves are generally MR-compatible, with the possible exception of the pre-6000 series Starr-Edwards valve, a caged ball device used clinically several decades ago. To the authors' knowledge, there has never been a report of an untoward incident with a heart valve prosthesis. The presence of sternal wires and bypass graft clips is not hazardous to the patient but results in MR signal artifact. Properly installed intravascular coils, stents, and filters are unlikely to dislodge but result in MR signal loss in the region of the metallic device.[29] Commonly encountered implanted devices that are potentially MR-hazardous include intracranial aneurysm clips and certain metallic ocular, cochlear, and penile prostheses. Technicians also must be aware of the potential danger associated with metallic devices that may accompany the patient, such as wheelchairs, intravenous (IV) poles, oxygen tanks, and iron-shot-filled hemostatic "sandbags." These devices may become dangerous projectiles in the vicinity of an MR system. A useful resource is the Web site that lists current devices and their degree of MR compatibility: http://MRIsafety.com/index.html.

A static magnetic field is not the only potential source of hazard. The rapidly changing magnetic gradients required for imaging can induce strong currents in conducting objects such as wires and cables. Further, the RF fields also can induce electric currents to flow. External devices that may cause harm to a patient by causing skin burns include pulse oximetry and ECG cables. MR-compatible cables, i.e., those designed to reduce the incidence of heating or induced currents, are

available and must be used in an MR facility. In addition, all non-MRI-compatible metal cables and detection devices must be removed from the patient before the scan is performed.

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Chapter 18A: MAGNETIC RESONANCE IMAGING OF THE HEART

CLINICAL APPLICATIONS

There are many applications of MR to the cardiovascular system, both clinical and research.[30] The current clinical indications are for assessment of function and morphology of the heart and great vessels. However, MR methods also have the potentialability to image perfusion (using the first transit of a paramagnetic contrast agent), assess viability after a myocardial infarction (MI), image the coronary arteries, and image and characterize atherosclerotic plaque.

Since MRI can generate images in any tomographic orientation, it can provide information for comprehensive assessment of the heart with excellent spatial resolution. The three-dimensional imaging ability of MRI allows accurate assessment of global and regional function. Such assessment in theory should be more accurate than methods that are predominantly two-dimensional, such as echocardiography and x-ray angiography, and methods with lower resolution, such as radionuclide approaches.

Assessment of Cardiac Morphology and Ventricular Function

The standard cardiac MRI exam begins with spin-echo images in the orthogonal planes of the body: transverse, coronal, and sagittal. To evaluate ventricular function, image planes should be oriented in relation to the intrinsic axes of the heart. Accordingly, cine cardiac MR images are obtained in the two-chamber (right anterior oblique), four-chamber, and short-axis views (Fig. 18A-8). Consequently, the resultant image orientation is comparable to that of other imaging modalities. Both static spin-echo (dark blood) and dynamic cine MR (bright blood) imaging allow comprehensive assessment of a wide variety of cardiac dimensions and volumes.

Measurements

"Computer calipers" are a standard feature of the software available on clinical MR systems. Linear point-to-point measurements of distances similar to that used on echocardiographic equipment provide a means to report standard dimensions. Since spin-echo images highlight morphologic detail, these images are used to evaluate the diameter of the great vessels and the cardiac chambers,[31-33] ventricular wall thickness,[34] left ventricular (LV) mass, pericardial thickness, cardiac and paracardiac masses, and congenital anomalies.

MRI generally provides images with excellent definition of endocardial surfaces, allowing ready measurement of left and right ventricular end-diastolic and end-systolic size within each myocardial slice. When area-length calculations are used for orthogonal long- and short-axis slices or for summing serial short-axis slices (Simpson's rule), end-systolic, end-diastolic, and stroke volumes of the left and right ventricles can be determined accurately. From these volumes, one can calculate cardiac output and ejection fraction. These volumetric parameters correlate well with other imaging techniques.[35-43] MRI allows routine quantitative assessment of regional ventricular function with visualization of all myocardial segments. In a similar fashion, the epicardial contour also may be outlined, and thus the volume of the myocardium, i.e., the volume between the epicardial and endocardial surfaces, can be calculated. Myocardial mass can be determined without geometric assumptions by multiplying the myocardial volume by the assumed value for the density of myocardial tissue.[44-48]

When the technique of phase-contrast imaging (phase-velocity mapping, velocity-flow mapping, or velocity-encoded cine MR is used), blood flow velocity can be determined (Fig. 18A-9). This method has been validated in a variety of in vivo models.[49-53] With this technique, blood flow in both the ascending aorta and the pulmonary artery can be determined simultaneously, allowing calculation of the ratio of pulmonary to systemic flow (Q_p/Q_s) for assessment of shunt size[54] or regurgitant volumes. Myocardial contractile velocity also has been determined by using PVM.

Ischemic Heart Disease

Several MR approaches are useful for detecting various aspects of ischemic heart disease. These include myocardial tissue characterization, postinfarct imaging of the intensity of contrast agents (e.g., hyperenchancement), stress-induced segmental dysfunction, perfusion imaging, and ischemia-induced changes in high-energy phosphate metabolism using spectroscopic methods (Table 18A-1). This section is divided into two main components: evaluation of stable and acute ischemic syndromes.

Table 18A-1: Ischemic Heart Disease Assessment by MR

Method	Established for Clinical Application	Ready for Clinical Application	Under Development (Emerging)	Research
Regional wall motion at rest	Cine, tagging			
Global ventricular function	Cine, tagging			
Regional and global stress		Cine, tagging		
Myocardial perfusion			Contrast agent	
Myocardial viability			Contrast agentDelayed hyperenhancement	
Myocardial metabolism				Spectroscopy (e.g., ^{31}P, ^{1}H)
Coronary artery disease			AngiographyPlaque characterization	

STABLE ISCHEMIC HEART DISEASE

A number of MR methods are useful for detecting and evaluating the severity of stable ischemic heart disease. Some of these methods have been applied widely and should be considered as the standard of care, some are promising but still under development, and some are still considered research (Table 18A-1).

Stress-Induced Segmental Dysfunction

Stress-induced impairment of regional LV function is an early and reliable sign of ischemia associated with significant coronary artery stenosis, preceding ST-segment depression, and angina pectoris.[55,56] Dobutamine can be used as a pharmacologic means of inducing stress and provides a way to induce ischemia-related wall motion abnormalities. Dobutamine infusion generally begins at 10 μg/min and is increased 5 μg every 2 min until angina occurs. ECGs are distorted in MR systems by the magnetic and RF fields. Thus, reliable ECG monitoring is not possible during MRI. Nevertheless, with symptoms, blood pressure, and pulse closely monitored, the test has been performed without life-threatening complications. Regional abnormalities of wall motion can be observed by using radionuclide cineangiography[57] and echocardiography.[58-61] MRI offers a noninvasive imaging approach with high spatial resolution and three-dimensional imaging for optimally accurate evaluation of regional LV function.[62,63] Van Rugge and colleagues used graded dobutamine infusion in conjunction with MRI in 45 patients with chest pain. Thirty-seven patients had angiographically significant coronary artery disease[64]; with peak dobutamine infusion, segmental dysfunction was observed in 30 patients, yielding an overall sensitivity for detection or coronary artery disease of 81 percent. None of the eight patients without significant coronary artery stenoses had abnormal wall motion; i.e., the specificity in this very small series was 100 percent. Furthermore, the sensitivity for detecting single-, double-, and triple-vessel disease was 75 percent, 80 percent, and 100 percent, respectively. The total duration of the examination is approximately 1 h.

Myocardial Perfusion Imaging Using MR Contrast Agents

Myocardial perfusion imaging (MPI) is used widely with radionuclides. However, it is now clear that MPI with MR methods can provide higher-resolution imaging without ionizing radiation. Although a substantial body of data has been acquired using MR MPI, this procedure should be considered developmental until a larger-scale multi center study is done.

Paramagnetic substances such as gadolinium and dysprosium cause a reduction in both T1 and T2. The magnitude of the decrease is related to the magnetic field strength and the concentration of the paramagenetic agent.[65] When a paramagnetic agent (e.g., gadolinium DTPA or gadoteridol) is given intravenously as a bolus, generally using a power injector, regional myocardial perfusion can be assessed. Currently, there are three classes of paramagnetic agents: extracellular, blood pool, and intracellular. The most commonly used is extracellular gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA), which actually distributes in the blood pool and extracellular space.

MRI records the first pass of the paramagnetic agent through the myocardium. A pulse sequence that markedly diminishes (or "nulls") the signal intensity of the myocardium is used. Thus, myocardium with the greatest concentration of contrast agent is assumed to be normally perfused. The portion of the myocardium with reduced signal is presumed to be underperfused or ischemic (Fig. 18A-10). The authors' initial experience in over 200 patients compared MR and radionuclide perfusion imaging using acquisitions at rest with thallium-201 or low dose ^{99m}Tc sestamibi and then with the first bolus injection of the gadolinium-based agent. A dipyridamole infusion was then initiated using this standard dose of 0.56 mg/kg over a 4-min interval. Two minutes after the infusion, practically simultaneous infusion of ^{99m}Tc sestamibi and gadoteridol was given. In the first 50 patients, sensitivity and specificity were significantly better with radionuclides. In the second 50 patients, radionuclides and MR showed equivalent sensitivity and specificity (probably related to a "learning curve").

Reading MR perfusion images requires some experience, since the approach is dynamic rather than static as it is with radionuclides.[66] One must evaluate the homogeneity with which the myocardium enhances as the paramagnetic agent enters the myocardium. One pitfall that it is

essential to know about is that the lower portion of the interventricular septum frequently demonstrates reduced signal in patients without significant coronary artery disease. Accordingly, if this territory is the only one with a "defect", one should not assume abnormal perfusion but instead an artifact of the MR method. Manning and associates[67] used GD-DTPA to assess myocardial perfusion at rest in patients with severe coronary artery disease. As was anticipated, the time to peak signal intensity was delayed, and peak signal intensity was reduced in regions of the myocardium perfused by a severely stenotic coronary artery. An alternative approach to detecting regions of compromised myocardium has been developed by Hundley and Wlleagues,[68] utilizing the ability of MRI to measure flow.

Using dipyridamole, Matheijssen and Coworkers[69] compared perfusion MRI with sestamibi single photon emission computed tomography (SPECT). Agreement in localization of the artery with significant occlusive disease was 80 percent between angiography and SPECT, 70 percent between angiography and MRI, and 90 percent between SPECT and MRI. MR perfusion studies have been limited by the need to use first-pass acquisition, resulting in the depiction of only one or two slices at the level of the mid-left ventricle. Walsh and associates have developed a method called the block regional interpolation scheme for k-space (BRISK) to acquire up to four tomographic slices through the ventricle by using a conventional MR scanner. This approach represents a great step forward, allowing a more extensive evaluation of perfusion within the short duration of the first pass of the paramagnetic bolus.[70-72] New contrast agents are under development. One strategy includes blood pool agents such as iron particles and a gadolinium agent that binds to albumin. Contrast agents that remain within the blood pool are less complex to analyze since they involve only one compartment. Iron particles have been under investigation, since they remain within the blood pool.[73] Another, more long-range approach for perfusion imaging was reported by Simor and Coworkers.[74] This group described an agent that appears to enter and remain within the myocardium, as thallium-201 or sestamibido.[74] Such agents, when clinically available, should allow myocardial perfusion imaging over many cardiac cycles rather than only one, as is the case with the "first-pass" approach. The use of such myocardial localizing agents should provide the highest-resolution perfusion images available by any technology.

MR Spectroscopy

MR spectroscopy provides another perspective for evaluating the myocardium and defining ischemia. This approach should still be considered research. Cardiac metabolism and energy reserve can be assessed by using spectroscopic methods to assess baseline and changes in the high-energy phosphates within the myocardium (Fig. 18A-11).[75-78] Studies in laboratory animals have demonstrated a rapid decrease in phosphocreatine (PCr) after coronary occlusion. The PCr-to-adenosinetriphosphate (ATP) ratio is used frequently to express changes in bioenergetics, particularly with myocardial ischemia.[79-81] Typically, a surface coil is placed on the anterior chest wall and ^{31}P spectroscopic imaging is performed before, during, and after hand-grip exercise stress. The patient is asked to grip as hard as possible. This is said to be the maximal level. Then, during the study, the grip is maintained at 30 percent of maximum.[82,83] Localized spectroscopic methods then examine PCr/ ATP in the anterior myocardium. Using isometric hand-grip stress, Weiss and coinvestigators[84] and Yabe and associates[85] reported significant decreases in PCr/ ATP ratios in patients with angiographically documented left anterior descending (LAD) coronary artery disease. In the NHLBI-supported WISE (Women with Ischemia Syndrome Evaluation), study to 20 to 30 percent of women with no significant coronary artery disease (CAD) but chest pain had a significant reduction in PCr/ ATP compared with age-matched controls. Such data suggest the importance of the PCr/ ATP stress test in detecting ischemia.

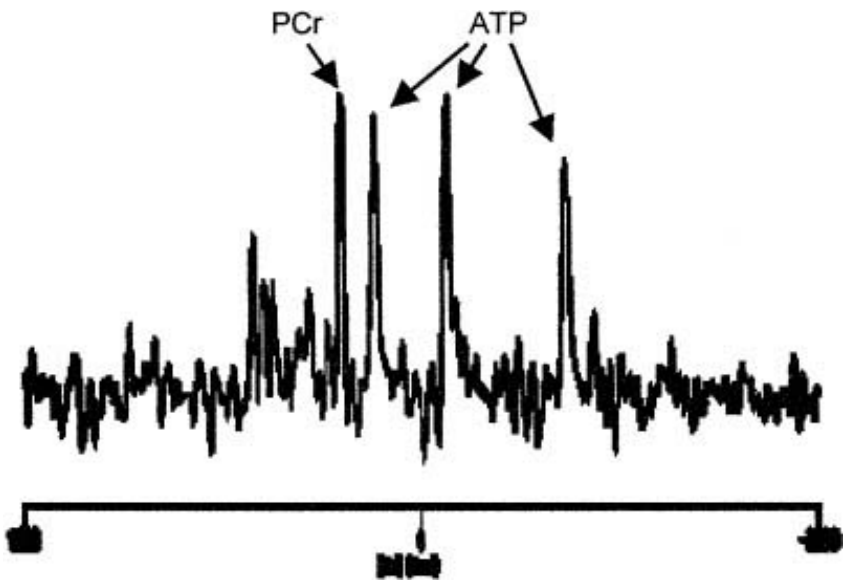

Figure 18a-11: Myocardial spectrum acquired from a healthy person, indicating the phosphocreatine (PCr) and ATP peaks.

ACUTE ISCHEMIC SYNDROMES

MR imaging can be used to differentiate between angina and acute MI. Morphology, function, perfusion, and coronary angiography may all be useful to differentiate reversible ischemia syndromes from MI. Infarct size, regional and global function, and viability can be evaluated. Further, the sequelae of myocardial infarction can be assessed.

Global and Regional Function

Wall motion and thickening can be readily assessed using a cine technique or a real-time approach[86-89] (Fig. 18A-12). Regional wall motion abnormalities and wall thickening by MRI correlate well with sites of dysfunction by x-ray cineventriculography.[90] End-diastolic wall thickness and the degree of systolic wall thickening demonstrated by MRI may be used as markers for predicting myocardial viability (Fig. 18A-13). Hofman and coworkers proposed employing cardiac pacing in combination with MR imaging.[91] Using ^{99m}Tc sestamibi SPECT imaging, Sechtem and coworkers[92] demonstrated that an end-diastolic wall thickness greater than 6 mm or a systolic wall thickening greater than 1 mm correlated with viable myocardium. This was supported by positron emission tomography (PET) imaging with ^{18}F-fluorodeoxyglucose and cine MR imaging of wall thickness and wall thickening to define viability.[93,94] Normal MR values of left ventricular dimensions have been reported by Lorenz and Wlleagues.[95] Wall function can be assessed quantitatively by using MR cine tagging approaches.[96,97]

Infarct Size

Within an hour of the onset of an MI, T1 and T2 relaxation times generally increase within infarcted myocardium; such prolongation of relaxation times provide a means to determine the location and extent of the infarction.[98-100] Whereas some investigators have claimed that infarct imaging with T1 and T2 is not specific,[101] others have demonstrated a good correlation between thallium-201 scintigraphy and T1 and T2 MR imaging in examining infarct size and location.[102,103] Using spin-echo imaging to emphasize T2 has demonstrated increased signal intensity in regions of infarcted tissue and provides a means to determine infarct size.[104,105] Furthermore, wall thinning and asynergy may be of value in assessing the extent of myocardial

tissue infarction.[106]

Paramagnetic contrast agents such as a chelate of gadolinium have been reported to be of value in differentiating between infarcted and noninfarcted myocardium. A phenomenon termed *delayed hyperenhancement* has been observed 3 to 15 min after contrast administration and has been found to correlate with zones of irreversible myocardial damage, whereas the absence of delayed hyperenhancement indicated reversible damage.[107] However, this observation may be controversial in view of the recent study of Rogers and coinvestigators.[108] In that study, delayed enhancement occurred in regions in which myocardial injury was reversible, while hypoenhancement occurred in regions with irreversible myocardial injury. The hyperenhancement phenomenon most likely is related to a delay in the uptake of the paramagnetic agent within the injured territory as a result of reduced blood flow and edema (Fig. 18A-14).[109] The ultimate significance of this finding awaits further study.

Myocardial Tissue Characterization

Changes in the biophysical properties of ischemic myocardium during an ischemic insult can be detected readily by using MR imaging. The relaxation times, T1 and T2, increase with several ischemic insults and are related largely to an increase in water content.[110-113] In animal models, the largest increase in relaxation times occurs in ischemic zones with moderate to severely reduced blood flow, whereas in zones in which the ischemia is total, there is little, if any, increase in myocardial T1 and T2. Other factors of less importance than edema that contribute to such changes in relaxation times include the presence of free radicals, the change in magnetic susceptibility related to the paramagnetic effects of deoxyhemoglobin as a result of hemorrhage, and lipid accumulation.[114,115] Spin-echo images with long echo times will emphasize T1 increases, depicting them as zones of increased intensity.

Complications of Myocardial Infarction

MR imaging provides exquisite morphologic and functional detail. Thus, it can be used to sensitively detect short- and long-term complications of myocardial infarction, including ventricular aneurysm, mitral regurgitation caused by papillary muscle necrosis, perforation of the interventricular septum, LV thrombus, and pericardial effusion. In addition to the regional wall thinning of infarcted myocardium, compensatory hypertrophy and LV chamber enlargement (remodeling) also may be demonstrated. Furthermore, pericardial effusions after infarction are readily demonstrated and quantified.

Coronary Artery Disease

It is possible, using MR angiography methods, to perform coronary artery imaging. In addition, several investigators have demonstrated the feasibility of characterizing the stability of atherosclerotic plaque by using MR methods. These topics are described in detail in Chap. 00.

Valvular Heart Disease

The ideal approach for evaluating patients with valvular heart disease must include an accurate assessment of the valve morphology and function and a means to assess myocardial structure and function and potentially energetics (e.g., using ^{31}P spectroscopy). Structural and functional changes related to valve dysfunction include atrial and/or ventricular chamber enlargement, ventricular wall thickening, poststenotic dilatation of the aorta and/or pulmonary artery, and atrial and/or ventricular thrombus.

MORPHOLOGY

Normal valve leaflets are 1 to 2 mm in thickness and are highly mobile throughout the cardiac cycle. Echocardiography provides high spatial and temporal resolution of the valve leaflets (see Chap. XX). Since the slice thickness of clinical MR images ranges from 5 to 10 mm, the spatial resolution is not adequate to assess the valve leaflets accurately and reproducibly. Nevertheless, spin-echo and gradient-echo images provide a reasonable approach for determining the number of leaflets, the degree of excursion, and approximate leaflet thickness.

With MRI, because of dimensional accuracy, high resolution, and three-dimensional aspects, the ventricular and atrial morphology and function can be assessed accurately without employing geometric assumptions. When the resultant information is used, MR imaging can be helpful in determining the approximate time for surgical intervention by defining chamber volumes and function. It has been demonstrated that preoperative LV size and ejection fraction are good predictors of LV function after surgical intervention for aortic and mitral regurgitation.

VALVE FUNCTION

The severity of valvular dysfunction can be assessed by two MR methods: cine gradient-echo imaging and phase-velocity imaging. In the former method, the chaotic motion of turbulent flow results in dephasing and consequently in a reduction of MR signal. Thus, a signal void is present within a normally signal-intense blood pool. The territory of MR signal void corresponds to the area of color Doppler signal by echocardiography[116-119] (Fig. 18A-15). The reduction in signal can be altered by changing acquisition parameters such as TE, TR, sampling size of the imaged volume element (voxel), and/or orientation of the imaging plane relative to the flow jet.[120,121] Thus, consistency of these factors must be maintained to assure appropriate interpretation. Similar to echocardiography, the volume of proximal flow convergence, which appears as a small cone-shaped MR signal void on the side of the valve opposite to the direction of regurgitant flow, is predictive of the severity of regurgitation.[122,123] MR has been used to measure regurgitant volumes and regurgitant fraction by measuring right ventricular (RV) and LV stroke volumes and thus determining the severity of regurgitation, assuming that regurgitant lesions involve only one side (RV or LV).[124-126]

In addition, gradient-echo imaging can be used to approximate the degree of aortic stenosis by observing the extent of turbulent flow (signal loss) in the ascending aorta.[127] However, it is possible to use phase-velocity imaging to assess flow velocities to 5 m/s.[128] In this way, the severity of aortic stenosis can be assessed more reliably.

In summary, MRI represents a reliable noninvasive means for assessing valvular and ventricular function to assist in determining the appropriate timing for valve replacement. PVM may be useful for the quantification of valve dysfunction.

Pericardial Disease

Normal pericardium on multislice spin-echo MR images appears as a thin, low-intensity signal (< 3 mm) between the high-intensity signal of mediastinal and epicardial fat and the medium-intensity signal of myocardium.[129,130] The lower signal intensity of the normal pericardium results from the amount of fibrous tissue (with long T1 and short T2 relaxation times). Sechtem and associates reported that the pericardium adjacent to the right ventricle could be visualized by MR in 100 percent of the subjects studied, whereas the pericardium along the lateral wall of the left ventricle could be visualized in only 61 percent of the subjects.[131]

PERICARDIAL EFFUSION

Normal pericardial fluid has a low signal intensity on spin-echo images. Such fluid leads to a zone of reduced signal intensity separating the pericardium from the myocardium and the epicardial fat. It has been postulated that the appearance is dark because of the nonlaminar flow of fluid within the pericardial sac as a consequence of cardiac motion. Such nonlaminar flow changes the spin phase and causes MR signal loss.[132] In gradient-echo images, the pericardial fluid appears bright as a result of this flow, clearly separating the parietal pericardium from the myocardium (Fig. 18A-16).

The ability of MRI to detect moderate or large pericardial effusions is comparable to that of echocardiography. However, MRI is able to detect small fluid collections better than echocardiography can. This is especially noteworthy in areas at the medial border of the right atrium or posterior to the LV apex.[133] Because of its lower cost and portability, echocardiography should be used as the first-line approach in assessing patients for pericardial effusion; however, MRI should be performed when a clinically suspected pericardial effusion is not detected on echocardiography. MRI is also useful for demonstrating loculated pericardial effusions.

PERICARDIAL THICKENING

In both MRI and computed x-ray tomography, a pericardial thickness of more than 4 mm is considered abnormal.[134] Pericardium visualized by MRI varies in thickness in different regions of the heart; thus, a standard imaging plane must be established. For this reason, transverse imaging at the levels of the right atrium and the right and left ventricles is recommended.

By demonstrating the presence or absence of a thickened pericardium, MRI can help distinguish between constrictive pericarditis and restrictive cardiomyopathy. Patients examined by MRI who had proven constrictive pericarditis had a pericardial thickening greater than 5 mm.[135] In addition, calcification of the pericardium, which demonstrates reduced signal intensity, also aids in the diagnosis of a pericardial rather than cardiomyopathic restrictive disease.

Cardiomyopathy

Evaluation of global and regional wall thickness and thickening, wall excursion, and chamber size is helpful in diagnosis and prognostication in cardiomyopathy. For example, a dilated cardiomyopathic ventricle with substantial regional wall motion abnormalities suggests an "ischemic" process. Further, valve dysfunction, ventricular outflow tract obstruction, and vena caval dilatation are readily detectable signs of cardiomyopathy. As was stated above MRI is an optimal means for detecting these conditions with excellent reproducibility.

HYPERTROPHIC CARDIOMYOPATHY

The diagnosis of hypertrophic cardiomyopathy is most sensitively made by visualizing the entire myocardium in view of its wide phenotypic variability. The most common pattern is associated with asymmetric hypertrophy. Nevertheless, a wide variety of patterns of wall thickening can be seen, from extensive and diffuse to limited and segmental, with no single morphologic expression considered typical.[136] Serial short-axis MR images systematically slice the ventricles from base to apex, allowing comprehensive evaluation of wall thickness (Fig. 18A-17). Cardiac MRI using this approach correlates well with echocardiography and x-ray cineventriculography in delineating the precise site and extent of hypertrophy.[137-139] Hypertrophy confined to the apex is a variant of hypertrophic cardiomyopathy that may be difficult to visualize by conventional echocardiography but is readily distinguished by MRI.[140-142] When the extent of turbulent flow (signal loss) in the LV outflow tract is defined, a semiquantitative assessment of the degree of dynamic LV outflow tract obstruction can be made with gradient-echo MRI.

DILATED CARDIOMYOPATHY

Typically, dilated cardiomyopathy is characterized by biventricular enlargement with depressed systolic function. MRI provides a noninvasive method for accurately determining RV and/or LV end-systolic and end-diastolic volumes, stroke volume, ejection fraction, thrombus, and/or valve dysfunction. Segmental wall thinning and regional dysfunction suggest a coronary artery disease etiology. However, one must be cautious in evaluating regional LV function, since the apex is frequently akinetic in dilated cardiomyopathy.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy is characterized by myocardial thickening with normal to reduced chamber volumes and frequently depressed LV systolic function. In addition, because of restricted diastolic ventricular filling, the atria and vena cavae commonly are dilated.[143] In patients with restrictive/constrictive hemodynamics, MRI frequently can distinguish between restrictive cardiomyopathy, which is managed medically, and constrictive pericarditis, which is managed surgically. The pericardium is thickened in constrictive pericarditis but usually is not thickened in restrictive cardiomyopathy. Occasionally, restrictive cardiomyopathy is caused by hemochromatosis. This condition frequently is characterized by a reduced or absent signal from the liver and spleen, since the reticuloendothelial system is laden with iron.

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

Because of the geometric shape of the right ventricle, segmental analysis is exceedingly difficult using current imaging technologies. The segmental morphology and function of the right ventricle can be evaluated extensively by using serial contiguous tomographic slices through the heart from base to apex, for example, by spin-echo and gradient-echo imaging. The hallmark of arrhythmogenic RV dysplasia is fatty infiltration with extreme thinning and akinesis of the RV free wall. Fat is identified readily by its increased intensity on T1-weighted MR images. The RV free wall is normally 3 mm in thickness, and thinning is more difficult to detect because of limitations of spatial resolution on traditionally gated cine MR studies. Also, it can be difficult to distinguish between the intramyocardial fat and the epicardial fat adjacent to the TV wall.[144] Analysis of RV function using gradient-echo or echo-planar MRI provides a means of observing focal RV free wall aneurysms and segmental dyskinesis[145] (Fig. 18A-18). Nevertheless, the resolution afforded by MRI allows other characteristics of arrhythmogenic RV dysplasia, such as conspicuous trabeculations and scalloping of the RV free wall, to be visualized.

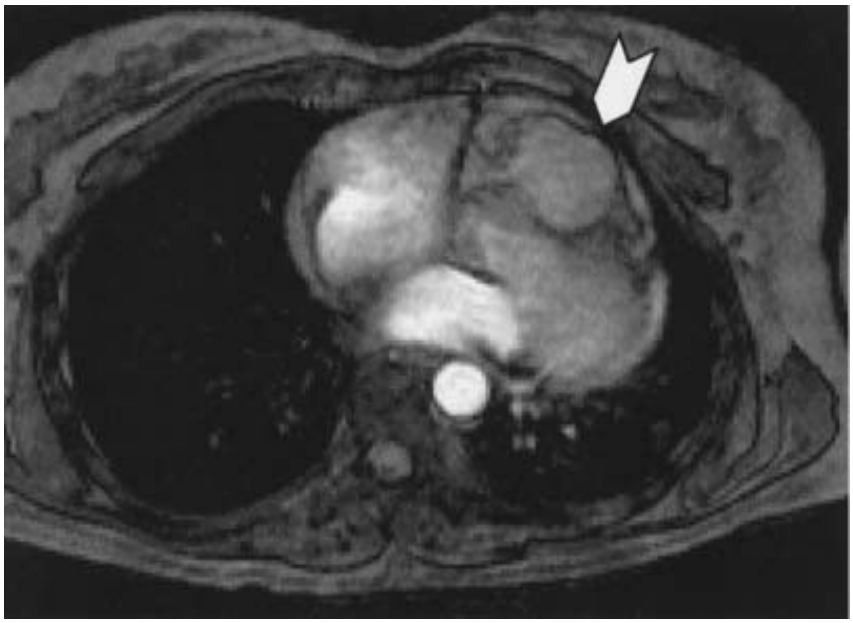

Figure 18a-18: Gradient-echo image of a patient with arryhythmogenic RV dysplasia (ARVD). Note the focal region of thinning of the right ventricular free wall (*arrow*). Another sign of ARVD is the appearance of lipid infiltrating the involved segment. However, this is not the case here.

Congenital Heart Disease

Transthoracic echocardiography is an ideal approach for noninvasive assessment of congenital cardiovascular anomalies in infants and young children, since this technique often requires no sedation and the ultrasound beam is not obstructed by calcified bone and has a nearer target than it does in older children, adolescents, and adults. As a child approaches adolescence or has a surgical repair, the echo assessment may become more difficult and sometimes incomplete. More often, invasive techniques must be performed to assess cardiac, vascular, conduit, or baffle structures adequately. Because of the morphologic detail afforded by MRI and MRA, virtually all common congenital anomalies have been reported in the literature.[146-149] Hence, many patients do not require cardiac catheterization to identify complex congenital anatomy accurately.

MR approaches can image the five necessary anatomic parameters for the initial evaluation of a patient with complex congenital heart disease: situs, ventricular loop, atrioventricular connection, location of the apex, and ventriculoarterial connections. Since MR methods are not influenced by body habitus or scar tissue, deep vascular structures such as the central pulmonary arteries and the ductus arteriosus are well visualized even in a postoperative patient. Baffles and conduit size and function can be evaluated fully by MR provided that no metallic (conductor or ferromagnetic) materials were used at the sites, which would interfere with image integrity because of substantial signal loss.[150] As was described previously, RV size and function are determined more accurately by MRI, which is most relevant in the management of patients with disorders such as transposition of the great vessels and interventricular and interatrial shunts or after repair of tetralogy of Fallot. In patients with coarctation of the aorta with or without aortic hypoplasia, angiography is no longer required unless knowledge of coronary anatomy also is desired.[151-154] Measurements of flow and velocity across shunts and within baffles and conduits also can be made by using PVM. By using such phase-velocity measurements, one can determine the magnitude of the shunt severity or the severity of stenosis noninvasively.[155,156] Furthermore, when phase-contrast cine MR is used, the size of an atrial septal defect can be defined accurately, thus assisting in determining the timing for optimal operative intervention.[157]

Intracardiac Masses and Thrombi

Masses within a heart chamber can be identified with either spin-echo (dark blood) or gradient-echo (bright blood) imaging. The MR intensity of the mass in the spin-echo image also may help characterize its pathology on the basis of T1 relaxation time. For example, cysts and lipomas have very high signal intensity, whereas lymphomas and myxomas have less intensity[158-162] (Fig. 18A-19). Thrombus is more difficult to identify since it is usually present in a dysfunctional ventricular segment or in the atrial appendages.[163] Within a cardiac chamber, slow-moving blood within the area of the akinesis or dyskinesis will contain signal and sometimes artificially appear as a mass. Gradient-echo and/or phase-velocity imaging can be used to differentiate clot from blood stasis. The contents of the atrial appendages, especially in patients with atrial fibrillation, also may resemble thrombus since the blood movement is typically sluggish. The most definitive assessment of atrial thrombi continues to be transesophageal echocardiography (TEE).

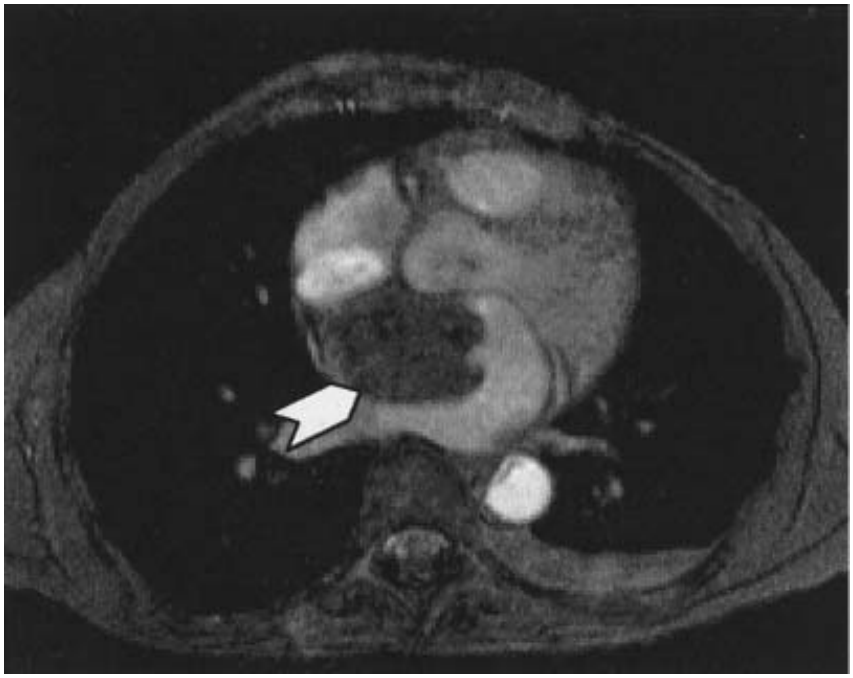

Figure 18a-19: A two-chamber gradient-echo images of a patient with a large left atrial mass (region with reduced signal). Note that the mass in fills about half the left atrial cavity.

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Chapter 18A: MAGNETIC RESONANCE IMAGING OF THE HEART

SUMMARY

Cardiovascular MR methods have gone beyond the status of a research tool to become the diagnostic method of choice for many conditions involving the cardiovascular system. This is a noninvasive modality that can generate unlimited tomographic planes, and operator interaction is not necessary. Further, there is no exposure to ionizing radiation. Resolution is high and real-time imaging is normally possible with new-generation MR systems. Also, it can generate spectra showing important metabolites such as ATP within the myocardium. Weaknesses include the lack of portability, the maintenance expense of the instrument, and the risk of the magnetic and RF fields that can displace or heat implanted devices. Despite its technical superiority, reimbursement for cardiac MRI is only somewhat higher than that for a two-dimensional echo/Doppler transthoracic echocardiographic study. Currently, MRI and MRA are most cost-effective when they replace an invasive procedure (e.g., aortography or TEE) or are performed when multiple diagnostic techniques would otherwise be required. For complex congenital heart disease in adults, aortic pathology, and cardiac or paracardiac masses, MRI is the imaging modality of choice. As physicians become more conversant with MRI in clinical practice, they will discover a diagnostic technology capable of answering questions that previously were unanswerable and improving the information provided by other technologies. If one generates images depicting ventricular and valve function, myocardial perfusion, viability, and coronary anatomy within a single time period, there is no better way to evaluate a patient with suspected cardiovascular pathology. This goal is imminently achievable.

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Figure 18a-13: Long-axis (*A*) and short-axis (*B*) views of the heart. Note the generalized myocardial thinning of the dilated left ventricle and dilation of the right ventricle (*B*). The mid-left ventricular anterilateral wall and the interventricular septum are particularly thin.

Figure 18a-14: A patient with an occluded left circumflex coronary artery that was opened by PTCA and stented. The MRI was performed 2 weeks after an acute MI. Images are seen in the short-axis (*A*) and long-axis views (*B*), and the regions of delayed hyperenhancement are arrowed. (Images provided courtesy of Robert M. Judd.)

Figure 18a-15: Transverse gradient-echo images are shown depicting mitral (*A*) and aortic regurgitation (*B*). In each case, turbulent flow caused by the regurgitant lesion results in loss of MR signal (*arrow*). Note reduced signal on the side of the valve opposite the direction of regurgitation (*white arrow*). This in part is consistent with proximal flow convergence.

Figure 18a-16: *A.* A coronal spin-echo image depicting a large pericardial effusion (*arrow*) *B.* A gradient-echo image depicting bright signal from a pericardial effusion (*white arrow*). Also note the circular region of reduced signal intensity related to postoperative sternal wire.

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Figure 18a-18: Gradient-echo image of a patient with arryhythmogenic RV dysplasia (ARVD). Note the focal region of thinning of the right ventricular free wall (*arrow*). Another sign of ARVD is the appearance of lipid infiltrating the involved segment. However, this is not the case here.

Figure 18a-19: A two-chamber gradient-echo images of a patient with a large left atrial mass (region with reduced signal). Note that the mass in fills about half the left atrial cavity.

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 18B:

MAGNETIC RESONANCE IMAGING OF THE VASCULAR SYSTEM

Authors: Valentin Fuster, Zahi A. Fayad, Stephen G. Worthley, Gerard Helft, Thomas K. F. Foo

INTRODUCTION

Over the last decade, there has been substantial growth in the role of cardiovascular magnetic resonance (CMR) imaging in evaluating cardiovascular structure and function in both clinical practice and research. CMR is an excellent diagnostic tool because of its noninvasive nature, lack of ionizing radiation, high spatial resolution, tomographic acquisition in any plane, and unique tissue contrast. This chapter reviews technical considerations in CMR, describes the established clinical CMR applications, and describes novel and promising approaches for the diagnosis of cardiovascular disease.

CMR relies on the same principles as do other MR techniques.[1-4] Since hydrogen (^{1}H) is the simplest and most abundant element in the human body, most MR studies are of hydrogen nuclei (protons) in water. During the examination, the patient is subjected to a strong local magnetic field, usually 1.5 tesla, that aligns the protons in the patient's body. These protons or spins are excited by a radiofrequency (RF) pulse and subsequently are detected with receiver coils. The detected signals are influenced by relaxation times (T1 and T2), proton density, motion and flow, molecular diffusion, magnetization transfer, changes in susceptibility, and so forth. Three additional magnetic fields (gradient fields) are applied during MR imaging: one to select the slice and two to encode spatial information. The timing of the excitation pulses and the successive magnetic field gradients determine the image contrast.

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Chapter 18B: MAGNETIC RESONANCE IMAGING OF THE VASCULAR SYSTEM

TECHNICAL CONSIDERATIONS

Introduction

In MR imaging, an image is encoded into its constituent spatial frequency components. To generate an image of a specific spatial resolution and image field of view (FOV), data for a minimal set of spatial frequencies, or k-space lines, must be sampled so that the object's spatial frequency distribution can be determined. With a single k-space line sampled after a single RF excitation pulse, the number of k-space lines in an image directly determines the total image acquisition time.

In CMR, cardiac motion and respiratory motion present unique challenges in obtaining images of the heart at specific time points in the cardiac cycle. To freeze the motion of the heart, image acquisition time must be shorter than 50 to 100 ms. Longer data acquisition periods lead to increased cardiac motion artifacts. If all the data (k-space data) needed to reconstruct an image cannot be acquired with a single R-R interval, data acquisition must be partitioned across several cardiac cycles, with each data segment being acquired at the same cardiac phase. This synchronization of data acquisition to the cardiac cycle [electrocardiogram (ECG)-gating] ensures that the heart is in the same spatial position or cardiac state for each data acquisition (k-space phase encoding) segment.

Similar to cardiac gating, acquisitions can be triggered by the respiratory cycle, hence the use of a device (e.g., respiratory bellows or belt) or method (e.g., navigator echoes[5]) that indicates expiration and inspiration. Therefore, data acquisition is performed only during a certain phase of the respiratory cycle. Cardiac and respiratory gating may be combined, but image acquisition is therefore increased.

Cardiac MR images can depict the anatomy of the vasculature at a single phase of the cardiac cycle and at multiple spatial locations (multislice imaging) or can be acquired at the same spatial location but at different temporal cardiac phases (multiphase imaging or cine). The multislice techniques can generate projectional angiograms similar to those of conventional x-ray angiography and provide structural anatomic information. Images acquired at multiple phases of the cardiac cycle then can be played back in a movie loop to provide a dynamic representation of the flowing blood[6] (see also Chap. 18A).

Black Blood Imaging Techniques

CONVENTIONAL ECG-GATED SPIN ECHO

The conventional single-phase, multiple-slice ECG-gated spin echo (SE) is the most common imaging sequence traditionally used for CMR. The SE technique generates images in which the blood signal appears dark ("black blood" images) because of the requirement that any spins excited by the initial 90° RF pulse dephase and are rephased by the subsequent 180° RF pulse. Flowing spins (such as blood) transiting through the imaged slice are affected by one but not both of the RF pulses. Hence, the spins flowing through the slice will not refocus and return a signal; i.e., the signal appears dark in the image. However, slow-flowing blood will not appear dark in SE

images as it may remain within the imaged slice and thus see both the 90° and 180° RF pulses. Saturation RF pulses usually are placed above and below the image planes to ensure that the blood signal is dark.

Long scan times make gated SE images extremely sensitive to respiratory motion and dependent on consistent ECG gating. To minimize the image artifacts from respiratory motion, respiratory view ordering (respiratory compensation) often is used.[7] However, this further extends the total scan time (10 to 20 min) and is sometimes ineffective.

ECG-GATED FAST SPIN ECHO

Conventional SE, with its acquisition of a single line of k-space data per slice excitation, is susceptible to respiratory artifacts, but this can be overcome by using techniques that provide shorter imaging times. When multiple k-space lines are encoded after a single 90° RF excitation pulse with a train of refocusing 180° RF pulses, the fast spin-echo (FSE), or turbo spin echo, sequence provides shorter imaging with reduced respiratory motion artifacts. The number of echoes acquired after the 90° excitation is called *echo train length* (ETL), or turbo factor. With an ETL of 8, the scan time for a T2-weighted sequence [repetition time (TR) = 2 R-R] is reduced to 32 heartbeats for a 128-phase-encoding image.

To ensure that signal from blood is suppressed adequately, a double-inversion recovery magnetization preparation pulse ("velocity-selective" inversion) is used.[8] As shown in Fig. 18B-1, a nonselective inversion pulse inverts all spins in the body. This is followed quickly by a slice-selective inversion pulse that restores the magnetization within the imaged slice. An inversion time (TI = ~600 ms) is selected to null signal from blood when the 90° RF excitation pulse is applied. To minimize image-blurring artifacts from T2 decay in a long echo train, the acquisition is segmented over to several heartbeats and the spacing between echoes [echo spacing (ESP)] is minimized. With an ETL of 32, a gated T2-weighted FSE image can be acquired in 16 heartbeats for 256 k-space lines. This allows fast data acquisition during suspended respiration and provides artifact-free images of the cardiovascular anatomy (Fig. 18B-2). One of the disadvantages of the current double-inversion recovery FSE sequence is that images are acquired a single slice at a time to avoid affecting the effectiveness of the inversion pulses used to null signal from blood.

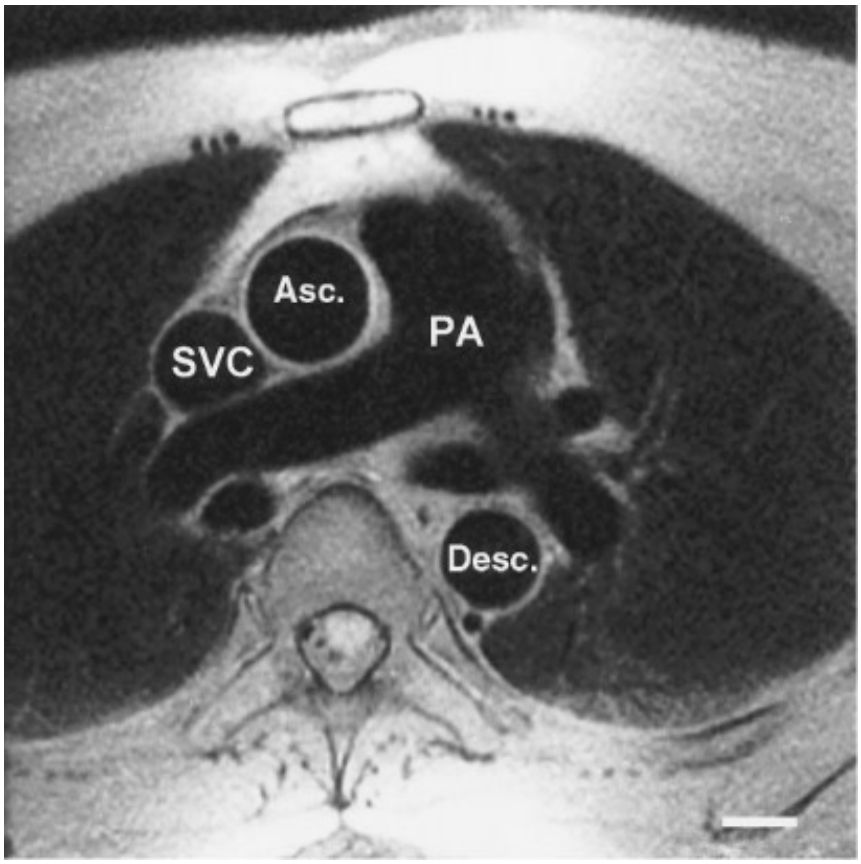


Figure 18b-2: Double-inversion recovery, fast spin-echo, proton-density-weighted magnetic resonance image from a normal subject. The signal from blood is suppressed, and therefore, the lumen is dark. The aortic wall of the ascending (Asc.) and descending (Desc.) aorta is clearly seen. PA = pulmonary artery; SVC = superior vena cava.

A recent extension of the FSE sequence is the single- or segmented-shot (half Fourier turbo spin-echo (HASTE) technique.[9,10] Image acquisition can be acquired in as a short a time as a single heartbeat.

White Blood Imaging Techniques

INTRODUCTION

So-called white blood imaging techniques refer primarily to gradient-recalled echo pulse sequences, which provide images that are T1-weighted. These techniques are characterized by short sequence TRs, flip angles less than 90°, and substantially greater signal intensity of the ventricular blood pool compared with that of the myocardium. The latter effect is due to the in-flow refreshment phenomenon, in which fresh unsaturated blood continues to course through the imaged slice and experience fewer RF pulses than does stationary tissue that remains in the imaged slice throughout the data acquisition period. Bright blood techniques can be subcategorized into time-of-flight (TOF) and phase-contrast techniques.

TIME OF FLIGHT

Conventional Gradient Echo (Cine)

Short TR-gated gradient echo-pulse sequence are used to generate cine images at multiple time frames in the cardiac cycle. Conventional cine pulse sequences run asynchronously to the cardiac

cycle, with the spatial frequency (phase)-encoding value updated on detection of the R-wave trigger. Each RF excitation pulse is applied at the same spatial location and is repeated at intervals of TR in the cardiac cycle. Since the sequence runs asynchronously, the RF excitation pulses may occur at varying time delays from the R wave from one cardiac cycle to the next. On detection of the next cardiac R wave, the k-space encoding value is updated and the acquired temporal data from the previous R-R interval are resorted and interpolated into evenly distributed time frames within each cardiac cycle. This method of gating also is known as retrospective gating because data from the current R-R interval are resorted only after the next R-wave trigger is detected.

As was noted earlier, conventional gradient-echo cine pulse sequences acquire only one k-space encoding view per heartbeat. The total image acquisition time is then of the order of 128 heartbeats. As this time is beyond the ability of patients to maintain an effective breath hold, conventional cine scans are subject to respiratory motion artifacts and require some form of respiratory gating or an intelligent k-space acquisition view reordering to maintain an artifact-free image. These measures, however, are only marginally effective and cannot substitute for a breath-held acquisition.

Segmented K-Space Techniques

Faster CMR techniques have been able to dramatically reduce the image acquisition time to as little as 10 to 15 heartbeats, making breath holding a feasible option to reduce respiratory motion artifacts. Faster scan times have been achieved by segmenting k-space and acquiring multiple k-space lines per R-R interval.[11] The scan time is speeded up by a factor equal to that of the number of k-space lines acquired per image per R-R interval. In this manner, a typical cine acquisition with a matrix size of 128 pixels in the phase-encoding direction can be completed in as little as 16 heartbeats, with eight k-space lines per segment (or views per segment). K-space is divided into several segments, with each k-space line in a segment acquired in a single R-R interval.

Because of the need to acquire data rapidly for several k-space lines to minimize motion-blurring artifacts, segmented k-space techniques are used almost exclusively with fast gradient-echo pulse sequences that have very short TR. Fast gradient-recalled echo acquisition also can be RF-phase spoiled to achieve better tissue-blood pool contrast. However, shorter TRs require smaller flip angles, and as a consequence, image signal-to-noise ratio is lower than that in conventional gradient-echo cine acquisitions.

Multiple phases of the cardiac cycle can be visualized by means of repeated acquisition of the same k-space segment within an R-R interval but assigning the data acquired at different time points in the cardiac cycle to different temporal phases.

In segmented k-space scans, the total scan time is inversely proportional to the number of views per segment (vps). The larger the number of views acquired per segment, the shorter the scan time. However, the reduction in scan time is obtained at the expense of reducing the image's temporal resolution. Significant motion of the heart during data segment acquisition time will result in a loss of spatial resolution from cardiac motion-related blurring. Minimizing artifacts from cardiac motion by decreasing the number of views per segment, conversely, would lead to an increase in the total scan time, reducing the ability to breath hold and reintroducing respiratory-related motion artifacts.

Fortunately, the minimum temporal resolution needed to sample cardiac motion, especially during systole, is about 40 ms. With fast gradient-echo pulse sequences, TR can be reduced to about 5 to 8 ms, permitting the collection of at least 5 to 8 k-space lines per segment. Similar to conventional cine acquisition, a higher effective temporal resolution can be obtained by means a simple interpolation or nearest neighbor viewsharing process.[12]

Each temporal phase image represents the cardiac motion at specific delays from the cardiac R-wave trigger, averaged over the acquisition time per segment. In Fig. 18B-3, it is clear that intermediate cardiac phases can be synthesized or interpolated by sharing k-space views between adjacent time segments to generate images averaged over different time points. The true image temporal resolution is unchanged, but the effective temporal resolution is doubled. View sharing thus can increase the number of phases reconstructed without affecting the manner in which the k-space data are acquired (Fig. 18B-3).

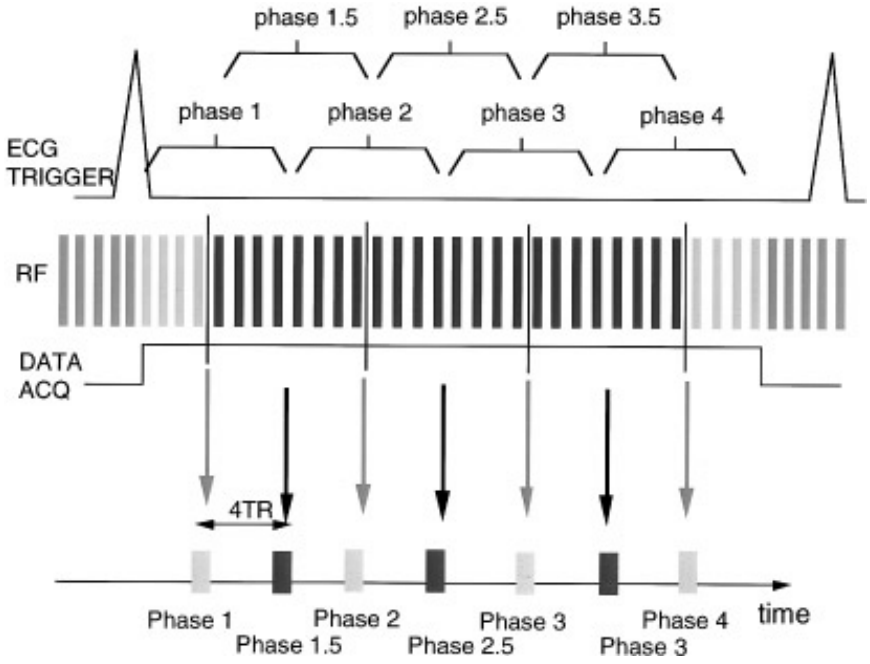


Figure 18b-3: Segmented k-space acquisition and view sharing. View sharing increases the effective temporal resolution by reconstructing images at different time points in the cardiac cycle, similar to the linear interpolation scheme applied to conventional cine scans. The true temporal resolution remains unchanged even though the effective (reconstructed) temporal resolution is doubled.

In addition to the acquisition of images at the same spatial location at different time points in the cardiac cycle (cine), a single-phase multislice acquisition can be performed. A segmented k-space gradient-echo multiplanar acquisition would then acquire images at different spatial locations, each at a different phase of the cardiac cycle. Although the image quality is somewhat limited, a wide range of pathologies can be detected on these images. Major structures such as the aorta, main pulmonary arteries, liver, spleen, and spine are viewed. Another application of this technique is the imaging of uncooperative and sedated patients for whom breath holding is not possible.

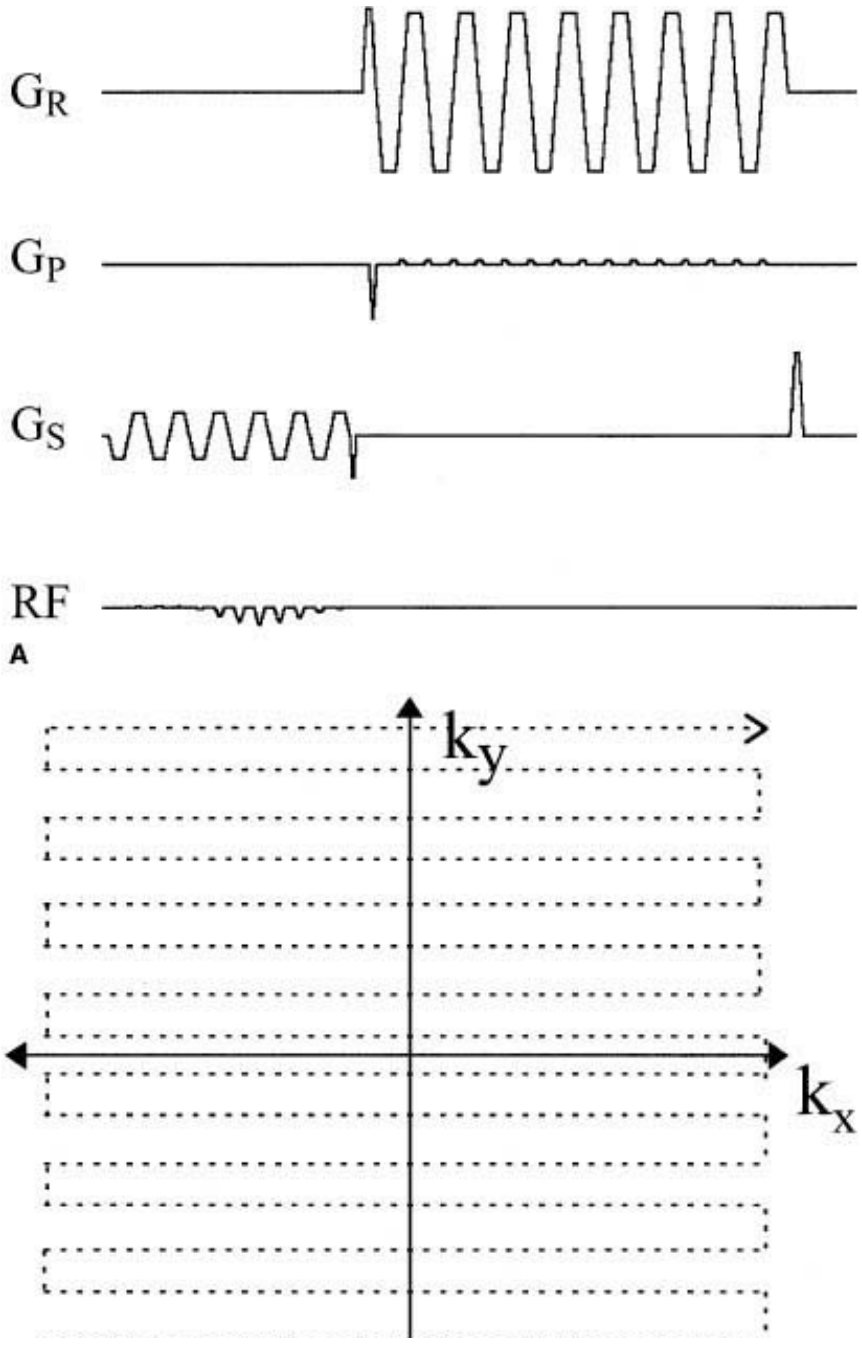
Fast Hybrid Imaging

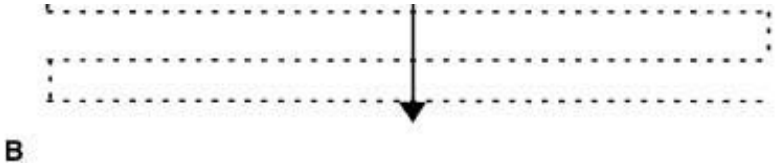
Very fast imaging techniques such as echo-planar imaging (EPI) and spiral imaging (see below) can achieve short scan times by acquiring a larger portion of k-space in each TR compared with conventional imaging. As will be discussed in this section, these techniques are prone to image artifacts. When multishot hybrid EPI and interleaved spiral techniques with relatively short echo train length and short echo spacing and sampling times are used, image artifacts are reduced while significant fast scan times are achieved compared with conventional imaging techniques. New gradient and receiver MR subsystems have substantially improved the performance of EPI and spiral imaging. Several CMR applications, such as real-time interactive scanning, coronary

imaging, first-pass myocardial perfusion, and fast functional cardiac imaging, are now possible with these techniques.

Conventional, Interleaved, and Hybrid EPI

In fast segmented k-space cardiac acquisitions, only one k-space line or view is acquired per RF excitation pulse. EPI is an acquisition technique that collects all lines (single-shot imaging) or several k-space lines (multishot imaging) per RF excitation.[13] As is shown in Fig. 18B-4, this is accomplished by effecting rapid gradient reversals of the readout gradient, generating a series of gradient echoes with each readout echo acquiring data for a single k-space line or view.[14] The number of gradient echoes after a single RF pulse is known as an ETL. As segmented k-space acquisitions reduced the scan time corresponding to a factor equal to the number of k-space lines acquired per R-R interval, interleaved EPI scans further reduce the scan time by a factor equal to ETL. The most significant benefit from using interleaved EPI sequences is that breath-holding times can be further reduced from 16s to 4s with comparable image spatial resolution.





B

Figure 18b-4: *A.* Pulse sequence timing diagram for multishot echo-planar imaging. Note the spectral-spatial RF pulse used for fat suppression. *B.* K-space trajectory traversed by one repetition of the pulse sequence shown in (*A*).

Unlike conventional EPI scans, not all the k-space lines necessary to reconstruct an image are acquired after a single RF excitation pulse. The data acquisition is interleaved between several RF excitation pulses, with between four and eight echoes acquired per RF excitation pulse.[15] The result is a hybrid EPI sequence that is inherently more efficient than conventional segmented k-space fast-gradient echo because multiple phase-encode lines are acquired in each TR. The smaller number of ETLs in a cardiac interleaved EPI acquisition significantly improves image quality, as there is less image blurring from changes in signal intensity across the multiple gradient echoes from T2* relaxation.

Different versions of EPI have been proposed for CMR applications. Single-shot EPI and dual-shot EPI have been used to multislice first-pass myocardial perfusion imaging.[14,16] Similarly, single-shot and multishot EPI and hybrid EPI have been used for faster functional cardiac imaging (multislice and phase imaging)[15,17] and for fast flow quantification.[18] Finally, three-dimensional (3D) multishot EPI also has been used for coronary imaging.[19]

Spiral Imaging

A different approach to cardiac imaging involves the use of spiral rather than rectilinear sampling of k-space.[20] In spiral imaging, the k-space trajectory usually starts at the center of k-space for each RF excitation pulse and proceeds to the higher k-space spatial frequency values in a spiral fashion. This imaging technique has the advantage of acquiring a greater number of data points than are acquired in a conventional rectilinear two-dimensional (2D) Fourier transform acquisition per RF excitation. A complete k-space matrix can be filled by using a single spiral (single-shot) or by using multiple interleaved spiral arms (interleaved spiral). Typically, 2048 and 4096 data points are acquired after each RF excitation pulse per spiral arm or interleave. Complete sampling of k-space is attained by interleaving several spiral arms (usually 16 to 24) in different acquisitions (Fig. 18B-5). Therefore, multiple slice locations (12 to 18) usually are obtained during a short breath hold. The fact that the k-space sampling always starts at the center of k-space for each spiral trajectory makes spiral scans less sensitive to motion- and flow-related artifacts. Longer TRs and larger flip angles usually are used in spiral acquisitions, providing an SNR advantage over small flip-angle fast gradient-echo imaging. The RF excitation pulse used with spiral imaging is usually a spectral-spatial pulse that provides excellent suppression of pericardial fat (Fig. 18B-5).[21]

To reconstruct spiral scans using 2D direct inverse Fourier transform (2DIFT), a uniformly sampled rectilinear grid must be calculated from the acquired k-space data before the 2DIFT operation. Calculating the rectilinear grid is referred to as *regridding*.[20] In practice, one disadvantage of spiral imaging is that the regridding process increases the time required for image reconstruction.

The primary and distinctive image artifact for spiral imaging is spatially localized blurring caused by off-resonance effects (e.g., the chemical shift of fat and magnetic field inhomogeneities). These artifacts are minimized by using the spectral-spatial RF excitation pulse, short sampling times, and

deblurring postprocessing methods.[22] The sampling time can be kept short by increasing the number of interleaves and using a high sampling bandwidth (64 to 125 kHz).

Studies have shown that spiral imaging can provide excellent high-resolution depiction of the coronary arteries[20] (see the section on coronary artery imaging, below) and cardiac cine imaging.[23]

Real-Time Imaging

The short scan times afforded by spiral trajectories and EPI imaging have enabled fast real-time imaging of cardiac motion. The images are acquired with no ECG gating and during free breathing at a frame rate of about 12 to 24 images per second at an in-plane resolution of ~2 mm.[24,25] The combination of higher-performance gradient subsystems and fast compute engines permits fast data acquisition and image reconstruction with minimal lag time.

This real-time imaging capability allows the user to change and localize scan planes of the heart and coronary arteries rapidly (Fig. 18B-6).

Phase-Contrast Cardiac Imaging

PRINCIPLES

Phase-contrast (PC) MR angiography[26] offers a different contrast mechanism to discriminate between flowing spins and stationary tissue. Rather than depending on the relative saturation of flowing blood and tissue, PC angiography derives image contrast from the differences in the phase accumulated by stationary and moving spins in a magnetic field gradient. The amount of phase accumulated is directly proportional to the flow velocity, allowing quantitative measurement of flow velocities, with stationary tissue having zero value for the phase. In addition, PC angiography allows discrimination of flow direction. Spins moving in the direction of a magnetic field gradient accumulate positive phase, while spins moving in the opposite direction accumulate negative phase. Hence, the magnitude of the phase determines the velocity, while the sign of the accumulated phase determines flow direction.

TIME-RESOLVED QUANTITATIVE FLOW MEASUREMENT

Time-resolved flow information can be obtained by using an ECG-gated fast gradient-echo acquisition and linear interpolation, similar to conventional cine pulse sequences. The difference here is that a pair of flow-encoding acquisitions must be acquired for each k-space view to quantify flow in a single direction (Fig. 18B-7). In a PC acquisition, two images are generated. The phase image contains information about the direction and magnitude of the velocity, and the magnitude image provides T1-weighted image contrast (Fig. 18B-8). When played in a cine loop, the multiple temporal PC images can provide visualization of changes in the flow (direction and velocity) as a function of the cardiac cycle (Fig. 18B-9).

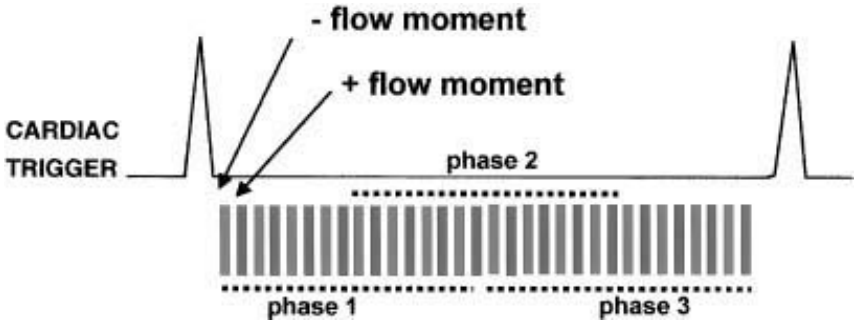


Figure 18b-7: Schematic showing the acquisition of a multiphase (cine) phase-contrast image data set. In this example, flow in one direction is encoded by the toggled flow-encoding gradients (positive flow moment and negative flow moment). As in a fast segmented gradient-echo cardiac acquisition, the R-R interval time is divided into segments, with each segment representing a cardiac temporal phase image (phases 1 and 3). View sharing can be used to generate intermediate phases (phase 2) by using data from each acquired segment.

Plots of the phase velocity as a function of time also can be made across a cross-sectional area of the vessel. If the cross-sectional area of the vessel is known and the flow-velocity time profile is integrated, an average measure of flow in milliliters per minute can be calculated. However, in these measurements, care must be taken to ensure that there are sufficient pixels across the target vessel to minimize errors in the flow measurement from partial volume inclusion of stationary spins.[27]

As in conventional cine acquisitions, the acquisition time for a gated cine phase-contrast scan (cine-PC) is a function of the patient's heart rate and the spatial resolution. A typical cine-PC scan can be completed in about 2 min. The respiratory deficiencies encountered in conventional cine scans are also present in cine-PC acquisitions.

Aortic flow and pulmonary arterial flow also can be measured and assessed against left and right ventricular function, respectively. The assessment of flow across valve leaflets in patients with valvular abnormalities also has been proposed. PC imaging has been shown to provide discriminate flow between the true lumen and the false lumen in aortic dissections and to separate thrombus and flow.

FAST CARDIAC PHASE CONTRAST

Segmented fast gradient-echo techniques also can be applied to PC (Fastcard-PC) scans to reduce the total scan time substantially.[12] Rather than acquiring one flow-encoded k-space view per cardiac cycle, several k-space views can be acquired with flow-encoding gradients, generating a series of flow-sensitized images at different temporal phases with substantially reduced total scan time.

Fastcard-PC scans have been used to evaluate flow in the great vessels and also in the measurement of coronary flow reserve.[28-30] With shorter scan times, PC-cine images can be acquired during a single breath hold. However, care must be taken to avoid using too large of a number of vps, as this may lead to low pass filtering or blunting of the temporal response of the PC measurements.[31]

Contrast-Enhanced 3D Imaging

Conventional and breath-hold SE and gradient-echo techniques define most vessel abnormalities; these are situations in which vessel anatomy is not seen with sufficient clarity because of artifacts. Contrast (e.g., gadolinium-chelates)-enhanced (CE) imaging is advantageous in displaying

detailed vessel anatomy and reducing artifacts.[32] The high signal provided by vascular contrast enhancement makes 3D image processing easier than it is with unenhanced images. CE MR angiography requires very short TR and echo time (TE) times and timing imaging to coincide with the arterial or venous phase of the contrast bolus. The resulting MR images can be rendered in multiple projections. If the patient is incapable of performing breath holding, a slower acquisition can be done over several minutes with a longer and/or slower infusion of contrast agent. However, the vessels may be degraded by respiratory motion.

Coil Selection

Early on, CMR was performed using a body coil, which has the primary advantage of a large FOV and uniform signal intensity. Conventional surface or phased-array coils that were not specifically optimized for cardiac imaging also have been used because of the lack of a cardiac-specific coil. These conventional receiver coils are optimized for general body-imaging purposes (spine, pelvis, etc.); therefore, they have poor sensitivity at larger depths and do not address the specific geometry of the heart within the chest. For example, a standard quatradure surface coil for spine imaging provides adequate images at depths of penetration of only up to 7 cm from the surface of the coil. When such a coil is placed on the anterior chest wall, the deep structures, such as the posterior wall of the left ventricle (located approximately 10 to 15 cm from the anterior chest wall) or the distal coronary arteries, can be well visualized.

Dedicated cardiac coils[33] are becoming commercially available. The FOV is somewhat smaller, and the signal intensity is not uniform. However, the cardiac coils are necessary for improved SNR and for good coverage of the heart and coronaries. Coil placement is very important for adequate SNR, and care must be taken to center the coil around the heart.

PREVIOUS | NEXT

Chapter 18B: MAGNETIC RESONANCE IMAGING OF THE VASCULAR SYSTEM

CLINICAL APPLICATIONS

Coronary Artery Imaging

INTRODUCTION

Coronary artery magnetic resonance imaging (MRI) is considered a very challenging area and often is referred to as one of the "holy grails" of CMR. Coronary arteries are small structures (3 to 4 mm in diameter), follow a tortuous course, and are intimate with many surrounding structures, making them difficult to visualize. Motion artifacts from cardiac and respiratory motion provide a further challenge to image quality. Existing coronary MR angiography (MRA) techniques[34-36] can visualize the proximal and middle portions of most coronary artery segments and some branches. Clinical applications include determining patency and direction of flow in native coronary arteries, evaluating the patency of coronary artery bypass grafts and native vessels after intervention, evaluating anomalous coronary arteries, and following up after surgical or medical therapy. The blind prospective detection of coronary artery lesions with coronary MRA is being evaluated with several MRI techniques. No single technique has emerged that can provide the sensitivity and specificity of catheter-based x-ray contrast angiography, although preliminary clinical studies appear promising. At this stage of development, coronary MRA can be used to exclude or confirm suspected clinically important coronary stenoses in patients referred for diagnostic contrast x-ray angiography. As techniques continue to improve, coronary MRA may become an integral part of the clinical evaluation and screening of patients with ischemic heart disease.

CORONARY MR IMAGING TECHNIQUES

Early Imaging

Early attempts at coronary MRA using conventional SE were inadequate. Reports by Lieberman and associates[37] and Paulin and coworkers[38] demonstrated the difficulty of visualizing long portions of artery as well as any stenosis that existed. Since that time, advances in MR technology have allowed more reliable visualization of the proximal epicardial vessels. In an attempt to improve image quality, current techniques combine ECG gating, suppression of respiratory motion (e.g., respiratory gating and compensation), fast image acquisition, and the suppression of signal from surrounding tissues.

2D SEGMENTED K-SPACE BREATH-HOLD METHODS

The most widely studied modality uses 2D segmented k-space gradient-echo imaging.[39] This method allows image acquisition (100 to 150 ms) during middiastole, a period of bulk cardiac diastasis and high coronary blood flow. Each cardiac cycle typically contains eight interleaved phase-encoding steps (vp = 8) and generates a single 2D image on a 128 × 256 matrix in a breath hold of 16 heartbeats (~15 to 20 s, depending on the heart rate) to minimize interference from respiratory motion. Typical parameters are a slice thickness of 3 to 5 mm, an FOV of 240 mm, and in-plane spatial resolution of 1.9 × 0.9 mm. To complete a study, 40 or more breath holds may be required. In this white blood technique, laminar blood flow appears "bright" (inflow of unsaturated spins) in normal regions and turbulent blood flow appears "dark" (dephasing of

signal) in areas of possible stenosis.[39-41] Coronary arteries usually are embedded in fat, which has high signal intensity on T1-weighted images. Suppression of the high signal from fat offers improved coronary visualization. This technique is called *fat suppression* and suppresses the signal from the pericardial and epicardial fat.

OTHER METHODS

Segmented k-space methods require repetitive excitation of the same slice of slab within each cardiac cycle. The result is (1) suboptimal intravascular blood signal caused by saturation effects resulting from the use of low flip angles and short TRs and (2) motion-induced artifacts caused by long acquisition times per cardiac cycle. Multishot echo-planar breath-hold imaging for coronary imaging has been used to alleviate these problems.[42]

Interleaved spiral imaging provides high temporal and spatial resolution with relative insensitivity to flow and motion artifacts.[20] This technique has shown great promise for coronary imaging (Fig. 18B-10).

A 2D breath-hold multislice segmented k-space gradient-echo technique that automatically tracks coronary artery motion by adjusting the slice offset to prospectively follow the coronary artery throughout the cardiac cycle has been proposed. This method increases the number of images in which portions of the coronary arteries are visible (Fig. 18B-11).[43]

Using the black blood fast spin-echo sequence with "velocityselective" inversion preparatory pulses[8] to null the signal from flowing blood high-resolution imaging of the coronary arteries also can be performed in a breath hold (Fig. 18B-12). The advantage of this sequence versus bright blood imaging techniques is being investigated.

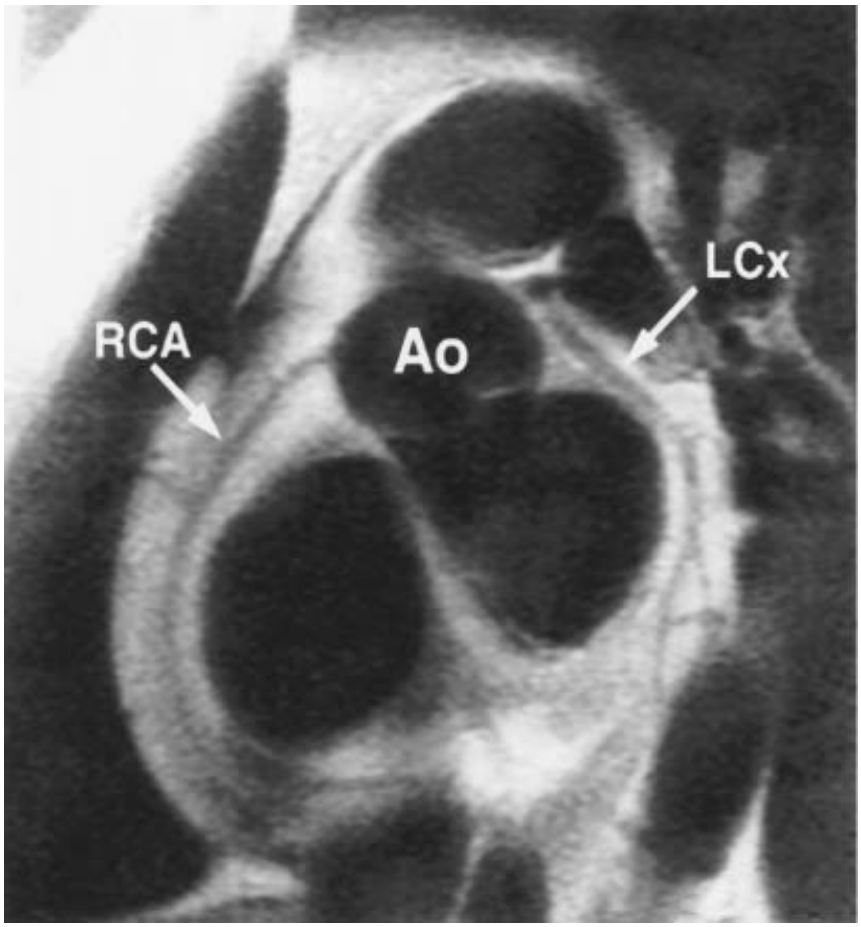


Figure 18b-12: Black blood imaging of the coronary arteries using a 2D double-inversion recovery fast spin-echo sequence. This image was obtained in a breath hold of 16 heartbeats. Long-echo train imaging (ETL = 32) and short echo spacing (ESP = 4 ms) were used. No fat saturation was necessary. The in-plane resolution was 0.5 mm, and the slice thickness was 3 mm. Ao = aorta; RCA = right coronary artery; LCx = circumflex.

Contrast preparation mechanisms such as magnetization transfer,[44] inversion recovery,[45] and T2 preparation[46] also can be employed to improve the delineation between the coronary artery and the surrounding myocardial tissue, especially for the left coronary artery distribution. These contrast preparation techniques are important because they improve vessel visualization by reducing partial volume effects.

3D IMAGING

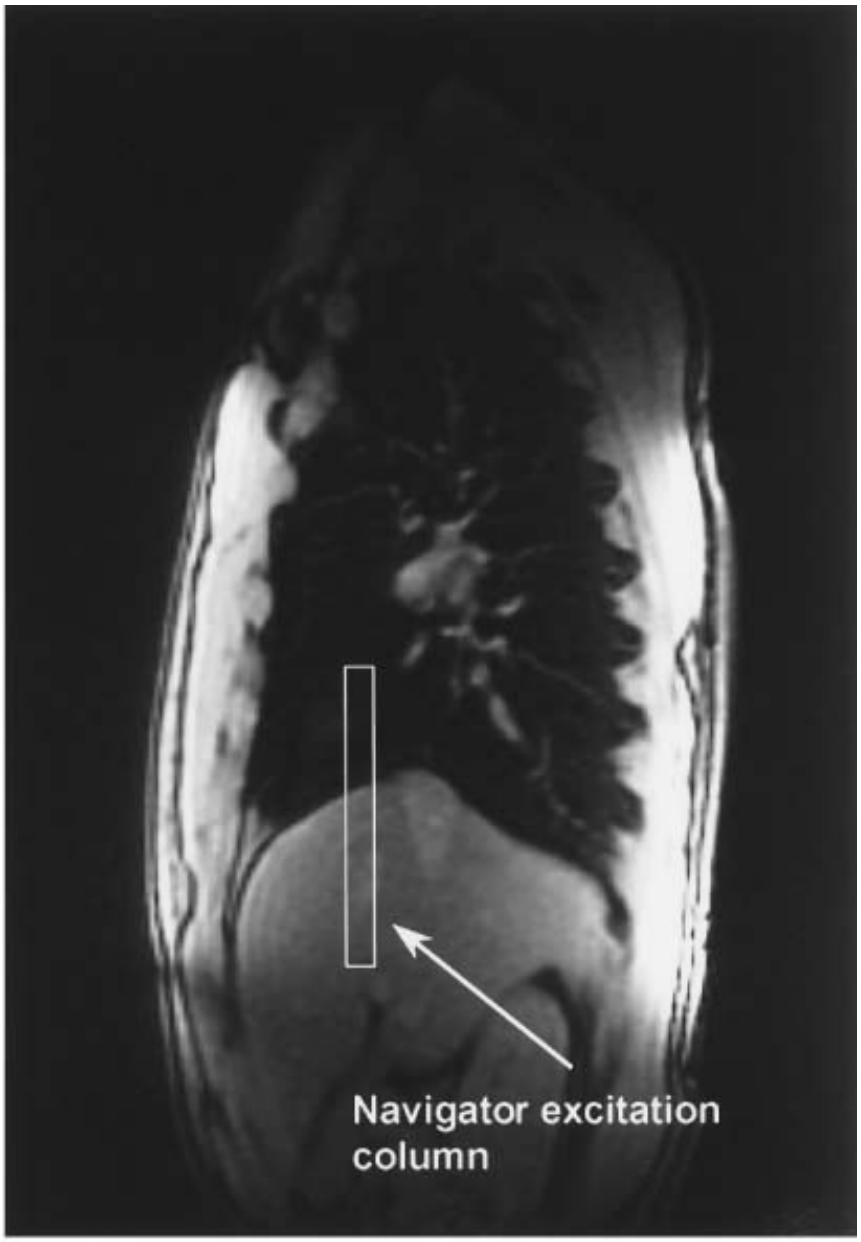
Three-dimensional imaging offers enhanced signal reception[47] with reconstruction capabilities used for visualizing tortuous vessels.[48] 3D imaging is prone to blurring and requires scan times that far exceed that of a breath hold.[49]

Attempts have been made to improve the free breathing 3D acquisition methods. Signal averaging,[50] respiratory feedback,[51] a respiratory monitoring belt,[52] and coached breathing[53] have all been used. New thin 3D slab acquisition is allowing imaging of the coronary arteries in a breath hold.[19]

NAVIGATOR ECHO IMAGING

Techniques used to suppress motion artifact may eliminate the difficult task of breath holding. Real-time navigator echo[5] has been successful in limiting respiratory motion artifacts. When the

lung-heart or lung-diaphragm interface is interrogated (Fig. 18B-13*A*), positional changes can be monitored through the respiratory cycle (Fig. 18B-13*B*) and image acquisition can be gated to respiratory motion according to the superoinferior position of the diaphragm (Fig. 18B-14).[54] The navigator data then are used to perform image correction prospectively[55,56] or retrospectively.[44,57] The navigator data also can be used to prospectively correct the slice position, allowing the use of wider gating windows with improved time efficiency.[45,46,58] Irregular breathing patterns may be problematic, and the accuracy with which the diaphragm is tracked determines to a great extent whether the coronary arteries are imaged at a constant position.[54]



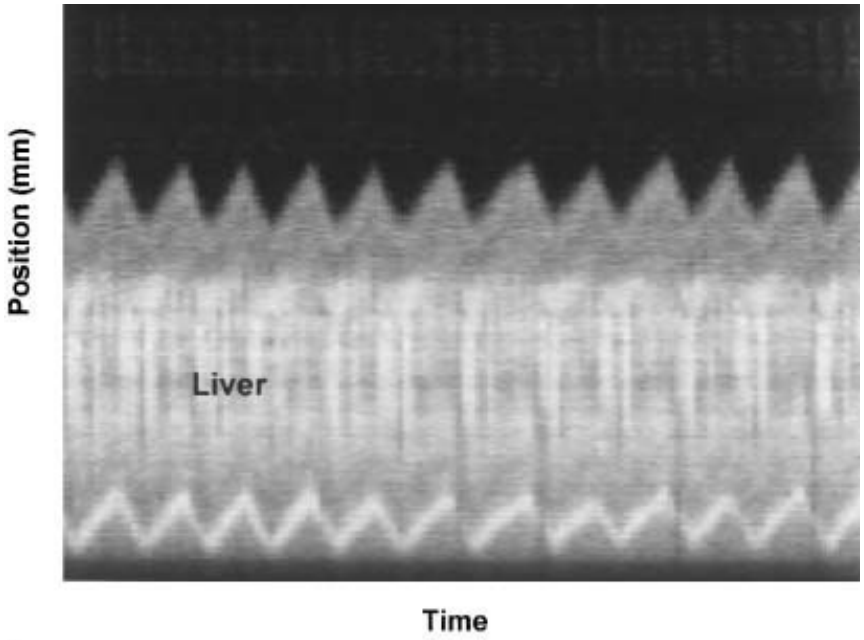


Figure 18b-13: *A.* A sagittal scout image in the region of the right hemidiaphragm showing the placement of a rectangular or cylindrical two-dimensional navigator echo column. The one-dimensional profile of the signal from this column is used to determine the displacement of the edge of the diaphragm from a specified reference position. *B.* An image composed of stacked one-dimensional navigator profiles as a function of time. The vertical axis has units of distance, and the horizontal axis is a function of time. The region of bright signal is the dome of the liver, and the lung field is indicated by the noise.

Typically, the acquisition parameters for a coronary MR study have an image FOV of 20 to 24 cm, with 1- to 1.5-mm sections. Since the volume acquisition is targeted over a specific vessel, the use of 16 to 20 partitions allows a 15- to 30-mm-thick region to be imaged, with the coronary artery approximately in the plane of acquisition. Scan times may range from 5 to 10 min for visualizing a single coronary artery distribution. The scan planes can be targeted for the different coronary artery structures (Fig. 18B-15).

CONTRAST-ENHANCED CORONARY ANGIOGRAPHY

Contrast-enhanced MRA has dramatically affected aortic, renal, and peripheral MRA through the use of both conventional extravascular (e.g., gadolinium-chelates) and new intravascular contrast agents. The latter include iron particle-based (e.g., iron particle-based AMI-227, Advanced Magnetics; iron particle and NC100150, Nycomed-Amersham; gadolinium-chelate, which binds to plasma albumin IS325, EPIX, and gadomer-17, Shering) contrast agents. Intravascular agents have several advantages over extravascular contrast agents: (1) higher T1 relaxivity, (2) higher concentration within the blood, (3) reduction of extravasation into the myocardium, and (4) blood signal remaining enhanced for a relatively long time. Early studies suggest that CE coronary MRA may play a role in improving coronary imaging (Fig. 18B-11).[59-61] The potential clinical applications of these agents awaits the results of large-scale multicenter clinical trials.

ANOMALOUS CORONARY ARTERIES

Not only is coronary MRA a noninvasive method, conventional x-ray angiography often may not be able to determine the exact pathway of an anomalous vessel. Both 2D and 3D coronary MR methods are proving to be well suited for the characterization of anomalous coronary arteries. Although rare, coronary anomalies must be defined accurately, as certain varieties carry the risk of

sudden cardiac death (Fig. 18B-16). MRA is an excellent way to identify anomalies and in some cases is superior to coronary angiography.[62,63] Coronary MRA should be considered a diagnostic tool in any suspected case.

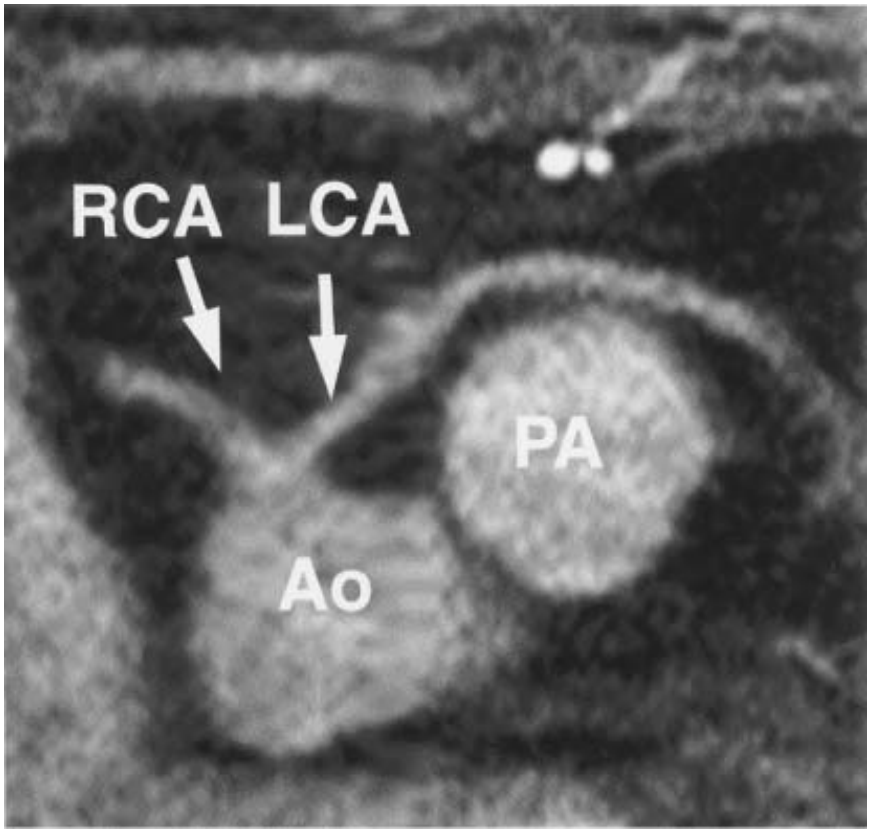


Figure 18b-16: A 53-year-old woman with multiple cardiac risk factors and recent onset of chest discomfort suggestive of angina. Thallium stress test was suggestive of reversible ischemia. 3-D navigator triggered MR angiogram (curved reformat) shows anomalous left coronary artery (LCA) originating from right cusp and passing anterior to pulmonary artery (PA). Ao = aorta; RCA = right coronary artery. (Courtesy Dr. Christine H. Lorenz, Barnes-Jewish Hospital at Washington University Medical Center, St. Louis, MO.)

CORONARY BYPASS GRAFTS

Conventional ECG-gated spin echo and gradient echo have been used to evaluate coronary bypass grafts. The more stationary position and the straight path of internal mammary and saphenous vein grafts contribute to the relative ease at which these vessels may be visualized by MRA. Routinely, contiguous transverse images are obtained through the area expected to contain each graft. The graft is deemed patent if laminar flow is detected by signal void (spin echo) or bright signal (gradient echo) in at least two contiguous anatomic levels. Laminar flow on only one level is considered indeterminate. The absence of laminar signal means the vessel is occluded. SE and gradient-echo methods have demonstrated equal accuracy.[64-66] Contrast-enhanced MRA has demonstrated improved accuracy in bypass graft evaluation.[67,68]

As with intravascular stents (see below), a major obstacle for bypass graft imaging is the local signal loss and artifact associated with implanted metallic objects such as ostial graft rings and homeostatic clips. These artifacts may make signal voids related to blood flow through a stenosis in the bypass graft indistinguishable. In addition, grafts with tight stenoses may result in insufficient contrast penetration to characterize graft patency. Therefore, identification of focal

stenoses within a graft may be extremely difficult and limited. The possible use of more MR-"friendly" materials may help alleviate this problem in the future.

STENTS

Since the introduction of coronary stents,[69] coronary stenting has been used commonly to treat obstructive coronary artery disease. Coronary stents typically are made of stainless steel or tantalum.[70] After implantation, they are endothelialized and incorporated into the vessel wall. Because of the strong magnetic field required by current MRI systems, there has been concern about the possible heating or even dislocation of previously implanted coronary stents in patients undergoing MRI. The current recommendation is to wait several weeks (~6 weeks) after stent placement before doing an MRI.[71] Additionally, the implanted stent may cause imaging artifacts and signal loss[72] because of its metallic nature[73] at the implantation site, prohibiting the visualization of the underlying structures (Fig. 18B-17).

Despite these challenges and limitations, coronary MRA after stent placement has been found to be safe[74] and possible for the assessment of coronary artery patency.[75] The use of more MR-"friendly" and artifact-free stents may provide a way to minimize this problem in the future.[76]

CORONARY BLOOD FLOW ASSESSMENT

Assessment of coronary blood flow with MR at rest and under pharmacologic stress offers the potential to identify noninvasively areas of the myocardium that merit revascularization in coronary artery disease (CAD) patients. MR flow measurement is based on modification of the MR signal of the flowing blood as it traverses the imaging plane. The use of phase-contrast MR imaging (velocity-encoded cine) is based on the principle that protons in the bloodstream experience a net change in the phase of precession proportionally to their velocity as they travel in a magnetic field gradient. The region of interest around the vessel perimeter is defined, and flow-velocity values are analyzed.

The main technical challenge for coronary flow determinations is the small diameter of the coronary arteries. Partial volume averaging results in overestimation of the flow velocity. Furthermore, cardiac motion and the currently limited spatial resolution of MR imaging introduce potential error in the measurement of coronary artery cross-sectional area and quantification of absolute coronary blood flow. Measurement of flow in the coronary sinus[29] and proximal aorta[77] can overcome the problems of partial volume averaging, motion, and low resolution. However, such global assessment of the coronary circulation is of little help in the study of focal coronary stenoses.

Various modifications of the phase-contrast approach[30,78,79] have been used to measure coronary flow at rest and after intravenous injection of adenosine or dipyridamole and after isometric exercise in patients with CAD.[80,81] A threefold to fivefold increase over resting blood flow and velocity can be measured after pharmacologic vasodilatation.[78,79] In patients with significant stenoses, the impaired coronary flow reserve has less than a twofold increase.

Similarly, MR coronary blood flow measurement has been used in native and grafted internal mammary arteries and saphenous vein grafts.[65,66,82]

CORONARY WALL IMAGING AND PLAQUE CHARACTERIZATION

The ability to define the components of a complex coronary atherosclerotic lesion (i.e., fibrous cap, lipid core, calcium, and hemorrhage) accurately could potentially allow risk stratification of patients for future acute coronary syndromes.[83] Given the excellent soft tissue contrast provided

by CMR imaging techniques, the ability of MR to differentiate between these plaque components has been investigated.[84-87] Experimental data have shown that MR is effective in identifying both the normal vessel wall components and atherosclerotic plaque in research conditions, often using high-field MR systems and performing imaging ex vivo to improve the spatial resolution.[88,89] In animal models, MR has been shown to be able to characterize the components of atherosclerotic lesions in transgenic mice and rabbits.[90-92] However, the ability to translate these techniques to the human coronary arteries in vivo has the same limitations that initially faced MR coronary angiography: motion (cardiac and respiratory), small vessel size, and tortuousity of the vessels. However, to visualize the components of a coronary atherosclerotic lesion, submillimeter resolution will be required.[93]

Experience with long-echo-train fast spin-echo imaging to null the signal from flowing blood and an optimized chemical shift pulse to null signal from perivascular and epicardial fat have shown great promise (Fig. 18B-18).[94,95] A cardiac phased-array surface coil for high-resolution coronary imaging (up to 460-μm in-plane spatial resolution) is used.[33] Normal and atherosclerotic human coronary wall imaging can be performed with high-resolution black blood methods. This may allow the identification of atherosclerotic disease before it becomes symptomatic. Further studies are necessary to identify the different plaque components and assess lesions in asymptomatic patients and their outcomes.

Aortic Imaging

CMR has been shown to be useful in both acquired and congenital abnormalities of the aorta. The noninvasive and high-resolution nature of MR makes it an ideal tool for imaging the deep structures of the thorax.

AORTIC DISSECTION

Among all the imaging modalities currently clinically available for the detection of aortic dissection, CMR appears to have the highest accuracy.[96,97] Furthermore, because of its noninvasive nature, it permits sequential imaging over time and thus allows patients at risk of and those who already have had an aortic dissection to be monitored. Using CMR, one can assess not only the intimal flap and site of tear with contrast-enhanced 3D MRA (Fig. 18B-19) but other important associated abnormalities, such as aortic wall thrombus/hematoma, aortic regurgitation, pericardial effusion, and branch vessel involvement.[98,99] It is the investigation of choice in hemodynamically stable patients. However, because of potential delays in patient access, transesophageal echocardiography (TEE) is indicated for unstable patients. Despite a high sensitivity for aortic dissection detection with TEE, it has a reduced specificity compared with MRI.[96]

The ability to detect aortic wall thrombus/hematoma has clinical implications, as it is considered a precursor for dissection.[100] MRI can accurately identify aortic wall thrombus/hematoma, as determined by aortic wall thickening (>7 mm), with a smooth surface and often areas of high signal intensity on T1-weighted images because of the presence of methemoglobin.[101]

AORTIC ANEURYSM

When contrast-enhanced three-dimensional MRA is used, high-quality imaging of the thoracic aorta can be performed (Fig. 18B-20), allowing not only detection of aortic dissection, as described above, but also visualization of aneurysms irrespective of the site or etiology; thus, it can assist in determining the appropriate timing for surgery.[102] CMR appears to be better able to accurately define complex aneurysm anatomy and branch vessel involvement than ultrasound for

abdominal aortic aneurysms.[103] Furthermore, CMR is able to detect mural thrombus (gradient- and spin-echo sequences) complicating an aortic aneurysm.[104,105] However, the advantage of CMR over simpler techniques (ultrasound and computed topography) in determining the timing of surgery in patients with aortic aneurysms is unclear.

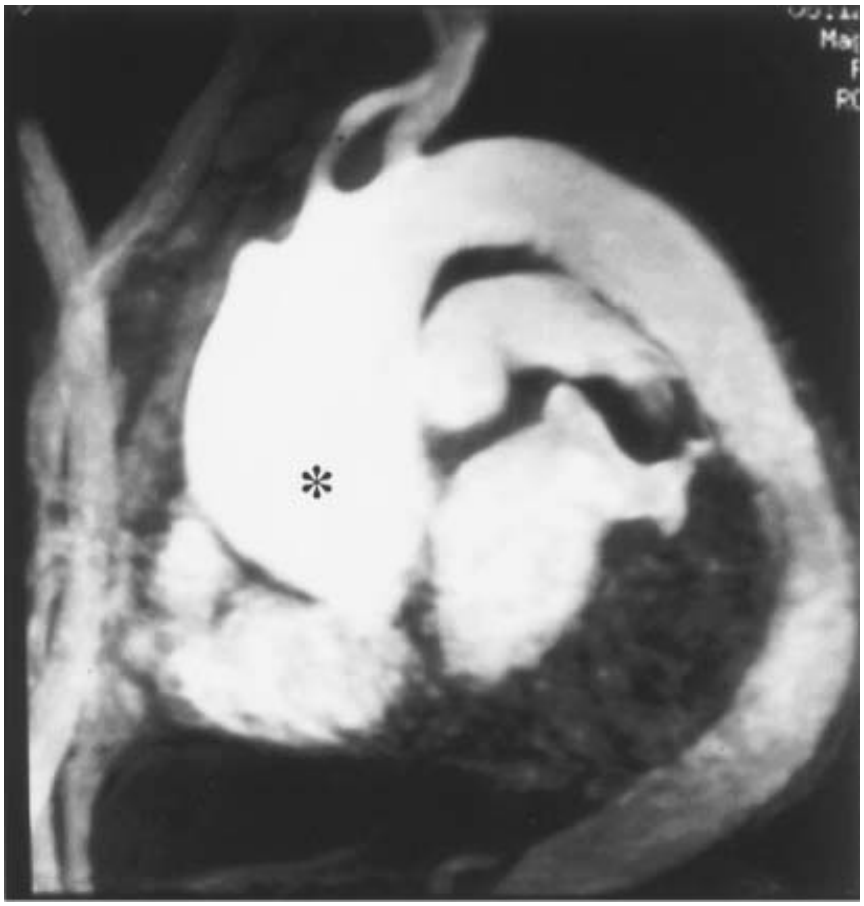


Figure 18b-20: Dynamic 3D imaging after the administration of Gd-DTPA. This MR image shows a severe aortic aneurysm in the ascending aorta (*asterisk*).

CONGENITAL ANOMALIES

In adults with congenital vascular anomalies, CMR is the diagnostic approach of choice because of its large field of view and the lack of the need for hyperosmolar contrast medium such as the radiopaque contrast medium used for x-ray angiography. MR angiography is useful for assessing the presence and severity of aortic coarctation, the effectiveness of balloon aortic angioplasty, and the etiology of postoperative complications, e.g., aneurysms or dissections.[106-108] The luminal dimensions of the aorta can be reproduced serially to assess the risk for aortic aneurysm rupture, as in patients with Marfan syndrome.[109,110] Frequently, concurrent problems such as pectus excavatum and scoliosis limit echocardiographic windows but do not limit imaging with MR. In fact, CMR and MRA provide more complete anatomic detail than does echocardiography and are optimal for assessing and following virtually all these patients. Anomalous aortic configurations such as vascular rings, right-sided aortas, and anomalous origins of branch vessels may be delineated by MRA not only to generate morphologic information but also to determine blood flow.

AORTIC ATHEROSCLEROSIS

Evidence is emerging confirming an association between ascending aortic and aortic arch plaque and atheroembolic cerebrovascular disease.[111] Pathologic and TEE studies have shown that aortic atheroma in these regions is an important cause of embolic cerebral infarction.[111] The risk of atherosclerotic plaque rupture and subsequent thrombogenicity appears to be modulated by the composition of aortic atheroma.[83] The ability to document noninvasively the size and composition (i.e., lipidic versus fibrotic components) of aortic atheroma could permit stratification of risk and allow monitoring of therapeutic approaches such as lipid lowering on the aortic atheroma. However, TEE is semi-invasive, and ultrasound techniques may be limited in their ability to differentiate the various components of complex atherosclerotic lesions.[112]

MR has been shown to accurately differentiate atherosclerotic plaque components in experimental and human models.[84,85,88-90,92] Furthermore, with black blood double-inversion recovery fast spin-echo sequences, there is the potential to visualize the aortic wall with submillimeter resolution, providing noninvasive data about atheroma size and composition (Fig. 18B-21).[86,87] This use for CMR remains under investigation and is an area of ongoing research.

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Chapter 18b: MAGNETIC RESONANCE IMAGING OF THE VASCULAR SYSTEM

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Figure 18b-11: A 2D multislice segmented k-space gradient-echo image of the right coronary artery (RCA). The imaging was performed using automated vessel tracking and increased the number of images in which portions of the right coronary artery were visible. Imaging was performed after the injection of gadolinium (0.10 mmol/kg).

Figure 18b-12: Black blood imaging of the coronary arteries using a 2D double-inversion recovery fast spin-echo sequence. This image was obtained in a breath hold of 16 heartbeats. Long-echo train imaging (ETL = 32) and short echo spacing (ESP = 4 ms) were used. No fat saturation was necessary. The in-plane resolution was 0.5 mm, and the slice thickness was 3 mm. Ao = aorta; RCA = right coronary artery; LCx = circumflex.

Figure 18b-13: *A.* A sagittal scout image in the region of the right hemidiaphragm showing the placement of a rectangular or cylindrical two-dimensional navigator echo column. The one-dimensional profile of the signal from this column is used to determine the displacement of the edge of the diaphragm from a specified reference position. *B.* An image composed of stacked one-dimensional navigator profiles as a function of time. The vertical axis has units of distance, and the horizontal axis is a function of time. The region of bright signal is the dome of the liver, and the lung field is indicated by the noise.

Figure 18b-14: Diagram showing the timing of the 3D navigator echo pulse sequence for imaging the coronary arteries. As shown in this figure, the navigator echo segment precedes the fat suppression segment and the image data acquisition segments. Each data acquisition segment consists of an RF excitation pulse to encode for one value of the k-space view in the slice or phase-encoding direction. A magnetization preparation segment also can be implemented into the sequence without affecting the navigator echo acquisition. In this scheme, prospective determination to enable or disable data acquisition for the current R-R interval depends on the ability of the MR imaging system to calculate the diaphragm displacement and arrive at an accept-reject decision within the time period of the navigator echo segment.

Figure 18b-15: Prospective navigator echo three-dimensional coronary artery images in double oblique planes after planar reformation in a healthy volunteer. In two separate acquisitions, the right coronary artery (RCA) (*A*) and the left main coronary artery/left anterior descending (LAD) artery (*B* and *C*) can be visualized clearly. Acquisition parameters were 24-cm field of view, 20 1.5-mm sections, and 256 × 224 matrix with partial Fourier reconstruction

Figure 18b-16: A 53-year-old woman with multiple cardiac risk factors and recent onset of chest discomfort suggestive of angina. Thallium stress test was suggestive of reversible ischemia. 3-D navigator triggered MR angiogram (curved reformat) shows anomalous left coronary artery (LCA) originating from right cusp and passing anterior to pulmonary artery (PA). Ao = aorta; RCA = right coronary artery. (Courtesy Dr. Christine H. Lorenz, Barnes-Jewish Hospital at Washington University Medical Center, St. Louis, MO.)

Figure 18b-17: A 55-year-old man with a single stent in the proximal left anterior descending artery (LAD). *A.* Oblique transaxial images with fat suppression. An area of signal void caused by the susceptibility artifact of the stent is visualized (*arrow*). *B.* Oblique transaxial images without fat suppression. The area of signal void caused by the susceptibility artifact of the stent is better visualized. The mid-LAD is seen only faintly (*arrow*). (From Duerinckx AJ, with permission. Duerinckx AJ, et al.[75])

Figure 18b-18: X-ray angiogram from a 76-year-old male patient showing high-grade stenosis in the proximal left anterior descending coronary artery (LAD) (*arrows, panel A*). The in vivo cross-sectional black blood MR image of the LAD lumen (obtained without fat saturation) (*panel B*) shows an obstructed lumen (elliptical lumen shape), while the wall image (obtained with fat saturation) (*panel C*) shows a large eccentric plaque with heterogeneous signal intensity (maximum thickness ~6 mm). LV = left ventricle; RV = right ventricle; RVOT = right ventricular outflow tract.

Figure 18b-19: Maximum intensity projection images. Dynamic 3D imaging after the administration of gadolinium. Patient had a history of ascending aortic dissection repair. Images show a residual aortic dissection (*arrow*) extending from near the origin of the right subclavian artery through the thoracic (*A*) and abdominal aorta into the right common iliac arrows (*B*). (Courtesy of Dr. Steven D. Wolff, Integrated Cardiovascular Therapeutics, Woodbury, NY.)

Figure 18b-20: Dynamic 3D imaging after the administration of Gd-DTPA. This MR image shows a severe aortic aneurysm in the ascending aorta (*asterisk*).

Figure 18b-21: T2-weighted CMR images from a patient with severe diffuse disease in the descending thoracic aorta. The plaques are different in appearance and characteristics from one location to another. Plaque characterization was based on the information obtained from T1-, proton-density-, and T2-weighted MR images. The inserts in each panel represent a magnified view of the descending thoracic aorta. Panel A shows a type Vc (fibrocellular) plaque. Panel B shows a lipid-rich plaque (type Va). MR images are 5 mm thick, were acquired with no interslice gap, and are displayed cephalad (*panel A*) to caudal (*panel B*). The origin of the right coronary artery (RCA) is clearly seen taking off from the aortic root (Ao).

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Part 2: GENERAL EVALUATION OF THE PATIENT
Chapter 19:

PET FOR THE NONINVASIVE STUDY AND QUANTIFICATION OF BLOOD FLOW AND METABOLISM IN HUMAN CARDIAC DISEASE

Author: Heinrich R. Schelbert

The study of the human heart with conventional radionuclide techniques remains confined to primarily ventricular function and relative distributions of regional myocardial blood flow (MBF). Positron emission tomography (PET) exceeds these capabilities. It offers the probing and defining regional functional processes in absolute units in the human heart spanning from MBF to biochemical reaction rates, substrate fluxes, and neuronal activity. The many positron-emitting, biologically active tracers, the quantitative imaging capability, and the in vivo application of tracer kinetic principles are unique to PET and account for this capability. The human heart's physiology and pathophysiology thus can be characterized more comprehensively. Also, novel insights into the function of the human heart can be gained, while, at the same time, PET can have a decisive impact on patient diagnosis and management. This chapter describes the key ingredients of PET and the tools for the evaluation and/or quantification of local functional processes in the human heart. It then examines how these tools can be applied to the diagnosis and characterization of coronary artery disease (CAD) and its consequences on regional myocardial function and discusses the impact of PET findings on patient management.

TOOLS FOR PROBING MYOCARDIAL TISSUE FUNCTION

Fundamental to the uniqueness of PET are (1) the quantitative imaging and high temporal resolution capability, (2) the in vivo application of tracer kinetic principles, and (3) the large number of physiologically active radiotracers.

Imaging with Positron-Emitting Radiopharmaceuticals

DEDICATED PET SYSTEMS

The quantitative imaging capability results from the physical properties unique to positrons. After losing their kinetic energy, they combine with an electron and "annihilate." The annihilation represents a conversion of mass into energy; i.e., the combined mass of the positron and the electron converts into two 511-keV photons that leave the site of the annihilation in diametrically opposed directions. If both strike two scintillation detectors connected by a coincidence circuitry at the same time, an annihilation event is registered. Its location in space can be defined by circular arrays of scintillation detectors. The near-simultaneous arrival of two 511-keV photons at the two scintillation detectors positioned in opposite directions allows the use of tomographic reconstruction algorithms analogous to those used with x-ray computed tomography. Accordingly, the spatial resolution throughout the image plane is rather homogeneous, unlike that obtainable with single-photon-emission computed tomography (SPECT), where the spatial resolution declines as a function of the distance between the imaged object and the scintillation detectors. Further, by acquiring "transmission" images with external rotating or circular sources of positronemitting isotopes, the images of the tracer tissue concentrations ("emission" images) can be corrected for photon attenuation so that the resulting tomographic images represent accurately the true regional radioactivity concentrations (mCi or MBq/cm^3). Current PET systems offer

spatial resolutions of as high as 4 to 5 mm full-width half-maximum (FWHM). Further, because modern tomographs are stationary circular devices, images can be acquired at sampling rates in the range of seconds. It is therefore possible with PET to rapidly measure changing radiotracer concentrations in tissues.

COMBINED SPECT AND PET

Several institutions use SPECT and PET for the evaluation of cardiovascular disease. For example, the distribution of MBF is determined with ^{201}Tl- or ^{99m}Tc-labeled tracers of MBF and SPECT and then compared with the distribution of myocardial glucose use by imaging [^{18}F]deoxyglucose with dedicated PET systems.[1-3] While this approach yields a diagnostic accuracy comparable with that achieved with dedicated PET systems, diagnostic difficulties can arise due to differences in the geometry of the heart and spatial resolution on SPECT and PET images, as well as artifacts on the SPECT images due to photon attenuation, especially of the inferior wall and the interventricular septum.[4,5]

MULTIPURPOSE IMAGING SYSTEMS

Most clinical applications of PET do not require assessment of functional processes in absolute units. This is particularly true for the identification of myocardial viability and, to some extent, for the detection of CAD. In view of the high cost of dedicated PET systems, lower-cost "hybrid" or "multipurpose" imaging systems are now available. Generally, two types of systems have emerged (Fig. 19-1). One is a SPECT-like system equipped with ultra-high-energy general-purpose collimators to accommodate the 511-keV photons of positrons instead of the 70- to 160-keV photon energies of conventional radiotracers. When used together with ^{201}Tl- or ^{99m}Tc-labeled flow tracers, the [^{18}F]deoxyglucose images provide diagnostic information comparable with that available with dedicated PET systems.[6-11] The second type of system entails a SPECT-like dual-head device with coincidence detection. While highly promising because of its superior spatial resolution, its use is still evolving, and clinical studies are scarce.[12] Initial studies demonstrate a spatial and contrast resolution that is superior to the high-energy-collimator SPECT system and approaches that of dedicated PET systems. Critical, however, is appropriate correction for photon attenuation that now seems feasible with 511-keV photon sources.[13] Both camera types also can be used for conventional single-photon-emitting tracers, hence the name *hybrid* or *multipurpose* systems.

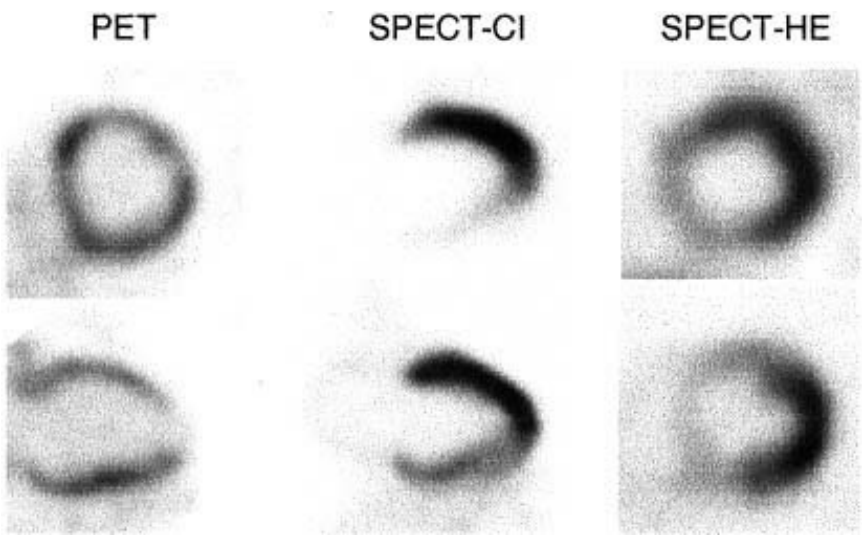

Figure 19-1: Examples of myocardial [18F]deoxyglucose images obtained with PET (*left*), a SPECT-like system with coincidence detection (CI, *middle panel*) (courtesy Dr. R. Henkins, Chicago, IL), and a SPECT system equipped with an ultra-high-energy-photon general-purpose collimator (HE). For the SPECT-CI images, the non-attenuation-corrected image is shown on top and the corrected image at the bottom.

Tracer Kinetic Principles

Positron-emitting isotopes of elements that constitute major parts of living matter such as carbon-11 (^{11}C), nitrogen-13 (^{13}N), and oxygen-15 (^{15}O) are inserted into biomolecules without disturbing their very physiologic properties. Their high specific activity (radioactivity per mass) permits administration of true tracer quantities without exerting a mass effect and perturbing the very process to be studied. Since their physical half-life is short, functional processes can be measured repeatedly or different aspects of the myocardial tissue function can be explored within the same study session. The radioactivity concentrations of these tracers in tissues such as arterial blood and myocardium and their changes over time can be determined noninvasively. The time-activity curves derived from serially acquired tomographic images at sampling rates of 1 to 10 s are fitted with operational equations that are derived from tracer kinetic models and yield quantitative estimates of regional functional processes. Tracer compartment models describe the distribution of the tracer radiolabel in tissue and its time-dependent changes. Because only the activity concentration of the tracer radiolabel can be measured externally, these models relate the externally derived signal to the metabolic fate of the tracer label and its relationship to the functional process under study. Such tracer kinetic models typically consist of functional rather than anatomic pools or compartments that contain the radiotracer or its metabolites. Exchange of radiotracers between compartments is described typically by first-order rate constants. Flux of a radiotracer through a given compartment depends on the flux rate of tracer or of its metabolite and on the size of the compartment. Tracer compartment models provide the basis for developing operational equations; applied to the externally derived radioactivity signal as, for example, tissue time-activity curves, estimates of regional functional processes are derived in absolute units.

Positron-Emitting Tracers of Myocardial Tissue Function

BLOOD VOLUME AND TISSUE CHARACTERIZATION

Blood can readily be radiolabeled with minute quantities of ^{15}O or ^{11}C carbon monoxide (CO). Once inhaled, the radiolabeled CO binds to hemoglobin, thereby tagging red blood cells. The latter serve to define the components of the myocardium in terms of vascular space, viable and normal myocytes, and scar tissue. One such characterization assumes that only living myocytes exchange water rapidly.[14] Transmission images represent the densities of the various tissues in the chest. They resemble low-spatial-resolution x-ray computed tomographic (CT) images and delineate the volume of the myocardium together with the blood in its cavities. The true extravascular volume is obtained by subtracting blood pool images from the transmission images. The fraction of the extravascular volume that exchanges water rapidly is then estimated with ^{15}O-labeled water and is referred to as the *water perfusable tissue index* (PTI). If all the extravascular volume does indeed rapidly exchange water, then the PTI approaches unity.[14] If a portion of the myocardium is injured irreversibly and scar tissue has formed, this fraction becomes less than unity.[15,16] Further, the PTI also will be reduced in diffuse interstitial fibrosis. Initial clinical investigations demonstrated that the fraction of irreversibly injured myocardium or of regional scar tissue formation does indeed indicate whether an impairment in contractile function is irreversible or whether a postrevascularization improvement is likely.[15] If functionally compromised but viable myocardium exchanges water as rapidly as normal myocardium, this may limit the predictive value of the PTI. In recent observations, a reduced PTI had a high negative predictive value, but a near-normal PTI predicted less accurately than [^{18}F]deoxyglucose an improvement in contractile dysfunction.[17] Moreover, the sum of viable and normal myocytes in a

given myocardial segment also serves as a reference to which transmural estimates of MBF or substrate metabolism can be related.[18]

MYOCARDIAL BLOOD FLOW

Several approaches exist for measurements of regional MBF in absolute units. Tracers such as ^{82}Rb or [^{13}N]ammonia are retained in myocardium in proportion to MBF.[19,20] Images of their regional activity concentrations in the myocardium depict the relative distribution of MBF at the time of tracer injection. Each tracer offers advantages and disadvantages. For example, ^{82}Rb is available through a generator based pushbuttonoperated infusion system and hence is easy to use clinically.[21] Its physical half-life of only 75 s affords repeat studies at only 10-min time intervals, enabling evaluation of changes in regional MBF in response to physiologic or pharmacologic interventions. The short physical half-life, however, can result in low-count and, thus, statistically noisy images. The longer physical half-life of [^{13}N]ammonia (10 min), by contrast, produces images of higher count rates and higher diagnostic quality but requires 40- to 50-min time intervals between studies.[20]

The various approaches yield comparable estimates of MBF in the human myocardium during rest and during pharmacologically induced hyperemia.[22-27] Some variability between studies probably derives from methodologic differences but also from intergroup differences in the hemodynamic state. Importantly, MBF in the normal myocardium depends largely on oxygen demand and thus on cardiac work as estimated from the rate pressure product.[28] Thus individual flow measurements should be interpreted within the context of the rate-pressure product.[29] Finally, gender-related differences in MBF have been reported. Compared with an age-matched group of males, women demonstrated higher MBFs both at rest and during hyperemia, which the authors attributed to higher high-density lipoprotein (HDL) cholesterol and lower triglyceride plasma levels in females.[30]

Repeat studies in the same normal volunteers report a 10 ± 11 percent *reproducibility* (average percentage difference of flows normalized to the rate pressure product) for rest MBF and a 12 ± 9 percent reproducibility for hyperemic MBFs.[31] Other studies report similar values for both, [^{13}N]ammonia and for [^{15}O]water.[32,33] Furthermore, the validity of the noninvasive measurements of MBF has been extensively established in animal experiments,[22,27,34-36] as well as in humans, using intracoronary flow velocity probes.[37]

MYOCARDIAL SUBSTRATE METABOLISM

Figure 19-2 depicts the major aspects of the myocardial substrate metabolism. According to this simplified depiction, the myocardium chooses between various substrates; foremost are free fatty acid (FFA), glucose, lactate, and ketone bodies. Selection of a given fuel substrate depends largely on its concentration in plasma and the overall hormonal milieu.[38,39] These in turn are governed by the dietary state, the level of physical activity, and the plasma concentrations of catecholamines, insulin, and glucagon. In the fasting state, circulating FFA levels are high and insulin levels are low so that as much as 70 to 80 percent of the myocardium's oxygen consumption can be accounted for by oxidation of FFA.[40] Conversely, oral glucose intake elevates the plasma glucose level and thus insulin levels while lowering FFA levels so that myocardium shifts its fuel selection to glucose.[39] Strenuous physical exercise increases plasma levels of lactate, which then becomes the major fuel substrate.[41,42] In fact, as much as 60 percent of the O_2 consumption can be accounted for by oxidation of lactate. On the other hand, catecholamines accelerate lipolysis so that circulating FFA levels increase, shifting the heart's substrate selection to FFA.

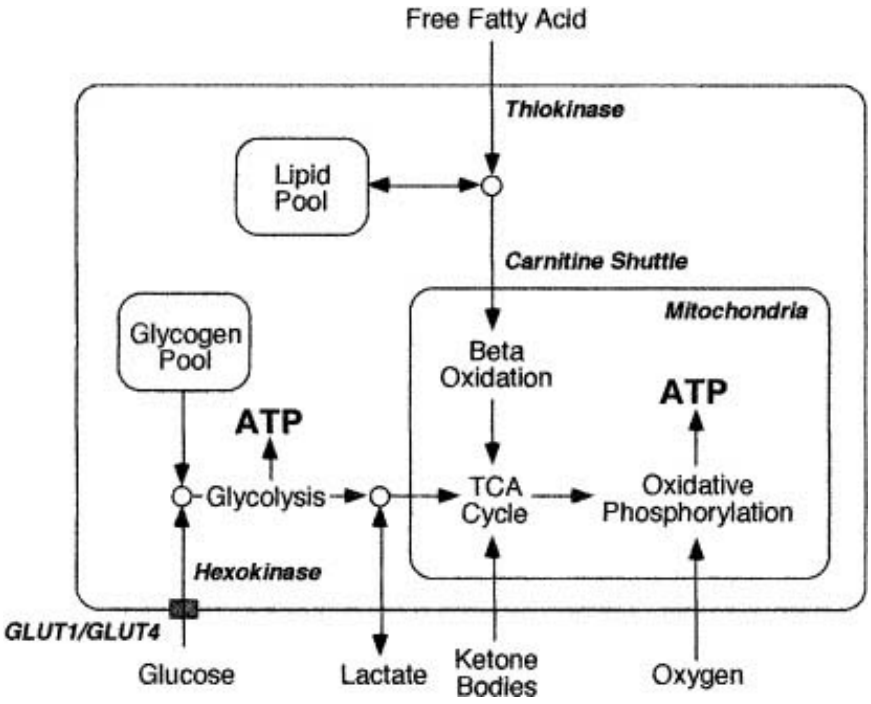

Figure 19-2: Highly simplified depiction of the myocardium's substrate metabolism (TCA, tricarboxylic acid; ATP, adenosine triphosphate; GLUT1 and GLUT4, glucose transporters 1 and 4).

Glucose enters the cell via facilitated transport systems, the largely insulin-independent glucose transporter GLUT1 and the largely insulin-dependent glucose transporter GLUT4. The hexokinase reaction phosphorylates glucose to glucose-6-phosphate. This compound then may be synthesized to glycogen or, alternatively, enter glycolysis with pyruvate as its end product. Converted to lactate, it may leave the myocardium or, if activated to acetyl-CoA, enters the tricarboxylic acid (TCA) cycle as the final oxidative pathway shared by most fuel substrates. Exogenous lactate can be converted via NAD^+ to pyruvate, which then again after esterification to acyl-CoA enters the TCA cycle. FFA also may enter two different metabolic pathways. On entering the cells, it is esterified by the thiokinase reaction to acetyl-CoA. This compound then enters an endogenous lipid pool, consisting mostly of glycerides and phospholipids, and/or proceeds via the carnitine shuttle to the inner mitochondrial membrane. It is there where β-oxidation cleaves of the long-chain acyl-CoA units' two-carbon fragments, which then engage in the TCA cycle. The TCA cycle metabolizes the two-carbon units into CO_2 and H_2O. The rate of flux through the TCA cycle is coupled closely with oxidative phosphorylation, where the energy resulting from the synthesis of oxygen and hydrogen ions is stored in the high-energy phosphate bonds of adenosine triphosphate (ATP). The latter is shuttled into the cytosol with transfer of energy to the high-energy phosphate bond of creatine phosphate. Other sites of high-energy production include glycolysis. The energy yields relative to oxygen differ between the various substrates; e.g., for 1 mol of oxygen, glucose yields 6.3, lactate 6, and FFA 5.7 mol ATP.[43]

Myocardial Glucose Utilization

The initial metabolic step of exogenous glucose metabolism can be evaluated and quantitated with [^{18}F]deoxyglucose (see Fig. 19-2). This radiolabeled glucose analog exchanges across the capillary and sarcolemmal membranes in proportion to glucose with which it then competes for hexokinase for phosphorylation to [^{18}F]deoxyglucose-6-phosphate.[44,45] The phosphorylated glucose analog is a poor substrate for glycogen formation, glycolysis, and the fructose-pentose

shunt; its rate of dephosphorylation is low in myocardium, and it is relatively impermeable to the cell membrane. The phosphorylated tracer thus becomes trapped in the cell so that images of the myocardial ^{18}F concentrations at 40 to 60 min after tracer injection reflect the relative distribution of glucose utilization rates. Because the compound traces only the initial steps of glucose utilization (up to the branch point between glycogen synthesis and glycolysis; see Fig. 19-2), it offers no direct information on glycolytic rates, glucose oxidation, or glycogen synthesis. Yet, in states of glycogen depletion, such as, for example, during ischemia, exogenous glucose serves as the major source of glycolytic flux so that [^{18}F]deoxyglucose may offer an estimate of the rate of glycolysis.

Myocardial Fatty Acid Metabolism

This aspect of the substrate metabolism can be evaluated with 1-[^{11}C]palmitate. The labeled long-chain FFA participates fully in the metabolic fate of its natural counterpart (see Fig. 19-2). Once esterified to acyl-CoA, a fraction of tracer label proceeds via the carnitine shuttle into mitochondria, where β-oxidation catabolizes the long-chain fatty acid into two-carbon fragments that are oxidized via the TCA cycle. The label is released from the myocardium in the form of $^{11}CO_2$. The remaining fraction of the initially extracted and activated tracer enters intracellular lipid pools, mostly those of di- and triglycerides and phospholipids. The biexponential morphology of the myocardial time-activity curve reflects the metabolic fate of the tracer. The slow turnover rate of the intracellular lipid pools accounts for the slow clearance phase, whereas the rapid clearance curve component corresponds to the fraction of tracer that enters β-oxidation and its rate of oxidation. Ischemia reduces the rate of FFA oxidation and of TCA cycle activity. The relative size and rate of the rapid clearance curve component on the ^{11}C myocardial time-activity curve typically decline during acute myocardial ischemia.[46,47] A disproportionately greater fraction of tracer label then enters the slower-turnover endogenous lipid pool. Used mostly as a tracer for the qualitative evaluation of regional myocardial fatty acid metabolism, recent studies suggest the possibility of quantitating myocardial fatty acid oxidation in milliequivalents of FFA per gram of myocardium per minute.[48]

Preferential use of a given fuel substrate (e.g., glucose, lactate, or FFA) depends on its concentration in arterial blood, which, in turn, depends on dietary state, serum levels or insulin resistance, and physical stress.[49] A change in the myocardium's preferential substrate use can be demonstrated with either [^{11}C]palmitate and [^{18}F]deoxyglucose or both.[49-51] In the presence of high FFA and low glucose and insulin levels, use of FFA as the preferred substrate is reflected on the [^{11}C]palmitate curve by the large relative size of the rapid clearance phase and its steep slope (both corresponding to increased fatty acid oxidation) and the low or even undetectable [^{18}F]deoxyglucose uptake. Ingestion of carbohydrates raises plasma glucose levels, stimulates insulin secretion, and depresses FFA levels. The shift to glucose use is reflected by a decline in the size and slope of the rapid-clearance phase of [^{11}C]palmitate and by an increase in myocardial [^{18}F]deoxyglucose uptake.

Myocardial Oxygen Consumption (MVO2)

While molecular ^{15}O oxygen is available for measurements of the (MVO_2,[52,53] the more widely applied approach entails rapid serial imaging with [^{11}C]acetate. The radiotracer clears rapidly from blood into the myocardium and produces high signal-to-background images.[54-57] It directly traces the rate of substrate flux through the TCA cycle as the final oxidative pathway common to most fuel substrates. The rate of clearance of ^{11}C activity from the myocardium on serially acquired images corresponds to the TCA cycle activity and, because of its close coupling to oxidative phosphorylation, to oxidative metabolism and MVO_2. Of note, the tracer yields rate

constants only, which can be converted into units of O_2 per minute per gram. Unlike [^{11}C]palmitate or [^{18}F]deoxyglucose, the clearance rate of [^{11}C]acetate from myocardium is relatively insensitive to changes in myocardial substrate utilization.[54] A tracer compartment model, based on biochemical assays of the tracer tissue kinetics of [^{14}C]acetate in isolated rat hearts[58] forms the base for estimating MVO_2 in absolute units in the human heart and, at the same time, of regional MBFs.[59,60]

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Chapter 19: PET FOR THE NONINVASIVE STUDY AND QUANTIFICATION OF BLOOD FLOW AND METABOLISM IN HUMAN CARDIAC DISEASE

CLINICAL APPLICATIONS

Clinical imaging of positron-emitting radionuclides with PET or PET-like devices is gaining momentum because of research showing the considerable potential for contributing to diagnosis, characterization, treatment, and monitoring of disease. New, lower-cost positron imaging devices and the availability of positron-emitting tracers through regional distribution centers have accelerated the pace of dissemination. Foremost in cardiology have been (1) the identification and characterization of CAD and (2) the detection of myocardial viability.

Identification and Characterization of CAD

GENERAL CONSIDERATIONS

Most studies with PET, such as, for example, those performed with [^{13}N]ammonia or ^{82}Rb, evaluate the relative distribution of MBF from the retention of tracer in the myocardium. More recent investigations use PET's quantitative capability for estimating regional MBF in milliliters of blood per minute per gram of myocardium in order to demonstrate abnormalities in vasomotion of the human coronary circulation during the early stages of coronary atherosclerosis.

Unlike other radionuclide approaches, PET employs almost exclusively pharmacologic stress for the detection of CAD and determination of its extent and functional significance. The transmission images, essential for correction of photon attenuation, must be acquired with the patient in exactly the same position as during the emission images. Both dipyridamole and adenosine afford the determination of the myocardial flow reserve as the ratio of hyperemic to rest MBFs. The now classic studies by Gould et al.[61] demonstrated a curvilinear, inverse correlation between stenosis severity and hyperemic flows or flow reserve. Thus the attenuation of the MBF response to dipyridamole induced hyperemia depends on the functional stenosis severity. As demonstrated by flow measurements with either [^{15}O]water or [^{13}N]ammonia, dipyridamole and adenosine as direct vascular smooth muscle dilators evoke interindividually variable hyperemic responses but induce on average four- to fivefold increases in MBF.[22,23,25,62] The magnitude of the hyperemic flow response is similar for dipyridamole (at a dose of 0.56 mg/kg over 4 min) and for adenosine (140 μg/kg/min).[26] Increases in the dipyridamole dose by 50 percent do not produce higher flows, nor do they reduce the interpatient variability in flow responses.[63] Additionally, the values of the normal flow reserve were derived from studies in young normal volunteers with an average age of 34 ± 16 years. This is important as evidence accumulates that flow reserve declines progressively with age[64-66] (Fig. 19-3). Contributing factors include an age-dependent *decline* in the vasodilator capacity and an agedependent *increase* in baseline MBF due to higher rate-pressure products as a major determinant of MBF. A progressive decline in vascular compliance is another possible explanation. Surprisingly, increases in the mean arterial blood pressure due to either isometric handgrip exercise or supine bicycle exercise attenuated the maximum flow response, most likely because of increased vascular resistance due to greater extravascular resistive forces.[63,67] These factors also may contribute to lesser flow increases during physical exercise when flow increases in proportion to MVO_2. Thus pharmacologically induced hyperemia may not necessarily prove to be more accurate in identifying functionally significant coronary stenoses. Even though flows in

remote myocardium may rise less with exercise depending on the level of cardiac work, higher intracavitary left ventricular (LV) pressures and regional wall stresses in ischemic or dysfunctional myocardium may enhance extravascular resistive forces so that flow responses in stenosis-dependent myocardium in fact may be even more attenuated. Because of differences between pharmacologically and physically stressed-induced ischemia, the vasodilator reserve as determined pharmacologically may not necessarily reflect truly the myocardium's ability to raise flow during physical exercise. An example is hypertrophic cardiomyopathy, where MBF during exercise failed to increase despite some residual flow reserve demonstrated with dipyridamole.[68]

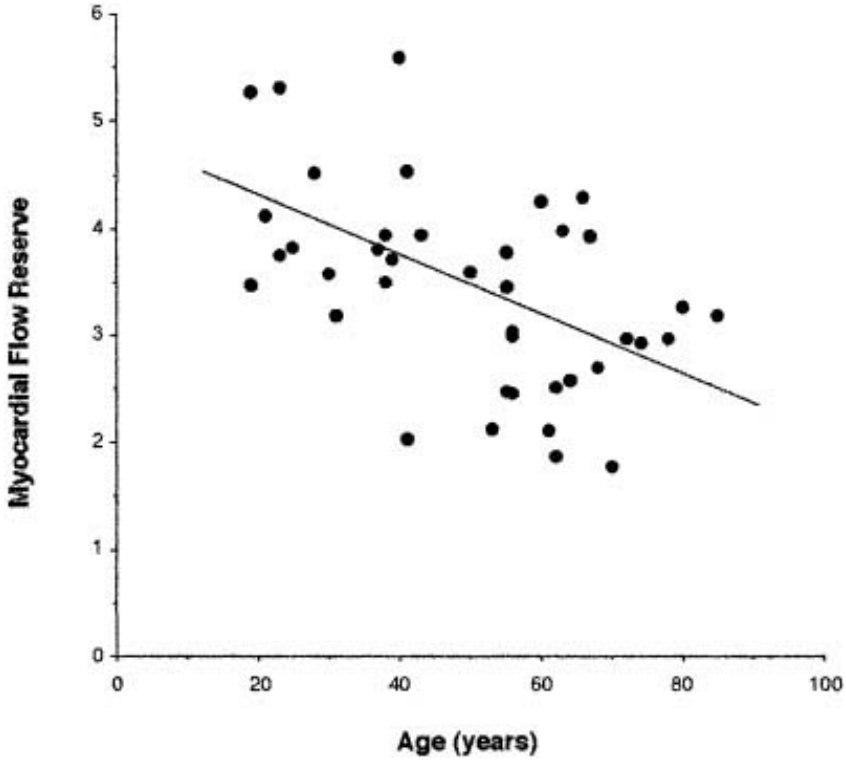

Figure 19-3: Progressive decline in myocardial perfusion reserve as a function of age in 40 normal volunteers. (Reproduced with permission of the American Heart Association from Czernin et al.[29])

Another important consideration with regard to pharmacologic stress is the variability of the hyperemic response. In normal individuals, responses range from about two- to sixfold increases in MBF. Several factors may account for this variability. Among these are (1) the coronary driving pressure, best reflected by the mean arterial blood pressure, (2) extravascular resistive forces as a function of wall tension and tension development, which in turn depend on the diastolic volume and the myocardium's contractile state, (3) β- and especially α-adrenergic control of the basic vasomotor tone,[69] (4) endothelial-dependent vasomotion, and (5) pharmacologic effects on vascular smooth muscle relaxation. The latter may be altered by antagonists of dipyridamole and adenosine, such as, for example, caffeine or theophylline-containing agents.[70] It thus is imperative that patients refrain from these substances for at least 24 h prior to a pharmacologic stress study.

Positive inotropic agents also are used for stress interventions. Dobutamine raises MBF in proportion to increases in cardiac work, as evidenced by increases in the rate pressure product.[71] In one study, intravenous infusion of dobutamine in normal volunteers at a rate of 40 μg/kg of body weight per minute increased the rate-pressure product by about 200 percent, which was

paralleled by a 225 percent increase in MBF.[71] Lower infusion rates produced lesser increases in the ratepressure product and thus in MBF.[72]

ASSESSMENT OF HEMODYNAMICALLY SIGNIFICANT CAD

For the detection of CAD, the relative distribution of MBF is examined at rest and during pharmacologic vasodilation. Either ^{82}Rb or [^{13}N]ammonia is used. Both are retained in myocardium in proportion to MBF so that the resulting images depict the distribution of MBF at rest and during hyperemia. The approach identifies flow defects at rest as well as attenuated responses of regional MBF to hyperemia as a consequence of a coronary stenosis (Fig. 19-4). The baseline and hyperemia flow images are analyzed by visual inspection combined with circumferential activity profile techniques or polar map approaches. While most studies rely on visual analysis, several laboratories employ quantitative image analysis. The regional tracer activity concentrations in a patient are compared with databases of normal displayed graphically in various cartographic forms, such as polar (or azimuthal) or cylindrical (Mercator-like) projections or surface rendered three-dimensional displays of the LV myocardium.[73-76]

Clinical investigations confirmed PET's high diagnostic performance for the detection of CAD.[77-83] Sensitivities range from 87 to 97 percent; and specificities from 78 to 100 percent. Most studies compared rest or stress-induced flow defects to arteriographic findings by visual analysis, and most defined a 50 to 70 percent diameter luminal narrowing as significant stenosis. Given the well-known limitation of visual analysis, Gould et al.[84] and, subsequently, Demer et al.[79] graded stenosis severity by estimates of coronary flow reserve by quantitative arteriography. Coronary arteries were classified as moderately to severely stenosed if the predicted coronary flow reserve was less than 3, as intermediate if the coronary flow reserve ranged from 3 to 4, and as minimal for coronary flow reserve values of greater than 4. According to this classification, 94 percent of vessels with moderate to severe, 49 percent of vessels with intermediate, and 5 percent of vessels with minimal stenosis were accurately identified with PET and pharmacologic vasodilator stress.

COMPARISON OF PET WITH CONVENTIONAL TECHNIQUES

The diagnostic accuracy of PET must be directly compared with that of more conventional approaches in order to define the diagnostic gain. (See also Chap. 16.) Demer et al.[79] indirectly compared their findings with those by another laboratory using ^{201}Tl SPECT but an identical angiographic approach for defining stenosis severity.[85] In this comparison, PET outperformed SPECT. Both studies defined stenosis severity by the angiographically predicted coronary flow reserve. Moderate to severe coronary stenoses were detected with a 95 percent sensitivity by PET and a 72 percent sensitivity by ^{201}Tl SPECT; intermediate stenoses were detected with a 49 percent sensitivity by PET, whereas none were detected by SPECT.

Other studies compared the PET with the SPECT approach in the same patients. An early study used supine bicycle stress and [^{13}N]ammonia in 48 patients with CAD and reported comparable diagnostic performances for PET and SPECT.[78] In another investigation of 202 patients, MBF was evaluated with ^{82}Rb at rest and again 4 min after the dipyridamole infusion.[80] About 8 to 9 min later, or a total of 12 to 13 min after the end of the dipyridamole infusion, ^{201}Tl was injected and SPECT imaging performed within 10 min. PET and SPECT exhibited comparable specificities, while PET demonstrated a significantly higher sensitivity than SPECT. The results were similar when only 132 of the 202 patients without prior cardiac events were analyzed. A third study reported somewhat different findings in 81 patients.[81] Again, all patients underwent rest and dipyridamole stress imaging with ^{82}Rb and PET; for the ^{201}Tl SPECT study, 38 (or 47

percent) of the patients underwent treadmill testing, and the remaining 43 (or 53 percent) underwent pharmacologic stress with dipyridamole. In that study, PET and SPECT exhibited comparable sensitivities; however, the specificity was higher for PET than for SPECT. The diagnostic accuracies were similar for patients submitted to treadmill stress testing and patients with pharmacologically induced hyperemia for SPECT imaging with ^{201}Tl.

Thus both studies demonstrate the high diagnostic accuracy for PET but differ in terms of higher sensitivities and specificities. The average decay half-time of 33 min for the hyperemic response amounts to an only 10 percent decline in the hyperemic response over a 4-min period[86] that is unlikely to fully explain the lower sensitivity of ^{201}Tl SPECT. The gain in specificity in the study by Stewart et al.[81] most likely resulted from the adequate correction of photon attenuation and thus a reduction of falsely positive findings. Although the reasons for the observed differences between both studies remain unclear, image analysis at different points of the receiver operating curve may be one possible explanation.

On balance, the reported studies demonstrate a statistically significant gain in diagnostic accuracy for the detection of CAD by PET. Although larger clinical trials are needed, especially in previously undiagnosed patients with normal MBF and normal wall motion at baseline, current information indicates an improved diagnostic accuracy that may eliminate additional diagnostic procedures. A recent report compared the effect of PET and of SPECT on the subsequent referral to coronary angiography in 1490 and 102 patients, respectively.[87] Pretest likelihoods for CAD were similar for both patient groups. However, the rate of angiography was significantly less (16.7 percent) after PET than after SPECT (31.4 percent), which produced an approximately 23 percent cost saving per patient.

EFFECT OF CORONARY STENOSES ON REGIONAL MBF

Recent investigations took advantage of PET's ability for measurements of regional MBF with [^{15}O]water or [^{13}N]ammonia in order to define the relationships between the angiographic stenosis severity, hyperemic flow responses, and vasodilator capacity.[88-90] These studies noted significant correlations between the anatomic stenosis severity and an attenuation of the hyperemic response to pharmacologic vasodilation. A similar correlation between MBF and coronary stenosis severity was observed when MBF was increased with dobutamine[41] (Fig. 19-5).[91] One study describes an inverse, nonlinear correlation between the cross-sectional area reduction of the stenosis and the flow reserve in the stenosis-dependent myocardium[84] (Fig. 19-6) that resembles the nonlinear correlation observed in animals.[61] In exploring the existence of such correlation in human CAD, the latter study excluded confounding factors such as stenoses in series or collateral vessels to stenosis-dependent myocardium.[89] While such correlation had in fact been expected in human CAD, the considerable scatter of the data about the regression line was not. Factors accounting for this scatter include possible inaccuracies in regional MBF measurements, the variability of the hyperemic response to pharmacologic vasodilation, age differences, and different baseline hemodynamic states. The scatter of the data may further point to a disparity between the anatomic and functional properties of human coronary artery stenoses. Different from the controlled and idealized coronary artery stenoses in the experimental setting, human coronary artery stenoses are of remarkably greater morphologic complexity, including eccentricity, variable stenosis inflow and outflow angles, and different lengths and irregular surfaces, that may not be fully appreciated by angiography nor be adequately accounted for by assumptions underlying model-based estimates of stenosis severity. It thus seems probable that the evaluation of flow, either semiquantitatively or quantitatively, renders more accurate functional information on the stenosis severity and, more broadly, on CAD. Moreover, estimates of an attenuated flow reserve obtained from static images of the relative distribution of MBF during

hyperemic stress clearly offer invaluable information on the functional significance of coronary artery stenosis. Yet, in view of the nonlinear response in flow tracer uptake to increases in blood flow, such "semiquantitative" estimates would tend to be less accurate than those available through true measurements of MBF.

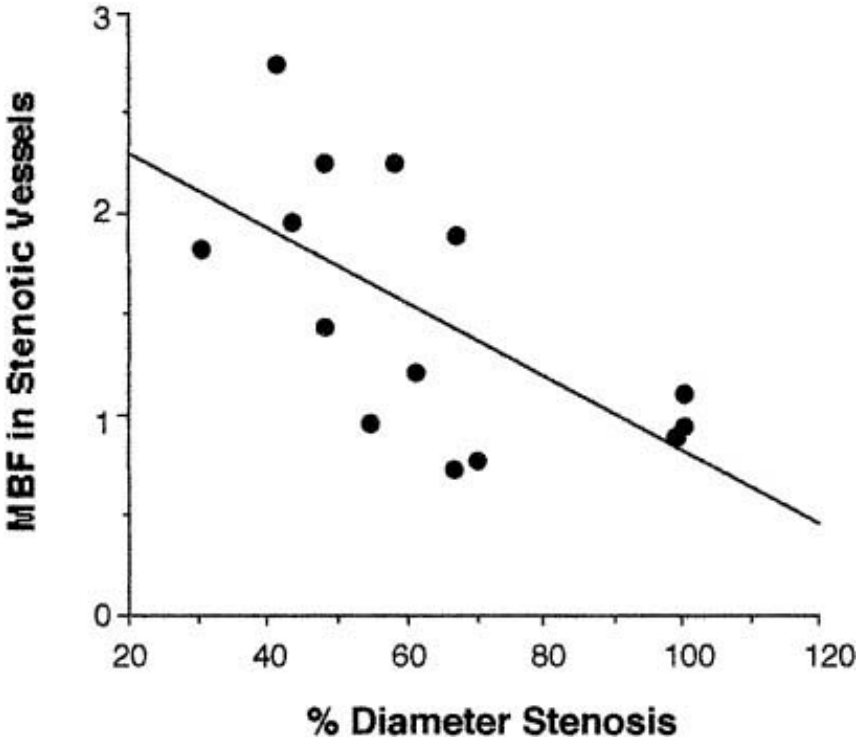

Figure 19-5: Correlation between coronary artery stenosis severity as determined by quantitative angiography and MBF in the stenosis-dependent myocardium during intravenous dobutamine infusion. (Reproduced with permission from Krivokapich et al.[228])

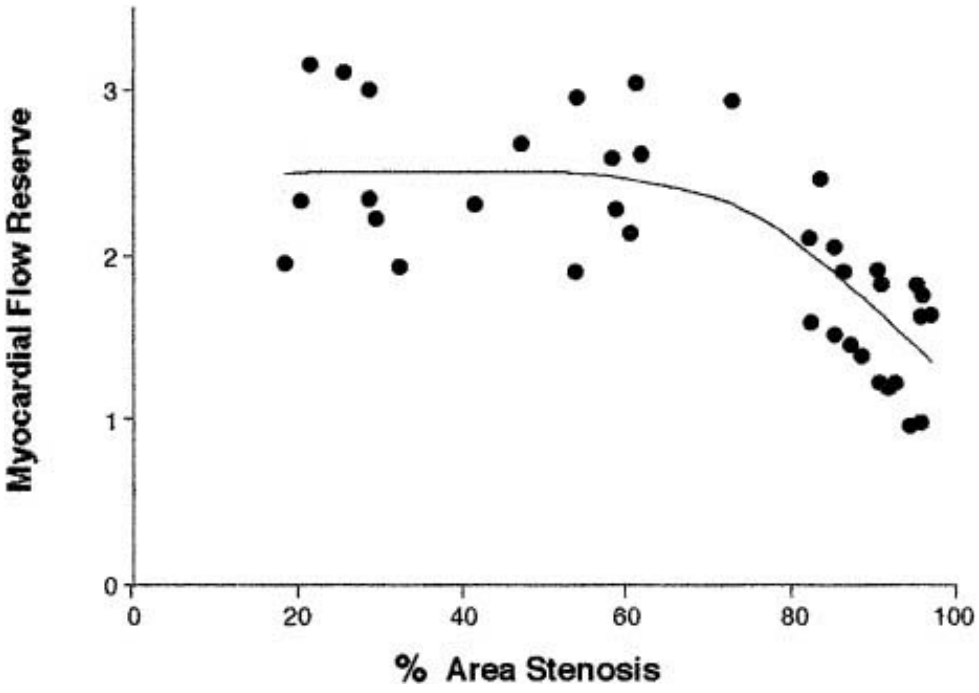

Figure 19-6: Myocardial flow reserve and coronary artery stenosis severity by quantitative angiography. Note the curvilinear relationship between the myocardial flow reserve as determined quantitatively from hyperemic and rest MBF measurements with [13N]ammonia. (Reproduced with permission of the American Heart Association from Di Carli et al.[89])

ASSESSMENT OF CORONARY VASOMOTION AND PRECLINICAL CAD

Noninvasive measurements of regional MBF offer the intriguing possibility to uncover vasomotor abnormalities of the human coronary circulation. If such abnormalities exist already during the early stages of CAD, it then may become possible to detect the disease during its evolutionary and preclinical stages. Such measurements further offer the prospect of monitoring disease progression as well as the responses to interventions aiming at regression of disease or slowing or halting its progression. Several lines of evidence support such possibility.

The now well-established beneficial effects of cholesterol lowering and especially of HMG-CoA reductase inhibitors have shifted the emphasis to the assessment of function rather than to the morphology of the human coronary circulation. Dietary and/or pharmacologic cholesterol lowering affect the anatomic stenosis severity only little, if at all, at least over the time periods studied, but strikingly reduced cardiac morbidity and mortality.[92] Hence the beneficial effects are attributed to plaque stabilization and improvements in endothelial function.[93]

Invasive studies of the human coronary circulation, performed during cardiac catheterization with intracoronary administration of direct vascular smooth muscle dilator agents such as adenosine or papavarine and of acetylcholine as a pharmacologic probe of predominantly endothelial-mediated coronary vasomotion, emphasize the importance of endothelial dysfunction early during the development of atherosclerosis (see Chaps. 36 and 37). For example, human coronary arteries with minimal atherosclerotic changes but no flow-limiting stenoses or even without any structural changes but in the presence of coronary risk factors alone revealed normal, predominantly vascular smooth muscle-mediated vasodilator capacities but attenuated or even highly abnormal endothelial-mediated flow responses.[94-96] These invasive studies test endothelial function at two sites of the coronary circulation, the large epicardial conduit and the coronary resistance vessel.[94-96] Measurements of regional MBF by PET offer the opportunity to probe the function of the human coronary circulation entirely noninvasively and mostly at the level of the resistance vessels.

PET-based measurements of MBF in asymptomatic patients with hypercholesteremia revealed an approximately 32 percent reduction in myocardial flow reserve or an approximately 18 percent reduction in hyperemic flow during adenosine administration.[97-102] In fact, the myocardial flow reserve was correlated with the ratio of plasma total cholesterol over HDL cholesterol.[97] Subsequent investigations confirmed these observations but also noted that elevated plasma triglycerides or, in young individuals, a family history of CAD alone or of hypertension was associated with diminished vasodilator capacities and myocardial flow reserves.[103-105] Other studies again observed diminished hyperemic responses in patients with diabetes,[104,106-108] and one study found a correlation between the hyperemic MBF response and the therapeutic control of the diabetic state.[109]

To some extent, these observations differ from those made by invasive techniques, where frequently the predominantly vascular smooth muscle-mediated vasodilator response to, for example, intracoronary papavarine or adenosine was preserved despite the presence of coronary risk factors, while primarily endothelial-mediated responses were markedly abnormal.[110] As Bache suggests,[111] however, the major resistance to flow through the coronary circulation resides at vessels in the diameter range of 100 to 400 μm. If increases in flow exert shear stresses on the

endothelium of the 400-μm vessels, then primarily endothelial-dependent mechanisms augment the flow response to predominantly vascular smooth muscle vasodilators. Conversely, as forearm blood flow measurements have shown, pharmacologic impairments of endothelial function reduce the maximal flow response to intravascular adenosine by about 25 to 35 percent.[112] Consequently, coronary risk factors such as low-density lipoprotein (LDL) cholesterol, triglycerides, and diabetes interfere with endothelial function and account for the diminished hyperemic response to adenosine or dipyridamole.

Another potentially important new concept for identifying diffuse coronary artery narrowing without discrete stenoses has been introduced recently.[113,114] Diffuse luminal narrowing causes a greater decline in pressure along the coronary artery. This then is associated with a progressive decrease in myocardial perfusion from the proximal to the distal portion of the coronary arterial system and hence in a longitudinal base-to-apex perfusion gradient. A similar longitudinal perfusion gradient likely exists during hyperemia in patients without CAD but with coronary risk factors.[115]

The predominantly endothelial-mediated coronary vasomotion can be assessed by the cold pressor test. In invasive studies, cold pressor testing evoked paradoxical changes in the diameter of the conduit vessels comparable with those evoked by intracoronary acetylcholine and, further, alterations at the level of the resistance vessels that correlated with those produced by intracoronary acetylcholine.[116-118] Observations with PET-based measurements of MBF in long-term smokers support the use of the cold pressor test for this purpose.[119] In these young smokers, vascular smooth muscle-mediated hyperemic flow responses to intravenous dipyridamole were normal, but cold pressor testing produced only modest, nonsignificant increases in MBF as compared with nonsmokers, where MBF rose in direct proportion to the cold-induced increase in cardiac work, as estimated by the rate-pressure product (Fig. 19-7). Similarly, abnormal flow responses to cold also were noted in postmenopausal women with and without CAD risk factors.[120]

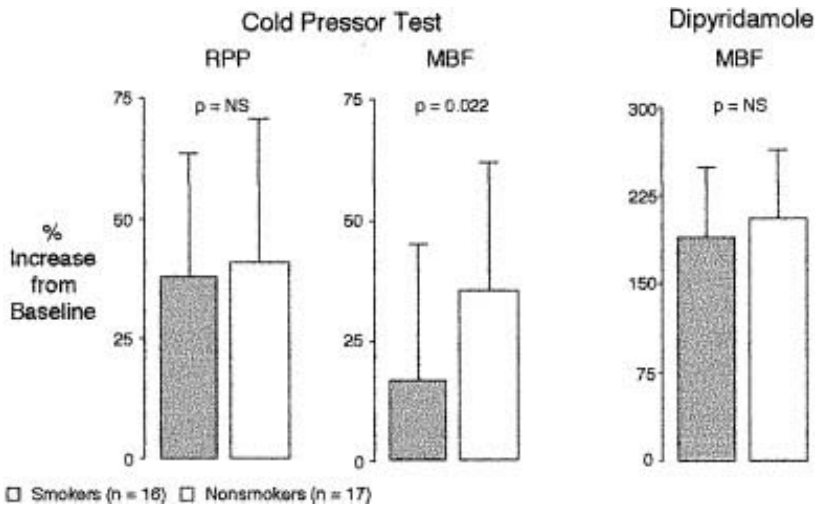

Figure 19-7: Increases in MBF in response to cold pressor testing and to intravenous dipyridamole in nonsmokers and long-term smokers (*shaded bars*). Note the comparable increases in MBF in response to dipyridamole in both groups. Also, cold pressor testing produced comparable increases in the rate pressure product (RPP), while the increase in MBF in long-term smokers was markedly attenuated as compared with normal individuals. (Data taken from Campisi et al.[119])

MONITORING RESPONSES TO RISK FACTOR MODIFICATION

Given their high degree of reproducibility, PET-based measurements of MBF are equally suited for monitoring responses in coronary vasomotion to pharmacologic interventions and risk factor modification. Early studies in only 13 participants in a 6-week cardiovascular conditioning program demonstrated this capability.[121] Dietary changes, regular exercise, and lifestyle modifications were associated with weight loss, decreases in heart rate and blood pressure at rest, and significant decreases in plasma total and LDL cholesterol. A 12 percent decline in MBF at rest was proportionate to the decrease in resting cardiac work. Cardiovascular conditioning also produced a 9 percent increase in hyperemic flow, and MBF reserve increased by a total of 20 percent. Rigorous lifestyle and risk factor modification had been shown previously with PET to result in smaller and less severe stress-induced perfusion defects.[122,123] More recent studies with PET-based measurements of MBF have demonstrated beneficial effects of cholesterol lowering by HMG-CoA reductase inhibitors.[124,125] In one study, a 6-month course of fluvastatin treatment produced a 26 percent increase in hyperemic MBFs (at 6 months but not at 2 months) and thus in vasodilator capacity.[124] Of interest was the delayed improvement in vasodilator capacity (Fig. 19-8). In these patients with CAD, the cumulative coronary function improved in myocardial territories subtended by both diseased and nondiseased coronary arteries. These observations differ with those of another study that demonstrated a significant improvement in vasodilator capacity only in territories with stress-induced perfusion defects but not in apparently normal myocardium,[126] whereas a third study demonstrated again a 20 percent improvement of hyperemic flows in remote myocardium.[125] Another study reported immediate (within 24 h) improvements in hyperemic MBFs following LDL cholesterol plasma apheresis.[127] In the latter study, however, plasma LDL cholesterol apheresis reduced total cholesterol by 42 percent and LDL cholesterol by 58 percent, which was greater than in the fluvastatin study with total and LDL cholesterol reductions of 29 and of 37 percent, respectively.[124]

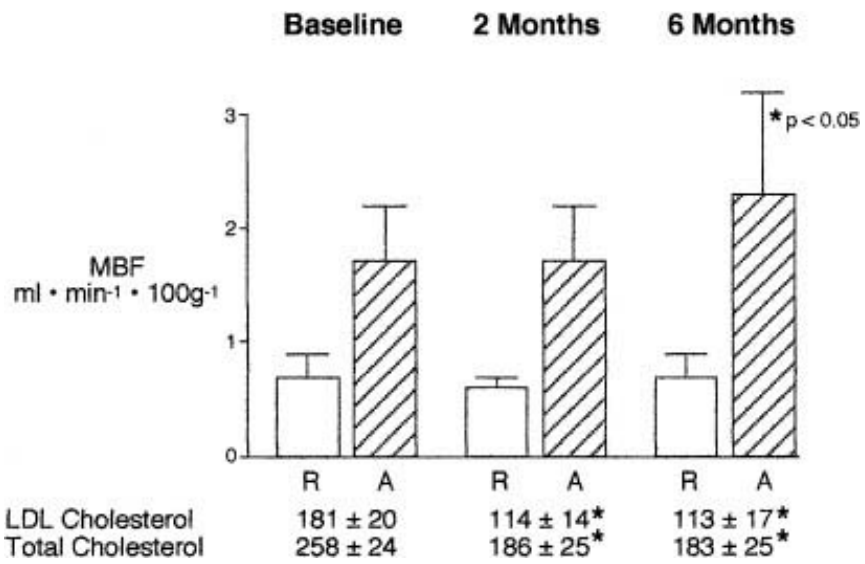

Figure 19-8: Changes in coronary artery vasodilator function in patients with CAD on a 6-month course of fluvastatin. The upper panel shows the MBF at rest and during adenosine hyperemia (A, *shaded bars*); the lower panel, the plasma levels for cholesterol in milligrams per deciliter. Note the delayed improvement of hyperemic MBF despite the significant decline in plasma total and LDL cholesterol at 2 months (*$p < 0.05$ versus baseline). (Data after Guethlin et al.[124])

Other investigations explored pharmacologic effects on predominantly endothelial-dependent

coronary vasomotion. For example, intravenous L-arginine (30 g) as the substrate of nitric oxide synthase (NOS) in long-term smokers normalized the MBF response to cold pressor testing, suggesting that endothelial function or, at least, the bioactivity of nitric oxide had normalized.[128] Whether increases in the substrate for NOS accelerate production of nitric oxide remains uncertain, especially in view of the low K_m, which renders the reaction relatively substrate-independent.[129] One possibility could be a nonspecific effect, perhaps on the oxidative stress, as recently demonstrated with cold pressor testing in response to acute administration of vitamin C.[130] Other possible mechanisms include competitive displacement of asymmetric dimethylarginine, an inhibitor of NOS with elevated plasma levels in hypercholesteremic patients.[131] An insulin-dependent mechanism is also possible, especially because L-arginine infusions prompted three- to fourfold increases in plasma insulin concentrations.[128] Similarly, hormone-replacement therapy in postmenopausal women without coronary risk factors can normalize the MBF response to cold, while the responses remain abnormal in postmenopausal women with coronary risk factors despite hormone-replacement therapy.[120]

Assessment of Myocardial Viability

Myocardial viability pertains to an impairment of myocardial contractile function that is potentially reversible. Distinction of such potentially reversible from irreversible impairment of contractile function often is of considerable clinical importance but remains diagnostically challenging. Both types of tissue injury share several features, including similar degrees of abnormal systolic wall motion, of reduced MBF, and of electrocardiographic abnormalities. Persistence of metabolic activity for sustaining vital, energy-requiring processes, however, including cellular homeostasis, depends on some residual MBF for removal of inhibitory metabolites as well as for supply of fuel substrates. Hence key features of viable myocardium include

- Impairment of systolic wall motion at rest
- Normal or reduced, but not absent, blood flow
- Preservation of cellular homeostasis
- Persistent metabolic activity for high-energy phosphate production
- Recruitable contractile reserve

GENERAL CONSIDERATIONS

Research studies in animals provided the base for the detection of myocardial viability. Known alterations in substrate metabolism during acute myocardial ischemia were demonstrated noninvasively with positron-emitting tracers of myocardial substrate metabolism.[132] Consistent with an impaired FFA oxidation was the diminished initial uptake of [^{11}C]palmitate and its delayed clearance from the myocardium.[46,47] Additionally, the known increase in glucose extraction and use was reflected by a regional increase in [^{18}F]deoxyglucose uptake.[133] Initial studies in patients with acute myocardial ischemia revealed blood flow and glucose metabolism patterns that were virtually identical to those in animals, e.g., enhanced [^{18}F]deoxyglucose uptake in hypoperfused dysfunctional myocardial regions. Unexpectedly, the same pattern existed in patients with chronic CAD but no signs of acute ischemia (Fig. 19-9). This raised the question of whether the observed blood flow-metabolism pattern was unique to acute ischemia or represented a more general metabolic pattern in chronically dysfunctional and hypoperfused myocardium. Also intriguing were observations in other CAD patients with regionally reduced [^{18}F]deoxyglucose uptake that paralleled the reduction in regional MBF[134] (see Fig. 19-9). A more systematic study in patients scheduled for surgical revascularization confirmed the hypothesis that the regionally enhanced [^{18}F]deoxyglucose uptake, in contrast to a reduction, reflected metabolic activity as evidence of viability in myocardium with complete or partial loss

of contractile function.[135] Restoration of tissue perfusion was followed by improved contractile function in myocardium with but not in myocardium without persistent glucose metabolic activity.

Possible Mechanisms of the Blood Flow Metabolism Pattern

The preceding observations established the clinical utility of these PET findings, but the underlying mechanisms remained uncertain. Patients with CAD revealed after supine bicycle exercise in stress-induced flow defects an augmented [^{18}F]deoxyglucose uptake when the radiotracer was administered 20 to 30 min after exercise and after the stress-induced flow defect had already resolved.[136] This implicated *myocardial stunning* as one possibility, subsequently supported by observations in animal experiments and in patients with either collaterized myocardium or unstable angina.[137-139] These studies demonstrated the evolution of a blood flow-metabolism pattern in chronically reperfused myocardium: An immediate postreperfusion decrease in glucose uptake was followed by an increase that subsequently declined to normal as contractile function returned.[137] The enhanced [^{18}F]deoxyglucose uptake was attributed to increased lactate release and thus anaerobic glycolysis that persisted even after blood flow had been restored.[140] The evolution of such metabolic pattern also may pertain to early postinfarction patients[141] but does not fully explain all observations in patients with chronic CAD. Another possibility includes *repetitive stunning*[142] as the reason for the persistent increase in [^{18}F]deoxyglucose uptake in dysfunctional myocardium. An impairment in contractile function associated with enhanced glucose use was noted in collateral-dependent myocardium only if the flow reserve was markedly restricted.[138] It limits the coronary circulation's ability to respond appropriately to transient and frequent increases in oxygen demand during daily life, leading to transient ischemic episodes, each followed by stunning and preventing recovery of contractile function.

Myocardial hibernation serves as another explanation.[143] The postulated downregulation of contractile function in response to diminished rest MBF is thought to be associated with an alteration of the myocardium's substrate metabolism with a dominant role for the more oxygen-efficient glucose. Hibernation in its truest sense then implies that the downregulated energy requirements match the available energy supply. A new supply-demand imbalance is established, but at a lower level. Such a new balance, however, will be a precarious one because even moderate increases in demand or decreases in supply disturb the steady state and cause ischemia. It is thus possible and likely that both *hibernation* and *stunning* coexist to varying extents in many patients. Observations in experimental animals suggest that sustained reductions in both blood flow and contractile function can be maintained for some time without significant necrosis, but development of structural alterations resembling those in patients with chronic CAD[144-148] supports the concept of hibernation.

Both concepts, repetitive stunning and hibernation, may, in their purest form, represent the two ends of a spectrum. As Fig. 19-10 illustrates, the spectrum begins with a reduction in myocardial flow reserve, where increased demand can no longer be matched by an appropriate increase in supply and which ends with a loss of the flow reserve and a decline in regional MBF at rest, associated with a downregulation of contractile function and adaptation of substrate metabolism. Such a spectrum could represent a temporal progression in coronary artery stenosis severity. Recent findings in chronically instrumented animals with a progressive decline in and ultimately loss of regional flow reserve associated with a decrease in rest blood flow support such a scenario.[148-151] Reductions in flow or flow reserve also may occur suddenly in view of the high incidence of blood flow metabolism mismatches in early postinfarction patients.[134,141,152] In acute animal studies, sudden moderate reductions in regional MBF are associated initially with evidence of acute ischemia (e.g., release of lactate and enhanced glucose uptake). An apparent resetting or adjustment of demand follows, and lactate release converts to uptake, high-energy phosphate stores are replenished, and a new supply-demand balance seems to have

returned.[144,153,154] Some debate focused on the issue of whether MBF at rest can indeed be chronically reduced.[155] Nevertheless, findings in chronic animal experiments, as well as substantial improvements in resting MBF following surgical revascularization, argue in favor of the possibility of a true chronic regional hypoperfusion.[148,150,151,156,157]

Ultrastructural and Histochemical Observations

Other attempts to gain mechanistic insights into the enhanced [^{18}F]deoxyglucose uptake include morphometric and histochemical analyses of biopsy specimens harvested from dysfunctional human myocardium during surgical revascularization. Prior autopsy studies indicated a general correlation between the degree of regional myocardial fibrosis and the severity of the impairment of regional contractile function. Yet there were exceptions.[158] In some instances, dyskinetic myocardium was free of fibrosis at autopsy, or conversely, some normally contracting myocardium contained as much as 40 percent fibrosis.[159] It also was known that "abnormal" myocytes (Fig. 19-11) existed in chronically dysfunctional myocardium.[160] More recent investigations noted correlations between the externally determined relative blood flows and relative [^{18}F]deoxyglucose concentrations with the morphometrically determined fractions of fibrosis, abnormal myocytes, and normal myocardium.[138,161,162] The various studies agree on a general correlation between relative blood flow and the percentage of tissue fibrosis (Fig. 19-12) but differ on the fraction of abnormal myocytes. In one study, this fraction is the same in reversibly and irreversibly dysfunctional myocardium,[161] whereas a second study notes a significantly greater fraction in reversibly than in irreversibly dysfunctional myocardium.[162] Because the centrally located glycogen granules are key features of such abnormal myocytes and a significant correlation exists between the fraction of such abnormal myocytes and the relative [^{18}F]deoxyglucose uptake, these abnormal myocytes have been considered the ultrastructural correlate of enhanced [^{18}F]deoxyglucose uptake in chronically dysfunctional myocardium. Other observations argue against this notion. Again, electron microscopy and histochemistry of biopsy samples from the center of the dysfunctional myocardial wall demonstrate highly different degrees of severity of morphologic alterations in myocardial regions with blood flow-metabolism mismatches.[163] Despite identical flow and glucose metabolism findings on PET, nearly half the patients in this study revealed only minimal, if any, morphologic changes, whereas the other half demonstrated severe structural abnormalities. Such variability in morphologic alterations argues against the structurally abnormal myocyte and especially the glycogen granules as an explanation of the enhanced [^{18}F]deoxyglucose uptake. More likely explanations include translocation and possibly upregulation of GLUT1[164] as a flux-generating step, uncoupling of glycolysis from glucose oxidation, regulated probably by malonyl-CoA and carnitine palmitate transferase I,[165,166] and possibly an ischemia-related loss of adrenergic innervation or function[167] associated with increased exogenous glucose use. In cardiac allografts, glucose use was about 70 percent higher in denervated than in reinnervated myocardium.[168]

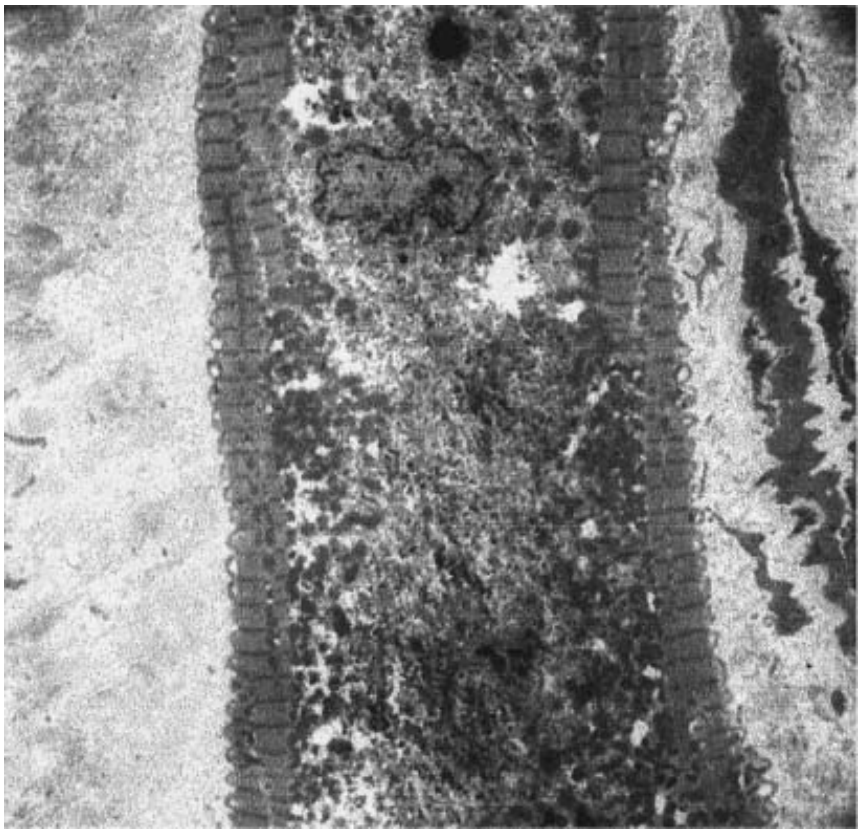

Figure 19-11: Abnormal myocyte in human chronically dysfunctional myocardium. Note the irregularly shaped nucleus, the loss of sarcomeres in the center of the myocyte, and the extensive deposition of glycogen. (Courtesy of M. Borgers, Maastricht, The Netherlands.)

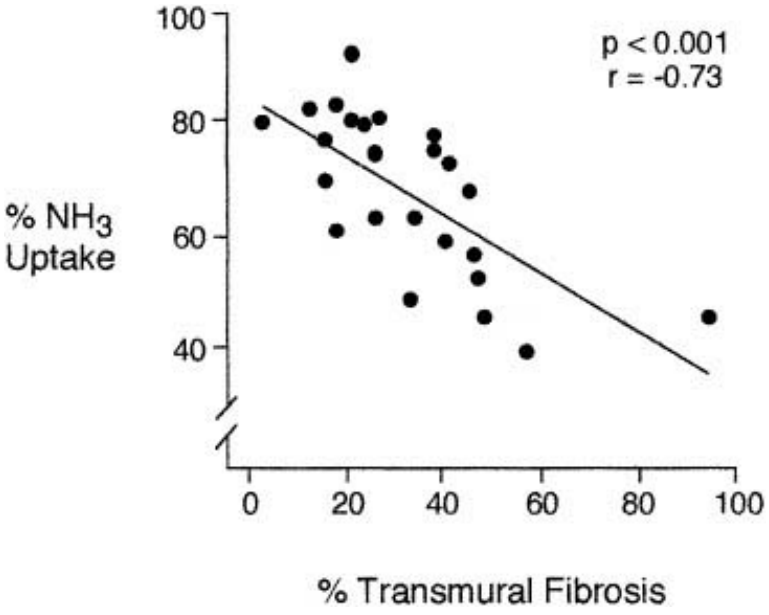

Figure 19-12: Inverse correlation between the fractional amount of tissue fibrosis by morphometry and MBF by relative [13N]ammonia tissue concentration (%NH_3 uptake). (Reproduced with permission of the American Heart Association from Depré at al.[162])

Myocytes in Chronically Dysfunctional Myocardium

Whether abnormal myocytes as described initially by Flameng et al.[160] and subsequently observed in biopsy material from mismatched myocardium point specifically in the direction of or are ingredients unique to any particular pathophysiologic mechanism underlying the chronic, though potentially reversible, impairment of contractile function remains uncertain. Two schools of thought exist. One holds that the morphologic alterations result from (1) contractile unloading, (2) increased wall stress (stretch), and (3) a metabolic substrate switch to preferential glucose use.[169] In fact, contractile unloading recently has been demonstrated to result in virtually identical structural changes.[170,171] The expression and distribution patterns of other features such as of α-smooth muscle actin, cardiotin, and titin,[169] as well as an increased expression of glucose transporter 1 (GLUT1) mRNA,[164] features that resemble those in embryonic and/or neonatal myocytes, suggested that the changes of abnormal myocytes may represent "dedifferentiation."[169] Histochemical analysis further uncovered alterations in the extracellular matrix, with increased amounts of collagen and fibronectin surrounding the abnormal myocytes.[169] Finally, similar to neonatal myocytes, these abnormal myocytes have been found to be relatively tolerant of ischemia.[172] The absence of true degenerative changes further has been claimed to support this possibility.

The other school of thought emphasizes a progressive deterioration rather than a stable state of the cell's morphology and therefore referred to *hibernation* as "incomplete adaptation to ischemia."[173] The process begins with few structural changes but a switch in substrate selection to glucose, either because of its greater oxygen efficiency or, alternatively, because of loss of enzymes essential for fatty acid oxidation, followed by loss of contractile protein and accumulation of glycogen and mitochondrial and nuclear alterations, ultimately leading to cell death and scar tissue formation (Fig. 19-13).[163] Other studies again report reduced expression of contractile and cytoskeletal proteins associated with increased expression of extracellular matrix proteins,[173] implying a progressive loss of contractile protein and of the cell structure that is paralleled by accelerated formation of tissue fibrosis and hence a progressive loss of viability that was further found to be associated with apoptosis and replacement fibrosis. Biopsies from patients with preoperatively viable myocardium but without a postrevascularization improvement in contractile dysfunction demonstrated an about threefold increase in mRNA of caspase-3, a promoter of apoptosis, together with an about 50 percent reduction in the expression of the antideath genes *Bcl-2* and *p53*, again consistent with continued cell death and replacement fibrosis.[174] Chronic animal experimental studies similarly have demonstrated significant increases in apoptotic myocytes in hibernating myocardium with reduced rest MBF and critically reduced or absent flow reserve.[151] The fact that myocyte apoptosis in these studies occurred scattered and not in clusters raises the question of whether apoptosis is indeed the end point of the progressively deteriorating abnormal myocyte or such apoptosis represents a process that occurs in parallel. To some extent this may depend on the duration and severity of the ischemic compromise. For instance, other animal studies with more sudden reductions in flow and shorter time periods report higher rates of myocyte apoptosis occurring in clusters.[175]

A progressive deterioration of reversibly dysfunctional myocardium is also consistent with clinical observations that point to the high prevalence of mismatch patterns in patients with prior myocardial infarctions[134,176] but note a declining incidence of blood flow-metabolism mismatches as a function of time after an acute myocardial infarction.[152] Moreover, the loss of the capability to improve global LV function if revascularization was delayed by more than 6 months[177] or an increase in fibrosis and loss of functional recovery after revascularization as a function of the duration of clinical symptoms[178] seem to support such progression. The blood flow-metabolism mismatch may represent a transient rather than a permanent state of reversibly dysfunctional myocardium. It is possible that reversibility can be maintained up to a certain point. Once this critical point has been reached, myocytes become committed to irreversibility and cell death.

In the clinical setting, prompt restoration of adequate tissue perfusion through interventional revascularization therefore will be essential, regardless of whether abnormal myocytes represent dedifferentiation or degeneration. It would seem that ultimately the return of contractile function will depend on the amount of connective tissue. Once fibrosis and scar tissue occupy more than 35 to 40 percent of the myocardium, dysfunction has been shown to be irreversible.[15,16] Also, the presence of structural changes in viable myocardium, as demonstrated with blood flow-metabolism imaging, implies that if the contractile machinery in abnormal or dedifferentiated myocytes can be reconstructed, the recovery of contractile function will not be immediate but slow, as animal experimental[179] and clinical investigations have indeed demonstrated.[180] The delay in cell repair also may explain the persistence of increased [^{18}F]deoxyglucose uptake after successful revascularization.[181]

Viability Assessment in the Clinical Setting

The classic and now most widely applied approach entails evaluation of the relative distribution of blood flow and exogenous glucose use with [^{18}F]deoxyglucose. Initial studies uncovered three distinct patterns:

- Normal blood flow and normal or enhanced glucose uptake
- Reduced blood flow but normal glucose uptake in excess of blood flow (mismatch)
- Reduced blood flow and proportionately reduced glucose uptake (match)

While these terms are purely operational, they infer, at least to some extent, the underlying pathophysiology accounting for the contractile dysfunction. Normal flow and/or metabolism may represent *stunned* myocardium, whereas the classic mismatch may be consistent with *hibernating* myocardium. Both patterns predict a postrevascularization improvement in contractile function, whereas the concordant reduction in blood flow and metabolism predicts that function will not improve.[135,182,183] It should be emphasized that the reduction in regional flow for both matches and mismatches may vary considerably between patients.

Because of the observed correlation between tissue fibrosis and relative flow tracer uptake, the evaluation of regional MBF alone can provide information on the presence of reversible contractile dysfunction (Fig. 19-12). [162] Severe reductions to less than 25 percent of normal or complete absence of blood flow reflects complete or nearly complete transmural scar tissue formation and hence nonreversiblity.[184] In another study, flow reductions of more than 60 percent were highly accurate in predicting nonreversiblity of contractile dysfunction.[185] Conversely, completely normal or only mild reductions (<20 percent) of MBF in dysfunctional myocardium argue against the presence of significant amounts of tissue fibrosis; it possibly reflects myocardial stunning and thus indicates functional reversibility. Mild to moderate flow reductions are less reliable discriminators. If combined with a metabolic study, the [^{18}F]deoxyglucose uptake in the case of a small nontransmural/infarction with otherwise normal myocardium would be reduced in proportion to blood flow.[186] Conversely, an increase in glucose uptake would indicate the coexistence of reversibly dysfunctional myocardium with scar tissue and predict an improvement in contractile function.

Another, again limited approach for identifying reversible contractile dysfunction is the use of [^{18}F]deoxyglucose alone. This approach assumes that regional reductions in [^{18}F]deoxyglucose greater than 50 percent relative to remote myocardium represent irreversible contractile function, whereas mildly reduced or normal uptake indicates the presence of reversible dysfunction.[187,188] While used for some time as a benchmark for defining the accuracy of ^{201}T1-based techniques for assessing myocardial viability,[187] only recently has the validity of this particular approach been tested against the postrevascularization outcome in regional contractile function.[189] Electrocardiographic gated image acquisition affords simultaneous evaluation of regional function

and metabolism and thus can further augment the predictive accuracy of the [^{18}F]deoxyglucose stand-alone approach.[190,191] A more recent report emphasizes the utility of measurements of exogenous glucose use in absolute units. Using a threshold value of 0.25 μmol/g per minute offered a 93 percent positive and a 95 percent negative predictive accuracy for the improvement of contractile dysfunction.[192] Nevertheless, this approach is severely limited when glucose use and hence [^{18}F]deoxyglucose uptake cannot be controlled sufficiently. In such instances, it may be difficult to distinguish between scar tissue, normal myocardium, and reversibly contractile dysfunction, which then could be readily clarified by evaluating the distribution of regional MBF.[193]

The pattern of normal blood flow and glucose metabolism in mildly to severely hypokinetic myocardium of severely depressed left ventricles is a difficult clinical problem. One study reports that of 32 such myocardial regions, only 8 regions (or 25 percent) improved following surgical revascularization.[194] Such regions therefore may represent remodeled LV myocardium. Conversely, an improvement in wall motion may be consistent with myocardial stunning. If suspected, careful evaluation of the coronary anatomy or, if unavailable, the addition of a pharmacologic stress study can aid in distinguishing between stunned and remodeled LV myocardium (Fig. 19-14).

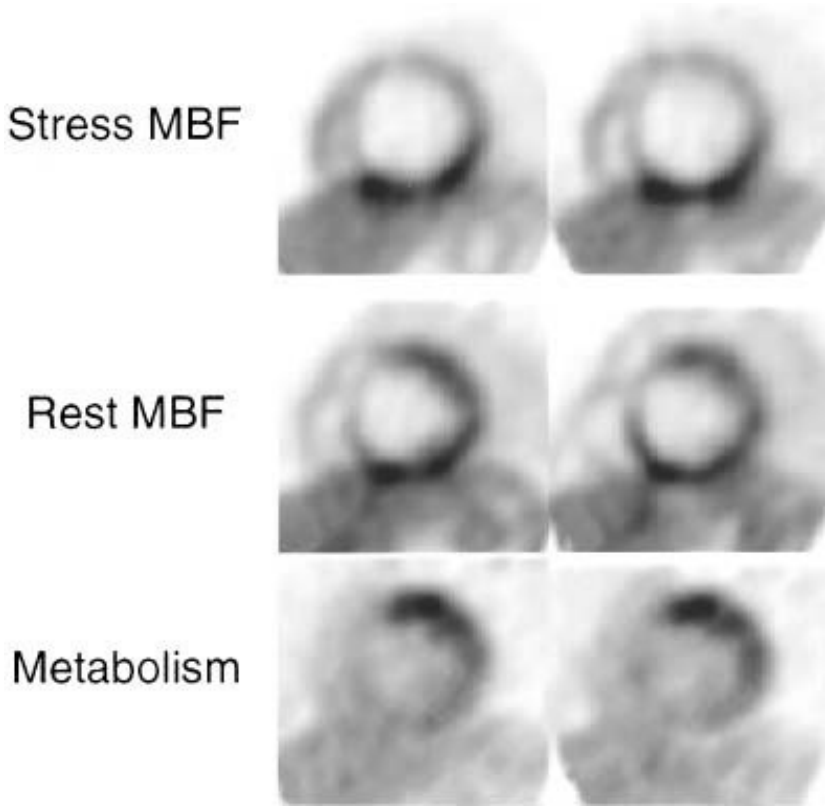

Figure 19-14: Two contiguous short-axis images through the mid-left ventricle in a patient with ischemic cardiomyopathy. The MBF images at rest (*middle panel*) reveal in the interventricular septum reduced but relatively well preserved flow in the anterior and anterolateral wall associated with regionally increased [18F]deoxyglucose uptake in the same portion of the left ventricle as seen in the lower panel (metabolism). The stress induced flow defect in the anterior and anterolateral wall (as seen in the upper panel) implicates stunning as the cause of the enhanced [18F]deoxyglucose uptake.

Alternate Approaches to Blood Flow and Glucose Metabolism Imaging

Several institutions use SPECT myocardial perfusion imaging with either ^{201}Tl or ^{99m}Tc-sestamibi and metabolic imaging with [^{18}F]deoxyglucose with dedicated PET systems. The reported predictive accuracies for segmental and global LV function approach those obtained with dedicated PET systems.[1] Nevertheless, such combined PET/SPECT approaches present at times with diagnostic limitations, especially because of considerable differences in contrast and spatial resolutions as well as artifactual reductions in tracer concentrations due to photon attenuation.[4,5] This can limit the ability to accurately estimate the extent of a blood flow-metabolism mismatch.

More recent approaches rely solely on the use of multipurpose SPECT-like systems, either equipped with ultrahigh-photon-energy general-purpose collimators or with coincidence-detection systems (see also Fig. 19-1). Little information thus far has become available on the clinical performance of coincidence-detection systems, whereas systematic studies with ultra-high-photon-energy general-purpose collimator SPECT systems using ^{201}T1- or ^{99m}Tc-labeled flow tracers and [^{18}F]deoxyglucose report predictive accuracies that are comparable with those reported with dedicated PET systems.[195,196]

Further, ^{201}Tl rest-redistribution imaging has been useful for identifying myocardial viability and for predicting the postoperative outcome of ischemic cardiomyopathy, although with a somewhat lower predictive accuracy (see Chap. 17). This approach suffers from instrumentation-related shortcomings, especially in patients with poor LV function, and consequently, poor signal-to-noise ratios. Thallium-201 offers a negative signal (reduced tracer uptake) as compared with [^{18}F]deoxyglucose, with a positive signal (enhanced tracer uptake) that is more readily accessible to visual analysis.[193] One study reporting that [^{18}F]deoxyglucose and PET identified myocardial viability in 18 of 20 patients with an average LV ejection fraction of 23 percent and only fixed ^{201}Tl defects on SPECT[197] is consistent with a more recent report of viability by [^{18}F]deoxyglucose in 17 of 33 patients (LV ejection fraction <35 percent) with fixed or minimally redistributing ^{201}Tl defects.[198] Further, a comparison study of ^{201}Tl and [^{18}F]deoxyglucose SPECT reports a generally excellent agreement between both approaches but observed disparities in patients with severely depressed LV ejection fractions, where [^{18}F]deoxyglucose revealed more viable myocardial segments than ^{201}Tl SPECT.[11]

In synthesizing the currently available information, it appears that ultimately the total fraction of scar tissue in a given myocardial segment determines largely whether or not contractile function will improve. Because of the linear correlation between scar tissue and relative MBF,[138,161,162] evaluation or even quantitation of regional MBF offers information on potential reversibility. On the other hand, if in viable though functionally compromised myocardium MBF is also reduced, then the augmented glucose use, as evidenced by the enhanced [^{18}F]deoxyglucose uptake, offers additional and critical information. This has prompted most investigators to predict the ultimate functional outcome from a combined assessment of blood flow and [^{18}F]deoxyglucose uptake.[199,200] Further, the temporal recovery of contractile function after revascularization appears to depend on the degree of ultrastructural changes of myocytes as well as the fractional distribution between myocytes with only mild and those with severe ultrastructural changes.[199] If, as postulated, only mild structural changes are associated with a full functional recovery within 3 months, more severe structural changes may require substantially longer time periods and, further, may account for the persistence of increased [^{18}F]deoxyglucose uptake even for many months following revascularization.[181]

CLINICAL ROLE OF PET VIABILITY ASSESSMENT

Among the various PET approaches, the blood flow and glucose metabolism approach has gained the greatest clinical acceptance. Viability assessments with PET can decisively affect therapeutic strategies in patients with advanced CAD and ischemic cardiomyopathy. The therapeutic options in these patients range from aggressive medical management to surgical revascularization and cardiac transplantation. While conservative pharmacologic approaches to the management of such patients has improved markedly over the past decade, the long-term survival of medically treated patients remains relatively poor.[201] Cardiac transplantation as another approach offers a better long-term survival and an improvement in the quality of life, but the supply of donor hearts has not kept pace with the increasing demand, so this therapeutic option remains limited (see Chap. 22). At present, the prevalence of ischemic cardiomyopathy in the United States alone amounts to about 2.5 million cases, thus affecting roughly 1 percent of the U.S. population. The decision to revascularize frequently depends on the answers to several questions. First, what is the leading cause of poor LV function? Second, if CAD has been identified as the culprit, is there enough viable myocardium so that surgical revascularization produces an improvement in LV performance and/or congestive heart failure symptoms? Third, will revascularization avert future catastrophic cardiac events and prolong survival? And finally, can the surgical risk be predicted, since this will influence the preoperative risk-benefit ratio?

Ischemic versus Idiopathic Dilated Cardiomyopathy

In addition to heart failure symptoms, ischemic cardiomyopathy shares several other features with idiopathic dilated cardiomyopathy, such as, for example, the LV enlargement, the often diffuse hypokinesis, the markedly depressed LV ejection fraction, and frequently, mitral regurgitation. Biventricular enlargement has been thought of as a feature characteristic of idiopathic dilated cardiomyopathy but also can be present in ischemic cardiomyopathy. Conduction abnormalities often limit the accuracy of electrocardiographic criteria to distinguish between both entities. Additionally, an intrinsic myopathic process including LV remodeling also may exist in a number of patients with CAD so that the major cause of the poor LV function may remain unknown or difficult to elucidate. Importantly, however, the therapeutic approach to both disease entities will differ strikingly (see Chap. 66).

Both disease entities, however, reveal remarkably different patterns of blood flow and substrate metabolism on PET. A comparative study in patients with ischemic cardiomyopathy and idiopathic dilated cardiomyopathy found the distribution of MBF to be characteristically homogeneous in idiopathic cardiomyopathy as compared with distinct flow reductions clearly corresponding in ischemic cardiomyopathy to the coronary vascular territories.[202] Similarly, uptake of [^{18}F]deoxyglucose was noted to be homogeneous in dilated cardiomyopathy, whereas matches and/or mismatches between blood flow and [^{18}F]deoxuglucose uptake were present in ischemic cardiomyopathy (Fig. 19-15). Combined imaging of blood flow and glucose metabolism distinguished with an overall accuracy of 85 percent between both disease entities.

Prediction of the Outcome in Global LV Function

Numerous clinical investigations have reported the high accuracy of [^{18}F]deoxyglucose imaging with PET in predicting the postrevascularization outcome in regional LV wall motion.[1,135,182,183,188,189,203-205] Even though some of these investigations employed permutations of the initially described blood flow-metabolism approach or relied only on the evaluation of regional [^{18}F]deoxyglucose uptake in dysfunctional myocardium,[188,189] the predictive accuracy, both positive and negative, continued to be high. Such studies have been important because they prove the concept of blood flow-metabolism patterns as accurate predictors of the outcome of regional wall motion after restoration of MBF. More relevant in the clinical setting is whether blood flow-metabolism patterns can predict the postrevascularization

outcome in global LV function.

Initial semiquantitative studies demonstrated some correlation between the extent of the blood flow-metabolism mismatch and the postrevascularization gain in LV ejection fraction.[135] Patients with blood flow-metabolism mismatches that occupied at least two or more of seven total myocardial segments revealed a statistically significant increase in the LV ejection fraction following coronary bypass grafting.[135] No such improvement was observed in patients with only one mismatch segment or with only matches. Subsequent studies reported significant gains in LV function in patients with blood flow-metabolism mismatches as compared with no improvement in those patients without metabolic evidence of viability. Fig. 19-16 summarizes the findings in 19 investigations including a total of 570 patients.[1,3,156,161-163,177,183,194,195,198,205-211] The gain in global LV function is most striking in patients with an LV ejection fraction of less than 35 percent, who had a 34 percent postoperative increase in the LV ejection fraction as compared with a 19 percent ($p < 0.02$) improvement in patients with an LV ejection fraction of more than 35 percent. Additionally, recent studies reported significant correlations between the percentage of the left ventricle with a blood flow-metabolism mismatch and the postrevascularization increase in the LV ejection fraction.[212,213] Thus the extent of a blood flow-metabolism mismatch has some predictive value on the postoperative gain in global LV performance[194,211] (Fig. 19-17). The absence of such improvement in one specific laboratory may be attributable to differences in the imaging and analysis approach used.[181,205] MBF is evaluated with ^{82}Rb at rest and during pharmacologic stress, and the distribution of MBF during stress is compared with the myocardial glucose uptake at rest. This approach identifies both stress induced ischemia and "viable myocardium" at rest. Hence blood flow and possibly wall motion at rest may be normal in some patients so that revascularization predominately improves the capacity of the left ventricle to respond to exercise.[205,214]

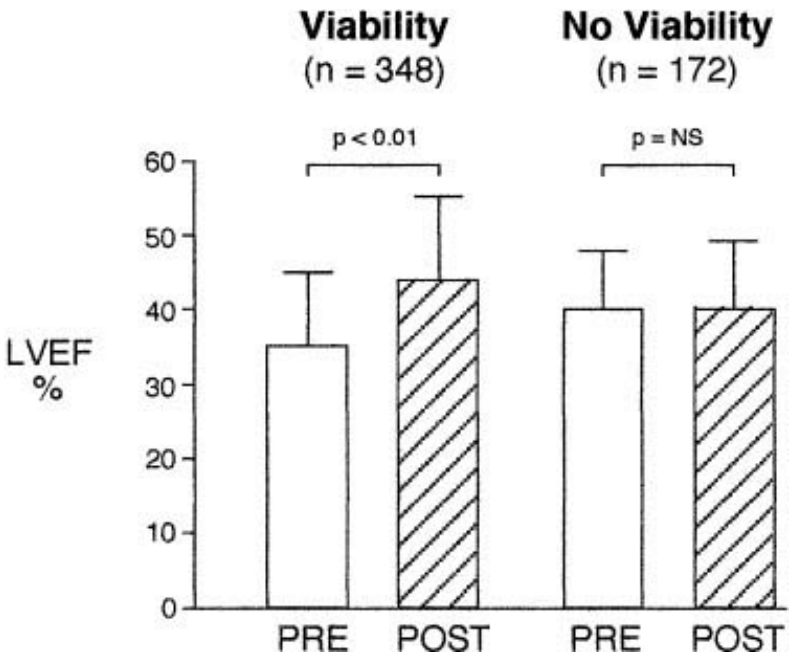

Figure 19-16: Summary of changes in LV ejection fraction from baseline (PRE) to following revascularization (POST) as reported for a total of 570 patients in 19 clinical investigations.[1,3,135,156,161-163,177,183,194,195,198,205,-211] Patients with metabolic evidence of reversible contractile dysfunction are shown on the left and those without on the right. The average LV ejection fractions are shown at baseline (PRE) and following surgical revascularization (POST).

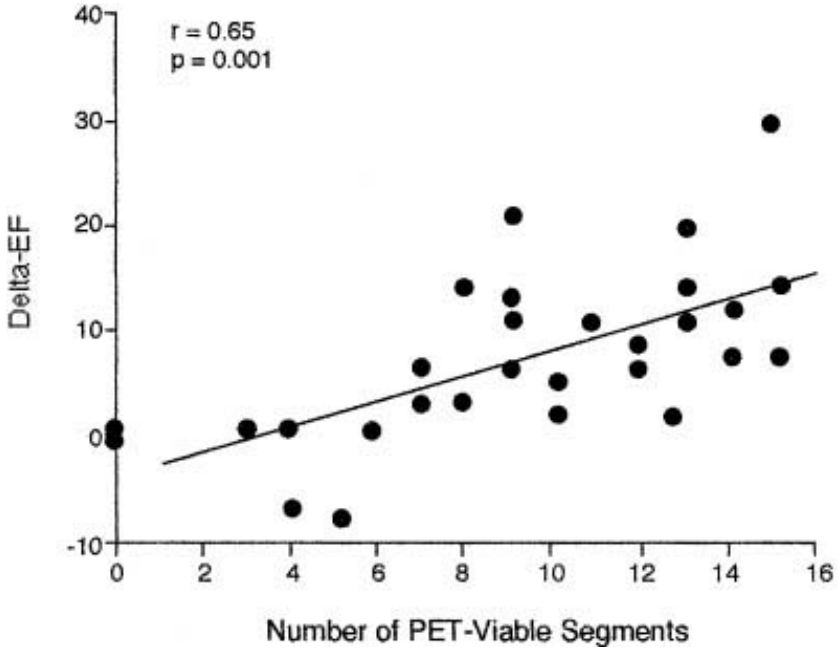

Figure 19-17: Postrevascularization improvement in LV ejection fraction as a function of the number of viable myocardial segments as determined by PET. (Reproduced with permission Pagano et al.[211])

The improvement in regional and especially global LV function may not occur immediately but slowly though progressively following revascularization. In a highly selected patient group, blood flow had been shown to recover promptly following revascularization by angioplasty, whereas contractile function remained initially unchanged.[180] On reexamination 67 ± 19 days later, no further improvements in regional MBF had occurred, but systolic wall motion had now significantly improved. The disparity between recovery of MBF and contractile function may be attributed to stunning and/or to rebuilding of the contractile machinery that had been lost in abnormal myocytes. Preliminary observations suggest a correlation between severity of the mismatch and the rate of recovery of contractile function. The rate of recovery appears to be faster when flow is relatively well preserved as compared with segments with more severe flow reductions and possibly more severe ultrastructural changes. Segments with largely preserved flows recovered faster than segments with more severe flow reductions.[215] The contractile function appears to recover or improve more promptly in myocardial regions without marked ultrastructural abnormalities or a lesser fraction of abnormal myocytes.[199] Finally, in addition to a slow recovery of contractile function in reversibly dysfunctional myocardium, other studies describe an associated decline in end-diastolic and end-systolic volumes, suggesting the possibility of a reversal of LV remodeling.[216]

Effect on Congestive Heart Failure-Related Symptoms

A related clinical question is whether such improvement is also associated with relief or amelioration of congestive heart failure symptoms. Several retrospective studies indicate such possible symptomatic improvement. Two investigations concluded that patients with blood flow-metabolism mismatches undergoing surgical revascularization demonstrated a significantly higher incidence of improvement in NYHA functional class than patients without mismatches or patients with matches but not submitted to regional revascularization.[217,218] Among the 52 patients with mismatches and congestive heart failure class III or IV, 81 percent of the 26 patients undergoing

revascularization revealed a significant improvement in congestive heart failure class as compared with only 23 percent of 26 patients treated conservatively.[218]

The amount of viable myocardium on blood flow and [^{18}F]deoxyglucose imaging contains information on the magnitude of the postrevascularization improvement in congestive heart failure symptoms.[219] The level of physical activity patients were able to perform prior to and 24 ± 14 months following coronary artery bypass grafting was graded on a specific activity scale and expressed in metabolic equivalents.[220] Among the 36 patients in this study with an average LV ejection fraction of only 28 ± 6 percent prior to revascularization, the extent of the blood flow-metabolism mismatch ranged from 0 to 74 percent (mean 23 ± 22 percent) on polar map analysis. When patients were grouped according to the extent of the mismatch, 11 patients with a mismatch occupying less than 5 percent of the LV myocardium revealed a statistically significant but only mild improvement in functional status (34 percent increase in metabolic equivalents) (see Chap. 17). Intermediate-sized mismatches (5 to 17 percent) in 8 patients were associated with a 42 percent increase in metabolic equivalents, whereas large mismatches, i.e., greater than 18 percent, in 17 patients were followed after revascularization by an average increase of 107 percent in metabolic equivalents. Furthermore, the improvement in functional status was linearly correlated with the anatomic extent of the blood flow-metabolism mismatch. Lastly, blood flow-metabolism mismatches of 18 percent or more were 70 percent sensitive and 78 percent specific in predicting an improvement in physical activity or functional status following successful surgical revascularization.

Impact on Long-Term Survival

Several studies examined the long-term fate of patients after being evaluated for MBF and metabolism with PET.[217,218,221,222] These studies presented compelling evidence for an increased prevalence of cardiac events in patients with blood flow-metabolism mismatches not submitted to interventional revascularization. They also implied that revascularization of blood flow-metabolism mismatches may avert future cardiac events.

Despite this general agreement, important differences emerged from these studies. One study in 129 chronic CAD patients followed for a time period of 17 ± 19 months found the presence of mismatches in the absence of revascularization to be independent predictors of the 17 nonfatal ischemic events.[221] Nevertheless, the LV ejection fraction and the patient's age contained the highest predictive values for the 13 cardiac deaths in this patient group. In patient series with more homogeneously depressed LV function, the predictive value of a low LV ejection fraction applied equally to all groups. As shown in Fig. 19-18, the cumulative long-term survival was lowest in the patient subgroup with blood flow-metabolism mismatches who were on medical treatment. Of note, all four subgroups were similar with regard to age and clinical and hemodynamic findings. There were no significant intergroup differences in the LV ejection fraction, which for the whole patient group averaged only 25 ± 7 percent. Of note, patients with mismatches who underwent revascularization revealed a significantly better cumulative survival that no longer differed significantly from that of the groups without mismatches (Fig. 19-18). In this study, the LV ejection fraction was without significant predictive value, whereas by Cox model analysis the extent of a mismatch had a significant negative effect on survival ($p < 0.02$), and revascularization of mismatch patients had a significant positive effect on survival ($p < 0.04$).[218] A second study in patients with similar uniform depression of LV ejection fraction reached similar conclusions.[217]

Assessment of Perioperative Risk

Surgical revascularization of patients with ischemic cardiomyopathy is associated with high

perioperative mortality and morbidity. Two investigations have explored the contribution of PET to the surgical risk assessment.[208,223] Both studies together include a total of 317 patients with ischemic cardiomyopathy and LV ejection fractions of less than 35 percent. The patients were categorized into two groups. Group one (35 and 88 patients, respectively, in each study) underwent coronary artery bypass grafting based on standard clinical criteria including LV size or ejection fraction, the suitability of the coronary anatomy for surgical revascularization, and the presence of comorbidities. The same criteria also were applied to the second group (41 and 153 patients per study), which, however, underwent blood flow metabolism imaging with PET in addition. Thirty-four of 41 patients (83 percent) in one and 110 of 153 patients (72 percent) in the other group demonstrated evidence of reversibly dysfunctional myocardium involving at least 20 to 30 percent of the left ventricle and subsequently underwent bypass grafting. Both studies consistently demonstrated lower perioperative mortalities in those patients who had undergone PET imaging (30-day mortalities of 0 and 0.9 percent) as compared with mortalities of 11.4 and 19.8 percent in the patients not evaluated by PET. Additionally, 1-year cardiac mortalities were lower for the PET-selected patients (3 and 10 percent, respectively) than for those not evaluated with PET (21 and 30 percent, respectively). PET-selected patients required less inotropic support or intraaortic balloon pumping and had better cardiac output and shorter stays in the intensive care unit. If further confirmation of such short-term benefits is established, PET evaluations of patients with ischemic cardiomyopathies would then offer important and possibly critical prognostic information on the immediate and long-term risks of cardiovascular surgery in patients with severe ischemic cardiomyopathy.

Lastly, the prevalence of reversibly dysfunctional myocardium is high. A survey of 283 patients with ischemic cardiomyopathy revealed a 55 percent prevalence of blood flow and glucose metabolism mismatches.[224] Half these mismatches involved 25 percent or more of the LV myocardium and thus would lead to significant gains in LV function and clinical symptoms after revascularization. The remainder of mismatches were smaller but, if not revascularized, may be associated with an increased long-term cardiac morbidity and mortality. Indeed, in the setting of ischemic cardiomyopathy, inclusion of PET in the diagnostic algorithm can be cost-effective and, at the same time, cost saving.[225,226] Clinical criteria for deciding on coronary artery bypass grafting in patients with ischemic cardiomyopathy have already been developed.[227] In addition to the diastolic dimension, the LV ejection fraction, and suitable target vessels, the criteria include the presence of viable myocardium affecting at least 15 to 20 percent of the LV myocardium.

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Part 3: HEART FAILURE
Chapter 20:

PATHOPHYSIOLOGY AND DIAGNOSIS OF HEART FAILURE

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DEFINITION OF TERMS AND CLASSIFICATION

Heart failure is a broad term that encompasses multiple etiologies, pathophysiologic mechanisms, and clinical presentations. There has been and continues to be much confusion regarding the definition and classification of heart failure. The definition of heart failure has changed remarkably throughout the years,[1] undoubtedly related to the difficulties integrating many simple bedside observations (water retention, scant and concentrated urine, distended neck veins, and enlarged heart) with intellectual elaborations of the laboratory. For the practitioner, heart failure is a clinical syndrome in which structural or functional alterations of the heart lead to secondary phenomena such as exertional dyspnea and circulatory congestion. The diseased heart is the centerpiece of the syndrome. It is perhaps useful to think of heart failure as a continuum that begins with structural or functional abnormalities of the heart that have few or no clinical manifestations. This is followed by an often slow progression, with changes such as chamber enlargement, hypertrophy, or in some cases impairment of ejection phase indices, leading eventually to the clinical manifestations that are apparent by history and physical examination. There is often an important time element between the very beginnings of impaired cardiac structure or function and the clinical manifestations of heart failure that are observed weeks, months, or years later. In some cases, such as in severe hypertrophic cardiomyopathy or mitral stenosis, left ventricular (LV) systolic function may be intact, and there may be no LV chamber enlargement. In acute myocardial infarction, structural and functional changes occur swiftly, and symptoms of heart failure may appear suddenly. Such patients may then recover and have a long latency period of few symptoms, only to manifest substantial chamber enlargement, impaired LV function, and clinical heart failure many months or even years after the index event. There is an important time domain that spans the onset of cardiac structural and functional changes (often asymptomatic) to the clinical syndrome that the physician recognizes at the bedside or in the office as "heart failure." Although it is the clinical manifestations such as cardiomegaly, exertional dyspnea, and circulatory congestion that define the syndrome to the clinician, the student of heart failure knows that the disorder often has its roots in more fundamental structural and functional impairment that begins long before the patient experiences signs and symptoms of dyspnea and circulatory congestion.

The clinical syndrome of heart failure must be distinguished from other causes of circulatory congestion where the heart is not the culprit. It is worth considering the definition of heart failure put forth by Professor Ludwig W. Eichna in his George E. Brown Memorial Lecture at the American Heart Association meeting in Philadelphia in 1959.[2] This definition makes the important distinction between *circulatory congestion* (which can be due to noncardiac causes such as renal failure) and *congestive heart failure* (CHF), where the myocardium is at fault. Eichna opined that "circulatory (venous) congestion is the hemodynamic disturbance responsible for the symptoms usually associated with congestive heart failure; removal of the congestion, regardless of how accomplished, relieves the symptoms. Circulatory congestion is a nonspecific hemodynamic disturbance and may arise when the heart does not fail as a pump. This is noncardiac circulatory congestion. The term *congestive heart failure* should be reserved for those states of circulatory congestion in which there is myocardial failure." Basically, Eichna is making

the important distinction between circulatory congestion of noncardiac cause (e.g., acute renal failure) and circulatory congestion due to "myocardial failure." The implication is that in *heart failure* there must be something structurally or functionally abnormal with the heart.

Heart failure remains largely a clinical or bedside diagnosis. There is no "gold standard" laboratory test. The combination of a careful history (breathlessness, fatigue, fluid retention) and physical examination (congested lungs, distended neck veins, tachypnea, gallop rhythm, and fluid retention) is how one makes the diagnosis. There should be some direct evidence of structural heart disease, and the echocardiogram is most useful in this regard. However, it remains a clinical, bedside diagnosis. One makes the diagnosis by a careful bedside or office examination and confirms the diagnosis by chest x-ray and/or echocardiography.

The bedside diagnosis of heart failure has been made somewhat more subtle in the past 20 years by the widespread contemporary use of potent loop diuretics. Some of the cardinal clinical features of heart failure may be unimpressive or even lacking.[3,4] Patients may present with a history of breathlessness and fatigue who have clear lungs, no venous distention, and no edema. The "congestion" may be lacking in some patients with "congestive heart failure," thus rendering the term *heart failure* more appropriate than *congestive heart failure*. Moreover, with the gradual erosion of bedside skills and more reliance placed recently on echocardiography, we have allowed the less sophisticated physician to equate the clinical syndrome of heart failure with the finding of a low ejection fraction. A low ejection fraction is *not* heart failure. No single laboratory test fulfills all diagnostic purposes. The heart may be small on chest x-ray. Echocardiography and cardiac catheterization may indicate normal systolic function. Impaired relaxation of the left ventricle may be the primary mechanism, emphasizing the need to perform echocardiography. Heart failure is a clinical syndrome with multiple etiologies, heterogeneity, and great plasticity. This is why it has been difficult to clearly define. The following definitions, though imperfect, have been used in the past by various authors.

Circulatory Failure

Circulatory failure is a nonspecific older term that is sometimes used to describe heart failure and includes the condition of *circulatory shock*. The basic concept of circulatory failure implies that there is inadequacy of the cardiovascular system in providing nutrition and blood flow to the cells of the body and inadequacy in removing metabolic products from cells. Circulatory failure can be due to cardiac and noncardiac causes. *Myocardial failure*, from acute or chronic injury, would be a cardiac cause of circulatory failure. Examples of cardiac circulatory failure would include acute myocardial infarction, acute inflammatory conditions such as lymphocytic myocarditis, chronic cardiomyopathy, and severe valvular heart disease. Noncardiac circulatory failure would include inadequate blood volume and insufficient oxyhemoglobin.

Circulatory overload or *congestion* is also an older general term referring to excess blood volume from either cardiac or noncardiac causes,[2] but it still carries some important conceptual considerations. *Noncardiac circulatory overload* may be divided into two categories: (1) conditions where the primary defect appears to be an increase in blood volume, as may occur with the accumulation of excess salt and water due to salt-retaining steroids, excess blood or fluid administration, acute glomerulonephritis, oliguria, or anuria, and (2) conditions where the primary defect appears to be an increased venous return and/or decreased peripheral resistance, as may occur with arteriovenous fistulas, beriberi, cirrhosis, or severe anemia, in which the increase in blood volume is secondary. Many patients with noncardiac circulatory overload eventually develop secondary "high output" heart failure.

Heart Failure

Heart failure also has been defined as a complex clinical syndrome that arises from a process of

ventricular dysfunction (acute or chronic) where the heart is unable to pump sufficient blood to meet the metabolic needs of the body at normal filling pressures, provided the venous return to the heart is normal. Ventricular systolic dysfunction is characterized by a loss of contractile strength of the myocardium accompanied by the compensations of ventricular hypertrophy and/or dilatation (ventricular remodeling). This syndrome, however, involves more than a circulatory disorder caused by impaired pump function. As ventricular dysfunction proceeds, there is activation of numerous neuroendocrine systems that, although "designed" to protect blood pressure, are directly toxic to the heart and contribute to progressive cardiomegaly and sodium retention. Heart failure is also generally associated with a very poor prognosis, even when symptoms are mild.[5,6] *Systolic LV dysfunction* or *failure* reflects a decrease in normal emptying capacity [usually with an ejection fraction (EF) of 45 percent or less] that is usually associated with a compensatory increase in diastolic volume. *Isolated diastolic ventricular dysfunction* or *failure* is present when the filling of one or both ventricles is impaired, while the emptying capacity is normal. It may be due to a thickened (hypertrophied) ventricular wall, infiltrative cardiomyopathies, and/or tachycardia, which limits the time for diastolic filling, resulting in increased ventricular filling pressures and eventually pulmonary edema.

Congestive heart failure denotes a clinical syndrome with complex and variable signs and symptoms, including dyspnea and increased fatigability, tachypnea, tachycardia, pulmonary rales, cardiomegaly, ventricular gallop sounds, and peripheral edema. In most patients, CHF and abnormal circulatory congestion occur as a result of both heart failure and subsequent changes in the peripheral circulation, accompanied by activation of the sympathetic nervous system and the renin-angiotensin system. In most patients with clinical CHF due to mechanical or myocardial abnormalities, the heart (pump) failure is preceded by a substantial period of *myocardial* dysfunction during which cardiac *pump* function and cardiac output (at least while at rest) may be maintained by compensatory mechanisms that include myocardial hypertrophy and ventricular dilatation. For this reason, in the early stages the patient may have little or no limitations or symptoms. Initially, the cardiac output may be within the range of normal at rest but fails to increase or may even decline during exercise or stress. Ultimately, the cardiac output is decreased even at rest. Associated changes include an increase in systemic vascular resistance (SVR) at rest and a failure of the SVR to decrease with increased metabolic needs.

When the intravascular circulatory congestion is present for any length of time with elevation of LV diastolic and pulmonary venous pressures, fluid transudation from the capillaries into the interstitial spaces increases. In the pulmonary circulation, pulmonary edema develops if the rate of transudation exceeds the rate of lymphatic drainage. Pulmonary edema is often detected initially by x-ray examination, and only later are audible rales detected on physical examination. In the systemic venous system, elevated jugular venous pressure is often visible and may be accompanied by dependent peripheral edema and hepatomegaly. In the majority of patients, CHF develops chronically and is associated with the retention of sodium and water by the kidneys.

Acute heart failure can develop during acute ischemia of the ventricle (i.e., a myocardial infarction), secondary tachycardia, or due to the rupture of a cardiac valve or structure. An acute shift of blood from the systemic to the pulmonary circulation can occur before the retention of significant sodium or water. The term *congestive heart failure* should not be used unless there is congestion of cardiac origin. When the cause of the pulmonary or peripheral congestion is not clear, however, it is usually preferable to describe the symptoms or signs, which are nonspecific, and to avoid improperly diagnosing heart failure.

CLASSIFICATION AND STAGES OF HEART FAILURE

Numerous classification schemes and definitions have evolved over the years (Table 20-1), including the antiquated "forward heart failure" and "backward heart failure" concepts that are no longer very useful. Even the New York Heart Association classification system, though widely

used, lacks precision.

Table 20-1: Classifications and Definitions of Some Common Types of Heart Failure

Heart failure A clinical syndrome with classic symptoms of breathlessness, fatigue, and exercise intolerance that are attributable to impaired myocardial function.
Congestive heart failure Similar to the preceding but with features of circulatory congestion such as jugular venous distention, rales, peripheral edema, and ascites.
Noncardiac circulatory congestion A syndrome that is clinically indistinguishable from congestive heart failure where there is no reason to ascribe the condition to structural heart disease. There must be a noncardiac cause such as acute renal failure.
Systolic heart failure A clinical syndrome with classic symptoms of breathlessness, fatigue, and exercise intolerance whereby the dominant cardiac feature is a large, dilated heart and impaired systolic performance. There may or may not be concomitant valvular disease.
Heart failure with normal systolic function Sometimes referred to as *diastolic heart failure,* this is a clinical syndrome characterized by breathlessness, fatigue, and exercise intolerance whereby the dominant cardiac feature is impaired diastolic function (usually diagnosed by echo) and normal or near-normal ejection phase indices. There is often LV hypertrophy and impaired filling of the heart due to altered LV stiffness or other evidence of diastolic dysfunction. Often, severe systemic hypertension is present. There may or may not be concomitant valvular disease, such as mitral insufficiency. This form of heart failure may coexist with systolic heart failure.
Right-sided heart failure A clinical syndrome characterized by tissue congestion including jugular venous distention, peripheral edema, ascites, and abdominal organ engorgement. There is marked impairment of right ventricular systolic performance, usually with right ventricular dilatation and severe tricuspid regurgitation. There are multiple causes of this syndrome, including severe left-sided heart failure, severe lung disease with chronic hypoxemia and pulmonary hypertension (so-called cor pulmonale), right ventricular myocardial infarction, and primary pulmonary hypertension.

New York Heart Association Functional Classification

I. *Patients with cardiac disease but without resulting limitations of physical activity*. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II. *Patients with cardiac disease resulting in slight limitation of physical activity.* These patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III. *Patients with cardiac disease resulting in marked limitation of physical activity*. These patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV. *Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort*. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

A more recent and useful "staging" scheme of heart failure is now being used more commonly by guideline committees and regulatory agencies and is more closely intertwined with prevention and therapy:

Stages of Heart Failure

Stage A. Patients at risk of developing heart failure because of comorbid conditions that are strongly associated with the development of HF. Such patients have no signs or symptoms of HF and have never manifested signs or symptoms of HF. There are no structural or functional abnormalities of the valves or ventricles. Examples: systemic hypertension, coronary artery disese, diabetes mellitus.

Stage B. Patients who have developed structural heart disease that is strongly associated with the development of HF, but have no symptoms of HF and have never manifested signs or symptoms of HF. Examples: left ventricular hypertrophy (LVH); enlarged, dilated ventricles asymptomatic valvular heart disease; previous myocardial infarction.

Stage C. Patients who have current or prior symptoms of HF associated with underlying structural heart disease.

Stage D. Patients with marked symptoms of heart failure at rest despite maximal medical therapy and who require specialized interventions. Examples include patients who cannot be safely discharged from the hospital; recurrently hospitalized; are in the hospital awaiting heart transplantation; are in a hospice setting; at home receiving continuous intravenous support for symptom relief; are being supported with a mechanical circulator assist device.

This newer staging scheme is very clinically oriented and allows physicians to target therapy in a more focused manner toward specific subsets of patients. In general, patients only progress forward in this schema, although occasionally patients may go from D to C.

Systolic and Diastolic Dysfunction

A useful distinction in ventricular failure is that between systolic and diastolic dysfunction (Table 20-2 and Fig. 20-1). These terms, however, are most appropriately defined in terms of altered ventricular architecture rather than systemic hemodynamics. *Systolic dysfunction* describes a large, dilated ventricle whose output is limited by impaired ejection, whereas *diastolic dysfunction* refers to a thickened, small cavity ventricle in which filling is limited. It is appropriate to reserve the term *systolic dysfunction* for a dilated, often eccentrically hypertrophied ventricle and *diastolic dysfunction* for a thick-walled, concentrically hypertrophied ventricle with a normal or small cavity, highlighting the important architectural differences between these two entities.

Table 20-2: The Differential Diagnosis of Systolic Heart Failure and Heart Failure with Normal Systolic Function (Diastolic Heart Failure)

Systolic Heart Failure	Diastolic Heart Failure
Large, dilated heart	Small LV cavity, concentric LV hypertrophy
Normal or low blood pressure	Systemic hypertension
Broad age group; more common in men	Elderly women more common
Low ejection fraction	Normal or increased ejection fraction
S_3 gallop	S_4 gallop
Systolic and diastolic impairment by echo	Diastolic impairment by various echo measurements

Treatment well established	Treatment not well established
Poor prognosis	Prognosis not as poor
Role of myocardial ischemia important in selected cases	Myocardial ischemia common

Diastolic heart failure (or heart failure with preserved LV systolic function) is increasingly recognized as a major and growing epidemiologic clinical problem.[7,8] As many as 40 percent of patients presenting with heart failure have preserved LV systolic function, and it may be an even higher proportion in hospitals caring for more elderly and inner-city patients. Diastolic heart failure often coexists with poorly controlled systemic hypertension. Factors contributing to altered LV diastolic function include myocardial fibrosis, hypertrophy, ischemia, and increased afterload.[9] Myocardial ischemia is an especially important mechanism to identify[10] because, like hypertension, it is usually treatable.

It is important to recognize that systolic and diastolic dysfunction frequently coexist in patients with heart failure and that systolic events can influence diastolic function.[11,12] The diagnosis of diastolic dysfunction can be challenging, but advancing echocardiographic techniques for this purpose have improved substantially. Limitations imparted by loading conditions, heart rate, and age to some extent have been overcome by new applications of continuous-wave Doppler, color Doppler M-mode, and Doppler tissue imaging.[13-15]

Women seem to be overrepresented in the group of patients with diastolic heart failure,[16] especially elderly women with hypertension, diabetes mellitus, and LV hypertrophy. For any given afterload stress, women seem to develop more hypertrophy than men. Patients with heart failure and normal systolic function have a lower mortality risk than patients with a reduced EF,[17] but they still have a fourfold mortality risk compared with control subjects who are free of heart failure.[18] Assessing LV architecture and function by echocardiography is important before initiating therapy in a patient with heart failure, since treatment for systolic dysfunction may be ineffective or even counterproductive if symptoms are due to abnormal diastolic properties with preserved systolic function. Knowledge of renal function and renal vasculature also may be important, especially in patients with severe hypertension. For example, many elderly patients with heart failure and severe hypertension have associated renal vascular stenosis.[19] Institution of an angiotensin-converting enzyme inhibitor in such a patient could lead to severe renal insufficiency. Likewise, prolonged aggressive use of diuretics in patients with severe LV hypertrophy and a small LV cavity may lead to a reduced stroke volume and hypotension. It is important, therefore, to have knowledge of myocardial architecture, anatomy, and function when planning therapy and in determining prognosis.

Generally, systolic ventricular dysfunction is characterized by an increase in end-diastolic volume (EDV) and a normal or somewhat reduced stroke volume (SV), resulting in a decrease in EF. This relationship of SV to EDV is normally described by the Frank-Starling relationship (Fig. 20-2). The increase in EDV is associated with an increase in ventricular end-diastolic pressure (EDP) in consonance with the resting pressure-volume curve. The filling pressures may be further elevated for a given EDV by concentric hypertrophy or a fibrotic wall. Conversely, they actually may be decreased by chronic overdistention (eccentric hypertrophy). The relation between LV wall force and fiber length is depicted in Fig. 20-3.

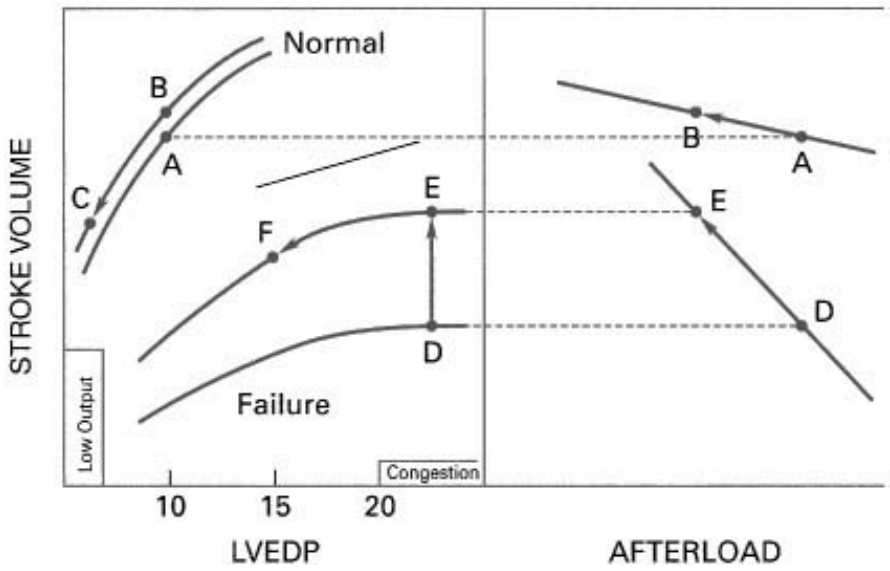

Figure 20-2: Relationship between stroke volume and left ventricular end-diastolic pressure (LVEDP) (*left*) and afterload (*right*). Normally, the ventricle operates on a sharply rising Frank-Starling curve with an LVEDP less than 12 mmHg (point *A*), where small changes in filling pressure yield large changes in stroke volume. Further, stroke volume is largely independent of the afterload. When failure occurs, ventricular function is characterized by a shift of the curve relating stroke volume to LVEDP to the right and downward. Low output may ensue if the curve is sufficiently depressed, while pulmonary congestion occurs as the LVEDP is increased. At the same time, this failing ventricle is now highly afterload-dependent, in that small changes in afterload produce large changes in stroke volume. When afterload is reduced in the normal heart (point *A* to point *B, right*), stroke volume rises very slightly. If, at the same time, venodilation reduces filling pressure, stroke volume falls to point *C* (*left*). The net result is a decrease in cardiac output. On the contrary, when afterload is reduced in the presence of severe ventricular failure, stroke volume is increased (point *D* to point *E, right*). Since the Frank-Starling curve is relatively flattened, a simultaneous decrease in filling pressure leads to a decrease in LVEDP with only a small decrease in stroke volume (point *E* to point *F, left*). The net reult of these opposing consequences can increase stroke volume. These results are observed clinically when a vasodilator is administered along with a diuretic in treating the failing ventricle.

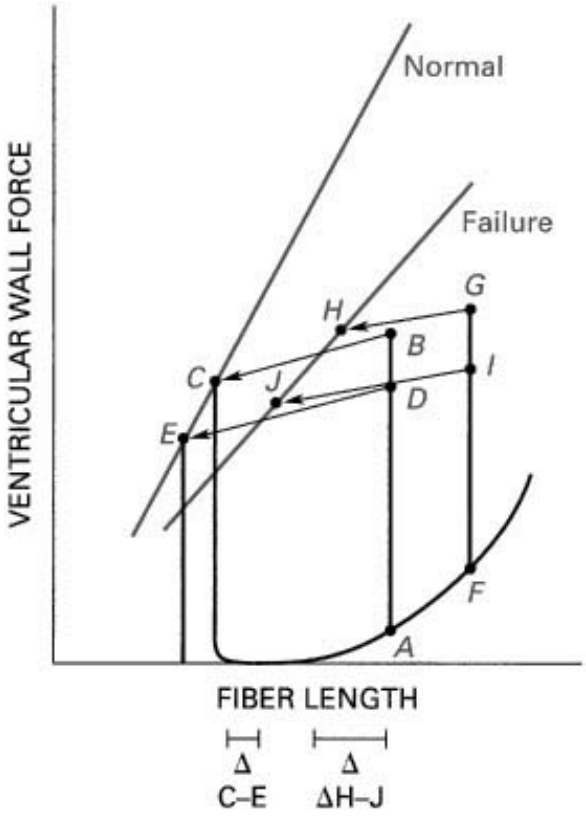

Figure 20-3: Relationship between LV wall force and fiber length. Hypothetical contractile cycles have been portrayed for the normal and failing ventricle. In the normal heart, contraction starts at point *A*, LV pressure rises until the aortic valve is opened (point *B*), the ventricle empties (point *B* to *C*), and relaxation ensues. When arterial pressure (afterload) is reduced (e.g., to point *D*), ejection starts at point *D* and proceeds to point *E*, which increases stroke volume. When the ventricle fails, the fiber length in diastole is increased, and ventricular contraction starts at point *F*. With systolic contraction, ventricular pressure rises to point *G*, and with ventricular emptying, fiber length decreases to point *H*. With a similar decrease in the afterload, wall force only needs to reach point *I* when ventricular emptying occurs to point *J*. As a result, for the same relative change in afterload, the increase in shortening is greater in the failing ventricle (Δ*H-J*) than in the normal heart (Δ*C-E*).

In patients with mild heart failure, the ventricular EDP and the cardiac output may be normal at rest, but the former may become elevated to abnormal levels during stress such as exercise or an increase in afterload. The ability to increase the cardiac output in response to the increase in oxygen consumption is also reduced (see below and Chap 3). In patients with more severe systolic dysfunction, both the early pressure and the EDP may be elevated even at rest. The elevated LV diastolic pressure increases pulmonary venous and capillary pressures and contributes to increased dyspnea as a result of changes in pulmonary compliance due to pulmonary congestion and edema. It is also apparent that before one reaches this stage of clinical heart failure, the body has used many compensatory mechanisms after the onset of the initial abnormality or stress and that these compensatory mechanisms eventually have failed to maintain the needs for cardiac output (see below).

Low-Output Heart Failure

The causes of overall heart pump failure may be classified in four main categories: (1) failure primarily related to work overloads or mechanical abnormalities, (2) failure mostly related to primary myocardial abnormalities, (3) failure related to abnormal cardiac rhythm or conduction disturbances, and (4) myocardial ischemia/infarction. Myocardial infarction resulting in a

quantitative loss of myocardium creates a special type of work overload. During the acute infarction, the EF falls as the EDV is increased to sustain a reduced SV, and the fall in EF is approximately proportional to the amount of myocardium lost. With time, the EF tends to remain at this reduced level. With healing of the infarction, the akinetic infarcted region becomes a scar that not only cannot contribute to ventricular emptying but may even contribute to the load. Thus the entire load falls on the remaining nonischemic myocardium. This load is further increased by the increased diastolic volume, which causes wall tension to be increased for any given pressure, even though the nonischemic myocardium hypertrophies in proportion to the amount of myocardium that is lost. Heart failure may ensue months or years later as a so-called ischemic cardiomyopathy resulting from progressive ventricular dilatation and reactive hypertrophy, termed *ventricular remodeling*, in the remaining nonischemic myocardium.

Cardiomyopathy

Virtually any form of heart disease eventually can lead to heart failure, and there are many causes of both "primary" and "secondary" heart failure. However, these distinctions are quite arbitrary and of little clinical value. *Primary heart failure* usually refers to "cardiomyopathy," a vague term that can include idiopathic dilated cardiomyopathy, familial dilated cardiomyopathy (an increasingly recognized cause of dilated cardiomyopathy), and hypertrophic cardiomyopathy. It simply depends on how one defines the term *cardiomyopathy*. Familial dilated cardiomyopathy is more common than previously believed.[20] It cannot be predicted by clinical or phenotypic techniques and requires family screening for identification. It is important to always consider familial dilated cardiomyopathy when evaluating patients with "idiopathic dilated cardiomyopathy" because it has a more unpredictable natural history and can present with a very rapid downhill course necessitating early referral to a heart transplant center.[21] Cardiac abnormalities are common in asymptomatic relatives of patients with dilated cardiomyopathy.[22] As many as 30 percent or more of patients with dilated cardiomyopathy may have an inherited disorder.[23] Single-gene defects may be important in the disease pathogenesis.[24]

Hypertrophic obstructive cardiomyopathy (HOCM) and nonobstructive hypertrophic cardiomyopathy are also often familial, affecting about 1 in 500 people in the general population. Most cases are inherited in an autosomal dominant manner with variable clinical penetrance and expression. Many different mutations have been described for at least seven abnormal sarcomeric proteins. Late-onset expression of HOCM may be a distinct clinical entity. Unfortunately, the genetic heterogeneity of this disease has made routine genetic testing impractical. Clinical screening may be warranted for members of families characterized by hypertrophic cardiomyopathy.

Unlike familial dilated or hypertrophic cardiomyopathy, alcoholic cardiomyopathy and "viral" cardiomyopathy (e.g., secondary to inflammatory myocarditis) may be overdiagnosed by clinicians. There are no specific clinical markers for so-called alcoholic cardiomyopathy, and there is no good evidence indicating an alcohol dose-response relationship. Apparently, a broad segment of the alcoholic population remains somehow immune to this complication. Nevertheless, patients believed to be "heavy" users of alcohol who present with dilated cardiomyopathy in whom heart failure resolves on cessation of alcohol use probably have "alcoholic cardiomyopathy." This observation should be a strong reason to encourage abstinence in patients with dilated cardiomyopathy of uncertain or possibly alcoholic origin.

Viral myocarditis can only be diagnosed by examining myocardial tissue (e.g., myocardial biopsy), since we now know that the "clinical" diagnosis of viral myocarditis is notoriously inaccurate. Only 5 to 10 percent of biopsies taken from the hearts of patients suspected clinically of having inflammatory myocarditis are actually "positive." Physicians should refrain from telling patients that their heart failure was due to a virus unless there is tissue verification. There are, of course, patients with mild or subclinical acute myocarditis who progress to heart failure and

present with "dilated cardiomyopathy." The prognosis of patients with proven inflammatory myocarditis may be somewhat better than that of patients with idiopathic dilated cardiomyopathy, since spontaneous improvement in LV ejection fraction is not uncommon.[25] However, others have found no difference in the 5-year survival between patients with myocarditis and idiopathic dilated cardiomyopathy (56 versus 54 percent, respectively).[26] Patients with active inflammatory myocarditis may suffer severe rejection earlier and more commonly after heart transplantation. Idiopathic giant-cell myocarditis is important to distinguish from inflammatory lymphocytic myocarditis because it has a worse survival rate and may respond better to heart transplantation.[27]

Anthracycline-induced heart failure is now increasingly recognized as a form of "toxic" heart failure.[28] It is clearly a dose-related phenomenon and may present as a "cardiomyopathy." A rapidly growing number of persons, including a fraction of the 150,000 adults in the United States who have survived childhood cancers, will develop anthracycline-induced cardiomyopathy.[29,30] There may be a long latency period (years) between treatment and onset of symptoms. Recently, Herceptin (recombinant humanized anti-HER2 antibody) has been approved for the treatment of breast cancer. About 27 percent of patients receiving both Herceptin and doxorubicin or Paclitaxel experience cardiac dysfunction,[31] which is a far greater percentage than those receiving anthracycline or Paclitaxel alone. Cardiac toxicity should be a major concern for patients receiving Herceptin, which is often used in conjunction with an anthracycline. Heart failure induced by these drugs is not a simple complication that can be "managed" by drug therapy but is a potentially lethal complication that requires skillful care. Other causes of toxic cardiomyopathy include cocaine, other cytostatic agents, interferons, interleukin-2, anabolic steroids, and a host of miscellaneous agents.[31]

The cause of LV systolic dysfunction in patients with chronic obstructive lung disease is unknown, although the combination of hypoxia and hypercapnia may be important. LV diastolic dysfunction in such patients is, in part, secondary to the pronounced right ventricular hypertrophy and dilatation with secondary elevation of LV diastolic pressure due to ventricular interdependence. The latter phenomenon is also important in the pathophysiology of acute pulmonary edema occasionally encountered in patients with acute pulmonary embolus.

Myocardial "Overload"

Myocardial failure may develop from many causes of "overload." It may evolve from pressure overloads in which myocytes hypertrophy to meet the load. Hypertrophied cells contract and relax more slowly[32] and may be subject to metabolic limitations. In addition, hypertrophied myocardial cells may have a shortened life span.[33,34] This is of considerable prognostic importance because cardiac myocytes appear to have little or no capacity to proliferate. When age-related myocyte loss is added to the picture, particularly in association with a late decrease in myocyte contractile activity, failure may ensue with ventricular dilatation. Loss of myocytes-whether segmental, as in acute myocardial infarction, or diffuse, as in myocarditis-sets up a vicious cycle that leads to reactive hypertrophy in remaining myocytes. As compensatory hypertrophy becomes more marked in some disease states, the unit contractility of the myocardium often declines because of molecular changes in the heart's contractile proteins and activation system. This is especially likely to occur in response to pressure overload, as in systemic arterial hypertension or aortic stenosis, but also ensues when myocytes are lost.

Ultimately, the myocardial failure (plus mechanical abnormalities that may be present) often leads to a decrease in systolic pump function that is sufficient to produce overall pump or heart failure. In most patients, significant dysfunction and failure of the myocardium occur before the clinical syndrome of CHF becomes apparent.

High-Output Failure

Some patients with high-output states or primary noncardiac circulatory overload may develop pulmonary congestion and edema secondary to an abnormal elevation of ventricular diastolic pressure at a time when the total cardiac output (systolic, or pump, function) and EF of the left ventricle are normal or even increased. The latter syndrome also can occur in conditions associated with an increase in blood volume from the accumulation of excess salt and water due to salt-retaining steroids, excess blood or fluid administration, acute glomerulonephritis, oliguria, or anuria. In other patients, it may occur with an abnormally increased venous return and/or decreased peripheral resistance, as might occur in patients with arteriovenous fistulas, beriberi, hyperthyroidism, cirrhosis, severe anemia, and large vascular tumors. Under such conditions, the chronic volume and/or pressure overload on the ventricle eventually may produce myocardial and ventricular systolic (pump) dysfunction or failure. Ultimately, this can both increase diastolic pressures and reduce cardiac output to abnormally low levels. When symptoms of pulmonary congestion or pulmonary edema secondary to elevated diastolic pressure occur while the cardiac output is still normal or elevated, the syndrome is sometimes referred to as *high-output failure*.

High-output heart failure is rare in the United States. For example, to have high-output heart failure from chronic anemia, a hematocrit of about 13 percent (9-16 percent) typically would be necessary.[35] This is an uncommon presentation in North America. However, this condition may be found in areas of the world where chronic parasite infestation can lead to severe, chronic anemia. As with low-output heart failure, patients with high-output heart failure have salt and water retention, reduced renal blood flow, and neuroendocrine activation.[35] Low concentration of hemoglobin in patients with anemia may lead to a relative inability to degrade nitric oxide (NO), leading to the vasodilation that is so typical of high-output heart failure. Low blood pressure may in turn activate neuroendocrine activity. Various conditions that increase cardiac output are depicted in Table 20-3.

Table 20-3: Conditions That Increase Cardiac Output

Bacteremia/sepsis	Fibrous dysplasia (Albright's syndrome)
Anemia (acquired or congenital)	Renal disease (acute or chronic)
Hyperthyroidism	Hepatic disease
Beriberi	Environmental temperature extremes
Arteriovenous fistulas (acquired or congenital)	Polycythemia vera
Pregnancy	Carcinoid syndrome
Paget's disease	Dermatologic abnormalities
Hyperdynamic heart syndrome	Erythroderma syndrome
Arterial hypertension	Kaposi's sarcoma

Left and Right Heart Failure

Left heart (*left-sided*) *failure* and *right heart* (*right-sided*) *failure* are clinical terms for conditions in which the primary impairment is of the left side of the heart or of the right side of the heart, respectively. Since both sides of the heart are in a circuit, it is apparent that one side cannot pump significantly more blood than the other side for any length of time in the absence of abnormal shunts, communications, or regurgitation. Furthermore, experimentally produced failure of one ventricle may produce significant hemodynamic and biochemical abnormalities of the other

ventricle, even without the usual hemodynamic manifestations of ventricular failure. Abnormal function of the left ventricle not only overloads the right ventricle from augmented pulmonary pressures but also may affect the right ventricle via the shared septum and the phenomenon of ventricular interdependence or interaction (see below). Altered elastic recoil of the left ventricle in diastole also may affect the right ventricle. Accordingly, when the pumping ability of one ventricle is primarily impaired, the output of the contralateral ventricle can be secondarily decreased; the biochemistry and hemodynamics of the contralateral ventricle also can be abnormal even in "pure" one-sided failure.

Right-sided heart failure commonly follows left-sided heart failure. In most situations, the expression *left-sided heart failure* is used clinically in reference to symptoms and signs of elevated pressure and congestion in the pulmonary veins and capillaries, whereas the term *right-sided heart failure* is used clinically in reference to symptoms and signs of elevated pressure and congestion in the systemic veins and capillaries. Actually, significant amounts of sodium and water retention, with subsequent peripheral edema formation, may occur with pure left-sided heart failure without hemodynamic evidence of right-sided heart failure. As noted previously, an increase in the diastolic pressure in either ventricle can increase the diastolic pressure or decrease the distensibility of the contralateral ventricle, especially if the pericardium is intact.

Compensated Heart Failure

Compensated heart failure is that condition in which the symptoms of heart failure are relieved, usually by therapy or compensatory mechanisms, although the EDV and EDP often remain elevated, and the EF remains reduced. As noted below and in Table 20-4, the usual "compensatory" mechanisms include increased sympathetic adrenergic stimulation of the heart, activation of the renal renin-angiotensin system, increased vasoconstriction, fluid retention by the kidney, increased venous return, increased ventricular preload, and cardiac dilatation and hypertrophy. Clinically, myocardial compensation and a decrease in congestion may be produced by improved ventricular performance. The term *compensated heart failure* frequently is used in reference to patients with CHF whose symptoms and signs of pulmonary or peripheral congestion have been relieved by therapy. In many such patients, reduced myocardial function and low cardiac output persist, although symptoms are relieved by an improvement in peripheral circulation and the reduction in edema and congestion.

NEXT

Chapter 20: PATHOPHYSIOLOGY AND DIAGNOSIS OF HEART FAILURE

MECHANISMS OF HEART FAILURE

Since virtually any form of heart disease can lead to heart failure, there can be no single causative mechanism. At the organ and the cellular level, there is likewise no single mechanism that is consistently operative. Identification of fundamental mechanisms remains an area of very active investigation (Table 20-5). Multiple alterations in organ and cellular physiology contribute to heart failure under various circumstances and at different points in time. Adaptive processes occur that affect the myocardium, kidneys, smooth and skeletal muscles, endothelium, peripheral vasculature, and multiple reflex control mechanisms, adding to the complexity of the syndrome (Tables 20-6 and 20-7). The schema of the sequence of events in heart failure is daunting (Fig. 20-4). Distinguishing primary etiologic forces from secondary epiphenomena has been very difficult. Identification of the precise mechanisms whereby heart failure evolves and quantifying the contributions of individual components (e.g., apoptosis) have remained elusive. Major gaps in our knowledge, such as what triggers the early activation of the sympathetic nervous system and withdrawal of vagal tone or how spontaneous resolution of heart failure occurs, have persisted despite intense investigation. Nevertheless, enough information has accrued to construct a reasonably coherent working hypothesis.

Table 20-5: Possible Mechanisms of Myocardial Failure

Loss of myocytes
Hypertrophy of remaining myocytes
Energy production and utilization
Oxygen and energy supply
Substrate utilization and energy storage
Inadequate mitochondria mass and function
Ventricular remodeling
Contractile proteins
Abnormal myofibrillar or myosin ATPase
Abnormal myocardial proteins
Defective protein synthesis
Nonuniformity of contraction and function
Activation of contractile elements
Membrane Na^+,K^+-ATPase defects
Abnormal sarcoplasmic reticulum function
Abnormal Ca^{2+} release
Abnormal Ca^{2+} uptake

Abnormal myocardial receptor function
Downregulation of beta adrenoreceptors
Decreased β_1 receptors
Decreased G_s protein
Increased G_1 protein
Autonomic nervous system
Abnormal myocardial norepinephrine function or kinetics
Abnormal baroreceptor function
Increased myocardial fibroblast growth and collagen
synthesis
Aging changes, presbycardia
Sustained tachycardia
Miscellaneous

Table 20-6: Compensatory Mechanisms in Heart Failure

Autonomic nervous system
Heart
Increased heart rate
Increased myocardial contractile stimulation
Increased rate of relaxation
Peripheral circulation
Arterial vasoconstriction (increased afterload)
Venous vasoconstriction (increased preload)
Kidney (renin-angiotensin-aldosterone)
Arterial vasoconstriction (increased afterload)
Venous vasconstriction (increased preload)
Sodium and water retention (increased preload and afterload)
Increased myocardial contractile stimulation
Endothelin-1 (increased preload and afterload)
Arginine vasopressin (increased preload and afterload)
Atrial and brain natriuretic peptides (decreased afterload)

Prostaglandins
Peptides
Frank-Starling law of the heart
Increased end-diastolic fiber length, volume, and pressure (increased preload)
Hypertrophy
Peripheral oxygen delivery
Redistribution of cardiac output
Altered oxygen-hemoglobin dissociation
Increased oxygen extraction by tissues
Anaerobic metabolism

Table 20-7: Neurohumoral Changes in Heart Failure

Increased sympathetic nervous system activity (increased norepinephrine, epinephrine)
Increased endothelin
Increased arginine vasopressin
Increased renin and angiotensin II
Increased aldosterone
Increased neuropeptide Y
Increased atrial and brain natriuretic peptides
Increased
Insulin
Cortisol
Growth hormone
Tumor necrosis factor-α
Interleukin 6
Vasoactive intestinal peptide
Adrenomedullin
Urodilatin
Increased dopamine
Increased prostaglandins (PGI_2, PGE_2)
Increased vasodilator peptides, (e.g., bradykinin)

NOTE: Measurements in individual patients vary significantly, and changes may not always be present.

To understand heart failure, it is useful to think in terms of evolutionary theory.[36] The cell, the organ, and the organism each has evolved adaptive responses to offset hostile environments, thus allowing a survival advantage. In many cases, heart failure may begin as an acute injury to the heart, such as an acute myocardial infarction or severe inflammatory myocarditis. In other cases, there may be a phenotypically silent mutation that is finally expressed (for unknown reasons), leading to structural and functional perturbations of such magnitude that the heart eventually fails. Valvular heart disease may lead to unusual loading conditions, forcing the myocytes to adapt by increasing their size (hypertrophy). In essence, there is an *index event* that in many cases is not clinically visible or may occur secondary to unknown toxins or an unusual mechanical load on the heart. The heart and its circulary physiology must somehow "adapt" to this "hostile" new environment.

In response to increased load, whether created by increased pressure or loss of myocytes, hypertrophy occurs that tends to normalize the load per cell. With an increased volume load, myocytes elongate and in rare cases may undergo division.[37,38] It is believed that hyperplasia and apoptosis involves less than 1 percent of the cardiac myocytes. Reprogramming of the cardiac myocytes occurs, resulting in a more fetal-like response leading to an increase in the size of the cardiac myocyte,[39,40] presumably rendering the surviving myocytes a short-term structural and functional advantage. The reprogramming requires altered signals, both mechanical and "chemical," to reach the nucleus of the cardiac myocyte in order to set into motion "new" gene transcription.[41] Ultimately, there is a transition from hypertrophy to heart failure,[42] which has been recognized for more than 100 years but is still not well understood.[34] In a sense, this "unnatural growth response" of myocyte hypertrophy leads to the obvious structural changes of LV remodeling, thus creating a large, dilated, and poorly functioning heart. The processes of cellular remodeling and subsequent architectural changes in cell and chamber size and shape are highly complex[41] and include many components other than myocardial cell hypertrophy. There is myocardial fibrosis, cell dropout, and myocyte slippage. As cardiac output falls, multiple neurohormones including renin and norepinephrine are "released" in an attempt to protect blood pressure and organ perfusion,[43] while atavistic counterregulatory natriuretic peptides are "released" in an attempt to offset vasoconstriction, hypertrophy, and volume conservation.[44] The story is undoubtedly much more complex than this[45] and includes a cornucopia of molecular mechanisms,[41,46] some of which primarily affect the cardiac interstitium and others the cardiac myocytes. The pathophysiologic changes observed in heart failure are partially depicted in Table 20-6 and Fig. 20-5.

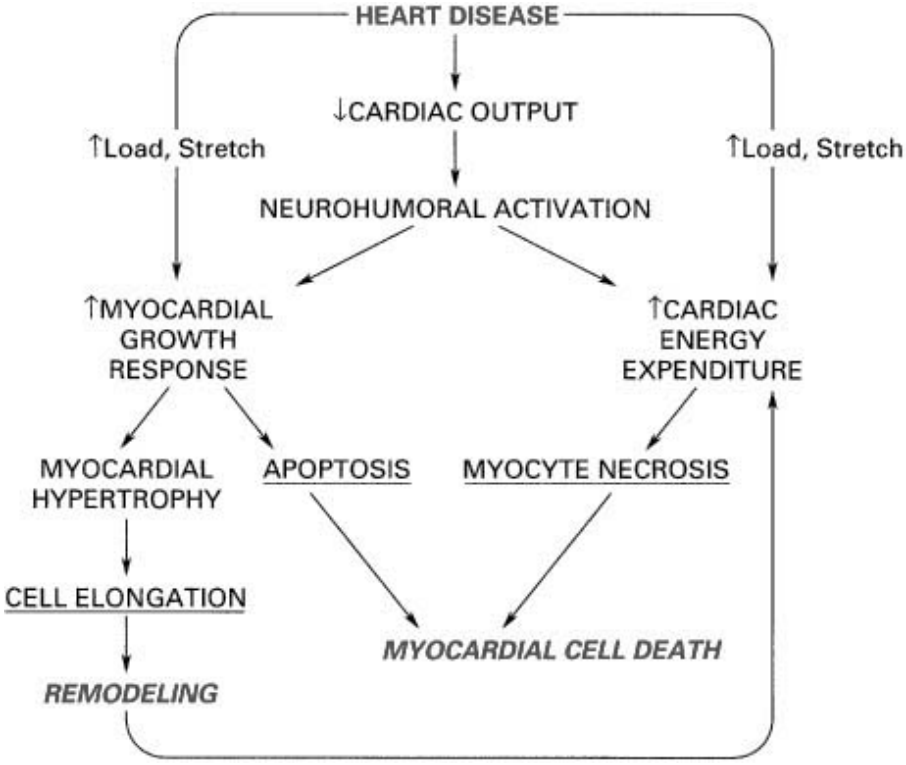

Figure 20-5: Possible mechanisms by which overloading can cause progressive deterioration of the heart ("cardiomyopathy of overload"). Several mechanisms, including myocyte stretch, activate a growth response that initiates myocardial hypertrophy in the overloaded heart (*left*). The same growth response may also activate signal transduction systems that cause programmed cell death (apoptosis). The hypertrophic response to overload, by causing sarcomeres to be added in series, can also lead to cell elongation and so accelerate remodeling; the resulting increase in wall tension, along with the overload itself (*right*), increases cardiac energy expenditure that, in the overloaded heart, can accelerate myocyte necrosis. Reduced cardiac output activates neurohumoral responses (*center*), which, by increasing afterload and β-adrenergic stimulation of the heart, also increase cardiac energy expenditure. Because many mediators of the neurohumoral response to a fall in cardiac output promote myocardial cell growth, neurohumoral activation can also accelerate both apoptosis and remodeling.

Maladaptive remodeling of cardiac myocyte size and shape begins long before clinical heart failure begins.[47-50] Alterations in myocyte proteins and mitochondria size and number and changes in myocardial interstitium and collagen content/architecture are seen in response to a variety of "injuries" including pressure overload,[51-53] volume overload,[54] and myocardial ischemia.[55,56] Additional phenotypic changes in heart failure include apoptosis[57,58] and side-to-side slippage of myocytes.[59] It is important to recognize that much of the neuroendocrine activation that occurs in a primordial attempt to conserve organ perfusion appears to facilitate this myriad of phenotypic change in the heart at the cellular level,[45] thereby possibly accounting for the success of neuroendocrine blockers as therapy for heart failure. Lastly, there is no single phenotypic change, protein expression, or signal-transduction pathway that is dominant. Rather, there is extraordinary redundancy in these mechanisms. This observation has important implications for therapy. For example, blocking one neuroendocrine system may lead to enhanced overactivity of other neuroendocrine systems. Blocking one signal-transduction pathway may lead the cell to hypertrophy through alternative pathways. Thus it is likely that polypharmacy will always be necessary in the treatment of heart failure.

In summary, heart failure often begins with an index event that results in loss of myocardium (e.g., acute myocardial infarction) or excessive overload (e.g., valvular heart disease, acute myocardial infarction, mutation leading to dilated or hypertrophic cardiomyopathy, etc.). Where hypertrophy cannot sustain the increased load, ventricular dilatation occurs, and the ventricle assumes a more globular shape (i.e., eccentric hypertrophy), thus allowing for maintenance of stroke volume despite a reduced EF. This provides short-term benefit. Absence of some dilatation probably would lead to shock and early death. Neuroendocrine activation presumably occurs in response to a perceived need to protect perfusion pressure, but

neurohormones also facilitate the LV remodeling process, thus contributing importantly to the pathogenesis and progression of heart failure. Despite the presumed coherency of this oversimplified working hypothesis, many gaps in our knowledge remain to be filled in, particularly with regard to the quantitative contribution that each phenotypic change makes toward the progression of heart failure. We still have much to learn.

Molecular, Physiologic, and Biochemical Alterations Occurring with Hypertrophyand the Progression to Heart Failure

Alterations are found in the failing heart in numerous contractile proteins, especially in heredity-based idiopathic dilated cardiomyopathies. In the latter situation, these alterations can be the sole cause of heart failure. Such alterations have been found in myosin, troponin T, and actin. These alterations in protein structure likely contribute to diminished myocardial performance. Alterations in gross cardiac structure and cellular components in heart failure resulting from systolic overloads are much more complex. Findings in animal models of overload-produced heart failure may vary from model to model, and observations made in human failing hearts may be different from those made in animal models. In the human failing heart, many changes in gene expression at the mRNA or protein level have been found in hearts harvested at the time of cardiac transplantation. These are hearts with end-stage myocardial disease in which many factors (such as receiving multiple inotropic drugs) may obscure actual pathogenesis. Despite these caveats, we have learned much from these studies, only some of which will be discussed here.

β-MYOSIN HEAVY CHAIN

Two myosin heavy chain (MHC) isoforms are present in mammalian heart, α- and β-MHC. The α-MHC is cardiac-specific and is more enzymatically active. The less active β-MHC is present in heart and also in slow-twitch skeletal muscle. The distribution of α- and β-MHC is developmentally and hormonally regulated. Mechanical stress, such as pressure overload, induces an α- to β-MHC transition in the ventricles of experimental animals, thus imparting a slower but more economical type of work for the overloaded heart. Either way, myosin remains the principal structural and contractile unit of muscle fiber. Lowes et al.[60] recently have demonstrated downregulation of α-MHC and upregulation of β-MHC using mRNA measurements from right ventricular endomyocardial biopsies from nonfailing hearts and failing human hearts. This alteration, if translated into protein expression, would decrease myosin ATPase enzyme velocity and slow the speed of contraction. Although such adaptive changes could be viewed to have an "economical" survival advantage in the face of increased load, slower contraction and relaxation may contribute to diastolic dysfunction.

SARCOPLASMIC RETICULUM FUNCTION

There is substantial evidence that defects in sarcolemma Ca^{2+} uptake (sarcolemmal transport via Na^{+},K^{+}-ATPase) and release by the sarcoplasmic reticulum (SR) are present in heart failure, especially at later stages.[61-63] Alternatively, uptake of Ca^{2+} by the SR may remain intact.[64] These alterations in Ca^{2+} transport may be secondary to quantitative alterations of gene expression of SR Ca^{2+} transport proteins, especially the sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA)[65] and phospholamban,[66] a reversible inhibitor of cardiac SR Ca^{2+}-ATPase activity. Other Ca^{2+} cycling proteins such as Na^{+}-Ca^{2+} exchanger proteins[67] and ryanodine receptors[68] also may be altered in heart failure. Unfortunately, these observations are not always consistent from model to model and may not always be relative to failing human hearts. Nevertheless, it is likely that heart failure is characterized by reduced myofilament activation and decreased Ca^{2+} available for activation as well as heightened cytosolar Ca^{2+} levels in diastole. Some studies have shown increased myofibrillar Ca^{2+} sensitivity[69] and altered Ca^{2+} kinetics.[70] These abnormalities of calcium metabolism may be of primary importance in some types of heart failure, and they may be secondary or epiphenomena in other types. Most abnormalities of myocardial contractile activation have been demonstrated only in the late stages of heart failure and therefore may be the result of maladaptive hypertrophy rather than a primary cause of ventricular dysfunction.

FORCE-FREQUENCY RESPONSE IN HEART FAILURE

The failing human myocardium is characterized by an abnormal force-frequency response that parallels the

severity of heart failure. Normally, increase in frequency of stimulation is accompanied by an enhanced force of contraction (Bowditch effect). In heart failure, an increase in heart rate by pacing an additional 50 beats per minute is accompanied by about a 30 percent decrease in myocardial performance as measured by dP/dt_{max}. It is likely that some impairment of systolic function in response to increased heart rate may be related to impaired LV filling, although a negative inotropic effect, as shown in isolated muscle to be due to alterations in intracellular Ca^{2+} handling, cannot be excluded. This feature of heart failure may help explain some impairment of cardiac function during exercise.[71,72]

ENERGY PRODUCTION AND USE

Oxygen deprivation, which is most often due to coronary artery disease, results in impaired relaxation and weakened contraction, as may be seen in angina pectoris. When transient, these are readily reversible. With prolonged ischemia, decreased contraction (dyskinesis) may persist for hours beyond return of blood flow and is termed stunning. If coronary blood flow is chronically reduced, myocardium may fail to contract normally (*hibernation*), even if necrosis does not ensue. With more serious loss of flow, infarction can occur. All these stages may produce substantial dyskinesia for which the remaining myocardium must sustain this load. The result is hypertrophy of the nonischemic portion of the ventricle; if this is inadequate, an increase in ventricular volume occurs using the Frank-Starling mechanism to sustain stroke volume.

In patients with heart failure, the total amount of oxygen consumed by the heart may be increased significantly because of the increased total mass, the increase in myocardial systolic wall tension due to the Laplace relationship, and perhaps some wasted contractile energy. This increase may result in the extraction of a greater amount of oxygen from each unit of coronary blood flow and a widening of the coronary arteriovenous oxygen difference. Many patients with heart failure are able to increase coronary blood flow during exercise; however, some patients with a dilated ventricle that increases in diameter during exercise may have a further widening of the coronary arteriovenous oxygen difference during exercise and a decrease in coronary blood flow reserve (see Chaps. 3 and 37). In the presence of severe LV hypertrophy, coronary blood flow per unit mass of myocardium is usually normal at rest. On the other hand, the capacity of the coronary vascular bed to dilate during reactive hyperemia, which is normally four- to fivefold, is reduced. In the presence of severe hypertrophy where filling pressures are elevated, tachycardia such as may occur with atrial fibrillation may reduce diastolic coronary perfusion, producing ischemic ventricular failure. While reduced perfusion is probably common in end-stage heart failure, a deficit in coronary blood flow or oxygen delivery has not been clearly demonstrated to be a primary cause of heart failure associated with hypertrophy, except in the presence of obstructive coronary disease (see below).

SUBSTRATE USE AND ENERGY STORAGE

Although the myocardial uptake of fatty acids and glucose per 100 g of myocardium is normal in heart failure,[73] there is conflicting evidence on whether or not there is a primary decrease in energy liberation by mitochondrial oxidative phosphorylation.[33,34,73-77] The reductions in stores of myocardial high-energy phosphate, creatine phosphate, and/or adenosine triphosphate (ATP) generally found in heart failure usually are thought to be secondary and to be the consequence of the failure rather than the primary cause of the failure.[73-82] There also may be reduced levels of creatine kinase and changes in the isoenzymes of creatine kinase in heart failure.[82]

The major consequences of the state of energy starvation that is probably seen in many, if not most, failing hearts are due to attenuation of important allosteric (regulatory) effects of ATP rather than reduction in the supply of substrate for the many energy-consuming reactions involved in contraction, relaxation, and excitation-contraction coupling. Because the normal systolic ATP concentration is around 5 to 10 m*M*, whereas the substrate-binding sites of most ATP-hydrolzing systems are saturated at ATP concentrations less than 1 m*M*, it is unlikely that ATP concentrations fall to levels below those needed to saturate known energy-consuming reactions except in the dying heart. These allosteric effects of high ATP concentrations, which do not require that the nucleotide be hydrolyzed, resemble those of a "lubricant" in that ATP accelerates ion pumps, ion exchangers, and passive ion fluxes through membrane channels. By facilitating the many calcium fluxes involved in excitation-contraction coupling and relaxation, these allosteric effects of ATP exert both inotropic and lusitropic effects.[76]

MITOCHONDRIAL MASS AND FUNCTION

There are conflicting data on whether or not there is a significant decrease in the mass of mitochondria relative to the mass of myofibrils that occurs in experimental cardiac hypertrophy.[80-82] It is possible that this is one of the limitations of severe hypertrophy. Defects in mitochondrial oxidative phosphorylation and in mitochondrial calcium metabolism also may be associated with myocardial failure.[83] Except in circumstances where coronary flow is limited, such as with large vessel obstructive disease (see Chap. 40) or purported microvascular obstructive or vasospastic disease, a primary role of energy limitation in the evolution of heart failure has yet to be demonstrated.[74] It is possible that it may play a role during periods of higher metabolic demand, such as tachycardia,[77] as noted previously.[84,85]

VENTRICULAR REMODELING (HYPERTROPHY AND DILATATION)

When one portion of the ventricle is disabled, an increase in intraventricular volume slowly occurs, presumably in response to a sustained venous return. This involves increased myocyte length, with the limit being at the level of the sarcomere at 2.2 μm. With systolic overloads, compensatory hypertrophy occurs with the addition of sarcomeres in parallel, leading to a lateral thickening of the myocyte while sarcomere length does not change.

Acute dilatation is also limited by the sarcomere, which at 2.2 μm attains maximum force. Beyond this point, stiffness of the sarcomere and the myocardium becomes very large, and resting tension rises to high levels. Such acute dilatation may lead to relative "side to side" slippage of myocytes. When distending forces become chronic, addition of new sarcomeres occurs in series. Dilatation of the ventricle also adds to the load by the Laplace relation, whereby tension in the wall rises with increased volume at the same pressure. This results in some lateral growth of myocytes, although elongation is the major alteration. In addition, functional mitral regurgitation may occur from excessive ventricular volume that adds to the volume overload. When increased systolic tension occurs, myocyte hypertrophy that occurs by laying down of sarcomeres in parallel is accomplished by biochemical alterations in both the contractile proteins and activating membrane systems (see Chap. 5).

In addition to the synthesis of sarcomeres in series with preexisting sarcomeres, "slippage" of myofibrils and myocardial fibers and rearrangement of myocardial fibers along cleavage planes of the left ventricle occur.[59] Thus, although overstretch of sarcomeres rarely may be present very transiently, it does not appear to be an important primary mechanism of chronic heart failure. There is evidence, however, that excessive stretch of myocytes can lead to myocyte death, apparently by the process of apoptosis (programmed cell death), which may lead to further heart failure. The effects of the law of Laplace with ventricular dilatation were noted earlier. Nonuniformity of myocardial contraction and functional mitral regurgitation also contribute to heart failure.

MYOCARDIAL RECEPTOR FUNCTION

One of the hallmarks of heart failure is decreased myocardial inotropic function. Although it is clear that no single mechanism accounts for the depressed inotropic state, reduction in myocardial β-adrenergic receptors and its subsequent second messenger cAMP may play an important role in this regard.[86] β-Adrenergic stimulation contributes importantly to the cardiac response to exercise,[87] and β-adrenergic desensitization and uncoupling may be at least partially responsible for the reduced chronotropic and inotropic response to peak exercise commonly found in patients with heart failure.[87] The β-adrenergic receptor abnormalities in heart failure appear to be due to desensitization and uncoupling of the β_1 receptor produced by local and not systemic alterations in catecholamines.[88] In severe heart failure, the norepinephrine (NE) stores in sympathetic nerve endings are well known to be depleted. In a sense, the failing myocardium becomes functionally denervated. cAMP responses are reduced by about 30 to 35 percent, leading to further contractile dysfunction.[79] It is possible that with rather selective downregulation of the β_1 receptor, there remains a relatively high proportion of β_2 receptors to mediate chronotropic and inotropic responses.[89] However, there is mild uncoupling of the β_2 receptor from its G protein and a mild upregulation of the $G\alpha_i$ subunit, further contributing to a depressed response to chronotropic and inotropic stimuli.[90-92] There is

also a profound decrease in cardiac β-adrenergic responsiveness with aging,[93] which has clinical implications because heart failure is heavily concentrated in the aging population.

The desensitization and uncoupling of β-adrenergic receptors occurs early with mild to moderate ventricular dysfunction. It is related to the degree of heart failure and is associated with a very reduced response to β-adrenergic stimulation with drugs such as dobutamine.[94] Long-term stimulation of β-adrenergic receptors may enhance myocardial β-adrenergic receptor kinase (β-ARK) activity,[95] leading to further desensitization and uncoupling of the β-adrenergic receptor. These observations generally support the previously counterintuitive concept of using β-adrenergic blocking drugs to treat patients with heart failure. Of some interest, β-adrenergic blockade with metoprolol, a relatively cardioselective β_1 blocker, upregulates the β_1 receptor, whereas carvedilol, a nonselective β_1 and β_2 blocker with additional α_1 blocking activity, does not increase β_1 receptor density.[96] Both drugs can improve LV function. This suggests that the improvement in cardiac function seen with chronic β blocker use is not simply due to upregulation of β-adrenergic receptors. Moreover, high plasma norepinephrine levels do not predict benefit from carvedilol,[97] suggesting that there is not a simple relation between activation of the sympathetic nervous system and β-adrenergic receptor function in heart failure.

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

Heart failure is characterized by many abnormal reflex control mechanisms. Peripheral vascular resistance is increased, there is defective cardiac parasympathetic control,[98] an abnormal response to upright tilt,[99] altered baroreceptor function,[100-103] and reduced cardiac sympathetic activity in response to a variety of stimuli.[104-106] Indeed, an early sign of heart failure is increased sympathetic tone accompanied by reduced vagal tone resulting in an increased heart rate even at rest.

The increase in systemic vascular resistance observed in well-established heart failure, a therapeutic target for short-term hemodynamic treatment with nitroprusside, is likely due to a combination of locally active heightened vasoconstrictors (norepinephrine, angiotensin II, endothelin, vasopressin, neuropeptide Y) and to structural changes in blood vessels related to fluid retention and reduced endothelial-dependent vasodilation. Early in heart failure there may be a fall in cardiac output, arterial pressure, and baroreceptor activity, leading to an "adaptive" increase in excessive neuroendocrine drive. The sympathetic nervous system and the renin-angiotensin-aldosterone axis are activated. Arginine vasopressin is released. Sodium and water retention occur, hypervolemia restores cardiac output and arterial pressure, and neuroendocrine activity may reach a steady state. However, as heart failure progresses, there is impaired cardiosensory activity that fails to reduce neuroendocrine drive. Cardiac afferent activity to the central nervous system, for unclear reasons, is reduced, leading to unhindered, efferent excitatory responses from the brain to the periphery. Reflex vasoconstrictor responses to unloading the heart are paradoxically blunted.[99,106] There are abnormal vascular responses to postural change.[107] Some of these changes lead to alterations in regional blood flow that accompany heart failure.[108] Heart rate variability is markedly reduced and is a hallmark in defining congestive failure. Further, decreased heart rate variability may provide independent prognostic value in the identification of patients at risk for premature death.[109]

Although the genesis of these abnormal reflex control mechanisms is still not clearly understood, the changes may be more functional than structural in origin. Heart transplantation reverses cardiopulmonary baroreflex control mechanisms to some extent,[110,111] but the improvement may be absent[112] or delayed[113] in some cases. The role that abnormal reflex control mechanisms plays in the progression of heart failure, like other neuroendocrine alterations, has been difficult to quantitate. Nevertheless, it is now increasingly clear that the sympathetic nervous system and the renin-angiotensin-aldosterone system greatly influence the progression and natural history of heart failure. The therapeutic implications derived from these observations have proven to be very important.[114,115]

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Chapter 20: PATHOPHYSIOLOGY AND DIAGNOSIS OF HEART FAILURE

MECHANICAL AND HEMODYNAMIC FEATURES OF HEART FAILURE

The term *heart failure* implies structural heart disease. The central problem of heart failure remains impaired cardiac performance, although many of the secondary "adaptive" responses become maladaptive and contribute substantially to progression of heart failure. An understanding of how these changes occur can provide insight into the pathophysiology of the syndrome.

As ventricular function becomes impaired, the Frank-Starling law of the heart becomes operative (see Fig. 20-2). Inadequate emptying of the ventricle leads to increased EDVs. This is referred to as *increased preload,* and it produces an increase in SV during the next contraction. The Frank-Starling law simply states that the increase in contractile force (i.e., contractility) is related to sarcomere lengthening (up to 2.2 μm). For any given amount of Ca^{2+} released into the myocyte, there is increased crossbridge formation and enhanced sensitivity of the myofilament to Ca^{2+} as the sarcomeres lengthen.

In the failing ventricle, the extent of shortening for a given diastolic fiber length and load (afterload) is reduced. The ventricle can maintain a normal or near-normal SV with an increased EDV and thus maintain end-diastolic fiber length for a period of time. Eventually, the filling pressure rises inordinately, limiting this compensation (see Fig. 20-1). Further, the clinically dilated ventricle tends to "give" like an overstretched elastic band, and end-diastolic volume may increase somewhat with no increase in LV end-diastolic pressure, reflecting a shift in the passive pressure-volume curve to the right. An obligatory reduction in ejection fraction occurs when SV is maintained in the face of a large EDV (EF = SV/EDV; normal EF = 0.62 ± 0.12). Eventually, further increases in EDP produce little change in EDV, thus flattening the SV-EDP curve (see Fig. 20-1). There is no true descending limb to Starling curve because increasing preload indefinitely ultimately will lead to mitral regurgitation.[116,117] As the heart dilates, the increase in wall stress according to the Laplace relationship also will increase afterload, which may account for any observed reduction in SV as the heart dilates further (i.e., the perception of a descending limb). It is important to keep in mind that LV performance depends not only on systolic pump function but also on active relaxation, passive diastolic properties, and vascular loading conditions. It is likely that at high LV end-diastolic pressure, valvular incompetence (mitral regurgitation) is a major cause of a decrease in cardiac output. Thus, in end-stage heart failure in the intact circulation, the Starling curve flattens out. It is possible under certain experimental conditions that the severely failing heart is able to utilize the Frank-Starling mechanism,[118] but a hallmark of heart failure is the inability of the chamber to respond robustly to an increase in preload.

Afterload and the Concept of the Laplace Relation

A characteristic feature of the dilated, failing heart is that it gradually becomes less sensitive to preload (EDV and fiber length) and more sensitive to afterload stress. At very high LV filling pressures (>30 mmHg) when the sarcomeres are fully extended and the preload reserve is exhausted, the SV becomes exquisitely sensitive to alterations in the afterload.[119] The impedance to ejection includes blood viscosity, vascular resistance, vascular distensibility, and myocardial wall tension. The afterload is the total load that the heart must work against during contraction. Much of the afterload is made up of ventricular myocardial wall tension. In the ventricle, the

tension on the walls increases as ventricular chamber volume increases, even if intraventricular pressure remains constant. Calculations of myocardial wall tension are defined by the Laplace equation and are expressed in terms of tension *T* per unit of cross-sectional area (dynes per centimeter).

Within a cylinder, the law of Laplace states that wall tension is equal to the pressure within the cylinder times the radius of curvature of the wall: $T = P \times R$ where *T* is wall tension (dyn/cm), *P* is pressure (dyn/cm^2), and *R* is the radius (cm). Basically, wall tension is proportional to radius. Because the heart has thick ventricular walls, wall tension is distributed over a large number of muscle fibers, thereby reducing tension on each. The equation for a thick-walled cylinder such as the heart is: $T = \frac{P \times R}{h}$ where *h* is wall thickness. The equation is sometimes stated as: $T = \frac{P \times R}{2h}$

Since the geometry of the ventricles is more complex than a cylinder, ventricular wall tension cannot be measured with precision. Wall stress, the force distributed across an area, is actually more correct but is seldom measured.

There are two fundamental principles that stem from the relationship between the geometry of the ventricular cavity and the tension on its muscular walls:

1. *Dilation of the ventricles leads directly to an increase in tension on each muscle fiber.*
2. *An increase in wall thickness reduces the tension on any individual muscle fiber. Therefore, ventricular hypertrophy reduces afterload by distributing tension among more muscle fibers.*

The wall tension is highest in the inner surface of the heart. The endocardial surfaces must do more work and therefore are also more vulnerable to reductions in coronary blood flow. Dilatation of the heart decreases cardiac efficiency, unless hypertrophy is sufficient to normalize wall stress. In heart failure, wall tension (or stress) is high, and thus afterload is increased. The energetic consequences of the law of Laplace may have some role in progressive deterioration of energy-starved cardiac myocytes in the failing heart.

Another major disadvantage of the dilated ventricle is the inability to decrease the average radius during contraction. In the normal heart, wall tension falls during ventricular ejection as the volume decreases, even though pressure is rising. In heart failure, given the dilated heart with reduced ejection, the average tension in the myocardial fibers actually may continue to increase from the beginning of the ejection until peak systolic pressure is reached,[120-122] adding additional afterload during ejection. The rate of myocardial fiber shortening is reduced, further contributing to diminished myocardial performance. It is difficult to overstate the importance of the law of Laplace when considering the syndrome of heart failure. This contrast is apparent in mitral insufficiency. With preserved contractility and a relatively small EDV, mitral insufficiency leads to rapid unloading of volume and reduced tension. When ventricular dilatation occurs with decreased ventricular contractility, ejection is reduced, and tension remains high during systole, leading to an unsteady state that cannot be maintained for long.

Ventricular dilatation, though initially adaptive as an attempt to sustain SV, eventually becomes a substantial disadvantage and contributes importantly to impaired myocardial performance. As the left and right ventricles dilate, functional mitral and tricuspid regurgitation can occur, adding to circulatory congestion. Stretched myocardial cells can induce programmed cell death (apoptosis), thereby contributing to further disease progression.[123] Any treatment that slows progressive

dilatation of the heart, such as angiotensin-converting enzyme inhibitors or β-adrenergic blockers, will likely have a powerful role in the treatment of heart failure. The plasticity of the process of progressive dilatation is now more apparent, with remarkable reversal of dilatation observed under specific circumstances such as cessation of alcohol use in patients with alcoholic cardiomyopathy and spontaneous improvement in patients with inflammatory myocarditis.

Myocardial Hypertrophy

Hypertrophy of myocardial myocytes occurs to meet the demand of increased rate of use of mechanical energy. It is basically a response to sustained hemodynamic overloading of the heart, be it a volume or pressure overload or a combination of the two. Ischemic heart disease leads to a reduction of contractile tissue, ventricular dilatation, and a volume overload on the remaining viable myocytes. In this sense, it is a form of volume overload hypertrophy. Up to a point, the increased mass of cardiac muscle is beneficial in that it tends to normalize wall stress and provides for a larger number of contractile elements (sarcomeres).

Experimentally, evidence of hypertrophy (e.g., synthesis of new mRNA) occurs within hours of imparting a new load on the heart.[124,125] Pressure- and volume-induced hypertrophy are associated with distinct myocyte phenotypes and differential induction of peptide growth factors.[126] The heart demonstrates remarkable plasticity in response to a variety of growth factors and hemodynamic loads.[41] Isolated cell deformation is a sufficient stimulus for induction of hypertrophic growth, but the modulating role of angiotensin II, norepinephrine, altered membrane ion channels, and numerous growth factors is of obvious importance. The changing mechanical loading conditions appear to be the primary driving force behind myocardial hypertrophy in heart failure, and other factors likely act more as important modulators or facilitators of the process. Hyperplasia, or an increase in new myocardial cells, may occur to some extent under conditions of excessive loading or myocyte loss.[127,128] However, the capacity for new cardiac myocytes to form is limited, and whether they are functionally useful is unknown. Rather, the primary response to altered load is the assembly of new working units or sarcomeres per myocardial cell. In general, pressure overload results in replication of sarcomeres in parallel, whereas volume overload leads to new sarcomeres both in parallel and in series.[129] There is, however, significant hyperplasia of fibroblasts,[130-136] which outnumber cardiac myocytes by 3:1 to 4:1. It is the fibroblasts that are the major source of the reparative and replacement collagen when myocytes are lost in the evolution of heart failure.

Classically, pressure overload induces a form of *concentric hypertrophy*, whereas volume overload causes a form of *eccentric hypertrophy*. Concentric hypertrophy typically occurs with aortic stenosis or severe hypertension and causes a thickened ventricular wall, usually with no increase in chamber diameter. Myocytes primarily are increased in diameter. Capillary growth to these thickened myocytes may be diminished.[137,138] In eccentric hypertrophy, usually a consequence of volume overload, there is a proportional increase in wall thickness and chamber diameter. Myocytes primarily elongate from new sarcomeres assembled in series.

There also may be *reactive hypertrophy* of remaining myocytes in response to myocardial infarction.[139] In actuality, such myocardial hypertrophy is often hybrid, with both myocyte elongation and increased thickness of individual cardiac myocytes being observed. Local activation of autocrine/paracrine angiotensin II may play a role in the regulation of the hypertrophic process[140] but may not be an essential component of this complex system.[141]

There is now evidence from animal experiments that cell elongation may contribute importantly to chamber dilatation.[142,143] However, other factors such as myocyte slippage and increased interstitial tissue also may help to explain the increase in heart size frequently encountered in patients with heart failure. It should be pointed out that the original increase in heart size is geared to maintain stroke volume and normal wall tension. When decompensated heart failure occurs, it

is apparent that the increase in wall thickness is insufficient to normalize wall tension. Afterload rises and performance worsens, contributing to decompensation.

Of course, other changes in the myocardium are occurring simultaneously, and hypertrophy is only one factor, albeit an important one. Biochemical changes, phenotypic changes in protein synthesis, altered excitation-contraction, slower velocity of shortening due to a slower acting myosin heavy chain, and reduced β-adrenergic receptor density are all occurring simultaneously. Mechanically, reduced velocity of contraction, delayed time to peak tension, and slower relaxation are observed in the myocardium of failing hearts. All these factors likely converge to produce clinical decompensation. Delayed ventricular relaxation may limit filling, leading to heightened filling pressure, pulmonary congestion, and shortness of breath. Force development and shortening capacity remain intact in the face of hypertrophy, and only in very late failure does contractility or contractile force decline. What ultimately happens to the patient may depend on the acuteness or chronicity of the load, the extent of hypertrophy and fibrosis, the amount of myocyte loss, the heart rate and synchrony of atrioventricular contraction, and a host of invisible perturbations occurring at the level of the cell (Fig. 20-6).

Diastolic Heart Failure

Diastolic heart failure is often present when there is limitation of exercise tolerance and dyspnea that cannot be explained by lung disease or the extent of underlying LV systolic dysfunction. Diastole is usually divided into several mechanical phases (Fig. 20-7). Investigation of patients with heart failure and normal systolic function, usually by echo, often indicates LV hypertrophy and abnormal diastolic function. Unfortunately, there is no agreement as to what constitutes abnormal diastolic function. Disturbances include alterations in relaxation (reduced rate of decline in wall tension), an upward shift of the LV diastolic pressure-volume relationship (a decrease in LV diastolic distensibility) (see Fig. 20-1), incoordinate wall motion during isovolumic relaxation, and altered ventricular inflow velocity. These measurements are influenced by loading conditions, ischemia, heart rate, and age, making it difficult to determine the actual contribution of diastolic dysfunction to heart failure. This is why some prefer the phrase "heart failure with intact or normal systolic function." Nevertheless, disturbances in diastolic function are common in patients with heart failure and are multifactorial. Diastolic impairment is frequently symptomatic in patients with LV hypertrophy, coronary artery disease, and diabetes mellitus. There also may be impairment of diastolic function due to an infiltrative process such as amyloid. For any given EDV, there is often a higher LV end-diastolic pressure, indicating increased chamber stiffness and a smaller cavity size.

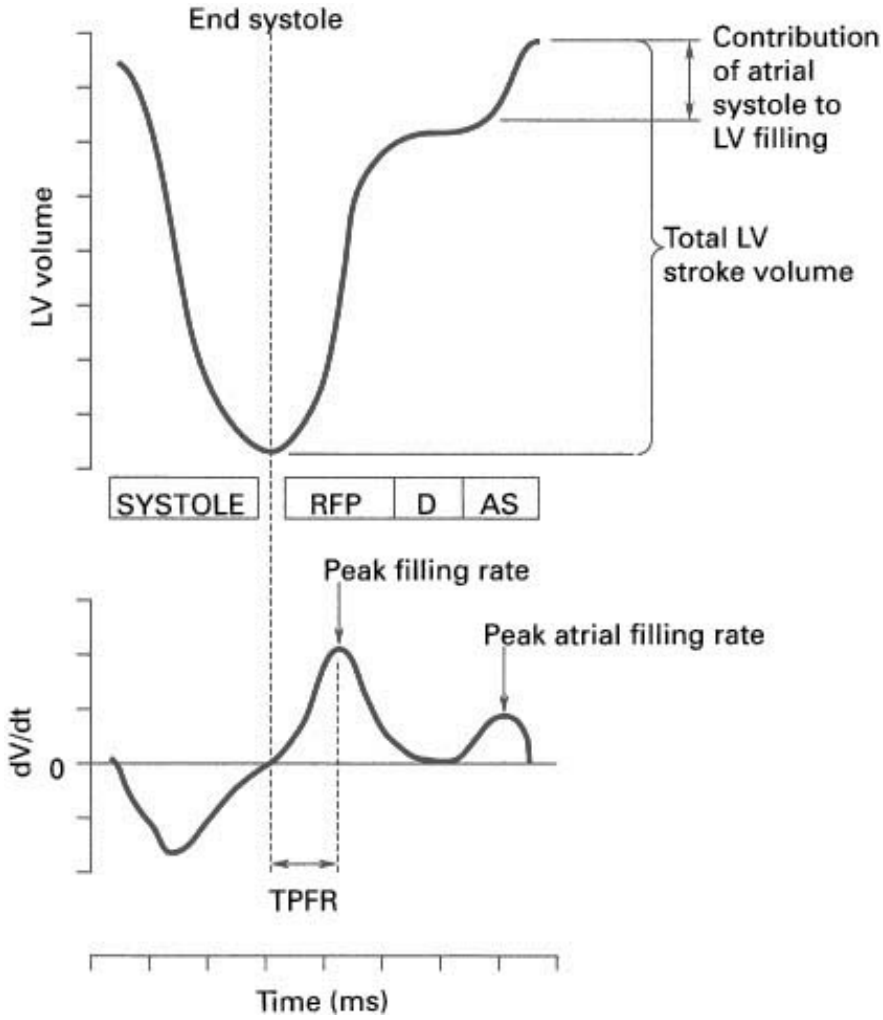

Figure 20-7: Idealized plot of left ventricular volume versus time (*top*) and the rate of change of volume (*dV/dt*) versus time (*bottom*), such as might be obtained from contrast or radionuclide ventriculographic studies. The representative cardiac cycle begins at end diastole. Subsequent events as depicted by the bars in the center of the figure are (1) systole, during which left ventricular volume decreases to a minimum and *-dV/dt* reaches its maximum; and (2) diastole, the beginning of which is signaled by the opening of the mitral valve and the onset of left ventricular filling. Diastole has three distinct phases in normal individuals: (1) the rapid filling phase (RFP), during which the left ventricle fills rapidly but passively and the peak filling rate occurs; (2) diastasis (D), during which relatively little left ventricular volume change occurs; and (3) atrial systole (AS), in which active atrial contraction fills the left ventricle to its end-diastolic volume. The diastolic parameters that have been derived from such analysis are the peak filling rate, the time to peak filling rate (TPFR), the percent contribution of atrial systole, and the first third filling fraction. (From Labovitz AJ, Pearson AC. Evaluation of left ventricular diastolic function: Clinical relevance and recent Doppler echocardiographic insights. *Am Heart J* 1987; 114:836-849. Reproduced with permission from the publisher and authors.)

As the population ages, one can expect to see more diastolic heart failure.[144] The development of atrial fibrillation with resulting reduced diastolic ventricular filling time commonly produces pulmonary edema in such patients. Although not as lethal as heart failure with a reduced ejection fraction, the prognosis of diastolic heart failure is poor. Diastolic abnormalities usually coexist with alterations in systolic function in patients with dilated cardiomyopathy.[145] The recognition, evaluation, and treatment of diastolic heart failure remain an obvious challenge,[146,147] but diastolic heart failure is an important component of the syndrome of heart failure and must be considered by all who care for patients with heart failure.

Hibernating and Stunned Myocardium

There is now a considerable body of evidence indicating that the myocardium can adapt its activity successfully to prevailing energetic circumstances.[148,149] *Hibernating* myocardium is a condition of reduced myocardial blood flow and impaired myocardial function that improves with revascularization. Myocardial *stunning* is the mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage. Hibernation is particularly important to recognize, diagnose, and treat because revascularization may be associated with a lower cardiovascular event rate.[150] The most commonly used tests for diagnosing hibernating myocardium are dobutamine echocardiography, thallium and sestamibi single-photon-emission computed tomographic (SPECT) myocardial perfusion imaging, positron-emission tomography, and magnetic resonance imaging (MRI) with gadolinium (see Chaps. 16, 18, and 19). Essentially, these imaging techniques are used to define myocardial viability.[151] Many large referral centers have developed their preferred method of assessment. LV function often improves or normalizes with revascularization when there is a "significant" amount of hibernating, but viable, myocardium as the major cause of LV dysfunction. When hibernating myocardium is documented, revascularization rather than heart transplantation is the appropriate therapy, provided the coronary arteries are suitable for revascularization.

Although the precise mechanism of hibernating myocardium has not been determined, the concept is very attractive to clinicians. It is as though the heart downgrades its myocardial function to the extent that blood flow and function are once again in equilibrium. There is no myocardial necrosis or symptoms of ischemia. These observations suggest that the heart can adapt to chronically low myocardial blood flow and that a new steady state between perfusion and contraction can be achieved and maintained. The pathophysiology is undoubtedly highly complex and is accompanied by phenotypic changes and morphologic alterations.[152] It is likely that hibernating myocardium represents a precarious though reversible state, and failure to revascularize it may lead to an increased rate of adverse events and a poor prognosis. Hibernating myocardium may be the end result of repetitive myocardial stunning, perpetuated by renewed episodes of ischemia.

The Cardiac Interstitium

Collagen and the interstitium are normally in a steady state but increase during hypertrophy and following loss of myocytes due to myocardial injury. In heart failure the interstitial space includes reparative and interstitial fibrosis. Contrary to previous concepts, the interstitium is a very dynamic structure, with both matrix removal and synthesis occurring simultaneously at all times. Connective tissue remodeling, either physiologic or pathologic, is in most cases a homeostasis between collagen synthesis and collagen degradation by matrix metalloproteases (MMPs). The matrix of the heart is a very complex scaffolding composed of fibrillar and ground substance proteins (collagen) that pattern around and between myocytes in a very precise and organized pattern. The matrix likely plays a very important role in maintaining an ideal ventricular shape.[153] Changes in the cardiac "skeleton" can contribute to impairment of both diastolic and systolic function.[154] In the failing human heart with advanced coronary disease (so-called ischemic cardiomyopathy), fibrosis is the major force of LV remodeling. Infarct scars may account for 30 percent of fibrosis, whereas microscopic fibrosis remote from the infarct may account for 70 percent of the total fibrous tissue found in the ventricles.[155] In general, interstitial loci of fibrosis are the "tombstones" of lost myocytes. It is likely that increased MMPs contribute to ventricular dilatation in heart failure.[156] Tissue inhibitors of MMPs (TIMPS) exist in the myocardium and are regulated independently of MMPs,[156] an observation with potentially important therapeutic implications. Enhanced protease activity in heart failure contributes to fibrillar collagen degradation, setting the stage for weakened connective tissue and disrupted organ integrity, myocyte slippage, and ventricular remodeling.

The growth of the interstitium in response to pressure and volume overload is highly complex and

involves fibroblasts and their ability to sense altered mechanical forces. Hormones, including the renin-angiotensin-aldosterone system[157] and endothelin,[158] also facilitate the production of collagen via their interaction with fibroblasts. Once abnormal loading conditions are removed, connective tissue hypertrophy regresses more slowly than myocyte hypertrophy. It is rather striking how the importance of this once considered inert ground substance has emerged over the past 15 years, previously hidden to investigators largely because it was essentially invisible by the usual techniques of light microscopy. It is now clear that the cardiac interstitium is very important in the syndrome of heart failure and contributes in many ways to the structural and functional alterations.

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Chapter 20: PATHOPHYSIOLOGY AND DIAGNOSIS OF HEART FAILURE

NONCARDIAC "ADAPTATIONS" IN HEART FAILURE

The Neurohumoral Hypothesis

A large number of neurohormones have been found to circulate in abnormal quantities in heart failure (Table 20-7). The natriuretic peptides [atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and clearance natriuretic peptide (CNP)] are considered counterregulatory because they tend to reduce right atrial pressure, systemic vascular resistance, aldosterone secretion, sympathetic nerve stimulation, and hypertrophy of cells and can enhance sodium excretion.[159] The predominant consequence of most neurohormone "release" in heart failure, however, is vasoconstriction coupled with salt and water retention. The regulation of body fluid volume is very complex but has a primitive relation to many of the neurohormones and their propensity to facilitate retention of sodium and water while at the same time protecting perfusion pressure. The integrity of the arterial circulation as a function of cardiac output and SVR is also determined by flexibility in renal sodium and water excretion.[160] Underfilling of the arterial bed by low cardiac output or vasodilation activates neuroendocrine reflexes that stimulate sodium and water retention. Sodium and water retention cease to be major problems after heart transplantation, indicating that there is no intrinsic renal dysfunction in heart failure. The kidney responds to a perceived reduction in arterial filling in an appropriate manner by retaining volume.

Decreases in blood pressure, stroke volume (pulse pressure), and perfusion (flow) in heart failure are sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles. When there is diminished activation of these receptors, as in heart failure, there is augmentation of sympathetic outflow, activation of the renin-angiotensin-aldosterone system, and nonosmotic release of arginine vasopressin (AVP).[160] Heightened peripheral vasoconstriction occurs along with increased blood volume, thereby "restoring" circulatory integrity and perfusion pressure. Of course, neuroendocrine activation has many important consequences at the cellular level, including facilitation of myocyte hypertrophy[41] and collagen synthesis.[136] Activation of the sympathetic nervous system contributes to tachycardia and arrhythmias and can be directly toxic to the myocardium.[161,162] Cardiac myocyte necrosis also occurs in response to low levels of angiotensin II.[163] Although neuroendocrine responses are not the primary cause of heart failure under most circumstances, they clearly contribute to the pathogenesis of the syndrome[164] (Fig. 20-8). The overly simplistic view that neurohormones in heart failure are a response to perceived "hypovolemia" is clearly incorrect.[165] Neuroendocrine mechanisms are now the targets of several important and successful therapeutic interventions in heart failure and hypertension[166] and have a key role in determining prognosis.[167] Angiotensin-converting enzyme inhibitors, β-adrenergic blockers, and aldosterone antagonists now have a prominent role in the treatment of heart failure, and new, more innovative neuroendocrine-blocking agents are being developed rapidly, adding strong support to the neurohumoral hypothesis.[164]

Norepinephrine

It has been recognized since the time of Starling that patients with heart failure manifest signs of a hyperadrenergic state. Vascular constriction, tachycardia, diaphoresis, and oliguria are clear signs of increased sympathetic drive. Starling's observations in 1897[168] were amplified in the early 1960s by the group from the National Institutes of Health (NIH), who verified increased plasma

norepinephrine (NE) levels in patients with heart failure.[169] Myocardial stores of NE were found to be depleted.[170] Later studies by various investigators using the more sensitive radioenzymatic technique measured plasma NE levels in patients with heart failure and described a correlation with functional class[171] and extent of hemodynamic dysfunction.[172]

NE synthesis begins in the body of the neuron with the synthesis of enzymes necessary to go from tyrosine to NE. The enzymes are transported down the neuron to the dendrites of the cell, where the actual synthetic steps take place. Dopamine is synthesized and transported into storage vesicles, where the final synthetic steps occur. These storage vesicles are both large and small, the large vesicles containing additional peptides such as neuropeptide Y. Following discharge of an axonal action potential, exocytosis occurs, allowing the vesicle contents to be released into the synaptic cleft. The vast majority of the NE is then taken back up into the cell for storage and rerelease (uptake 1). Some NE is taken up by effector organs and metabolized (uptake 2), and only a small quantity is released into the plasma (≈5 percent), where it circulates as plasma NE. There are now microneurographic techniques than can be used to directly measure sympathetic traffic direction[173] and "spillover" techniques that can measure specific organ sympathetic activity.[174] It now seems clear that increased cardiac sympathetic traffic precedes more generalized sympathetic activation in the course of heart failure.[175] However, the plasma NE level has served as a useful research and prognostic guide for the study of patients with heart failure.[176]

It is overly simplistic to consider NE to be "good" or "bad" for patients with heart failure. Those with severe New York Heart Association (NYHA) class IV heart failure may be quite dependent on catecholamine support[177] and often require a continuous dobutamine infusion to maintain suitable organ perfusion prior to heart transplantation. However, there is no question that NE is toxic to the myocardium and is responsible in part for progressive LV remodeling.[178,179] The favorable and detrimental effects of sympathetic drive are depicted in Table 20-8. These observations imply that blocking the sympathetic nervous system effects are most likely to benefit NYHA class I-III patients, whereas such action potentially could worsen the condition of class IV patients who manifest congestion.

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The Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis of heart failure (Fig. 20-8), and consistent benefit has been derived from angiotensin-converting enzyme inhibitor therapy in patients with heart failure. The mechanisms responsible for the release of renin from the renal cortex have been studied exhaustively[180] and include sympathetic drive to the kidneys, hyponatremic perfusate to the macula densa of the kidney, and the use of diuretics and a low Na^+ diet, which tends to promote a relative volume contraction. Renin proteolytic enzyme has little biologic activity, but it interacts with angiotensinogen to split off two amino acids to form angiotensin I, which is then cleaved by the angiotensin-converting enzyme found locally and widely in the vascular system, especially the lungs, to produce angiotensin II, a peptide with a vast range of biologic activities. Angiotensin II in turn stimulates release of aldosterone from the adrenal cortex, which also has an array of biologic effects, including Na^+ and H_2O retention and kaliuresis.

There now are at least four recognized angiotensin II (AT) receptors, but much of the activity is subserved by the AT_1 receptor. The AT_1 actions include arterial vasoconstriction, cell growth (hypertrophy), apoptosis in myocytes, polydypsia, NE release, sensitization of blood vessels to NE, AVP release, and aldosterone release. The AT_2 receptor appears to subserve somewhat counterregulatory effects, including antigrowth/antiremodeling, apoptosis in vasculature,

vasodilation, and activation of the kinin-nitric oxide-cGMP system.[181] Since AT_1 receptor-blocking drugs (so-called ARBs) increase angiotensin II levels, they may enhance unoccupied AT_2 receptor activity. Angiotensin II levels tend to "escape" the pharmacologic effects of chronic angiotensin-converting enzyme inhibition and may stimulate AT_2 and AT_2 receptor activity. It is also now clear that the RAAS is not solely a classic endocrine system but has autocrine and paracrine activity that may be particularly important in cardiovascular, brain, and renal tissue. With our current knowledge that angiotensin-converting enzyme inhibitors remarkably reduce all cardiovascular events and the onset of new diabetes mellitus in patients with cardiovascular disease, it is difficult to overstate the role of the RAAS in the pathogenesis of heart and vascular disease, including progressive heart failure.[182-184]

Arginine Vasopressin

Patients with heart failure sometimes may have water retention in excess of Na^+ retention, which leads to hyponatremia. The hyponatremia is due in part to nonosmotic release of AVP, which acts on the kidney to reduce clearance of free water.[185] Release of AVP in heart failure probably occurs via activation of carotid baroreceptors.[160] Plasma AVP levels are often but not always increased in patients with LV dysfunction[186] and heart failure.[187] AVP acts on the V_2 receptors in the collecting duct of the kidney via adenylate cyclase to translocate aquaporin-2 water channels from cytoplasmic vesicles to the apical surface of the collecting duct. AVP also increases aquaporin channel-2 synthesis. Activation of V_1 receptors in vascular tissue contributes to heightened vascular resistance and myocardial dysfunction in heart failure.[188] Recognition of the role of AVP in the pathogenesis of heart failure has led to the development and investigation of selective and dual V_1-V_2 receptor blockers as potential adjunctive treatment.

Natriuretic Peptides

A family of natriuretic peptides including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and clearance natriuretic peptide (CNP) have evolved over time, encoded by separate genes, each with a tissue-specific distribution, regulation, and biologic activity.[159] These natriuretic peptides are often increased in patients with heart failure, and BNP may even be a marker for asymptomatic LV dysfunction or early heart failure.[189,190] ANP is a 28-amino-acid peptide that is normally synthesized and stored in the atria and to some extent in the ventricles. It is released into the circulation during atrial distention. BNP is synthesized mainly by the ventricles and is released in LV dysfunction or early heart failure. For the most part, these peptides act via guanylate cyclase receptors to promote vasodilation (ANP, BNP, CNP) and natriuresis (ANP, BNP). They also may attenuate NE release, RAAS activity, and the growth/hypertrophy of target cells-hence the term *counterregulatory hormones*.

Patients with heart failure are relatively resistant to the natriuretic effects of these peptides when they are administered exogenously, perhaps due to decreased Na^+ delivery to the collecting duct as a result of diminished glomerular filtration or increased Na^+ reabsorption in the proximal tubule.[160] Nevertheless, BNP infusion has a remarkable positive hemodynamic effect in patients with heart failure,[191] and drugs designed to inhibit degradation of natriuretic peptides (so-called neutral endopeptidase inhibitors) have been combined with angiotensin-converting enzyme inhibitor activity as potential therapy for hypertension and heart failure. The role of natriuretic peptides as potential therapy continues to evolve.

Endothelin

Endothelins are a family of vasoconstrictor peptides produced by vascular endothelial cells[192,193] whose normal function is as yet unclear. Although blood levels are increased in patients with heart failure,[194,195] endothelin-1 (ET-1) is more of a paracrine than an endocrine hormone. In heart failure, myocardial tissue ET-1 levels are increased, possibly more due to decreased clearance by the lungs than to increased synthesis.[196] Endothelial cells synthesize ET-1 rapidly and convert so-called big endothelin-1 into endothelin by an endothelin-converting enzyme. The synthesis of ET-1 is enhanced by angiotensin II, NE, growth factors, insulin, hypoxia, oxidized low-density lipoproteins (LDLs), shear stress, and thrombin.[193] Its synthesis is antagonized by ANP and prostaglandins.

Endothelin acts on at least two types of G protein-coupled receptors, A and B. The ET-A receptor subserves smooth muscle vasoconstriction and cell proliferation/hypertrophy and mainly resides on vascular smooth muscle cells. The ET-B receptor, which is mainly endothelial, subserves vasodilation that is probably mediated by a variety of mechanisms including increased production of nitric oxide and prostaglandins and activation of potassium channels. ET-1 also can act on the heart to cause hypertrophy, on the adrenal gland to release aldosterone, and on the kidney to promote Na^+ and H_2O retention.[193] The importance of ET-1 in the pathogenesis of heart failure is highlighted by the development and clinical testing of several new endothelin antagonists.[197] Endothelin-blocking agents are believed to hold promising vasodilator, natriuretic, and antiremodeling effects.

Additional Neurohormones

Many other neurohormones are believed to be important in the pathogenesis of heart failure, including neuropeptide Y, vasointestinal peptide, bradykinin, prostaglandins, adrenomedullin, and urodilatin. As we grow to better understand heart failure, some of them may emerge as "systems" to block or enhance, depending on their primary function.

Cytokines

In 1990 it was reported by Levine et al.[198] that circulating tumor necrosis factor alpha (TNF-α), a proinflammatory cytokine, was increased in cachectic patients with chronic heart failure. Since then, a large body of work has emerged indicating that proinflammatory cytokines such as TNF-α may play a fundamentally important role in modulating abnormal myocardial structure and function in late stages of heart failure.[199-201] This group of proinflammatory cytokines also includes interleukin 1 (IL-1) and interleukin 6 (IL-6). These proteins, largely products of macrophages and lymphocytes, are also expressed under some circumstances by myocardial tissue. Each of these cytokines can influence the expression of the other two, and each can modulate cardiovascular performance when expressed at sufficiently high levels. Experimentally, a continuous infusion of TNF-α leads to time-dependent depression in LV function[202] and provokes a hypertrophic growth response in adult cardiac myocytes.[203] When there are large quantities being produced, TNF-α spills over into the circulation and acts as an endocrine "hormone" leading to metabolic wasting and cachexia.[204,205] Overexpression of TNF-α in a transgenic mouse model leads to a phenotype consistent with cardiomyopathy.[206] TNF-α acts via two different membrane receptors. The transduction signal pathways are not fully understood, but in the heart they may mediate cell growth, negative inotropy, and apoptosis. The emergence of these important observations has lead to the launching of a clinical trial with etanercept (a fusion molecule that binds circulating TNF-α) for the treatment of patients with late-stage heart failure.

Renal Retention of Salt and Water

Since its earliest clinical descriptions, a hallmark of heart failure has been renal retention of Na^+ and H_2O, resulting in signs and symptoms of fluid retention. The precise mechanism whereby the

heart signals the kidney in the early stages of heart failure to retain Na^+ and H_2O is still unknown, although in the late stages reduced cardiac output and impaired renal blood flow likely play a major role. In early heart failure, when normal cardiac output is maintained via compensatory mechanisms and renal blood flow is not reduced, there is still some Na^+ retention. Curiously, some patients with advanced heart failure rarely demonstrate peripheral edema or ascites. This suggests that in some cases counterregulatory natriuretic peptides may be acting to maintain natriuresis. Perhaps release of ANP and BNP in the early stages of heart failure offsets the tendency to retain Na^+, thereby maintaining Na^+ balance. Salt and water retention usually becomes evident in the syndrome of heart failure as adequate perfusion and protection of blood pressure become more imperative.[207] The RAAS is dominant in this regard.[208] Angiotensin II preserves glomerular filtration rate in patients with heart failure even when renal perfusion is severely compromised, and this effect is achieved independently of this hormonal system's propensity to support systemic blood pressure.[209] Intraglomerular hydraulic pressure and therefore glomerular filtration are preserved by the constriction of glomerular efferent arterioles via angiotensin II.[210] Increased intrarenal formation of angiotensin II during a reduction in renal artery pressure maintains efferent arteriolar tone and, consequently, the effective filtration pressure.[211] The resulting high level of filtration fraction favors changes in the postglomerular circulation that promote avid proximal fluid reabsorption via elevated peritubular capillary oncotic pressure.[212] Increased aldosterone acts principally on the cortical collecting tubules to conserve Na^+. Because the plasma volume and blood pressure vary considerably from day to day, there is no consistent relation between the RAAS and fluid retention.

The mechanisms of Na^+ and H_2O retention in heart failure are complex and determined by multiple other factors. Sympathetic nervous system traffic to the kidney favors sodium retention. Increased AVP activity diminishes free water clearance. The prostaglandins normally dilate afferent glomerular arterioles to enhance intraglomerular flow and pressure, and their inhibition by nonsteroidal anti-inflammatory agents may lead to a marked reduction in filtration and sodium retention. Enhanced Na^+ reabsorption of heart failure also occurs in the ascending loop of Henle, as well as in the cortical and medullary collecting ducts. Eventually, the "goal" of plasma volume expansion is met, but at the expense of circulatory and tissue congestion.

Endothelial Dysfunction, Nitric Oxide, Exercise Intolerance, and Sleep Disorders

Data from many animal and human studies indicate that endothelium-dependent vasodilation is abnormal in a number of disease states, including atherosclerosis, hypertension, heart failure, hyperhomocysteinemia, insulin resistance, and hypercholesterolemia. Treasure et al.[213] observed abnormal endothelial-dependent dilatation of the coronary arteries in patients with dilated cardiomyopathy. Peripheral resistance vessels in both experimental animals[214] and patients with heart failure[215] demonstrate endothelial dysfunction. Data collected to date would suggest that the endothelial dysfunction in heart failure (i.e., failure to vasodilate in response to a specific endothelial-dependent vasodilator) may be due to a reduced release of nitric oxide during stimulation.[216] The basal release of nitric oxide may be preserved or even enhanced in heart failure[217] and may be compensatory by antagonizing neuroendocrine vasoconstrictor forces. However, impairment of endothelium-dependent peripheral vasodilation may be a factor contributing to exercise intolerance in patients with chronic heart failure, perhaps by limiting nutritive skeletal muscle flow during exercise.[218] This dysfunction of the endothelium may be related to deconditioning in later stages of heart failure, and with training, it is largely reversible. Further, abnormal endothelium-dependent responses in heart failure are reversible following heart transplantation.[219]

The roles of nitric oxide and nitric oxide synthase in the failing heart are much more complex.[220,221] Nitric oxide inhibits the positive inotropic response to β-adrenergic stimulation in

the failing heart. While smaller physiologic amounts of constitutive nitric oxide (cNOS) are necessary for normal function and have an antioxidant effect to protect cells, high levels of nitric oxide in the heart may exert proapoptotic and cytotoxic effects. The inducible isoform of nitric oxide synthase (iNOS) is overexpressed in human heart failure[222] and therefore may contribute to worsening heart failure. On the other hand, there is decreased myocardial nitric oxide synthesis during decompensation of experimental heart failure.[223] The relative roles of nitric oxide also may differ at different stages in the evolution of heart failure.

In addition to a reduced myocardial force-frequency response, inability to fully use the Starling effect, chronotropic incompetence and diminished myocardial β-receptor density, endothelial dysfunction, reduced nutritive blood flow, and disuse atrophy of skeletal muscles limits exercise tolerance in patients with heart failure. The latter effects appear to be excessively dependent on a glycolytic metabolism,[224] in part due to reduced metabolic efficiency in performing external work. Possible mechanisms include changes in muscle fiber recruitment, selective atrophy of oxidative fibers, and physical deconditioning. The mitochondrial content of skeletal muscle is reduced[225] in heart failure. Increased expression of the inducible isoform of nitric oxide synthase in skeletal muscle is correlated with reduced mitochondrial creatine kinase expression and exercise intolerance.[226] Apoptosis is frequently found in skeletal muscle of patients with heart failure and is associated with exercise impairment.[227] Exercise capacity and EF are very poorly correlated in heart failure, suggesting that impairment in nutritive blood flow is not the dominant reason for exercise intolerance.

Pulmonary dysfunction is common in patients with heart failure and also may contribute to exercise intolerance. The amount of intrathoracic space available for ventilation may be decreased by alveolar and interstitial edema, by pleural effusions, or by an increase in blood volume. Increased pulmonary vascular congestion decreases lung compliance and increases the work of breathing. Excessive ventilation during exercise is a hallmark of heart failure. Acute reduction in pulmonary capillary wedge pressure has no effect on the augmented ventilatory response, and the extent of excessive ventilation does not relate to either resting or exercise pulmonary capillary wedge pressure.

The potential mechanisms resonsible for exercise intolerance, a uniform feature of heart failure, are numerous (Table 20-9). Exercise intolerance is clearly multifactorial and is a potent prognostic indicator used the to help determine the optimal timing of heart transplantation (e.g., $V(r)_{O_{2,max}}$ of less than 50 percent predicted for size and age). Exertional symptoms generally correlate with maximal exercise capacity,[228] although exertional symptoms frequently underestimate the severity of functional disability. Although EF does not correlate with exercise performance ($V(r)_{O_2}$), if the latter is markedly reduced (e.g., $V(r)_{O_2}$ <12 mL/kg/min) along with a low EF, the prognosis is especially grave. Cardiopulmonary exercise testing should be done in patients with heart failure to assess functional capacity. Importantly, exercise tolerance can improve with training, which should be encouraged in patients with classes I to III heart failure symptoms.

Table 20-9: Mechanisms of Exercise Intolerance in Heart Failure

Inability of endothelium to respond to vasodilator stimulus
Reduced nutritive blood flow to skeletal muscle
Inability to increase stroke volume in response to exercise
Chronotropic incompetence
Reduced myocardial force-frequency response
Diminished myocardial β-adrenergic receptor density
Skeletal muscle atrophy
Shift from slow- to fast-twitch fiber types
Atrophy of fast-twitch type II fibers
Reduced level of skeletal muscle mitochondrial enzymes
Reduced skeletal muscle mitochondrial size
Increased skeletal muscle apoptosis
Reduced lung compliance
Excessive ventilatory response to exercise
Generalized deconditioning

Periodic breathing (Cheyne-Stokes) is common in patients with heart failure. It can be caused by lung edema, which can excite carbon dioxide responses through vagal reflexes. Enhanced sensitivity to carbon dioxide may predispose some patients with heart failure to the development of central sleep apnea.[229] Cheyne-Stokes respiration in heart failure is associated with a poor prognosis.[230] Successful treatment of Cheyne-Stokes respiration with nocturnal nasal oxygen improves sleep, exercise tolerance, and cognitive function in patients with heart failure.[231] Severe untreated sleep-disordered breathing can further impair LV function, leading to arterial oxyhemoglobin desaturation and arrhythmias.[232] Central sleep apnea may occur in as many as 40 percent of patients with heart failure, and 10 percent suffer from obstructive sleep apnea.[233] Obstructive sleep apnea increases afterload and heart rate during sleep but is responsive to continuous positive airway pressure.[234]

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Chapter 20: PATHOPHYSIOLOGY AND DIAGNOSIS OF HEART FAILURE

DIAGNOSIS AND EVALUATION OF PATIENTS WITH HEART FAILURE

History

The dominant and most recognizable symptom of congestive heart failure is "shortness of breath." The clinical term for this shortness of breath is *dyspnea*, and it is described by patients as the sensation of being unable to get enough air with each inspiration. Frequently, dyspnea is first noted by the patient on exertion and often dismissed by the patient as part of aging. As the heart failure progresses, the sensation of dyspnea occurs with less and less exertion, until the patient experiences symptoms at rest.

Despite all the advances in the field of cardiology, the mechanism of dyspnea remains poorly understood. When patients develop acute heart failure, they are often hypoxemic secondary to pulmonary edema and a resulting decrease in oxygen diffusing capacity. Patients with chronic stable heart failure, even if clinically compensated, still experience dyspnea, despite a lack of overt pulmonary edema. The explanation for the dyspnea in this latter group of patients is likely multifactorial, including increased physiologic dead space, increased airway resistance, reduced lung compliance, and fatigue of the respiratory muscles. Additionally, there may be some as yet undefined signals from the pulmonary J-receptors and respiratory muscles that contribute centrally to the sensation of dyspnea.[235,236]

The classic respiratory symptom triad of heart failure includes dyspnea, orthopnea and paroxysmal nocturnal dyspnea (PND). Orthopnea is the sensation of shortness of breath in the supine position. Patients may describe the need for more pillows under their head to sleep or even needing to prop the head of the bed up. PND relates to sudden, nocturnal dyspnea, often awakening the patient from sleep and requiring the patient to sit or stand up and ambulate to improve breathing. Onset of these symptoms indicates progression of the underlying heart failure and may culminate in a Cheyne-Stokes respiratory pattern.

The other typical complaint of patients with heart failure is fatigue. Since everyone feels fatigued at some time, this a vague, subjective complaint that does not easily lend itself to measurement. Often, the interviewer must inquire about specific tasks or ask the patient to provide examples of how the fatigue occurs. The patient often will describe being physically exhausted by activities that presented no difficulty weeks or months prior to the interview. Some may be able to separate fatigue from dyspnea, but the two complaints frequently coexist. Like dyspnea, the underlying mechanism of fatigue remains unclear. It is likely multifactorial and may be in part due to a reduced cardiac output with resulting poor tissue perfusion, excessive activity of the neuroendocrine system, elevated cytokine levels, or deconditioning of skeletal muscles.

Wheezing and cough are additional common complaints of patients with heart failure. Symptoms of circulatory and organ congestion also can occur and include nausea, vomiting, and discomfort from hepatic and bowel edema. Right upper quadrant abdominal pain can be severe in acute heart failure and is due to distention of the hepatic capsule. Peripheral edema is also a frequent complaint of patients with heart failure, though, curiously, some patients never manifest it. Along with dyspnea, ankle swelling is a common early symptom that often brings the patient for treatment. This is generally more prominent at day's end; with sleeping, fluid reabsorption with redistribution into the chest may lead to orthopnea.

The initial evaluation of the patient suspected of having heart failure should include a thorough past medical history and review of systems. This can be beneficial in defining the etiology of the patient's cardiac dysfunction. Since ischemic heart disease is the most frequent cause of heart failure in the United States, coronary risk factors such as diabetes mellitus, hypertension, cigarette smoking, hyperlipidemia, and family history need to be assessed and vigorously treated. Poorly controlled hypertension can cause heart failure that is unrelated to coronary artery disease. Relatively mild hypertension in the diabetic may result in a specific cardiomyopathy. Excessive alcohol or illicit drug use also can lead to cardiomyopathy. A

comprehensive list of cardiomyopathies, though far from exhaustive, is found in Table 20-10. Dietary needs and therapeutic compliance need to be assessed in all patients. They must know that excessive salt intake can lead to diuretic resistance and acute decompensation. Patient education regarding signs, symptoms, treatment, and prognosis is critical for the well-being of the patient. End-of-life wishes regarding resuscitation and intubation also should be discussed at a time when the patient is stable and can participate in meaningful dialogue.

Table 20-10: Classification of Cardiomyopathies

Dilated cardiomyopathy (idiopathic)
Hypertrophic, cardiomyopathy
Restrictive cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Unclassified cardiomyopathy
Ischemic cardiomyopathy
Valvular cardiomyopathy
Hypertensive cardiomyopathy
Inflammatory cardiomyopathy
Metabolic cardiomyopathy
Infiltrative cardiomyopathy
Muscular dystrophy-associated cardiomyopathy
Neuromuscular disorder-associated cardiomyopathy
Toxic cardiomyopathy
Peripartum cardiomyopathy

SOURCE: Adapted from Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies *Circulation* 1996; 93:841-842.

Physical Examination

The physical examination in heart failure is not relegated solely to the cardiovascular examination. A complete examination is necessary because peripheral findings can provide additional insight into the extent and chronicity of the disease process. The patient's overall appearance can be very enlightening. A generalized wasting with skeletal muscle loss, referred to as *cardiac cachexia*, is usually indicative of severe and late-stage heart failure.

A complete cardiovascular examination encompasses both peripheral and cardiac findings (see Chap. 10). On palpation of the heart, the point of maximal impulse is often laterally displaced and diffuse. An LV heave often can be appreciated, as can a right ventricular heave if the pulmonary artery pressures are elevated or if right-sided heart failure has begun. In the case of severe valvular aortic stenosis, a palpable thrill, LV heave, and radiation of the murmur into the carotids is often present. On cardiac auscultation of the apex, an S_3 gallop rhythm is indicative of decompensated heart failure. An S_4 gallop in a patient with coronary artery disease, hypertension, or aortic valve stenosis makes the examiner consider a stiff ventricle due to cardiac hypertrophy. A pericardial knock can be found in constrictive pericarditis, an unusual cause

of circulatory congestion. The systolic murmur of mitral regurgitation can be found in either primary (organic valve disease) or secondary (due to LV dilatation) mitral valve incompetence. Severe mitral regurgitation can occur with no or little audible murmur. Additionally, the murmurs of aortic stenosis, aortic insufficiency, tricuspid regurgitation, and less commonly, a ventricular septal defect can provide further evidence of the etiology and extent of CHF. A loud P_2 (i.e., audible at the apex of the heart) can indicate elevated pulmonary artery pressures in either the acute or chronic setting.

The vascular examination provides important information. An increased resting heart rate is common. An new irregular pulse in a previously compensated patient can implicate new-onset atrial fibrillation as the source of an unexplained decompensation. Bilateral carotid "bruits" radiating from the heart with a decreased and delayed (*parvus et tardus*) pulse can indicate severe aortic stenosis. However, in the absence of the bruit and any aortic stenosis murmur, a decreased pulse waveform may indicate a poor stroke volume and therefore low cardiac output. This is also usually reflected by a narrow pulse pressure. Poor capillary refill and cool extremities can indicate a severely restricted cardiac output. An elevated jugular venous pressure is an indicator of high right-sided pressure and volume overload. Careful examination of the jugular venous pressure is most useful when determining diuretic dosage. A prominent *v* wave can be seen in severe tricuspid regurgitation, which is often accompanied by a pulsatile liver. Pedal edema is often observed in heart failure, and scaly, discolored, and ulcerated lower legs denote a chronic edematous state (*stasis dermatitis and ulceration*).

The pulmonary examination can be relatively normal in chronic compensated heart failure. However, rales due to alveolar fluid accumulation accompanied by hypoxemia often are found in acute or decompensated heart failure. Decreased breath sounds at the bases and dullness to percussion are found with pleural effusions. On occasion, wheezing rather than rales will be heard, which is termed *cardiac asthma*.

Diagnostic Studies

Routine blood work sometimes can provide some insight into the etiology of heart failure and the extent of decompensation. Noncardiac factors may increase failure or make it initially evident. Fever or anemia may help to explain decompensation in a previously stable patient with severe coronary disease. A low serum sodium level (hyponatremia) often is observed in patients with advanced heart failure and can be a poor prognostic sign. Prerenal azotemia is found in patients with poor cardiac output and resulting renal hypoperfusion, whereas a rise in the creatinine level may indicate renal dysfunction that can be primary or secondary to heart failure. Other laboratory values of import are noted in Table 20-11.

Table 20-11: Recommended Tests for Patients with Signs or Symptoms of Heart Failure

Test Recommendation	Findings	Suspected Diagnosis
Electrocardiogram	Acute ST-T-wave changes	Myocardial ischemia
	Atrial fibrillation, other tachyarrhythmia	Thyroid disease or heart failure due to rapid ventricular rate
	Bradyarrhythmias rate	Heart failure due to low heart
	Previous myocardial infarction (e.g., Q waves), left ventricular performance	Heart failure due to reduced contractile tissue
	Low voltage	Pericardial effusion
	Left ventricular hypertrophy	Diastolic dysfunction
Complete blood count	Anemia	Heart failure due to or aggravated by decreased oxygen-carrying capacity
Urinalysis	Proteinuria	Nephrotic syndrome

	Red blood cells or cellular casts	Glomerulonephritis
Serum creatinine	Elevated in renal failure	Volume overload due to renal dysfunction
Serum albumin	Decreased	Increased extravascular volume due to hypoalbuminemia
T_4 and TSH (obtain only if atrial fibrillation, evidence of thyroid disease, or patient age >65)	Abnormal T_4 or TSH	Heart failure due to or aggravated by hypo/hyperthyroidism

SOURCE: From Konstam M, Dracup K, Baker D, et al. *Heart Failure: Management of Patients with Left-Ventricular Systolic Dysfunction. Quick Reference Guide for Clinicians No. 11.* AHCPR Publication No. 94-0613. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Human Services; June 1994.

The standard 12-lead electrocardiogram should be part of the routine evaluation. Pathologic Q waves can indicate previous myocardial infarction. Evidence of LV hypertrophy can be found in patients with aortic stenosis or chronic systemic hypertension. New atrial fibrillation in a patient with previously compensated heart failure may explain recent decompensation. The chest x-ray also provides information beyond radiographic pulmonary edema and pleural effusions. An enlarged cardiac silhouette is usually found in dilated cardiomyopathy or can be due to a large pericardial effusion. Taking note of the various chambers can provide insight into valvular involvement and can indicate the presence of right-sided heart failure.

The echocardiogram is the most important imaging tool for evaluating patients with symptoms of heart failure. The overall systolic function and chamber size can be evaluated quickly. Global LV dysfunction can be differentiated from the regional abnormalities more commonly found in ischemic cardiomyopathy. Valvular stenosis and incompetence can be defined and graded. Furthermore, mitral regurgitation can be evaluated to determine if it is a primary valvular problem or secondary to the LV dilatation and related to LV chamber enlargement. This information may provide insight into the potential benefit of mitral valve repair or replacement, as well as the type of surgical technique required. Importantly, diastolic function of the heart can be evaluated by echocardiography. Abnormalities of diastolic function are a component of all cardiomyopathies but are particularly important in patients with normal *systolic* function. Finally, dobutamine stress echocardiography can help to define ischemic and hibernating myocardium, which may be necessary when considering coronary revascularization. The use of coronary angiography in patients with heart failure, however, is still somewhat controversial. It should be strongly considered when there is angina.

Radionuclide imaging is sometimes preferred when evaluating patients with heart failure. It is perhaps more quantitative than echocardiography. Additionally, positron-emission tomographic (PET) scanning is useful in distinguishing nonviable myocardial scar from dysfunctional but viable myocardium (Table 20-12) when considering coronary revascularization.

METABOLIC EXERCISE TESTING

The addition of gas-exchange measurements to exercise stress testing creates a noninvasive test that provides a wealth of information and can be performed safely in a symptom-limited fashion in patients with heart failure.[235] In addition to the evaluation of potential ischemia and objective assessment of functional capacity, the patient's maximal oxygen consumption at peak exercise ($V(r)_{O_{2,max}}$) and anaerobic threshold can be evaluated.[236-239] As an initial evaluation, metabolic exercise testing can provide insight into the patient's functional disability and allow the physician to council the individual patient on physical limitations and rehabilitation. When a patient's maximal oxygen consumption is less than 50 percent of expected for age and body size and/or if the $V(r)_{O_{2,max}}$ is below 14 mL/kg per minute, the patient may be a candidate for heart transplant evaluation.[240,241]

CARDIAC CATHETERIZATION

Swan-Ganz (right-sided heart) catheterization is performed frequently in patients with heart failure. Even so, its use in this patient population remains a point of contention among experts in the field. In general, the diagnosis of heart failure can be made on physical examination. Prognosis also can be estimated reasonably by noninvasive means.[242] The major benefit of right-sided heart catheterization (RHC) resides in the ability of the physician to demonstrate hemodynamic changes in response to pharmacologic treatment. The primary use of RHC should be in patients with worsening heart failure requiring intravenous agents in an intensive care unit setting. Sometimes it is necessary to use RHC when LV filling pressure is uncertain and the patient is clearly deteriorating.

The need for coronary angiography in patients with heart failure is controversial. It should be strongly considered if angina is present. In a country where ischemic heart disease is rampant and post-myocardial infarction patients are surviving more frequently to develop ischemic cardiomyopathy, diagnostic coronary angiography is performed frequently. It may not be possible to distinguish clinically ischemic cardiomyopathy from nonischemic dilated cardiomyopathy. The prognosis of patients with heart failure is worse when there is underlying coronary artery disease and is related to the extent of coronary artery disease.[243]

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CONCLUSIONS

Heart failure is a complex clinical syndrome that is growing in magnitude as the population ages. It is difficult to define but relatively straightforward to diagnose. Heart failure implies underlying structural and functional changes in the heart that contribute importantly to the clinical syndrome. Although the molecular underpinnings of heart failure are still incompletely understood, the importance of pathophysiologic principles such as reduced preload reserve and enhanced sensitivity to afterload is now well recognized. Neuroendocrine and inflammatory responses are common in patients with heart failure and serve as important therapeutic targets. There is no single cause or unifying mechanism of heart failure. There can be a diversity of signs and symptoms, most of which can be evaluated at the bedside. The echocardiogram in conjunction with a careful history and physical examination remains the primary diagnostic test. Ancillary evaluation includes use of the chest x-ray, electrocardiogram, exercise test, and in some cases, cardiac catheterization with coronary angiography.

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Figure 20-3: Relationship between LV wall force and fiber length. Hypothetical contractile cycles have been portrayed for the normal and failing ventricle. In the normal heart, contraction starts at point *A*, LV pressure rises until the aortic valve is opened (point *B*), the ventricle empties (point *B* to *C*), and relaxation ensues. When arterial pressure (afterload) is reduced (e.g., to point *D*), ejection starts at point *D* and proceeds to point *E*, which increases stroke volume. When the ventricle fails, the fiber length in diastole is increased, and ventricular contraction starts at point *F*. With systolic contraction, ventricular pressure rises to point *G*, and with ventricular emptying, fiber length decreases to point *H*. With a similar decrease in the afterload, wall force only needs to reach point *I* when ventricular emptying occurs to point *J*. As a result, for the same relative change in afterload, the increase in shortening is greater in the failing ventricle (ΔH-J) than in the normal heart (ΔC-E).

Figure 20-4: Schema of the sequence of events in heart failure. An increased load or myocardial abnormality leads to myocardial failure and eventually to heart failure. This results in increased sympathetic activity, increased levels of renin-angiotensin-aldosterone, pulmonary and peripheral congestion and edema, and decreased cardiac output reserve. Endothelial dysfunction also occurs, with decreased endothelial-dependent vasodilatation and with increased plasma levels of endothelin-1, a very strong vasoconstrictor. See text for details.

Figure 20-5: Possible mechanisms by which overloading can cause progressive deterioration of the heart ("cardiomyopathy of overload"). Several mechanisms, including myocyte stretch, activate a growth response that initiates myocardial hypertrophy in the overloaded heart (*left*). The same growth response may also activate signal transduction systems that cause programmed cell death (apoptosis). The hypertrophic response to overload, by causing sarcomeres to be added in series, can also lead to cell elongation and so accelerate remodeling; the resulting increase in wall tension, along with the overload itself (*right*), increases cardiac energy expenditure that, in the overloaded heart, can accelerate myocyte necrosis. Reduced cardiac output activates neurohumoral responses (*center*), which, by increasing afterload and β-adrenergic stimulation of the heart, also increase cardiac energy expenditure. Because many mediators of the neurohumoral response to a fall in cardiac output promote myocardial cell growth, neurohumoral activation can also accelerate both apoptosis and remodeling.

Figure 20-6: Evolution of myocardial damage to left ventricular function and ultimate congestive heart failure. The syndrome of congestive heart failure is the end result of processes that evolve in response to initial myocardial damage and/or cardiac overloads. The initiating event may be myocyte loss, either segmental, as with acute myocardial infarction, or diffuse, as with idiopathic cardiomyopathies and myocarditis; systolic overload, such as hypertension or aortic stenosis; or diastolic overload, such as mitral regurgitation or aortic regurgitation. Major loss of myocytes may also stimulate the renin-angiotensin and adrenergic systems, which may contribute to ventricular and vascular remodeling. All of these overloads create an increased workload for the heart, as characterized by Laplace relationship, where tension (T) is equal to the product of pressure (P) and ventricular radius (r) divided by twice the wall of thickness (h). The initial adaptations to these overloads, termed *ventricular remodeling*, are an increase in both myocyte length and diameter as well as an increase in ventricular volume to maintain adequate stroke volume and hence cardiac output. If hypertrophy is adequate to normalize the tension load, a relatively steady state may be maintained. Myocytes continue to be lost as a function of aging per se, however, and this tends to lead to further myocyte hypertrophy and cardiac dilatation. Moreover, the aging process may be amplified by hypertrophy. Should there be a sudden increase in end-diastolic pressure within the ventricle, an added factor of relative myocyte slippage within the wall tends to occur, which may lead to a further decrease in myocytes across the ventricular wall, further increasing ventricular wall tension. This may create a downward spiral in which progressive cell loss leads to further ventricular remodeling and continued ventricular dilation. As noted above, the entire process of ventricular remodeling may occur

asymptomatically, and myocardial damage progresses to left ventricular dysfunction, which is characterized by an increasing diastolic volume and thus a reduced ventricular ejection fraction. Symptoms associated with congestive heart failure occur when decreased left ventricular reserve limits cardiac output response to exercise. As the process of heart failure evolves, abnormalities of endothelial function in the peripheral arterioles lead to reduced ability of the peripheral vasculature to dilate in response to metabolic need. As these abnormalities occur, abnormal skeletal muscle blood flow occurs in response to exercise and decreased exercise tolerance. In addition decreased renal perfusion leads to further activation of the renin-angiotensin-aldosterone system (RAAS), with increased aldosterone secretion and sodium retention. The combination of these two events leads to decreased exercise capacity and peripheral edema, important components of the symptom complex of congestive heart failure. Decreased cardiac performance promotes neurohumoral responses characterized by activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, leading to peripheral vaso-constriction and sodium accumulation. These factors feed back to increase the ventricular remodeling process and to amplify cardiac damage. Thus, initial myocardial damage progresses to ventricular dysfunction and ultimately to congestive heart failure. It is important to note that the myocardial damage and left ventricular dysfunction are often asymptomatic, and by the time symptomatic heart failure ensues, the disease process is far advanced. [Revised from LeJemtel TH, Sonnenblick EH. Heart failure and maladaptive processes: Introduction. *Circulation* 1993; 87(suppl VII):VII1-VII4. Reproduced with permission from the American Heart Association and the authors.]


Figure 20-7: Idealized plot of left ventricular volume versus time (*top*) and the rate of change of volume (*dV/dt*) versus time (*bottom*), such as might be obtained from contrast or radionuclide ventriculographic studies. The representative cardiac cycle begins at end diastole. Subsequent events as depicted by the bars in the center of the figure are (1) systole, during which left ventricular volume decreases to a minimum and *-dV/dt* reaches its maximum; and (2) diastole, the beginning of which is signaled by the opening of the mitral valve and the onset of left ventricular filling. Diastole has three distinct phases in normal individuals: (1) the rapid filling phase (RFP), during which the left ventricle fills rapidly but passively and the peak filling rate occurs; (2) diastasis (D), during which relatively little left ventricular volume change occurs; and (3) atrial systole (AS), in which active atrial contraction fills the left ventricle to its end-diastolic volume. The diastolic parameters that have been derived from such analysis are the peak filling rate, the time to peak filling rate (TPFR), the percent contribution of atrial systole, and the first third filling fraction. (From Labovitz AJ, Pearson AC. Evaluation of left ventricular diastolic function: Clinical relevance and recent Doppler echocardiographic insights. *Am Heart J* 1987; 114:836-849. Reproduced with permission from the publisher and authors.)


Figure 20-8: Schema of events in congestive heart failure leading to symptoms. Note that fatigue and other symptoms of limited cardiac output are primarily related to decreased ejection, whereas peripheral and pulmonary edema are related to Na+ and water retention from increased sympathetic tone and increased renin-angiotensin-aldosterone. See text for details.

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Part 3: HEART FAILURE
Chapter 21:

DIAGNOSIS AND MANAGEMENT OF HEART FAILURE

Authors: Thierry H. LeJemtel, Edmund H. Sonnenblick, William H. Frishman

The management of patients with chronic heart failure is increasingly complex, since congestive heart failure (CHF) represents the end result of many cardiovascular, pulmonary, and systemic diseases that require specific and aggressive therapy.[1-3] Moreover, ventricular dysfunction generally precedes clinical symptoms by months or years.[4] Thus, the initial aim of therapy is to treat the primary etiology and prevent or slow the progression of or even reverse left ventricular (LV) systolic dysfunction independent of symptoms. This goal most often is achieved on an outpatient basis. Once symptoms of CHF occur, their control becomes a primary focus. Ultimately, the severity of symptoms may require hospitalization with parenteral therapy. Overall, successful management of patients with CHF rests on in-depth knowledge and treatment of the processes responsible for ventricular dysfunction and ultimately the symptoms that evolve. Despite the diversity of the initial processes, three guiding principles remain central.

The first guiding principle in CHF management is the concomitant, continuous, and aggressive pursuit and treatment of the underlying disease or diseases that led to the development of CHF. For example, hypertension requires vigorous and adequate therapy. When CHF is due to obstruction of the coronary arteries, a demonstration of reversible myocardial ischemia, even in the absence of angina, can lead to a coronary revascularization procedure that in turn can lead to an improvement in myocardial function. Similarly, slowing the progression of coronary artery disease through the use of both antithrombotic and lipid-lowering therapies along with cessation of cigarette smoking is as important as is the treatment of the clinical symptoms of ischemic CHF.

The second guiding principle in managing patients with CHF is to define precisely the stage of the disease when therapy begins. The syndrome of CHF is a dynamic process, and the therapeutic goals and end points vary as the process evolves. Symptoms, even as judged by exercise testing,[5] do not correlate with the severity of ventricular dysfunction as judged by measurement of the ejection fraction.[6] Thus, symptoms should not be used to guide therapy in the early stages of the disease. Minimal serial measurement of the ejection fraction remains the guide to advancement of the primary diseases, and symptoms and their relief may not predict survival. Prevention of sudden death is an important therapeutic outcome in patients with asymptomatic or mildly asymptomatic LV systolic dysfunction. It may be a limited therapeutic goal in extremely symptomatic patients who are not candidates for cardiac transplantation or LV assist devices, in whom symptom relief becomes a primary concern.

The third guiding principle in managing patients with severe CHF is the recognition that a key determinant of successful therapy is the intensity of care; this requires frequent visits, in-home monitoring, and meticulous attention to management details such as diet, daily activity level, daily weight, and the doses of the medications being used, with an appreciation of their adverse effects.[7,8] The importance of this principle is illustrated by the careful approach that is required to both successfully initiate and increase the dosage of beta-adrenergic blockade therapy in patients with symptomatic LV systolic dysfunction.

To plan an appropriate therapy, an accurate clinical diagnosis is necessary, with an understanding of the pathophysiology involved. Details of diagnostic approaches are presented elsewhere (see

Chap. 20).

PREVENTION OR REVERSAL OF LV DILATATION AND HYPERTROPHY

Besides primary prevention of the processes that are associated with LV systolic dysfunction and the development of CHF (coronary artery atherosclerosis, hyperlipidemias, hypertension, diabetes), secondary prevention of LV dilatation has been achieved most successfully over the past decade by modulating heightened activity of the neurohumoral activity of the sympathetic and renin-angiotensin-aldosterone systems. As will be discussed, below deactivation of both systems has led to attenuation or reversal of the remodeling process that accompanies the syndrome of CHF. However, the extent to which these systems should be deactivated is still poorly understood, especially late in the syndrome of CHF. Of interest, the dissociation between LV systolic performance and functional capacity that is present at baseline in patients with CHF seems also to be observed during therapeutic interventions. Further, the substantial improvement in LV ejection fraction that frequently occurs during long-term beta-adrenergic blockade does not necessarily translate into improved functional capacity. Current therapeutic investigations regarding the progression of LV dilatation and hypertrophy are focusing on cytokine receptor antagonists and endothelin receptor antagonists.[9,10]

NEXT

Chapter 21: DIAGNOSIS AND MANAGEMENT OF HEART FAILURE

PATHOPHYSIOLOGY AND DIAGNOSIS OF CONGESTIVE HEART FAILURE

The dynamic process by which ventricular dysfunction evolves into CHF can be conveniently described in three phases[11] (Fig. 21-1). The clinical characteristics of each phase and its duration depend heavily on the specific primary etiology involved. Myocardial damage with massive myocyte loss and fibrotic repair may be rapid, as occurs with an acute transmural myocardial infarction or a viral myocarditis, or may evolve over years, as occurs with overloads resulting from systemic hypertension or valvular disease.[12,13] In the absence of overt clinical symptoms, such as chest pain with a myocardial infarction or sudden (flash) pulmonary edema, the initial damage may go undiagnosed. In this situation, a two-dimensional echocardiogram can be helpful in documenting the presence and extent of LV dysfunction and segmental wall motion abnormalities. Ventricular dilatation is not uncommon in largely asymptomatic patients.

The second stage in the evolution of heart failure involves an adaptation to myocardial damage termed *ventricular remodeling*. This involves myocardial hypertrophy in response to myocardium that is lost or overloaded and ventricular dilatation, which helps sustain cardiac output (Fig. 21-1). In general, heart failure begins with increased loading of the ventricle with pressure or volume or with loss of myocardium leading to ventricular dysfunction. In a sense, loss of myocardium, whether segmental as occurs with myocardial infarction or diffuse as occurs with cardiomyopathies, creates an overload for the myocardium in that less myocardium must maintain the work of the heart. Once an overload is created, the myocardium responds with changes in growth and architecture that constitute ventricular remodeling. This includes increases in myocyte length as well as lateral dimension. With an increased pressure load, myocytes respond by laying down more contractile units in parallel, thus increasing the lateral dimensions of the myocyte and its force potential. This form of hypertrophy tends to normalize the tension in the ventricular wall. When volume is increased, whether because of increased flow from an insufficient valve or increased diastolic filling pressure that results as a compensation for lost myocardium, myocytes elongate in order to maintain force and shortening. Acutely, this occurs within the limits created by the physiological lengthening of the sarcomere, i.e., the Frank-Starling length-tension curve. With a sustained diastolic load, sarcomeres are added in series, resulting in increased myocyte length. Since augmented diastolic volume itself results in increased ventricular wall tension [wall tension (T) = pressure (P) × dimension (r)/wall thickness (h)], lateral growth (hypertrophy) of myocytes commonly accompanies myocyte lengthening. In addition to hypertrophy of myocytes, other dynamic events occur in the myocardium.

Myocytes may be lost diffusely when excessive overloads occur through the process of apoptosis and focal necrosis with replacement fibrosis. With sustained diastolic loads, ventricular dilatation proceeds with not only marked myocyte lengthening but also with apparent displacement of myocytes or groups of myocytes one to the other, a process labeled *myocyte slippage*. While hypertrophy of myocytes is readily demonstrable, hyperplasia of myocytes also may be observed.[14,15] Taken together, hypertrophy, myocyte hypertrophy, further myocyte loss, and hyperplasia, along with ventricular wall restructuring, constitute ventricular remodeling. With systolic overloads, this generally is characterized by increased ventricular wall thickness with normal intraventricular volumes (e.g., normal ejection fraction). When the hypertrophy cannot sustain required systolic tension, whether because of a primary decrease in force production by a given myocyte[16] or because of loss of myocytes, ventricular dilatation occurs and a fall in the ejection fraction is observed. Generally, it proceeds silently unless it is heralded by an acute

myocardial infarction. Thus, except for clinical symptoms, such as dyspnea and exertion, that may reflect an increased diastolic filling pressure resulting from a thickened ventricular wall, ventricular remodeling generally progresses unobserved.

The factors that mediate progressive ventricular remodeling (hypertrophy) are both physical forces and hormonal factors (e.g., angiotensin). During this evolution of ventricular remodeling, neurohumoral activation occurs.[17] Activation of the sympathetic nervous system with parasympathetic withdrawal leads to tachycardia and peripheral vasoconstriction. Activation of the renin-angiotensin system causes further vasoconstriction and salt accumulation through stimulated aldosterone secretion. Both of these latter factors, along with excessive stretch of the myocardium, can lead to further myocyte loss, with fibrosis along with further myocyte hypertrophy, while ventricular dilatation may induce functional mitral and/or tricuspid insufficiency, creating an additional hemodynamic load (Fig. 21-2).[18]

The third phase in the evolution of heart failure evolves from these adaptive changes, with development of symptoms of CHF, characterized by decreased exercise tolerance, pulmonary and systemic congestion, and central and peripheral edema. The interval between the initiation of ventricular dysfunction and the onset of symptoms, during which ventricular remodeling occurs, may extend over a long period, but if the damage is related to an acute myocardial infarction, this period can be very short. With more chronic processes, such as those which occur with hypertension or idiopathic cardiomyopathies, this period may extend over months or years. Indeed, when patients were first identified with asymptomatic LV dysfunction in the Studies of Left Ventricular Dysfunction (SOLVD) trial (discussed below), their average ejection fraction was already reduced to 28 percent, indicating that extensive ventricular damage had already occurred (Fig. 21-3). At this point, exercise performance, as represented by peak oxygen consumption, was moderately reduced, but not to an extent that limited exercise performance or produced symptoms. Circulating norepinephrine was increased slightly, while plasma renin levels (slashed lines) were not, except when diureties had been administered (open bars). Once symptoms occurred, there was a progressive increase in circulating norepinephrine and plasma renin. A progressive decline in exercise capacity was documented as patients progressed from New York Heart Association (NYHA) class I to class IV. The reduction in exercise performance was relatively greater than the decrease in the ejection fraction. This relates to the finding that with inactivity, the capacity for peripheral vasodilatation is reduced, limiting skeletal muscle performance. Ventricular dysfunction may involve the left ventricle, the right ventricle, or both. In addition, such abnormalities may be amplified by overloads created by valvular insufficiency (e.g., mitral or tricuspid) or systolic overloads (e.g., aortic stenosis, arterial or pulmonary hypertension). Separating the effects of myocardial dysfunction from such imposed overloads is difficult. Moreover, functional mitral and/or tricuspid insufficiency resulting from ventricular dilatation imposes a further volume load on an already damaged myocardium.

Abnormalities of ventricular function can be usefully divided into problems of ventricular filling (diastole) and problems of ventricular emptying (systole). Even in the presence of normal systolic ventricular performance, abnormalities of ventricular filling, termed *diastolic ventricular dysfunction*, may be observed, and these abnormalities require specific diagnostic consideration (Fig. 21-4). This is characterized by an increased ventricular filling pressure for any end-diastolic volume (EDV) resulting from reduced compliance of the ventricle. Thus, with normal EDV and stroke volume (SV), filling pressures may be markedly increased, leading to signs of pulmonary congestion despite a normal ejection fraction. Such a situation may occur with LV hypertrophy, especially when associated with a rapid heart rate, which further limits the time for ventricular filling. It also can occur with an aging heart, where diffuse myocyte loss can occur with replacement fibrosis and reactive myocyte hypertrophy.[19]

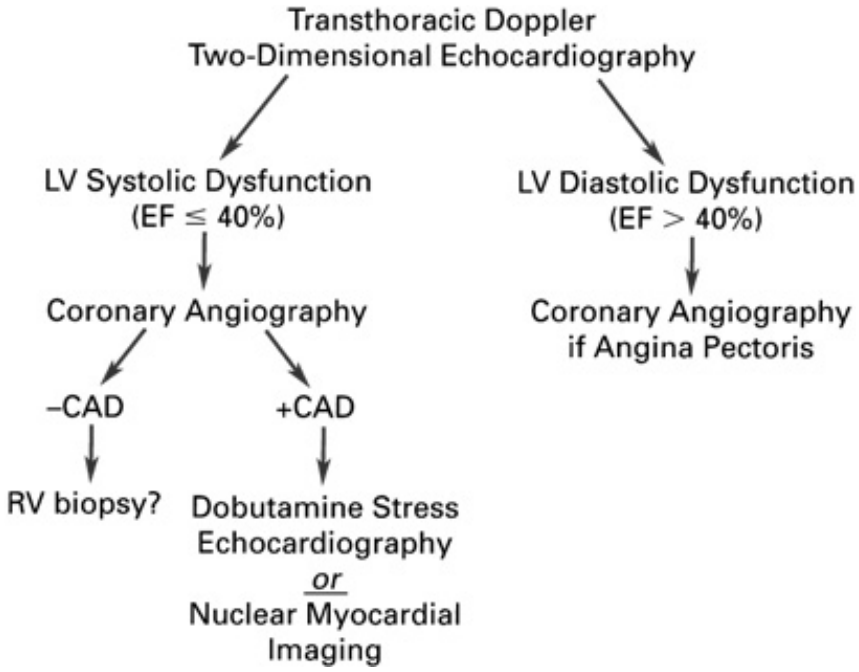

Figure 21-4: Evaluation of patients with congestive heart failure. Transthoracic Doppler and two-dimensional echocardiography provide a central modality to evaluate ventricular function and valvular abnormalities. Ventricular wall thickness and both end-diastolic and end-systolic volumes can be determined. With an ejection fraction (EF) more than 40 percent, coronary angiography is indicated in the presence of angina pectoris or evidence of significant ischemia. With an EF less than 40 percent, coronary arteriography is indicated since the underlying ischemic depression may be amenable to reperfusion by angioplasty or coronary bypass surgery. Nuclear imaging techniques are used to define viable ischemic myocardium, while stimulation of such myocardium with dobutamine or extrasystolic potentiation may indicate recoverable hibernating myocardium. Right ventricular biopsy may be indicated in the absence of coronary artery disease to rule out processes such as amyloid or sarcoid.

Systolic ventricular dysfunction is characterized by a reduced ability to generate pressure isovolumically and a decreased capacity to eject blood in systole. As is known from classic physiology, the SV depends on the diastolic volume as well as the afterload, which is directly related to the arterial pressure. If the afterload is reasonably normal, there is a linear relation between SV and EDV, and the resultant slope (SV/EDV) is termed the *ejection fraction*. If the slope of the relation linking end-systolic pressure and LV volume is reduced, as occurs when the ventricle is depressed, the SV at any EDV is reduced, resulting in a decreased ejection fraction. If the afterload is approximately normal, this reduced ejection fraction can serve as a measure of *reduced systolic ventricular performance*. Since the extent of shortening of myocardium is reduced as afterload is increased, an increased systolic ventricular pressure can by itself reduce SV and hence tend to decrease EF, as can occur in severe aortic stenosis. Similarly, with severe mitral insufficiency, which decreases afterload through a low-impedance pathway into the left atrium, an increased SV tends to occur, yielding an artificially increased ejection fraction. Thus, with these considerations in mind, the ejection fraction can provide a useful indicator of systolic ventricular performance.

Although complex indices of systolic ventricular function have been described on the basis of myocardial muscle function,[20] the measurement of the ejection fraction has served as the clinical standard, whether determined noninvasively by echocardiography and nuclear imaging techniques or invasively with angiography. In addition to an overall depression of myocardial function, focal abnormalities of ventricular wall motion, described in terms of hypokinesis and akinesis, may produce major alterations in overall LV function, as seen in coronary artery disease. While a segment of the LV wall may be replaced by fibrotic scar, focal abnormalities of contraction may

occur in viable myocardium when coronary perfusion is transiently reduced, leading to a prolonged decrease in contraction; this is termed *stunning*. Alternatively, with a sustained reduction in coronary blood flow that is still adequate to sustain viability, contraction can be persistently reduced or absent; this is termed *hibernation*.[21,22] These important alterations can occur simultaneously in a given patient and are hard to separate.[22] Defining these abnormalities in coronary heart disease with heart failure is extremely important, since reversal of transient or persistent ischemia with vascular reperfusion may be vital for restoring segmental contraction and improving overall ventricular function.[21,23] Various techniques have been employed to identify such tissue, including echocardiographic studies using a catecholamine stress[24-28] and angiographic studies using nitroglycerin[29] or extrasystolic potentiation after a premature ventricular contraction.[21,30,31]

Once ventricular dysfunction is manifest, abnormalities of reflex control of the circulation ensue. As CHF progresses, decreased baroreceptor sensitivity occurs with augmented sympathetic tone and reduced parasympathetic tone (Fig. 21-2).[32] This results in an increase in heart rate along with reduced beat-to-beat heart rate variability and loss of the Valsalva overshoot. These changes also help establish the diagnosis of heart failure.

With reduced ventricular function, exercise performance tends to be reduced as measured by a reduced maximum O_2 uptake on a treadmill (VO_2). However, this reduction in exercise performance does not always correlate with a reduced ejection fraction,[5] since it also reflects the *training* state of the peripheral circulation.

Clinical Assessment in Directing Therapy

Clinically, the initial diagnosis of heart failure is made by the patient's history, physical findings on clinical examination, and data obtained from routine chest x-rays and electrocardiography (ECG). The history obtained from patients tends to reflect pulmonary or systemic congestion or both, with complaints of shortness of breath, initially with effort and on lying down, generally associated with easy fatigability and, commonly, peripheral edema. Common factors in the history often include diabetes mellitus, ischemic events, and hypertension. On physical examination, peripheral vasoconstriction and tachycardia are common, along with the presence of pulmonary rales and physical signs of pleural effusion. Cardiac findings may include a fourth heart sound (S_4), reflecting a stiffened or hypertrophied ventricle, and a third heart sound (S_3), reflecting more profound LV failure. Murmurs can be auscultated that may relate to valvular organic abnormalities, although functional mitral and tricuspid insufficiency can occur as a function of LV and/or right ventricular (RV) dilatation per se. Peripheral venous engorgement and an enlarged liver, along with peripheral edema, are detected as RV failure ensues. If RV failure is severe, clinical symptoms associated with LV failure, such as severe shortness of breath, actually may be lessened.

Precipitating factors for developing CHF should be looked for, such as anemia, infection, dietary indiscretion, acute arrhythmias (especially atrial fibrillation), poor compliance with treatment, pulmonary embolism, and occult myocardial infarction.

Nuclear imaging techniques, computed tomography, and magnetic resonance imaging have been useful in assessing ventricular volume, shapes, and motion and have provided an excellent assessment of ventricular function. However, two-dimensional echocardiography provides much of the necessary information in a practical and cost-effective manner and remains the clinical standard. Its accuracy and usefulness depend on the care expended in performing the procedure and the professional oversight utilized in both detecting and interpreting the findings that are obtained. Echo-Doppler examination not only provides information about systolic and diastolic volumes, and thus ejection fraction, but also allows for the evaluation of valve structure and function, including regurgitation and stenosis. Reasonably accurate measurements of gradients,

and thus valvular orifices, can be made, and this can help direct therapy.

In defining the etiology of heart failure, segmental wall motion abnormalities with hypokinetic and contralateral hyperkinetic segments suggest an ischemic etiology. Indeed, after an acute myocardial infarction, a two-dimensional echocardiogram obtained within a few days is essential. The finding of ventricular dilatation within a few days of an acute anterior wall infarction tends to predict progressive LV dilatation with a falling ejection fraction. Among patients sustaining an anterior wall infarction without initial ventricular dilatation, approximately one-third will show ventricular dilatation at 3 months. In contrast, ventricular dilatation rarely occurs after inferior wall infarctions, except when the region involved is large, extending from the base of the heart to the apex. After an acute myocardial infarction,[33] LV enlargement, as measured by two-dimensional echocardiography, is associated with an increased incidence of adverse cardiovascular events. When LV diastolic volumes of patients with an infarction are divided into quartiles, patients in the fourth quartile have a mortality rate of 45.5 percent, while patients in the third quartile have a mortality rate of 21.1 percent and those in the first and second quartiles both have a mortality rate of 16.7 percent.[34] If LV dilatation occurs much later, however, two-dimensional echocardiography will not differentiate between the causes of heart failure, i.e., coronary artery disease or other etiologies. Moreover, patients with a primary cardiomyopathy also may exhibit segmental wall motion abnormalities. As was noted above, stimuli that elicit latent contraction, such as low-dose dobutamine, stress, and premature ventricular contractions, may help identify patients with dilated left ventricles and severe coronary artery disease who also have *hibernating* or *stunned* myocardium.[22,35,36]

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Chapter 21: DIAGNOSIS AND MANAGEMENT OF HEART FAILURE

THE TREATMENT OF CONGESTIVE HEART FAILURE

As was noted initially, the treatment of heart failure requires close attention to both the primary etiology and the relief of symptoms while attempting to reduce the risk of death from the process. This includes vigorous control of hypertension, if present, and an evaluation for treatment of myocardial ischemia. As was noted above and discussed further relative to surgical approaches to heart failure, noncontractile but viable myocardium, whether resulting from stunning or from hibernation, requires definition with consideration of coronary reperfusion.[22,37] Valvular disease that imposes an excessive volume or pressure overload must be considered relative to the need for surgical correction. For example, critical aortic stenosis with heart failure is an urgent indication for aortic valve replacement, when possible, not medical therapy. To those ends, there is a multifactorial approach to therapy[38] that varies with the etiology and stage of the heart failure process (Fig. 21-5).

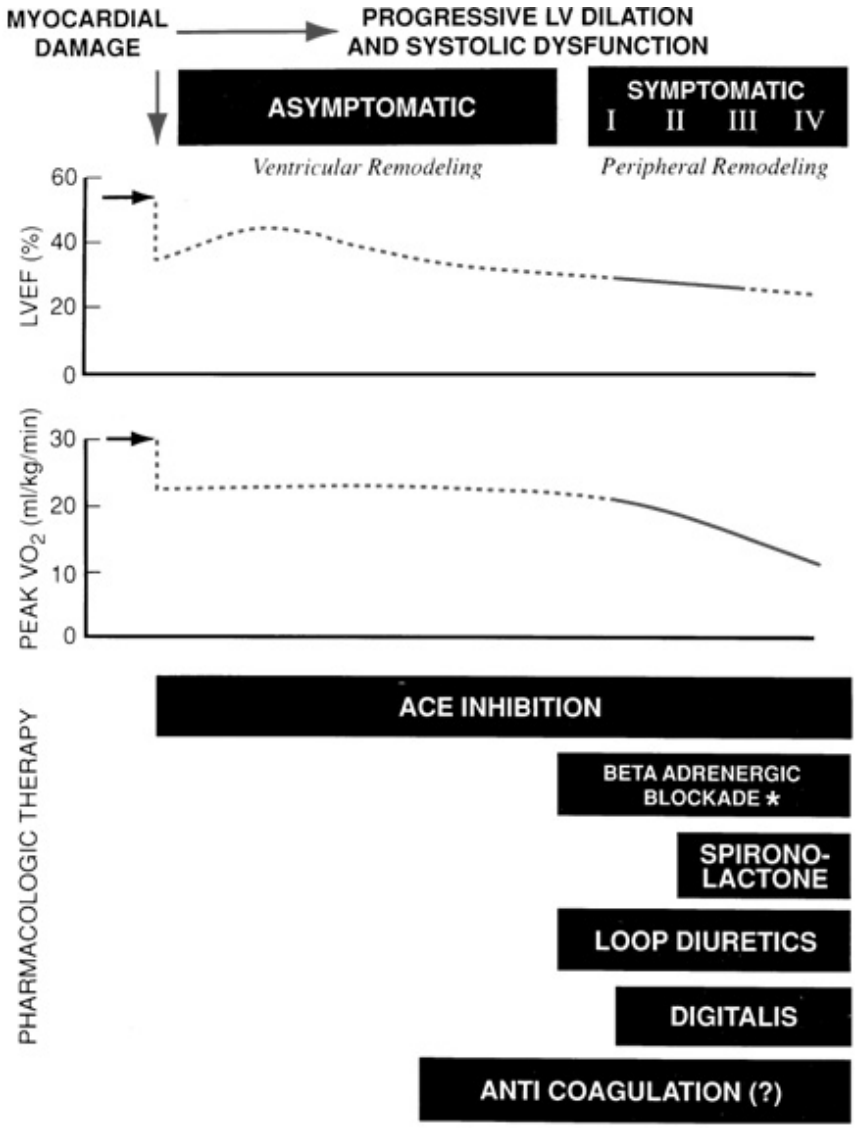

Figure 21-5: figuremeasure taged use of therapeutic agents in heart failure. Initial approaches include control of factors that may cause progression of heart failure and/or augment its manifestations.

Hypertension requires control. Unanticipated tachycardia may augment oxygen needs while reducing the time in diastole for coronary flow to take place. The reduction in the diastolic time can lead to marked elevations of left ventricular (LV) diastolic pressure as well as increased ischemia. Moreover, atrial fibrillation will deprive ventricular filling of the "atrial kick" and lead to further elimination of diastolic pressures. These considerations are of special importance with ventricular hypertrophy and resultant diastolic dysfunction. During the "remodeling" phase of ventricular failure, the patient may be asymptomatic. Nevertheless, inhibition of the renin-angiotensin system is indicated to reduce the rate of ventricular remodeling and slow ventricular dilation. Beta-adrenergic blockade reverses ventricular remodeling and improves survival in patients with class II to III symptoms. * Reflects the inconsistent effects of beta-adrenergic blockade in patients with class IV symptoms. In the Copernicus trial, carvedilol was beneficial, while in the BEST trial, bucindolol appears to be detrimental. Once symptoms ensue, loop diuretics generally are needed for fluid control. Digitalis glycosides also are indicated for neurohumoral benefits in reducing sympathetic tone and enhancing parasympathetic tone while providing modest inotropic support. These actions appear to improve morbidity without necessarily altering mortality.

General Principles in the Pharmacologic Treatment of CHF

Therapy is tailored to the phase of heart failure. In the initial phase, where ventricular damage is a primary concern, identification of etiology is essential with appropriate therapy. Thismight be termed treatment of ventricular dysfunction and its causes. Hypertension must be controlled aggressively. Even mild hypertension should be treated in the presence of the diabetic state to attempt to prevent large- and small-vessel coronary disease. Overt or silent ischemia should be identified and treated. Early inhibition of the neurohumoral responses to initial cardiac damage with both beta-adrenergic blockade and inhibition of the activated renin-angiotensin-aldosterone system (RAAS) requires consideration. This is particularly the case as one moves into the phase of ventricular remodeling in which inhibition of progressive ventricular damage is essential. It is important to remember that what bothers the patient, such as edema and shortness of breath, is generally not life-threatening, while therapy that may reduce mortality, such as beta blockers, may do nothing to alleviate symptoms. Thus, both agendas must be addressed. In general, mortality has been used to measure efficacy. Improvement in symptoms has been difficult to assess, and a combined end point of mortality and the need for hospitalization has been useful. As the syndrome of CHF ensues, pharmacologic treatment is directed to three demonstrable hemodynamic end points: (1) reducing volume overloads and maintaining a stable volume state, (2) reducing preload and afterload to enhance ventricular performance, and (3) improving ventricular contractility when necessary. An additional pharmacologic aim is to reduce heightened neurohumoral activity, which is seen in patients with heart failure, with the hope of limiting abnormal loading created by these systems and preventing the progression of the heart failure process. The ultimate aim is to reduce morbidity and perhaps extend life.

INACTIVATION OF THE RENIN-ANGIOTENSIN SYSTEM AND ALTERNATIVE THERAPIES

Neurohumoral activation plays an important role in the progression of the syndrome of chronic LV systolic dysfunction/heart failure. After initial increases in sympathetic tone and decreases in parasympathetic tone, the renin-angiotensin system is activated.[39] This generally occurs when diuretics are initiated or, in their absence, with the onset of the clinical symptoms of CHF. With release of renin from the kidneys, angiotensinogen, which is circulating in the blood, is converted to inactive angiotensin I, which in turn is converted to the highly active angiotensin II by a converting enzyme that is ubiquitously located along vascular walls. Angiotensin II in turn stimulates aldosterone secretion by the adrenals, which results in sodium accumulation and also produces marked arteriolar constriction, which augments peripheral vascular resistance. Both phenomena, which increase ventricular preload (filling pressure) and afterload (systolic pressure), contribute to the clinical picture of CHF. In addition to these actions, angiotensin II serves as a growth factor, adding to myocardial hypertrophy and apparently fostering fibrosis. It also may contribute to subtle myocyte loss by enhancing apoptosis.[40]

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The initial impetus toward the use of angiotensin-converting enzyme (ACE) inhibitors for the treatment of patients with CHF was the desire to duplicate with one agent the hemodynamic effects produced by the combination of nitrate and hydralazine.[41] In the late 1970s, combined administration of nitrate and hydralazine was shown to enhance LV systolic performance and alleviate symptoms in patients with

CHF.[42] In severe heart failure, this resulted from the combined action of nitrates to reduce diastolic filling pressures (preload) and hydralazine to reduce peripheral arterial resistance (afterload). The result was reduced filling pressures accompanied by an increased cardiac output. Initial hemodynamic studies with captopril (Table 21-1) demonstrated substantial lowering of ventricular filling pressures, a modest increase in cardiac output, and a reduction in systemic arterial pressure without tachycardia.[41] In a landmark randomized, placebo-controlled study, the administration of captopril for 3 months produced sustained improvement in LV performance, improvement in the functional class, and increased duration of maximal exercise,[43] resulting in U.S. Food and Drug Administration (FDA) approval of captopril for the treatment of CHF. In the first weeks of the study, exercise duration also improved in patients on placebo. This initial improvement in exercise duration on placebo probably is due to familiarization with exercise equipment and increased patient motivation.

Several aspects of long-term therapy with ACE inhibitors in patients with CHF are worthy of mention:

1. The magnitude of the initial hemodynamic change does not predict the long-term clinical response. Some of the beneficial effects of lower ventricular filling and systemic arterial pressures may relate to increased levels of kinins, resulting from decreased enzymatic destruction that also is mediated by ACE inhibitors.[44] Whether sustained elevation in kinin levels exerts long-term clinical benefits is uncertain. The dissociation between acute hemodynamic effects and long-term clinical benefit suggests that the mechanisms underlying the benefits of ACE inhibitors may be related to structural and functional changes in the peripheral vasculature. Improvement in peak aerobic capacity (VO_2) has been directly related to enhanced perfusion of skeletal muscle at maximal exercise.[45] The exact mechanisms that mediate the benefits of ACE inhibitors on the vasculature are poorly understood. The time differential between the acute, immediate hemodynamic and the more delayed functional benefits suggests that the cellular alterations produced by ACE inhibitors, rather than just the relief from heightened vasoconstriction, may mediate the clinical benefits. Improvement of vascular endothelial function, which is reversibly depressed in CHF, as through the response to local administration of acetylcholine, is so far the best documented vascular effect of ACE inhibitors in patients with CHF.[46,47] Improved vascular endothelial function during long-term ACE inhibition may be mediated in part via the kinins pathway. Whether lowering tissue levels of angiotensin II (AII) affects vascular smooth muscle structure and function is unknown. However, AII is a smooth muscle growth factor, and its reduction may reduce smooth muscle mass and thus affect vascular tone and compliance.[48]
2. The impact of long-term ACE inhibition on LV systolic function appears to be modest. Thus, the absolute increase in LV ejection fraction observed in large multicenter randomized trials ranged from 1 to 3 absolute units.[49] With long-term use of ACE inhibitors, LV end-diastolic and systolic volumes are only modestly altered and somewhat disparate in patients with CHF. Initial reduction in LV end-diastolic volume during long-term ACE inhibition appears to be related largely to decreased loading of the failing ventricle rather than structural cardiac alterations, since LV volume increases within a few days after the withdrawal of ACE inhibition.[50] More recently, LV end-diastolic volume was noted to increase steadily during long-term ACE inhibition in patients with CHF while remaining unchanged in patients treated with AII type 1 receptor blockade (ARB) in addition to ACE inhibition.[51] However, persistent diastolic unloading with these agents may reduce the progression of dilatation.
3. Long-term use of ACE inhibitors has significant natriuretic effects. From a hormonal point of view, a decrease in AII tends to reduce aldosterone secretion, with a resultant lessening of sodium accumulation and a reduced potassium loss. However, aldosterone synthesis is modulated by factors other than AII, such as potassium levels, corticotropin, and endothelin, among others.[52] During long-term treatment with ACE inhibitors, levels of aldosterone remain elevated in up to 38 percent of patients of with CHF.[53] Thus, one cannot assume that long-term ACE inhibition alone can reliably lower plasma aldosterone levels. Increased diuresis with the consequent reduction in the dose of loop diuretics has been reported during long-term therapy with captopril.[54] This natriuretic effect of captopril may be related to the increase in renal blood flow demonstrated after the administration of captopril, despite the concomitant reduction in systemic arterial pressure.[55]

A major impetus for an increasing use of ACE inhibitors in patients with LV systolic dysfunction and CHF derives from the experimental work of Pfeffer and associates.[56] Ligation of the left anterior descending

coronary artery in rats resulted in a large infarction and progressive ventricular dilatation. Long-term therapy with captopril reduced LV dilatation and shifted the pressure-volume curve favorably to the left. The process of LV enlargement in those experiments was largely dependent on the size and location of the myocardial infarct as well as the patency of the infarct-related artery. It was theorized that by lowering LV diastolic wall stress, long-term therapy with ACE inhibitors could favorably alter the loading conditions of the left ventricle and reduce LV enlargement, thus enhancing the survival of patients after a myocardial infarction.[57] A short-term trial in humans with acute myocardial infarction suggested that ventricular dilation could be attenuated with ACE inhibition (captopril).[58] A subsequent study with postinfarction patients with an ejection fraction less than 40 percent demonstrated a 21 percent reduction in mortality after 4 years.[58a] Of note, a similar reduction in reinfarction was observed.

In addition to the work of Pfeffer and associates,[56] several large survival trials were launched and completed exploring the effects of ACE inhibitors in patients with heart failure.[59] Beneficial effects of an ACE inhibitor on mortality in patients with CHF was first demonstrated with enalapril. The results of the Cooperative North Scandinavian Enalapril Study (CONSENSUS) involving 253 patients with symptoms compatible with NYHA functional class IV showed that after an average follow-up of 188 days, 68 of the 126 patients randomized to placebo died, while only 50 of 127 patients randomized to enalapril died, a reduction in mortality of 27 percent ($p = .003$).[60] The entire reduction in total mortality was found to occur among patients with progressive heart failure, whereas no difference was observed in the incidence of sudden death. After the initial dose of enalapril was reduced from 10 to 2.5 mg, only 3.2 percent of the patients could not tolerate enalapril because of symptomatic hypotension.

The second Veterans Administration Cooperative Vasodilator Heart Failure Trial (V-HeFT II) randomized 804 men with peak aerobic capacity <25 mL/kg per minute to enalapril or to hydralazine plus isosorbide dinitrate. At 2 years, the mortality was lower in the enalapril group than it was in the hydralazine plus isosorbide dinitrate group (18 percent versus 25 percent, $p = .016$; reduction in mortality, 28 percent).[61] The reduction in mortality, particularly in patients with less severe symptoms (NYHA classes I and II), was attributable to a reduction in sudden death. V-HeFT II also confirmed previous findings that treatment with long-term ACE inhibitor was associated with a minimal absolute increase in the LV ejection fraction, i.e., 2 percent with enalapril and 45 percent with hydralazine plus nitrate.

The SOLVD Study assessed the effect of ACE inhibition with enalapril in patients with symptomatic and asymptomatic LV systolic dysfunction as evidenced by an ejection fraction <35 percent.[62,63] Two thousand five hundred sixty-nine patients who had CHF as defined by the need for therapy and a mean ejection fraction of 24.8 percent were enrolled in the treatment arm of SOLVD and randomized to placebo or enalapril. Over a period of 48 months, 510 of the 1284 patients randomized to placebo died, while only 452 of the 1285 patients randomized to enalapril died [risk reduction, 10 percent; 95 percent confidence interval (CI), 5 to 26 percent; $p = .0036$]. The chief difference in mortality was due mostly to progressive heart failure, as the number of deaths classified as arrhythmogenic without worsening CHF was similar in the placedo and enalapril arms. Four thousand two hundred twenty-eight patients who were not treated for CHF and thus were considered asymptomatic had a mean ejection fraction of 28 percent and were enrolled in the prevention arm of SOLVD. Over a period of 37.4 months, 334 of the 2117 patients randomized to placebo and 313 of the 2111 patients randomized to enalapril died (risk reduction, 8 percent; 95 percent CI, 8 to 21 percent; $p = .030$). In the placebo group, 818 patients developed heart failure or died compared with only 630 patients in the enalapril group, i.e., 38.1 versus 29.8 percent (risk reduction, 29 percent; 95 percent CI, 21 to 30 percent; $p < .001$).

Of great note was a common effect of enalapril in both the treatment and prevention arms of the SOLVD trials to reduce the incidence of recurrent myocardial infarction, i.e., 288 in the enalapril group versus 362 in the placebo group (risk reduction, 23 percent; 95 percent CI, 11 to 34 percent; $p < .001$).[64] Similarly, 499 patients in the enalapril group and 595 in the placebo group developed unstable angina (risk reduction, 20 percent; 95 percent CI, 9 to 29 percent; $p < .001$). Whether this reduction in the incidence of acute coronary events in patients with coronary artery disease is associated with long-term ACE inhibition with enalapril or is related to the improvement in endothelium vasomotor dysfunction, which was subsequently demonstrated with quinapril, another ACE inhibitor, is not known.[46,65] It is also possible that ACE inhibition plays a role in stabilizing atherosclerotic plaques, perhaps by reducing smooth muscle growth. Importantly, as is noted below, the same considerations have been raised by the Survival and Ventricular Enlargement (SAVE) trial of ACE inhibition in the depressed heart after myocardial infarction.

The impetus for an earlier use of an ACE inhibitor in patients with LV dysfunction and heart failure also has been provided by the results of the Heart Outcomes Prevention Evaluation (HOPE) study.[66] Therapy with ACE inhibitors traditionally has been recommended in patients with CHF related to LV systolic dysfunction, as defined by an LV ejection fraction <40 percent (to 35 percent) in most clinical trials. By demonstrating that long-term administration of ramipril, a tissue-specific ACE inhibitor, improved life expectancy in patients with vascular disease or diabetes and one cardiovascular factor who did not have any evidence of LV systolic dysfunction, the findings of the HOPE trial indirectly but strongly argued for the use of ACE inhibitors at a pre-LV dysfunction stage in patients with clinical conditions known to be associated with the development of chronic heart failure.[67] These results also emphasize the vascular benefits of ACE inhibitors, since other morbid vascular events, such as stroke, were reduced significantly. Since the conditions that lead to LV systolic and diastolic dysfunction are similar, the early use of ACE inhibitors is warranted in patients with both LV systolic and diastolic dysfunction. Besides the already mentioned effects of ACE inhibitors on skeletal muscle vasculature and the prevention of subsequent acute coronary events by ACE inhibitors in patients enrolled in the SOLVD and SAVE trials, the results of the HOPE trial point out the importance of the vascular effects of ACE inhibitors in mediating their clinical benefits. To a large extent, in the majority of patients with CHF, deterioration of LV function is related to progressive systemic and coronary vascular processes that now can be altered favorably by ACE inhibitors. The vascular benefits of ACE inhibitors appear to be additional to those provided by aspirin, beta-adrenergic blockers, and lipid-lowering agents.[66]

The fact that ramipril exerted vascular benefits in patients who were receiving aspirin is of particular importance, as the attenuations of the hemodynamic effects of ACE inhibitors have been reported in patients receiving aspirin.[68] The negative interaction between ACE inhibitors and aspirin presumably is due to interference with kinin-mediated synthesis of prostaglandin. The loss of benefit from ACE inhibitors noted in patients treated with aspirin in some large trials contrasts with the findings of the HOPE trials and others.[69] In view of the importance of the kinin pathway in vascular biology, one would expect that if a negative interaction exists between ACE inhibitors and aspirin, it would have been observed in patients enrolled in the HOPE trial. Whether the use of ticlopidine or clopidogrel is preferable in a subset of patients with LV dysfunction, CHF, and renal insufficiency who are treated with ACE inhibitors is unknown.

By preventing events related to myocardial ischemia and the progression of atherosclerosis, ACE inhibitors are becoming the cornerstone of both treatment and prevention in patients with LV dysfunction, independent of the presence or absence of symptoms. Whether patients should be treated for vascular protection with ACE inhibitors other than those specifically approved for the treatment of LV systolic dysfunction and CHF is unclear. So far no study has included clinical end points to show an advantage of one ACE inhibitor over another. Tissue-specific ACE inhibitors appear more apt to exert vascular benefits than do ACE inhibitors with low tissue specificity.[47] Tissue specificity is probably most relevant at low doses of ACE inhibitors; at maximally recommended doses of ACE inhibition, tissue specificity is less likely to be relevant. Overall, in several clinical trials and in daily practice the dose of ACE inhibitors is strikingly low.[62,63] The patients randomized to ACE inhibition in the SOLVD trial received only 11 mg of enalapril daily.[62] Several small studies and one large study [Assessment of Treatment with Lisinopril and Survival (ATLAS)] randomized patients to 2.5 to 3.5 mg or to 32.5 to 35 mg of lisinopril and showed that high doses of ACE inhibitors produce greater hemodynamic and clinical benefits.[70] Moreover, recent data suggest that even what is currently considered a maximal dose of ACE inhibitors may in fact be insufficient to completely block formation of AII via the ACE pathway, independent of the possible contribution of enzymatic pathways other than ACE to the generation of AII.[71] Thus, every effort should be made to increase the dose of ACE inhibitors to the maximally recommended or tolerated dose in every patient with LV systolic dysfunction and CHF. Unfortunately, this practice is not followed routinely.

In view of the clear benefits observed, all patients with documented LV dilatation should be treated with ACE inhibitors. The only patients with LV dysfunction who should not be treated with ACE inhibitors are pregnant women, patients with documented angioedema or anuria during earlier exposure to ACE inhibitors, and patients with severe bilateral artery stenosis. The benefits of ACE inhibitors have not been looked for in patients with serum creatinine levels >2.5 mg/dL, since those patients have been excluded from clinical trials. The important effects of ACE inhibitors on cardiovascular protection that are independent of any renal effects argue in favor of a trial of ACE inhibitors in patients with CHF with severe chronic renal insufficiency as defined by a serum creatinine level >3.0 mg/dL. However, patients with

serum levels of creatinine >3.0 mg/dL require careful follow-up, including daily monitoring of renal function after the initiation of ACE inhibitors at the lowest possible dose. Since inhibition of AII production leads to dilatation of the efferent artery of the glomerulus, a decrease in glomerular perfusion pressure occurs and a modest rise in serum creatinine (0.5 to 1.9 mg/L) is anticipated. This poses no problem unless the creatinine continues to rise, in which case ACE inhibition needs to be reduced. Indeed, in the presence of diabetes, renal protection is afforded by ACE inhibition, and the rise in creatinine, which is reversible, does not reflect ACE inhibitor-induced renal damage.[72] Moreover, ACE inhibitors that are in part excreted by the liver are preferable in this clinical situation. Overall, it is always recommended to avoid prescribing nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with CHF, but this is particularly important in patients with decreased renal function. Renal function is likely to deteriorate further after the initiation of ACE inhibitor therapy in patients treated with NSAIDs. Patients with plasma levels of potassium >5.0 mmol/L at baseline, particularly if they are diabetic with renal tubular acidosis, require daily measurement of electrolytes and renal function at the initiation of ACE inhibitor therapy.

A potential drug-drug interaction with aspirin and ACE inhibitors has been described, with a potential loss of the protective effects of ACE inhibition on patient survival in heart failure. However, this finding has not been substantiated in recent analyses of large clinical data bases.[69]

ALTERNATIVES TO ACE INHIBITORS

Angiotensin II Receptor Antagonists

Several ARBs are approved by the FDA for the treatment of hypertension (losartan, valsartan, irbesartan, candesartan, telmisartan and eprosartan) (Fig. 21-6). Although trials are in progress involving the use of ARBs alone or in combination with ACE inhibitors in heart failure, none have been approved for this purpose. The first comparison of ACE inhibition with captopril (150 mg daily) and ARB (losartan 50 mg daily) was undertaken in 722 patients with CHF who were over 65 years old. The results suggested that losartan may be preferable to captopril.[73] The rate of death and hospitalization for heart failure was 9.4 percent in patients randomized to losartan and 13.2 percent in patients randomized to captopril (risk reduction 32 percent; 95 percent CI, 4 to 55 percent, $p = .075$). The results of ELITE I were not confirmed by a subsequent study of identical design that included over 3000 patients, ELITE II.[74] In fact, while the number of deaths or hospitalizations was similar during the first 12 months of the study, thereafter fewer patients randomized to captopril died or were hospitalized for heart failure compared with patients randomized to losartan. Thus, the results of ELITE II failed to confirm the hypothesis derived from ELITE I, suggesting that ARBs may be superior to ACE inhibition for the treatment of patients with CHF. Of note, the design of ELITE II and the number of patients studied do not allow one to conclude that the two interventions are equal, based on a lack of statistical difference between the number of events noted in patients randomized to captopril and that in patients randomized to losartan. The ELITE II trial also must be viewed as inconclusive since there remains a question of adequate dosage and, as noted below, the potential for the concomitant use of ACE inhibition and ARBs.

The present use of ARBs for the treatment of CHF is limited to patients who experience intolerable cough or angioedema while receiving ACE inhibitors. Patients who cannot tolerate ACE inhibitors because of worsening renal function or hyperkalemia are likely to experience similar side effects with ARBs.

Another potential use of ARBs for the management of CHF is to counteract the attenuation of the benefits of ACE inhibition that may occur with time, a phenomenon often referred to as *ACE escape*. After long-term (1 year) ACE inhibition, plasma AII levels rise above initial values and LV antiremodeling and the decrease in norepinephrine levels effects attenuate.[75-77] Whether this is due to ACE inhibition becoming partial with time or whether AII is generated via pathways other than the converting enzyme is controversial.[78] Independent of the underlying mechanisms that mediate ACE escape, the addition of ARB to ACE inhibition negates the detrimental effects of elevated levels of tissue and circulating angiotensin.[79]

Several experimental and small studies have clearly demonstrated the added benefits of combined ARB and ACE inhibition on LV performance, functional capacity, and safety.[80-84] The safety of combining ARB and ACE inhibition has been well documented in the Valsartan Heart Failure Trial (Val-HeFT), which has safely randomized 4000 patients treated with adequate doses of ACE inhibitors to 320 mg daily of valsartan or to placebo. The results of Val-HeFT are not yet known, but enrollment and maintenance into the trial

were uneventful. The addition of ARBs to ACE inhibitors is extremely well tolerated even in patients who do not tolerate high doses of ACE inhibitors because of symptomatic hypotension.[82] This may be explained by the fact that ARBs are specific vasodilators that lower vascular resistance primarily to essential organs such as the heart, brain, and kidneys. In contrast, as a result of the concomitant increases in kinin levels, ACE inhibitors are also nonspecific vasodilators that lower vascular resistance to cutaneous tissues and splanchnic beds.[85] In addition, ARBs are associated with a greater improvement in plasma fibrinolytic parameters than that achieved by ACE inhibitors.[86] Whether the beneficial effects of combined ARB and ACE inhibition on functional capacity and LV performance and dimensions will translate into added benefits in life expectancy over those provided by ACE inhibition alone is being evaluated in the Val-HeFT trial with valsartan and the CHARM trial with candesartan.

Other Vasodilators

Vasodilator agents may be used as adjunctive therapy in the management of heart failure. The combination of hydralazine and isosorbide dinitrate is an alternative therapy when ACE inhibitors are contraindicated or cannot be tolerated. Daily doses of hydralazine up to 300 mg in combination with isosorbide dinitrate 160 mg in the presence of cardiac glycosides and diuretics probably have some effect in reducing mortality in patients with chronic heart failure but not in reducing hospitalization for heart failure.[87] At these doses, the combination increased exercise performance more than enalapril did.[61] The effects of hydralazine and nitrates, alone or in combination, when added to ACE inhibitors are unknown. There is no evidence of proven benefit when either nitrates or hydralazine is used alone, but nitrates often are prescribed without hydralazine. Nitrates also may be used effectively for the treatment of concomitant angina. Early development of hemodynamic tolerance (tachyphylaxis) to nitrates may occur with frequent dosing (every 4 to 6 h) but is less with intervals of 8 to 12 h[88] or in conjunction with ACE inhibition. Also, hemodynamic tolerance may be less during coadministration with hydralazine.[89]

Prostacyclin, which is a potent systemic vasodilator used in the treatment of primary pulmonary hypertension, has not been shown to improve mortality outcomes in patients with heart failure despite improvements in hemodynamics. Similarly, alpha blockers, despite their potent vasodilatory activity, have not shown benefit in patients with chronic heart failure; this probably is related to hemodynamic tolerance with prolonged drug treatment.

Calcium Antagonists

Calcium antagonists are not recommended for the treatment of CHF because of their negative inotropic effects. However, second-generation dihydropyridine-type calcium antagonists such as amlodipine and felodipine may be considered for the treatment of concomitant arterial hypertension or angina. Some second-generation calcium antagonists are still under investigation with respect to their long-term effect on mortality in chronic heart failure, in addition to baseline therapy including ACE inhibition. Preliminary data indicate either no effect[90] or a positive outcome in restricted patient populations, i.e., in patients with idiopathic dilated cardiomyopathy.[91] Although in these studies the second-generation dihydropyridine agents evaluated appeared to be safe and seemed not to increase mortality, there are no reasons to recommend these agents for the treatment of heart failure caused by systolic dysfunction; rather, they can be recommended as adjunctive medication for ischemia. As a result of the potential benefits noted below, however, beta blockers should be preferable to calcium blockers for patients with CHF and ischemia.

A study is in progress evaluating the dihydropyridine agent amlodipine as an adjunctive therapy for patients with congestive cardiomyopathy. Similarly, the selective T-channel calcium antagonist mibefradil, a drug that has no apparent effect on myocardial function,[92] has been studied. No beneficial effects of mibefradil on survival were demonstrated in patients with heart failure, and unfavorable drug-drug interactions, especially with amiodarone, led to the withdrawal of mibefradil from the market.[93] The use of calcium blockers in patients with diastolic dysfunction (e.g., verapamil) has been reported, but there are no long-term outcome studies with this form of treatment. The use of verapamil in the treatment of patients with hypertrophic cardiomyopathy has been well defined.[92]

BETA-ADRENERGIC BLOCKADE

In view of the marked benefits afforded by beta-adrenergic blockade in patients with heart failure after a myocardial infarction, beta-adrenergic blockade was advocated 25 years ago by Waagstein and colleagues for the treatment of patients with dilated cardiomyopathies.[94] In the BHAT trial, in which propranolol was begun 7 to 21 days after an acute MI and continued for 24 months, 5 lives per 100 were saved when heart failure was present, and only 2 lives when heart failure was absent.[95] Just as the use of ACE inhibitors in patients with CHF did not become widely accepted until the positive results of large survival trials such as CONSENSUS I, SOLVD, and V-HeFT II were known, the use of beta-blocking agents did not gain broad acceptance until large survival trials demonstrated the benefits of beta-adrenergic blockade on survival in patients with CHF.[96,97] The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) evaluated the effects of bisoprolol, a $beta_1$ -selective adrenergic blocker, on mortality from all causes in patients with CHF treated with standard medical regimens, including ACE inhibitors.[98] This multicenter placebo-controlled trial was conducted in Europe and enrolled 2647 patients with CHF characterized by functional class III-IV according to the NYHA and an LV ejection fraction <40 percent. Treated patients received up to 10 mg of bisoprolol. The trial was discontinued prematurely because mortality from all causes was significantly lower in the bisoprolol group than it was in the placebo group. Of the 1320 patients receiving bisoprolol, 156 died; of the 1327 patients randomized to placebo, 228 died. The estimated annual mortality rate was 8.8 percent in the bisoprolol group and 13.2 percent in the placebo group (hazard ratio, 0.66; 95 percent CI, 0.54-0.81 percent). The most common dose of bisoprolol was 10 mg in 564 patients, followed by 5 mg in 176 patients and 7.5 mg in 152 patients. Sudden death and hospitalization for worsening CHF were 42 percent and 32 percent lower in patients randomized to bisoprolol, respectively. In summary, in a trial that did not include a run-in period and thus did not select patients who tolerated beta-adrenergic blockade, bisoprolol lowered the risk of mortality from all causes by 32 percent. Bisoprolol was equally efficacious in patients with ischemic cardiomyopathy and patients in functional classes II and IV. However, in view of the overall low mortality rate of patients randomized to placebo, one may question how many patients were really in functional class IV before prerandomization.

In the Metoprolol CR/XL Randomised Intervention Trial (MERIT-HF), the effects of a controlled-release/extendedrelease formulation of metoprolol (CR/XL) on mortality was studied in patients with CHF treated with a standard medical regimen, including ACE inhibitors.[99] The 3991 patients with LV ejection fractions <40 and functional class II-IV were randomized to metoprolol (target dose 200 mg) for 2 months or to placebo after a 2-week single-blind placebo period. The study was terminated prematurely on the recommendation of the safety committee after a mean follow-up of 12 months. One hundred forty-five of the 1990 patients randomized to metoprolol died, and 217 of the 2001 patients randomized to placebo died ($p = .0062$). The mortality rates were 7.2 percent and 22 percent per patient-year of follow-up, respectively, with a relative risk of 0.66 (95 percent CI, 0.53-0.81 percent). Sudden death and death from aggravated heart failure were less frequent among treated patients: 79 versus 132, 0.59 (0.45-0.78), $p < .0002$, and 30 versus 58, 0.51 (0.33-0.79), $p = .0023$. The mean daily dose of metoprolol was 159 mg, with 87 percent of patients receiving more than 100 mg and 64 percent receiving the target dose of 200 mg. In summary, as demonstrated with bisoprolol, metoprolol CR/XL lowered mortality from all causes by 34 percent in patients with CHF already treated with ACE inhibitors and diuretics. As was noted in the CIBIS II trial, most of the patients enrolled in the MERIT-HF trial had moderate CHF, as evidenced by the low mortality of patients in the placebo group. Few patients in functional class IV participated in MERIT-HF. Thus, too few patients in functional class IV were randomized to active therapy in both the CIBIS II and MERIT-HF trials to assess the safety and efficacy of bisoprolol and metoprolol in this population. Both the CIBIS II and MERIT-HF trials demonstrated that mortality from all causes can be reduced by a selective $beta_1$-adrenergic agent in patients with mild to moderate CHF. Metoprolol is about 80-fold more selective for the human $beta_1$ than for the $beta_2$ receptor, and bisoprolol is approximately 120-fold more selective.[100]

While both $beta_1$ and $beta_2$ receptors are present in the normal human myocardium, $beta_2$ receptors predominate in the human failing myocardium, since $beta_1$ receptors are downregulated.[101] Thus, selection of a nonselective beta-blocking agent may seem preferable when the therapeutic aim is to protect the heart from beta-adrenergic stimulation. In the United States, most of the experience in treating patients with beta-adrenergic blockers has been gained with nonselective agents such as carvedilol and bucindolol. In addition to being a nonselective beta-adrenergic blocker, carvedilol has alpha-blocking and antioxidant properties, while bucindolol has direct vasodilating properties.[102]

Carvedilol is the only beta blocker currently approved by the FDA for the treatment of patients with

CHF.[102] Since a long-term survival trial has not been conducted with carvedilol, its approved use is for delaying the progression of myocardial disease and heart failure. The U.S. Carvedilol Program was composed of four trials and was stopped prematurely by the safety committee because of a highly significant reduction in mortality in treated patients (65 percent, $p < .0001$) compared with placebo.[102-107] The four trials were the Multicenter Oral Carvedilol in Heart Failure Assessment (MOCHA), the Prospective Randomized Evaluation of Carvedilol in Symptoms and Exercise (PRECISE), and the "mild" and "severe" heart failure trials.[103-106] The intended duration of these trials was 6 months. The primary end points were submaximal exercise for the MOCHA and PRECISE trials; a composite end point of death, reduction in cardiovascular hospitalizations, and a need to increase heart failure medications for the "mild" heart failure trial; and quality-of-life evaluation for the "severe" heart failure trial. The MOCHA and PRECISE trials had completed enrollment by the time the program was interrupted. Whereas primary end points were not reached expect in the "mild" heart failure trial, the average LV ejection fraction increased substantially in patients randomized to carvedilol in all the trials, while LV ejection fraction remained unaltered in patients randomized to placebo.[103-106] The improvement in LV ejection fraction was noted in patients who were already receiving optimal standard therapy, including ACE inhibitors. A dose-related reduction in mortality and enhancement of LV ejection fraction was noted in the MOCHA trial.[103] Cardiovascular hospitalizations were fewer and symptoms were alleviated in patients randomized to carvedilol in the PRECISE trials.[104] Lastly, global heart failure assessments were improved in patients randomized to carvedilol in the "severe" heart failure trial.[106] Thus, although the primary end points were different, the carvedilol trials demonstrated substantial reduction in mortality and dose-dependent improvement in the ejection fraction. This improvement was present in both ischemic and nonischemic cardiomyopathies, although it was greater in the latter group.

The Australia-New Zealand (ANZ) trial included an initial phase of 6 months and a longer phase with an average follow-up of 19 months.[108] Submaximal exercise, the end point of the initial phase, remained unchanged in patients randomized to carvedilol. During the second phase of the ANZ trial, fewer patients randomized to carvedilol died or were hospitalized.

The effects of beta-adrenergic blockade on LV function and dimensions are unique. No other pharmacologic intervention has been shown to reverse LV remodeling and improve LV ejection fraction so consistently in patients with CHF caused by LV systolic dysfunction. In all clinical trials in which patients received beta-blocking agents for at least 3 months, LV ejection fraction increased.[102] Long-term administration of selective and nonselective beta-blocking agents increases LV ejection fraction consistently to a much greater extent than is achieved by vasodilator therapy. The long-term benefits of beta-adrenergic blockade on LV performance are in contrast with the deterioration that may be observed initially. The time course of the effects of beta-adrenergic blockade includes an initial reduction in LV ejection fraction during the first weeks of treatment, a return to the initial ejection fraction at 4 weeks, and a substantial increase ranging from 5 to 10 absolute units at 3 months.[109] Thereafter, from 4 to 12 months, LV end-systolic and end-diastolic volumes and mass steadily decrease, a phenomenon often referred to as *reversed remodeling*.[110] Reversal of LV remodeling has been documented with carvedilol at 12 months in a substudy of the ANZ trial.[111] At 1 year, LV ejection fraction was greater and LV end-diastolic volume index was 14 mL/m^2 smaller in patients randomized to carvedilol than was the case in patients randomized to placebo.[111]

Not every patient benefits from long-term adrenergic blockade. In those who benefit, the rise in ejection fraction averages 10 percent. Increases in LV ejection fraction up to 15 to 20 percent with a normalization of LV volumes have been observed in individual patients. Systolic blood pressure and myocardial contractility, as evaluated by LV maximal rate of rise of pressure (dp/dt), are predictors of the response to long-term beta-adrenergic blockade in terms of LV ejection fraction.[112] The higher systolic blood pressure and LV dp/dt are, the more likely the ejection fraction is to increase during long-term beta-adrenergic blockade. Thus, patients with mild to moderate CHF and LV systolic dysfunction are the optimal candidates for beta-adrenergic blockade. Conversely, beta-adrenergic blockade is unlikely to benefit, and at present is not recommended for, patients in functional class IV with extremely reduced ejection fractions. Despite the fact that patients in functional class IV are the least likely to benefit from long-term beta-adrenergic blockade, they are the most likely to decompensate at the initiation of therapy as a result of their lack of cardiac reserve. Exacerbation of LV dysfunction at the initiation of therapy often leads to worsening CHF and hospitalization. The Beta Blocker Estimation of Survival Trial (BEST), a large randomized, placebo-controlled study of the effect of bucindolol, a third-generation beta-adrenergic blocking agent with

direct vasodilating properties, on the survival of 2708 patients with NYHA functional class III and IV, was stopped because of the lack of benefit seen. A preliminary report indicates that whereas bucindolol reduced mortality in patients in functional class III, it did not do so in patients in functional class IV.

The long-term and acute effects of beta-adrenergic blockade on LV performance have important therapeutic and pathophysiologic implications. First, the deterioration in LV performance that is observed routinely during the first weeks of therapy mandates that beta-adrenergic blockade be initiated at the lowest dose possible of a given agent in stable patients with CHF. Since beta-adrenergic blockade is aimed at altering the progression of the syndrome of CHF and not at providing acute relief of symptoms, effective beta blockade can be reached progressively by increasing doses of beta blocker agents every 2 to 3 weeks. When CHF is associated with angina or excessive tachycardia and effective beta blockade is needed for control of symptoms, the doses of beta blockers can be increased every few days under close in-hospital monitoring. An important unresolved issue concerning beta-adrenergic blockade in CHF is the treatment of patients whose symptoms worsen to functional class IV while they are being treated with beta-blocking agents. No data are available to provide guidelines to manage these patients. A pragmatic approach is to hospitalize patients who decompensate while receiving beta blockade and treat them with temporary inotropic support with a specific phosphodiesterase inhibitor, such as milrinone, which does not require beta receptors for its activity. Patients who improve are kept on a beta-adrenergic blocker, and inotropic support is discontinued after a few days. Beta-adrenergic blockade should be tapered off and withdrawn in patients who fail to improve. The pathophysiologic implication of successful beta-adrenergic blockade is that the process of LV dysfunction can be reversed by pharmacologic means even in patients with markedly reduced LV function. Thus, a certain amount of plasticity that was previously unrecognized remains in dilated fibrotic left ventricles. The cellular and molecular mechanisms that reverse myocyte dysfunction, thereby enhancing global LV performance, are poorly understood (Table 21-2). Since patients with both ischemic and nonischemic cardiomyopathy benefit from long-term beta-adrenergic blockade, dysfunction of surviving myocytes is a common characteristic of CHF independent of its etiology.[113] Patients with nonischemic cardiomyopathy were initially thought to experience greater benefit from long-term beta blockade compared with patients with ischemic cardiomyopathy. Since it is practically impossible to compare patients with different etiologies of CHF at a similar stage of their disease process, definite conclusions concerning the effects of long-term beta-adrenergic blockade as a function of the etiology probably should not be drawn.

Table 21-2: Possible Mechanisms by Which Beta-Adrenergic Blockers Improve Ventricular Function in Chronic Congestive Heart Failure

1. Upregulation of beta receptors
2. Direct myocardial protective action against catecholamine toxicity
3. Improved ability of noradrenergic sympathetic nerves to synthesize norepinephrine
4. Decreased release of norepinephrine from sympathetic nerve endings
5. Decreased stimulation of other vasoconstrictive systems, including renin-angiotensin-aldosterone, vasopression, and endothelin
6. Potentiation of kalikrein-kinin system and natural vasodilatation (increase in bradykinin)
7. Antiarrhythmic effects raising ventricular fibrillation threshold
8. Protection against catecholamine-induced hypokalemia
9. Increase in coronary blood flow by reducing heart rate and improving diastolic perfusion time; possible coronary dilation with vasodilator-beta blocker
10. Restoration of abnormal baroreflex function
11. Prevention of ventricular muscle hypertrophy and vascular remodeling
12. Antioxidant effects (carvedilol?)
13. Shift from free fatty acid to carbohydrate metabolism (improved metabolic efficiency)
14. Vasodilation (e.g., bucindolol, carvedilol)
15. Antiapoptosis effect
16. Improved left atrial contribution to left ventricular filling

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The selection of a beta-adrenergic blocker for the treatment of CHF is at the present time somewhat academic, since carvedilol is the only beta blocker approved by the FDA for this indication in the United

States. The rationale for selecting a nonselective agent over a selective beta$_1$ antagonist has been mentioned previously. Studies comparing a selective versus a nonselective agent are few and have enrolled small numbers of patients. Their results are controversial. In a 6-month study of 67 patients randomized to carvedilol or metoprolol, Kukin and associates demonstrated no significant difference between these agents.[114] In contrast, carvedilol was reported to enhance LV function and reverse LVE remodeling in patients with dilated cardiomyopathy who were failing metoprolol therapy.[115] Similarly, compared with metoprolol, carvedilol was found by Gilbert and colleagues to produce greater improvement in functional class and LV performance in patients with idiopathic dilated cardiomyopathy.[116] Lastly, the antioxidant properties of carvedilol were recently documented in vivo by demonstrating an inhibition of reactive oxygen species generation by leukocytes.[117] The clinical relevance of the antioxidant action of carvedilol remains to be determined in patients with CHF. A large trial comparing the respective benefits of carvedilol and metoprolol in patients with CHF is under way [Carvedilol or Metoprolol Evaluation Trial (COMET)]. Whether enough events will occur in the patients enrolled in the COMET trial to detect a meaningful difference between these agents is uncertain. In addition, a trial is in place [Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS)] that is examining the effects of carvedilol in class IV patients.

In summary, in the absence of an indication such as reversible airways obstructive disease, advanced heart block, or episodic decompensation, all symptomatic patients with CHF, except those in functional class IV, should be treated with long-term beta-adrenergic blockade.[3,101,102] Treatment should be initiated at the lowest possible dose and advanced to full beta blockade over 1 to 2 months as tolerated. Patients who do not tolerate the full dose should be kept on intermediate doses that still result in substantial improvement in LV function and a reduction in mortality.[102] Beta-adrenergic blockade is the only pharmacologic intervention that reverses LV remodeling, whereas ACE inhibition is the only intervention that improves the vascular processes. Thus, beta-adrenergic blockade is not an exclusive intervention but a complementary intervention. Both ACE inhibition and beta-adrenergic blockade are essential interventions for the treatment of CHF.

DIURETICS

Sodium accumulation tends to occur in the early stages of CHF, with peripheral edema accompanied by weight gain. Diuretics, along with salt restriction, remain the best therapeutic tool for treating the edematous state in heart failure. Despite the advent of new agents for treating symptomatic CHF, diuretics continue to be among the most commonly prescribed drugs in the world.

The mechanism for edema is generally multifactorial and includes renal vasoconstriction, increased aldosterone and vasopressin activity, and/or increased venous pressures. Increased sympathetic nervous system activity (tone) tends to occur early in the course of heart failure. Activation of the renin-angiotensin axis tends to occur somewhat later, commonly when diuretics are begun.[39] This leads to increased aldosterone, leading to sodium accumulation and potassium loss. Even with asymptomatic LV dysfunction, avidity of the kidneys for sodium and water is enhanced greatly, and peripheral edema constitutes an early physical sign that brings the problem of CHF to the physician's attention. Salt and water retention leads to an expanded intravascular volume, with an increase in LV filling pressures to maintain cardiac output.[118] With continued worsening of LV function, progressive volume expansion continues and LV end-diastolic pressure rises along with venous hydrostatic pressure in both the systemic and pulmonary beds. This alteration in Starling forces favors transudation of intravascular fluid into the interstitial compartment, culminating in edema formation.[119] Eventually a point is reached at which additional increases in LV filling pressure fail to augment cardiac output, and with progressive increases in peripheral arterial vasoconstriction, renal perfusion is reduced. By this time, overt heart failure is established, and the kidney's ability to excrete a salt load is severely impaired.[118] Important mediators in this process are (1) activation of the renin-angiotensin-aldosterone axis, (2) stimulation of the sympathetic nervous system, (3) increased levels of antidiuretic hormone leading to water retention and hyponatremia, and (4) resistance to atrial natriuretic peptide (ANP), which is an endogenous hormonal vasodilator and diuretic.

The appropriate use of diuretics depends on the stage of disease and severity. With mild fluid accumulation characterized by peripheral edema, pulmonary rales, and weight gain, oral diuretics are indicated. Long-acting but less potent diuretics, such as hydrochlorothiazide and chlorthalidone, may be adequate. Intermittent use of more potent loop diuretics, such as furosemide, bumetanide, and torsemide, may allow

one to regain dry weight more rapidly. Efficacy can be assessed by daily weights, and diuretic regimens can be adjusted appropriately.

Loop Diuretics

The most potent diuretics are those whose action occurs in the medullary thick ascending limb of Henle because of the percentage of filtrate reabsorption that occurs at this segment of the nephron. In the euvolemic state, about 20 percent of filtered sodium load is reabsorbed in the thick ascending limb, compared with only 7 percent in the distal tubule and 5 percent in the collecting duct.[120] Drugs in this diuretic class include furosemide, bumetanide, torsemide, and ethacrynic acid. The loop diuretics are more than 98 percent protein-bound and therefore are not freely filtered by the glomerulus. Rather, they access the tubular lumen, where they act by secretion via an organic anion transporter.[121] This secretion of loop diuretic may be impaired and their action may be limited by the presence of elevated levels of endogenous organic acids, as occurs in renal failure, and by probenecid, salicylates, and NSAIDs. Once in the lumen of the tubule, the loop diuretics compete with chloride for binding to the $Na^+/K^+/2Cl$ contransporter situated on the apical membrane of cells of the medullary thick ascending limb, thus inhibiting the reabsorption of both sodium and chloride.[122] The urinary diuretic concentration best represents the fraction of drug delivered to the thick ascending limb and significantly correlates with the natriuretic response after diuretic administration.[123]

Furosemide is the most widely used loop diuretic. In normal patients, the oral bioavailability of furosemide is 50 percent. After an oral dose, the onset of action occurs within 30 to 60 min, peaks at 1 to 2 h, and has a duration of action of 6 h, with a half-life of 50 min.[121,124] Furosemide may be given intravenously over 1 to 2 min; after intravenous administration, diuresis begins within 15 min and peaks at 30 to 60 min. The duration of action is up to 2 h when the drug is given intravenously. Sixty percent of furosemide is excreted unchanged in the urine; the rest is conjugated with glucuronic acid in the kidney.[121,124] In renal insufficiency [glomerular filtration rate (GFR) >30 mL/min)], the elimination half-life is prolonged, although the diuretic response is impaired, largely owing to reduced drug delivery to its site of action within the tubule.[125]

In CHF, the pharmacokinetics of oral furosemide are also altered; furosemide absorption is delayed, which leads to a delay in the time at which peak concentration occurs.[123] Altered pharmacodynamic properties of furosemide occur independent of the route of administration, resulting from adaptations within the glomerular microcirculation and renal tubule that are present during chronic diuretic administration.[123] Bumetanide is 40 times more potent than furosemide and is available in both oral and intravenous formulations. In normal patients, the bioavailability is 80 percent after an oral dose, and the onset of diuretic effect occurs within 30 min and peaks within 1 h. The duration of action of oral bumetanide is between 3 and 6 h, with a half-life between 1 and 3.5 h.[124,126] Similar to furosemide, the delayed absorption of oral bumetanide in heart failure results in lower peak concentrations as well as a delayed time to peak concentration.

Torsemide is a newer loop diuretic that differs from others in its class in that 80 percent of a dose undergoes hepatic metabolism. Because only 20 percent of the drug is excreted unchanged in the urine, its half-life is altered minimally in renal failure.[127] Torsemide is absorbed rapidly and is 80 to 90 percent bioavailable. In patients with chronic renal insufficiency or with cirrhosis, the natriuretic response after torsemide is unaffected by the route of administration.[128] Maximal sodium excretion occurs within the first 2 h after either routine. In healthy individuals, the half-life of torsemide is 3.3 h, but it is prolonged to 8 h in cirrhosis.[127,129] When selecting an oral agent in patients with heart failure, the physician may find oral torsemide to be advantageous since its absorption is unimpaired and is less variable than that of oral furosemide.[130] In fact, the pharmacokinetics of torsemide in CHF patients are comparable to those in normal persons. As is the case with all loop diuretics, however, dose-response curves for torsemide in patients with CHF are shifted downward and to the right, suggesting altered drug pharmacodynamics and a diminished diuretic response. The efficacy of loop diuretics often is reduced significantly in patients with decompensated heart failure. Impaired drug absorption has been implicated as one cause of variable efficacy. Reduced gastric and intestinal motility, an edematous bowel wall, and decreased splanchnic blood flow may delay absorption. The total amount of furosemide absorbed over 24 h, however, is similar to that found in normal individuals.[131-133]

In patients with stable, compensated heart failure who are given oral furosemide, the time to peak urinary excretion is prolonged to about 190 min (normal, 90 min) and peak urinary excretion rate is reduced by 50 percent.[123] Furosemide and bumetanide, when given in doses of equivalent potency, induce a similar natriuretic response in patients with heart failure.[123] The pharmacokinetic properties of intravenous furosemide are unaltered in heart failure patients compared with normal individuals.[134]

The effectiveness of loop diuretics is limited by two phenomena in patients with chronic heart failure and normal renal function. The *rebound phenomenon* consists of a decrease in sodium excretion below baseline after the effect of the loop diuretic has worn off. The *braking phenomenon* refers to an increase in tubular sodium reabsorption by the distal tubule that occurs during long-term administration of loop diuretics.

In decompensated heart failure, the intravenous route of administration is preferable when possible, since the onset of diuresis is shorter and more predictable (Fig. 21-7). In patients with CHF that is refractory to standard doses of intravenous furosemide, higher doses may be efficacious. In 20 patients with severe CHF that was previously resistant to lower intravenous doses of furosemide,[135] intravenous furosemide was administered at doses of 500 to 2000 mg daily for a mean of 10 days, with increased diuresis, weight reduction, and symptomatic improvement. Other investigators observed a similar clinical improvement, as assessed by NYHA classification criteria, in 17 of 21 patients using high-dose oral furosemide (>500 mg daily) for 1 month.[136]

Continuous intravenous rather than intermittent administration of loop diuretics is an effective method of overcoming diuretic resistance in heart failure. In a randomized crossover study comparing continuous versus bolus bumetanide in patients with chronic renal failure (mean GFR, 17 mL/min), a greater net sodium excretion was observed during continuous infusion despite comparable drug excretion.[137] In CHF, continuous infusion of furosemide produces a similar natriuresis at serum concentrations 20 times lower than those after a comparable effective bolus dose.[138] Only one prospective, randomized crossover study is available that compares the continuous infusion of furosemide (loading dose 30 to 40 mg followed by infusion at a rate of 2.5 to 3.3 mg/h for 48 h) with intermittent intravenous bolus administration (30 to 40 mg every 8 h for 48 h) in NYHA class III and IV heart failure.[139] When it was infused continuously, furosemide's pattern of delivery produced more effective drug utilization, that is, sodium excretion relative to total furosemide excretion, whereas with intermittent bolus furosemide, wide fluctuations in urine output and sodium excretion were observed. Theoretically, an infusion of furosemide at a constant rate may be safe than using intermittent intravenous dosing, although a larger study is needed to confirm this.[140]

In summary, loop diuretics with salt restriction monitored by weight measurement by scale remain the basis for the treatment of edema. As CHF progresses, increasing oral doses of loop diuretics tend to be needed. In severe CHF with hospitalization, intravenous loop diuretics, commonly at higher doses, become essential. As will be discussed below, other agents, such as metolazone, may be required as well to increase and sustain sodium loss. Limitations to diuretic use remain hyponatremia and a progressive increase in serum creatinine, which may require careful dose reductions (Table 21-3).

Table 21-3: Stepwise Approach to Loop Diuretic Resistance

1. Enforcement of strict low-sodium diet
2. Use of effective doses of loop diuretics
3. Combination administration of long-acting thiazide with loop diuretic to offset the antinatriuretic rebound effect observed after administration of short-acting loop diuretics
4. Constant intravenous infusion of loop diuretic

Thiazides

The thiazide diuretics may be reasonable first-line natriuretic agents in early LV dysfunction when renal perfusion is not yet significantly compromised. In overt ventricular failure, however, thiazides are usually ineffective or inadequate. Thiazides are 50 percent protein-bound, and more than 95 percent of the dose is

excreted unchanged in the urine.[124] They gain access into the tubular lumen through both glomerular filtration and tubular secretion. In the kidney, they inhibit sodium chloride reabsorption in the early distal tubule, where they compete for the chloride site on the apically located Na^+/Cl cotransporter.[141,142]

Hydrochlorothiazide is the most widely prescribed drug in this class of diuretics. Seventy-one percent of an oral dose is absorbed. The onset of diuresis occurs within 2 h, peaks between 3 and 6 h, and continues for up to 12 h.[124] Hydrochlorothiazide's pharmacokinetics follow a two-compartment model of elimination (α phase, 5 h; β phase, 6 to 15 h), and the half-life is prolonged in patients with decompensated heart failure and those with renal insufficiency.

Metolazone is a quinazoline diuretic and is similar to the thiazides in structure and mechanism of action.[124,143] Although its major effect occurs in the cortical diluting segment, metolazone has a minor inhibitory effect on proximal tubular sodium reabsorption. Metolazone is lipid-soluble and easily accesses the tubular lumen during states of renal insufficiency, unlike the thiazides.[144] Another advantage of metolazone is its longer duration of action (12 to 24 h).[124,143]

Potassium-Sparing Diuretics

Aldosterone, an endogenous adrenal hormone, normally increases sodium reabsorption with the simultaneous excretion of potassium. Aldosterone levels are increased in heart failure, to some degree because of its augmented secretion induced by angiotensin II. In heart failure, an increase in aldosterone activity may cause significant sodium retention, potassium depletion, and magnesium depletion. Increased aldosterone activity also can be harmful by causing an augmentation of sympathetic stimulation and a decreased activity of the parasympathetic nervous system, thus contributing to baroreflex dysfunction, a poor prognostic finding in patients with heart failure. Aldosterone also may promote the formation of patchy myocardial fibrosis, leading to arrhythmias and further depression of LV dysfunction.

Spironolactone, a lipid-soluble potassium-sparing diuretic, competes with aldosterone for binding to its receptor in the principal cell of the collecting duct and thus leads to diuresis.[124] Spironolactone is particularly advantageous during states of reduced renal perfusion because its delivery to its site of action is not dependent on GFR. Spironolactone may be a useful adjunct to hydrochlorothiazide in offsetting its effect of producing hypokalemia resulting from sodium-potassium exchange. Since the exchange of sodium for potassium is reduced, potassium loss is reduced and hypokalemia may be corrected. Indeed, potassium supplements given for hypokalemia generally should be stopped to avoid hyperkalemia. If the use of spironolactone is warranted in a severe heart failure patient receiving an ACE inhibitor, therapy may be initiated at a dose of 25 mg a day. Because of the risk of hyperkalemia, serum potassium concentration should be monitored closely not only during concomitant therapy with ACE inhibitors or AII receptor blockers but also during periods of declining renal function. If the serum potassium concentration exceeds 5.5 meq/L, the spironolactone dose should be reduced to 25 mg every other day. Alternatively, after 8 weeks, the spironolactone dose may be increased to 50 mg a day in patients with stable serum potassium concentrations who are experiencing worsening heart failure symptoms. Maintenance doses of 50 mg a day or greater should be limited to patients with refractory or severe heart failure who have evidence of pulmonary or peripheral edema caused by an increased incidence of hyperkalemia. In this particular patient population, however, doses as high as 200 mg a day may be necessary. However, once a patient's condition has stabilized, the dose of spironolactone should be decreased to the maintenance level (25 to 50 mg a day) used before the heart failure exacerbation.[145]

The use of spironolactone also has been associated with reduced mortality in CHF, perhaps by helping to maintain potassium levels, thus reducing the risk of arrhythmic death in patients with heart failure,[146] or by inhibiting other pathologic processes influenced by aldosterone.[147] Spironolactone also has been shown to improve endothelial dysfunction, increase nitric oxide bioactivity, and inhibit the conversion of angiotensin I to angiotensin II, providing additional mechanisms for its beneficial effects on cardiovascular mortality.[148]

Amiloride and triamterene are similar to spironolactone in that they are potassium-sparing and act on the principal cell; however, they must be delivered intralumenally to be effective. More specifically, they reduce sodium flux into principal cells by blocking the apically located sodium channel.[124] When used

alone, the potassium-sparing diuretics are relatively weak. In heart failure, they are useful when used in combination with a loop diuretic to overcome diuretic resistance and reduce potassium wasting.[149]

Combined Use of Diuretics

Numerous reports have demonstrated a rapid, profound diuresis (1 to 2 L daily within 24 to 48 h), accompanied by clinical improvement, after the addition of metolazone to furosemide in patients with CHF (Fig. 21-7) who were previously resistant to furosemide alone.[150-157] Metolazone, a thiazide-like diuretic, is particularly advantageous since it has a prolonged duration of action, is lipophilic, and remains effective in states of renal impairment. In a study comparing metolazone with a thiazide, however, when either was used in combination with a loop diuretic, no significant difference in sodium excretion or urine output was observed between the two drugs.[157] Spironolactone, when used in combination with a loop diuretic (Fig. 21-7), also has been associated with an improvement in diuretic response in patients with CHF previously resistant to loop diuretics.[149]

In summary, thiazides, potassium-sparing diuretics, and aldosterone inhibitors (e.g., spironolactone), along with loop diuretics, provide potent tools to reduce salt accumulation in CHF. Early in CHF, their use is mainly to reduce or eliminate peripheral edema and help relieve pulmonary congestion. Once dry weight is approximated, intermittent and reduced diuretic use is advisable to avoid electrolyte problems. Daily weights are the best guide to the adequacy of this therapy. Early in CHF, thiazides with potassium-sparing diuretics may be all that is necessary, although loop diuretics provide increased diuresis. Indeed, loop diuretics can be used intermittently on top of thiazides when needed. It is possible that the early use of diuretics can hasten the evolution of CHF by increasing reflex neurohumoral responses that may have adverse consequences, such as activation of the renin-angiotensin system.[39] As CHF progresses, the loop diuretics in increasing amounts are generally required. Here again, a scale for weight provides guidance for the dose. With excessive diuresis in very severe CHF, increasing renal insufficiency may be induced by hypovolemia, and this in itself may increase loop diuretic dose, its used intravenously, and the need for the concomitant use of thiazides (metolazone) or spironolactone.

INOTROPIC AGENTS

The use of inotropic agents in the treatment of CHF is predicated on the finding that a major contributing factor in reducing ventricular performance results from depression of myocardial contractility and that this can be reversed, or at least improved, by inotropic drugs. The fact that there is reduced myocardial contractility in failing heart muscle, whether from a sustained work overload of pressure or in response to losing myocardium, has been well demonstrated and appears to be due largely to inadequate Ca^{2+} availability for activation. All currently available inotropic agents act to increase Ca^{2+} for activation in both normal and failing myocardium. This is the case whether the mechanism of action is via cyclic AMP system excitation (e.g., catecholamines) or occurs by sarcolemmal Na^{+}-K^{+}-ATPase inhibition (e.g., digitalis glycosides). The problem remains whether this increase in intracellular Ca^{2+} can benefit pump function while doing no harm, such as enhancing the propensity for arrhythmia or theoretically producing further myocyte loss. Moreover, agents that reduce afterload may enhance ventricular emptying without these potential hazards. In end-stage, severely decompensated CHF, inotropic agents (e.g., dobutamine) may be temporarily lifesaving (Fig. 21-7), and at somewhat earlier stages, they may reduce morbidity (e.g., digitalis glycosides). In earlier stages of CHF, the benefits of inotropic agents may not outweigh the risk, and their use is relegated to later stages in the disease process (Figs. 21-5 and 21-7).

Digitalis Glycosides

Digitalis glycosides have had a long and venerable history in the treatment of CHF and are the only oral inotropic agents available currently for this purpose (Fig. 21-8). In 1785, William Withering[158] reported on his use of the digitalis leaf as a purported diuretic agent to treat anasarca, presumably caused by CHF. Indeed, the major effects of digitalis initially were thought to be on the kidneys, although important effects on heart rate were noted. Only during the latter part of the nineteenth century did it become apparent that there was a direct action of digitalis glycosides to increase cardiac contractility,[159] while in the earlier part of the twentieth century the effects of digitalis on the peripheral circulation and the autonomic nervous system were noted.[160] Despite this long history, the risks and benefits of digitalis administration in patients

with sinus rhythm have remained controversial. The controversy was partially addressed in a large randomized, placebo-controlled clinical trial of digoxin use in CHF.[161] Overall, digoxin was shown to be safe with a significant reduction in morbidity, expressed in terms of less need for hospitalization, but not in mortality. The benefit in terms of hospitalization for heart failure appears greatest in those with lower ejection fractions. As will be discussed later, with serum digoxin levels below 1 μg/mL, the neurohumoral and autocrine effects of digoxin predominate over the inotropic effects.

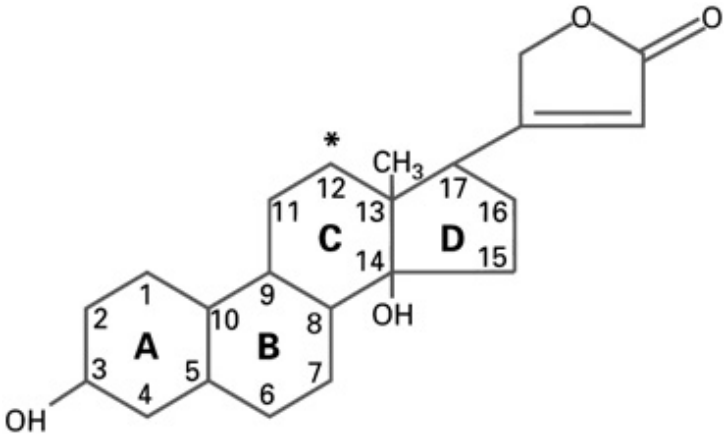

Figure 21-8: Structure of digitalis molecule. * Digitoxin becomes digoxin with OH placement at C_{12}. (From Sonnenblick EH, LeJemtel TH, Frishman WH. Digitalis preparations and other inotropic agents. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics*. New York, McGraw-Hill; 1997:241. Reproduced with permission from the publisher and authors.)

Digitalis glycosides have important effects on multiple systems in addition to augmenting the contractility of the myocardium.[162,163] Electrophysiologically, digitalis glycosides speed conduction in the atrium while inhibiting conduction at the atrioventricular node. This has made them useful for rate control in atrial fibrillation. In the normal circulation, digitalis glycosides also produce generalized arteriolar vasoconstriction while affecting the central nervous system to enhance parasympathetic tone and reduce sympathetic nervous system activation. Digitalis glycosides sensitize baroreflexes to decrease efferent sympathetic activity, which acts to reduce sinus node activity and thus reduce heart rate. The precise mechanism for these effects is unclear. The increase in baroreflex sensitization also increases parasympathetic tone, even in mild heart failure, while central vagal nuclei also are stimulated. The broad enhancement of parasympathetic activity with digitalis glycosides helps explain the sinus heart rate slowing observed after digitalis glycosides even with sinus rhythm as well as their therapeutic efficacy in controlling supraventricular arrhythmias. As is discussed below, in the failing state, the effects of sympathetic withdrawal may be dominant, leading to reduced arterial vascular resistance, while in the normal circulation, arterial vasoconstriction may be dominant. Integration of these various actions adds to the inotropic activity and the therapeutic usefulness of digitalis glycosides.

The positive inotropic action of digitalis glycosides to increase the contractility and alter the electrophysiology of heart muscle occurs through binding to and inhibition of the enzyme Na^+-K^+-ATPase on the surface membrane of myocardial cells, which results in an increase in the cytocyclic Ca^{2+} concentration.[164,165] Na^+-K^+-ATPase is an energy-requiring "sodium pump" that extrudes three Na^+ ions, which enter the cell during depolarization in exchange for two K^+ ions, thus creating an electric current and a negative resting potential.[166] Contraction is initiated with an action potential that depolarizes the surface membrane of the cell. This is created by a rapid inward current of Na^+ into the cell that opens sarcolemmal Ca^{2+} channels, permitting Ca^{2+} to enter the cell. This Ca^{2+} releases substantially more Ca^{2+} from stores in the sarcoplasmic reticulum within the cell, which in turn activates the contractile mechanism by binding to a component of the troponin-tropomyosin system that had been maintaining the resting state. With Ca^{2+} bound to troponin, actin and myosin can interact to produce force and shortening. The greater the amount of activating Ca^{2+}, the greater the force and the shortening.[165,166] When Ca^{2+} is released from troponin and taken up by the sarcoplasmic reticulum, relaxation occurs.[165] The relatively small amount of Ca^{2+} that

enters the cell with activation ultimately is removed by an electrogenic Na^+/Ca^{2+} exchange that extrudes one Ca^{2+} for three Na^+ ions. When intracellular Na^+ is increased, less exchange occurs and the net amount of intracellular Ca^{2+} is increased. Thus, by inhibiting the Na^+-K^+-ATPase, digitalis glycosides produce a decrease in intracellular K^+ and an increase in intracellular Na^+ that increases intracellular Ca^{2+} (Fig. 21-9).[165,166] In general, the main way in which all inotropic agents, including digitalis glycosides, increase contractility is by increasing the amount of Ca^{2+} available for activation.[167] This is the case in both normal and failing myocardium. In the failing heart, there is also a decrease in the Ca^{2+} released into the cytosol with activation.[168,169] Digitalis glycosides increase this intracellular Ca^{2+} that augments Ca^{2+} stores in the sarcoplasmic reticulum, resulting in a subsequent increase in previously reduced myocyte contraction.

Digoxin

Although there are numerous digitalis glycosides with varying durations of action and metabolic fates, digoxin has a relatively rapid onset and an intermediate duration of action. Digoxin has its most beneficial hemodynamic actions when substantial ventricular depression is evident along with CHF. In this circumstance, it augments myocardial performance while reflexly reducing peripheral resistance.[170] Acutely, digoxin also reduces cardiac norepinephrine spillover and reduces efferent sympathetic nerve activity in skeletal muscles in patients with CHF.[170] Slowing of the heart rate, whether via enhanced parasympathetic tone and reduced sympathetic activity to reduce sinus rate or via control of heart rate in atrial fibrillation (as discussed below), greatly benefits ventricular filling and reduces pulmonary congestion.[171] In the treatment of CHF, digoxin generally is employed along with diuretics and vasodilator agents. Thus, by reducing peripheral resistance, digoxin and peripheral vasodilators act in a complementary manner.

In acute heart failure, either caused by massive sudden loss of myocardium, as may occur with a myocardial infarction, or with increasing decompensation in severe chronic CHF, characterized by acute pulmonary edema, severe limitations of cardiac output, and perhaps hypotension, more rapidly acting inotropic agents such as intravenous dobutamine and milrinone (discussed below) may be required (Fig. 21-7), together with loop diuretics and vasodilators. This situation may occur in the setting of rapid deterioration of a patient with more chronic heart failure or after a large myocardial infarction.[172] In this circumstance, the main aim is to increase cardiac output and reduce filling pressures as a setting for longer-term stabilization. While rapidly acting inotropic agents are being used, digitalis may be administered cautiously for its longer-term effects. In the setting of myocardial infarction, the situation is more complex. Because of a fear that arrhythmias may be induced or oxygen consumption may be increased, which might be detrimental, digoxin generally is avoided in the first few days after infarction,[172] although in a longer-term treatment of CHF, digitalis, especially if dosing is carefully controlled, may be of value along with other agents, especially ACE inhibitors.

For chronic CHF, digoxin is of use over the long term when administered in association with loop diuretics and ACE inhibitors. Benefits are most evident in patients with NYHA class III or IV CHF. In this circumstance, the response of the circulation is characterized by a decrease in venous pressures and ventricular filling pressures and an increase in cardiac output. Heart rate is slowed, and the ejection fraction tends to rise, while peripheral resistance falls with little or no change in arterial pressure. These salutary effects are attributed to a combination of augmented myocardial contractility and restoration of baroreceptor sensitivity, which results in enhanced parasympathetic and decreased sympathetic tone. Whereas myocardial oxygen consumption may increase in the normal heart from the increased contractility, in heart failure it tends to be reduced as a result of a decrease in heart size, and thus ventricular wall tension, and a slowing of heart rate. Earlier concepts supported the view that digoxin is of greatest benefit when atrial fibrillation is present and controlled. It is now clear that efficacy is also present when a patient with heart failure is in sinus rhythm.[173] Withdrawal of digoxin from such patients led to rapid deterioration even when both diuretics and ACE inhibitors were used.[174,175] While digoxin has been associated with an increase in the ejection fraction, vasodilators have been shown to cause more significant increments in exercise performance.[176] These considerations would justify the combined use of these agents. Whereas the use of ACE inhibitors may be indicated when the ejection fraction is reduced and symptoms are limited (class I, II), digoxin probably should be reserved for use with more overt symptoms (class III, IV).

While digoxin can be given once a day without tolerance or tachyphylaxis, the dose is a matter at issue.[177]

In general, a serum level of 0.5 to 1.5 mg/L is felt to be therapeutic.[178] This level may vary from patient to patient, and a clear dose-response relation has not been established. Indeed, some of the greatest benefits may be gained from lower doses (e.g., 0.125 mg/day), which may induce the neurohumoral benefits of lower sympathetic and higher parasympathetic tone while reducing the incidence of possible toxic side effects,[177] as is discussed below. There appear to be no adverse effects from digoxin usage in terms of mortality in patients with CHF,[161] and the substantially increased morbidity noted when the drug is withdrawn[174,179,180] suggests such a result. Effects on mortality with digoxin are complicated by the fact that the nature and progression of the underlying process, which led to failure in the first place, may be the ultimate determinant of mortality. If morbidity is reduced substantially with digoxin, as has been demonstrated,[161] a neutral effect on ultimate mortality would be acceptable. This was demonstrated in the Digitalis Investigation Group (DIG) Study (sponsored by the National Institutes of Health), a controlled trial in patients with CHF that showed no effect on survival compared to placebo, a reduction in hospitalizations, and a low incidence of digoxin toxicity.[161]

Digoxin has been shown to be of limited value in the treatment of right-sided heart failure, which can occur in cor pulmonale or with left-to-right shunts. Digoxin also has limited value in acute LV failure caused by acute myocardial infarction, although it is useful in the subsequent treatment of ischemia-related CHF. Nevertheless, since mortality may be increased after infarction by digoxin, especially when clear evidence of heart failure is absent, its use is best reserved for patients with overt CHF.

Toxicities from digitalis glycosides can be numerous and are somewhat dependent on the serum level. Central nervous symptoms include loss of appetite and nausea, and visual changes may be seen. Cardiac limitations include atrioventricular block, premature ventricular extra systoles, and ultimately ventricular tachycardia and fibrillation. Monitoring serum levels may be useful in a patient with sinus rhythm, while the ventricular rate provides an adequate guide to dosing in the presence of atrial fibrillation. Except in dire circumstances, such as a suicide attempt, cessation of therapy is adequate. In the former circumstances, antibodies to digoxin may be indicated.

Catecholamines

As was noted above, positive inotropism is based on enhancing the delivery of Ca^{2+} to the contractile system to increase force and shortening. Increasing Ca^{2+} in the serum effects this transiently, while digitalis glycosides increase Ca^{2+} for activation by inhibiting sarcolemmal Na^{+}-K^{+}-ATPase. Catecholamines increase activating Ca^{2+} via beta-adrenergic receptors and the adenyl cyclase system (Fig. 21-9).

Beta receptors are located in the sarcolemma and constitute a complex structure that spans the membrane.[181] The beta receptor is connected with G proteins (Fig. 21-9) that either activate (G_s) or inhibit (G_i) a secondary enzyme system, adenylate cyclase, which, when activated by G_s, induces the formation of 3′-5′ cyclic adenosine-monophosphate (cyclic AMP). Cyclic AMP in turn activates certain protein kinases, which lead to intracellular phosphorylation of proteins that enhance both the entry and the removal of intracellular Ca^{2+}.[182] When more Ca^{2+} is provided to the troponin-tropomyosin system, a greater interaction between actin and myosin occurs, increasing force and shortening. Increasing the rate of Ca^{2+} removal from the cytoplasm speeds the rate of relaxation.

In a normal heart, norepinephrine is synthesized and stored in the sympathetic nerve endings that invest the entire heart, including the atria, conduction system, and ventricle.[183] When these nerve endings are depolarized, norepinephrine is released from granules in nerve endings into myocardial clefts containing beta-adrenergic receptors, which, when activated, turn on the sequence of events noted above. Not only does this enhance Ca^{2+} entry into the myocyte to augment contraction, it also phosphorylates phospholamban, which enhances relaxation.[182] Subsequently, most of the released norepinephrine is taken back up and restored in the sympathetic nerve endings. Released norepinephrine also is inactivated by two enzymes, catechol *O*-methyltransferase (COMT) and monoamine oxidase (MAO), and the products are excreted largely by the kidneys.[182]

In very severe heart failure, stores of norepinephrine in the ventricle are largely depleted and the sympathetic nerve endings fail to take up norepinephrine normally.[184] Rapid turnover of whatever

norepinephrine stores remain is suggested by increased cardiac norepinephrine spillover in CHF. At the same time, circulating norepinephrine released from peripheral sympathetic nerve endings may be increased, especially in severe failure.[185] In less severe heart failure, the serum norepinephrine levels tend to be normal despite increased sympathetic nerve activity.[186]

In both normal and failing myocardium, activation of the adenyl cyclase system can augment contractility. Agents that do this may be divided into two categories. The first category consists of the catecholamines (e.g., norepinephrine, epinephrine) and their synthetic derivatives (e.g., dobutamine, isoproterenol), which act via cell-surface adrenergic receptors (Fig. 21-9).[182] The second includes agents that inhibit the breakdown of cyclic AMP by inhibiting phosphodiesterase type III (e.g., amrinone, milrinone, and pimobendan), resulting in an increase in cyclic AMP.[186] Some of these agents, such as pimobendan, also may increase myofibril sensitivity to calcium and then further augment contraction.[187]

Catecholamines constitute an endogenous hormonal system that exerts reflex control of the heart and circulation. Their effects depend on localized, controlled neural release and receptor specificity in terms of action. Dopamine is the naturally occurring precursor of both norepinephrine and epinephrine (Fig. 21-10).[188] While epinephrine is released from the adrenal medulla, norepinephrine is the primary mediator in the heart and the peripheral circulation.[182]

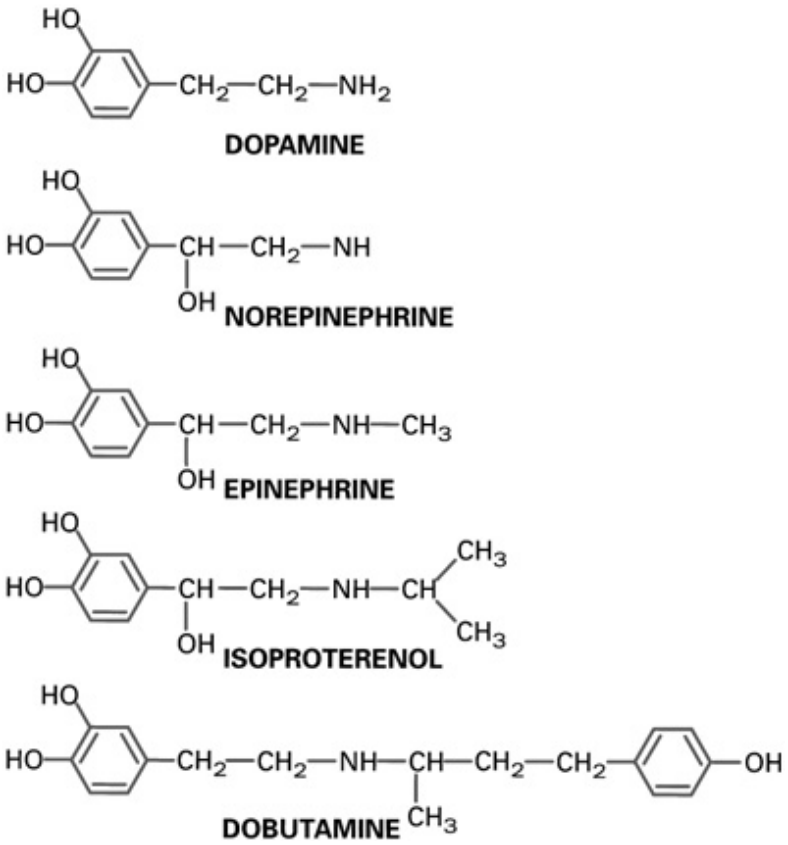

Figure 21-10: Structure of catecholamines.

The actions of both endogenous and exogenous catecholamines depend on their activation of specific alpha- and beta-adrenergic receptors (Tables 21-4 and 21-5).[182] Alpha receptors include alpha$_1$ receptors, which are postsynaptic and are located in vascular smooth muscle and in the myocardium. In smooth muscle, they mediate vasoconstriction; in the heart, weak positive inotropic and negative chronotropic effects. Alpha$_2$ receptors are presynaptic and, when stimulated, decrease norepinephrine release from peripheral nerve endings as well as sympathetic outflow from the central nervous system. Alpha$_2$ receptors also may mediate vasoconstriction in specific peripheral vascular beds.

Table 21-4: Adrenergic Receptor Activity of Sympathomimetic Amines

	$Alpha_1$	$Beta_1$	$Beta_2$	Dopaminergic	Dose
Dopamine	+++	++	+	++++	<2 (μg/kg)/min: vasodilation effects on peripheral dopaminergic receptors2-10 (μg/kg)/min: inotropic effects, $beta_1$ receptor activation;5-20 (μg/kg)/min: peripheral vasoconstriction, alpha effects
Norepinephrine	++++	++++	0	0	Initiate with 8-12 μg/min; maintain 2-4 μg/min
Epinephrine	+++	++++	++	0	
Isoproterenol	0	++++	++++	0	0.5-5 μg/min
Dobutamine	+++	++++	++	0	Start at 2-3 (μg/kg)/min and titrate upward

SOURCE: From Sonnenblick EH, LeJemtel TH, Frishman WH. Digitalis preparations and other inotropic agents. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics.* New York: McGraw-Hill; 1997:246. Reproduced with permission from the publisher and authors.

Table 21-5: Physiologic and Pharmacologic Actions of Catecholamine Receptors

Receptor	Receptor Activity	Primary Location
$Beta_1$	Positive inotropic and chronotropic action; increased AV conduction	Heart (atria, ventricle, AV node)
$Beta_2$	Peripheral vasodilation	Arterioles, arteries, veins, bronchioles
$Alpha_1$	Arteriolar vasoconstriction	Arterioles
$Alpha_2$	Presynaptic inhibition of norepinephrine release	Sympathetic nerve endings, CNS
Dopaminergic-1	Renal and mesenteric vasodilation, natriuresis, diuresis	Kidneys

NOTE: AV = atrioventricular; CNS = central nervous system.
SOURCE: From Sonnenblick EH, LeJemtel TH, Frishman WH. Digitalis preparations and other inotropic agents. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics.* New York: McGraw-Hill; 1997:246. Reproduced with permission from the publisher and authors.

Beta-adrenergic receptors can be divided into $beta_1$ and $beta_2$ subtypes. $Beta_1$ receptors are located in the myocardium, where they mediate positive inotropic, chronotropic, and dromotropic effects.[186] Their activation occurs primarily through norepinephrine released from neurons in the heart. $Beta_2$ receptors are located in vascular smooth muscle, where they mediate vasodilatation, and in the sinoatrial node, where they are chronotropic. In general, $beta_2$ receptors are activated by circulating catecholamines released from peripheral sites such as the adrenal medulla.

Another type of receptor, which has been termed the *dopaminergic receptor,* is localized to the mesenteric and renal circulation and mediates arterial vasodilatation. The physiologic and pharmacologic actions of various catecholamines depend on which receptor they activate, both in the heart and in the periphery (Tables 21-4 and 21-5).

Norepinephrine has potent alpha$_1$ and beta$_1$ activity. When norepinephrine is released from cardiac nerve endings, as occurs in normal exercise, myocardial contractility and heart rate are augmented. When norepinephrine is administered exogenously, its major action is to stimulate alpha$_1$ receptors, leading to marked peripheral arterial vasoconstriction. Thus, norepinephrine has been used to increase arterial blood pressure in the presence of severe hypotension to maintain blood flow to vital organs. Long-term renal vasoconstriction from continued norepinephrine administration may produce ischemic renal damage, including acute tubular necrosis, so that prolonged use, i.e., for more than 24 to 48 h, is usually untenable. For a failing heart, this peripheral vasoconstriction also provides an undesirable added pressure load (afterload), which tends to vitiate the potential benefits of beta$_1$ stimulation.

Dopamine[188] has both alpha$_1$ and beta$_1$ activity but also stimulates dopaminergic receptors in the renal vasculature to produce arterial dilation and increased renal blood flow. Its beta$_1$ effects in the heart occur largely through the release of endogenous norepinephrine, which may be largely depleted in a failing heart. As doses of dopamine are increased, conversion to norepinephrine also occurs, which tends to produce relatively more pressor effects than myocardial inotropic stimulation (Table 21-4). As such, the benefits of dopamine administration, if any, occur at low doses (e.g., 0.02 mg/kg per minute), where it may induce renal arterial vasodilatation. In general, it is employed in association with more potent inotropic agents (e.g., dobutamine).

Dobutamine[189,190] is a synthetic variant of the catecholamines whose structure has been altered to optimize the hemodynamic response in the dog, characterized by an increase in cardiac output and a decrease in ventricular filling pressure with little change in heart rate. Since arterial pressure also rises modestly, peripheral vascular resistance must of necessity fall. The positive inotropic activity of dobutamine is mediated by direct stimulation of beta$_1$-adrenergic receptors in the myocardium (Table 21-4). It is unclear why a concomitant increase in heart rate does not always occur. One possibility is that an increase in cardiac output that increases arterial pressure serves to buffer any increase in heart rate reflexly. Given its capacity to increase cardiac output and reduce filling pressures without substantial changes in heart rate, dobutamine has been used widely to treat severe acute LV failure in the absence of profound hypotension, which is poorly responsive to diuretics and vasodilators (Fig. 21-7). This may be seen after a very large myocardial infarction or in acute decompensation in the course of chronic CHF. In the presence of severe hypotension, the beta$_2$ stimulation of dobutamine may be harmful, and the administration of an alpha$_1$-stimulating vasoconstrictor such as norepinephrine or higher-dose dopamine also may be necessary to increase arterial peripheral resistance.

Dobutamine infusion generally is begun at 2 μg/kg per minute and titrated to optimize cardiac output while reducing LV filling pressure. Tachycardia is avoided carefully to avoid increasing myocardial oxygen demands and inducing ischemia. The effects on myocardial oxygenconsumption (MVO_2) are complex.[190] While the increase in contractility will increase MVO_2, a decrease in heart size will tend to reduce it. The end result is generally a modest increase in MVO_2 induced by dobutamine. With a better maintained arterial pressure and reduced LV diastolic pressure in the absence of tachycardia, coronary perfusion pressure also may be increased. The major side effects of dobutamine are an excessive increase in heart rate with high doses and ventricular arrhythmias, both of which may mandate dose reduction and even drug discontinuation. Tachyphylaxis also may occur to a variable degree. In general, once hemodynamic benefits are attained, dobutamine is withdrawn slowly. In some cases this has not been possible, and sustained administration becomes necessary, which may require portable pumps for administration at home. The outcome in this circumstance is generally dire.

In chronic CHF, the patient commonly is maintained on vasodilators such as ACE inhibitors, loop diuretics, and digoxin. Nevertheless, episodes of acute decompensation may intervene, characterized by increased pulmonary congestion and edema and reduced renal function with increasing fluid accumulation (Fig. 21-7). The in-hospital addition of dobutamine, with or without milrinone (see below), using a Swan-Ganz catheter to monitor hemodynamics, provides for an increase in cardiac output with a decrease in filling pressures, which, with added diuretics, may help restore a steady state for a variable period. Dopamine, at a low dose, commonly is used concomitantly to augment renal blood. This generally requires a short hospitalization and temporary hemodynamic monitoring. In CHF, norepinephrine is used only for a

limited time to treat severe hypotension and shock unresponsive to dopamine and dobutamine, and then the outcome is generally very poor.

Phosphodiesterase Inhibitors and Other Agents

The adenyl cyclase-cyclic AMP system also can be activated beyond the beta receptor. Hormones such as glucagon activate the system and can increase myocardial contractility acutely despite $beta_1$ blockade.[191] While intravenous glucagon administration is useful in overcoming beta-adrenergic blockade when necessary, glucagon may induce gastric atony and nausea, and this has limited its more generalized use.

Amrinone and milrinone are prototypes of cardiotonic agents that activate the adenyl cyclase system through inhibition of the enzyme that breaks down cyclic AMP, phosphodiesterase (PDE) III.[192,193] Type III PDE inhibitors decrease the breakdown of cyclic AMP in the myocardium and increase cyclic guanidine monophosphate (cyclic GMP) in vascular smooth muscle, resulting in an increase in myocardial contractility as well as arterial and venous vasodilatation. Other members of this class of drugs include enoximone and pimobendan, although only intravenous amrinone and milrinone have been approved by the FDA for the treatment of acute heart failure. The mechanisms by which vasodilatation occurs are not completely understood. Increased cyclic GMP induces phosphorylation of myosin light-chain kinase, which decreases sensitivity to calcium and calmodulin. In the heart, inotropism may relate not only to increased cyclic AMP-mediated calcium availability for contraction and increased rates of its removal for relaxation but also to increased sensitivity of the contractile system for calcium.[194] Both amrinone and milrinone,[193] which are available as intravenous agents, have substantial ability to augment cardiac output while reducing both RV and LV filling pressures. The lowering of filling pressures is greater than that seen with dobutamine. Dilatation of the pulmonary arterial vasculature is also a very useful therapeutic effect. Arterial pressure tends to be reduced, while an increase in heart rate may occur. Since dobutamine increases cyclic AMP and milrinone reduces its breakdown, the combination of these agents is substantially more potent than is either agent alone.[193] When either dobutamine or milrinone is utilized, ectopic activity may be increased; this requires careful supervision in their use. PDE III inhibitors are also orally active and produce the same hemodynamic improvement seen with intravenous use. In longer-term oral use, however, increased mortality was seen with the use of milrinone, especially in the presence of class IV heart failure.[195] This increased mortality might have been due to the relatively short action of this agent (90-min half-life), which leads to large peaks and valleys in dosing and concomitant arrhythmias. For the time being, this has vitiated clinical study of these agents in oral formulations, but more stringent control of the use of this class of agents as adjuncts to other agents ultimately may increase their value, especially in improving quality of life in the terminal and short-term outcome of very severe CHF.

NEWER INOTROPIC AGENTS

Agents under investigation include the inodilatory benzimidazoline PDE inhibitors, such as levosimendan, which acutely increase cardiac output and reduce filling pressure while improving exercise tolerance in patients with CHF.[196] Levosimendan and other drugs in this class (MCI-154, EMD 53998, EMD 57033) may have additional effects to enhance calcium binding to troponin-C, a calcium-sensitizing action (Fig. 21-9).[196-198] Theoretically, this could enhance the contractile response for a given amount of cytolytic Ca^{2+}, which could lead to less arrhythmogenicity. This may be an important consideration since the activation of the cyclic AMP system may be detrimental in inducing tachycardia and arrhythmias. Clinical trials evaluating the efficacy and safety of levosimendan are in progress. Preliminary results from one study that compared levosimendan to dobutamine [Levosimendan versus Dobutamine (LIDO)] demonstrated comparable hemodynamic activities with less chest pain and arrhythmia with levosimendan. The critical issues to be addressed, now that acute efficacy is apparent, are whether these agents will improve symptoms, i.e., reduce morbidity, and/or improve mortality.

ADJUNCTIVE THERAPIES

As was mentioned earlier, patients with heart failure require treatment of underlying disease processes that may be aggravating the myopathic process. Systemic hypertension should be treated vigorously. In diabetes, hyperglycemia should be controlled. Aspirin prophylaxis and cholesterol-lowering drugs should be used in patients with coronary artery disease. It is not known whether estrogen replacement therapy in

postmenopausal women can modify the course of heart failure.[199]

Heart failure patients with mental depression have an increased mortality risk. The tricyclic antidepressant drugs have been associated with myocardial depression and probably are contraindicated in heart failure patients. However, the selective serotonin reuptake inhibitors have a favorable risk profile in cardiac patients and could be considered an adjunctive treatment for relieving mental depression. However, many of these drugs interfere with the hepatic cytochrome P450 system, and that might affect the metabolism of drugs being used to treat heart failure (see Chap. 81).

Beta blockers should be considered in all patients who survive a myocardial infarction with or without ventricular dysfunction. As was described earlier, carvedilol, metoprolol, and bisoprolol should probably be the beta blockers of choice in patients with symptomatic mild to moderate CHF of ischemic or nonischemic origin. Propranolol, metoprolol, atenolol, or timolol should be used in myocardial infarction survivors who are asymptomatic with and without LV dysfunction.

Patients with CHF are liable to develop venoembolic disease and systemic emboli from intracardiac mural thrombi. These embolic events are major causes of morbidity and mortality in CHF. In patients with atrial fibrillation and CHF, with and without mitral stenosis, anticoagulation is indicated. In patients with normal sinus rhythm and cardiomyopathy, the role of prophylactic anticoagulation with warfarin is not well defined.[3] A cohort analysis of the SOLVD population focused on the relation between warfarin use and the risk of all-cause mortality and found a beneficial effect with an anticoagulant.[200] Most of this benefit appeared to relate to reduced ischemic events. It is more difficult to anticoagulate patients with CHF because of drug-drug interactions, malabsorption of medications, varying perfusion of the liver, and malnutrition.[201] Patients with CHF who have developed a phlebothrombotic process or who have definite evidence of ventricular mural thrombi and systemic embolism should receive warfarin despite the potential problems with the regulation of anticoagulation in these patients.

Patients with heart failure have a markedly increased prevalence of ventricular ectopy and incidence of sudden death. These patients should be assessed for hypokalemia, hypomagnesemia, hypoxia, infection, and the use of antidepressant drugs. Many antiarrhythmic drug regimens have negative inotropic actions and may aggravate the heart failure process. Amiodarone and beta blockers have been used in patients with LV dysfunction with less risk involved and are probably the drugs of choice when treatment of ventricular ectopy is considered.[202,203] There is little evidence to show that antiarrhythmic drug therapy changes the natural history of advanced CHF.[203] Amiodarone also can be used to treat atrial arrhythmias with and without digoxin and calcium channel blockers.

DIASTOLIC DYSFUNCTION

Diastolic dysfunction of the left and right ventricles often leads to all the signs and symptoms of systolic dysfunction, but the therapeutic approach varies for these two conditions. Often, there is significant LV hypertrophy present, and aggressive management of systemic hypertension is required.[202,204] These patients develop significant congestion, and so diuretics are often necessary. With hypovolemia from other diseases, however, patients are prone to develop hypotension. The effects of diuretics in these patients should be monitored carefully. Digoxin is probably of no use unless the patient is in atrial fibrillation, and vasodilating drugs with peripheral venodilator actions may cause hypotension. The role of ACE inhibitors, angiotensin II receptor blockers, and other vasodilator drugs are not well defined in this condition, and they may cause hypotension. Large clinical trials have begun to include patients who have diastolic dysfunction as the primary cause for clinical heart failure. Studies with the ACE inhibitor perindopril and the angiotensin receptor blocker candesartan are in progress.

Tachycardia must be avoided. Rate-lowering calcium blockers (verapamil, diltiazem) are useful drugs of choice for reducing elevated blood pressure, keeping the heart rate under control, and improving ventricular compliance.[205] Beta-adrenergic blockers are first-line therapy for maintaining relative bradycardia to maintain time for diastolic ventricular filling. However, their effects on ventricular compliance are not as well defined. Both verapamil and beta blockers can be used with caution in patients with heart failure caused by hypertrophic cardiomyopathy.

DRUG THERAPIES UNDER INVESTIGATION

Natriuretic Peptides and Their Enhancers

Conventional diuretics are associated with undesirable stimulation of the renin-angiotensin axis, sympathetic nervous system, and vasopressin. ANP and brain natriuretic peptide (BNP), by contrast, induce diuresis and natriuresis while concomitantly suppressing the renin-angiotensin axis with dilation of peripheral vascular beds.[206-210] In heart failure, despite high endogenous ANP and BNP levels, a state of intense sodium avidity prevails.[206,207,210,211] Attempts at restoring the efficacy of ANP in heart failure include infusing ANP intravenously and administering a neutral endopeptidase inhibitor. Prolonged infusion of ANP in patients with moderate CHF (NYHA class II to III) has been associated with doubling of the urine flow rate and a three- to fourfold increase in sodium excretion.[212] When ANP is infused in patients with moderate to severe CHF (NYHA class II to IV), however, the natriuretic and diuretic response is attenuated.[207,208]

Favorable hemodynamic responses have been observed after ANP infusion, including a fall in pulmonary capillary wedge pressure (PCWP), plasma renin activity, and systemic vascular resistance and an increase in cardiac output.[207,208,213] When ANP and furosemide are administered concomitantly, urine volume and sodium excretion are not augmented, although in this setting ANP does maintain its inhibitory effect on the renin-angiotensin axis and on sympathetic discharge.[214]

Neutral endopeptidase (NEP) inhibitor administration is associated with a rise in endogenous ANP levels resulting from the inhibition of ANP metabolism.[210,215-219] In a canine model of CHF, Cavero and coworkers reported that at similar ANP levels, NEP inhibitor treatment was associated with a better diuretic and natriuretic effect than was an ANP infusion.[215] In human studies, however, the two modalities appear to have similar natriuretic and diuretic effects. In 1989, Northridge and colleagues were the first to report diuresis after NEP inhibitor infusion in six patients with mild CHF (mean ejection fraction, 37 percent).[218] A 60 percent increase in the 4-h urine sodium excretion was observed, associated with a three- to fivefold rise in ANP levels.[218] The same investigators compared the renal and hemodynamic effects of NEP inhibitor administration to low-dose furosemide in mild CHF.[220] Eighteen patients were randomized to receive an NEP inhibitor, candoxatrilat 200 mg twice daily, candoxatrilat 400 mg twice daily, or furosemide 20 mg twice daily. The administration of a NEP inhibitor was associated with diuresis; however, the change in urine flow rate and sodium excretion from baseline was greater in the low-dose furosemide group. Although its diuretic effect was modest, the NEP inhibitor was associated with desirable hemodynamic effects, including marked preload reduction (PCWP decreased 40 percent), and with no stimulation of plasma renin activity. In comparison, the group given furosemide experienced only a 15 percent reduction in PCWP and a threefold rise in plasma renin activity.

The natriuretic properties of NEP inhibitors are mediated by inhibition of sodium reabsorption within the renal tubule, since they do not alter renal hemodynamics (GFR or renal plasma flow) significantly. This is supported by their association with an increased fractional excretion of lithium, a marker of proximal tubular reabsorption.[215,217] In addition to inhibiting ANP degradation, the NEP inhibitors inhibit the breakdown of bradykinin and BNP. They also have been shown to enhance prostacyclin synthesis, another mechanism by which they may exert a natriuretic effect.[221,222] In the most severe stages of CHF (NYHA class III to IV; ejection fraction, 22 percent), an impaired renal response to NEP inhibitor treatment can be expected. Munzel and colleagues[209] reported an unpredictable natriuretic response to candoxatrilat in nine patients with severe CHF. Three patients had no diuresis, five had a minimal response, and one (cardiac index > 2.5 L/min) had a good diuresis. The natriuretic response correlated closely with the cardiac output, which theoretically was most likely related to renal perfusion status.

In contrast to ANP, the natriuretic effect of BNP infusion is surprisingly and significantly more pronounced in patients with CHF than in normal patients, even when similar BNP levels are infused.[210] Yoshimura and colleagues infused BNP in normal patients and in those with NYHA class II to IV CHF and observed a fivefold rise in urine flow rate and a tenfold increase in sodium excretion in the CHF group.[210] In normal patients, diuresis and natriuresis were only three- to fourfold that of baseline, respectively. BNP infusion also was associated with a reduction in PCWP, systemic vascular resistance, and aldosterone levels as well as a rise in ANP levels.

It is unclear why high-dose BNP infusion is not associated with an attenuated natriuretic response in CHF, as is seen with ANP infusion. Like the process in ANP, inhibition of NEP 24.11 with candoxatril prevents the metabolism of BNP, increasing BNP levels by about 50 percent.[222] Because of its enhanced natriuretic effect at high infusion rates and prolonged duration of action compared with ANP, BNP appears to be the most promising natriuretic peptide candidate for future investigation and potential clinical therapeutic use.

When the BNP nesiritide is infused in patients with CHF, it reduces pulmonary capillary wedge pressure and systemic vascular resistance while increasing stroke volume and cardiac index. It suppresses plasma aldosterone but does not change plasma renin, norepinephrine, or epinephrine. It increases renal plasma flow and GFR as well as insulin excretion without affecting blood pressure and heart rate.[223] Nesiritide was recently considered by the FDA for intravenous clinical use in the treatment of acute heart failure, but excessive hypotension caused by treatment in studies has delayed its approval.[224] A recent study demonstrated that twice-daily subcutaneous injections of nesiritide can improve hemodynamics in patients with CHF, and this may provide a new therapeutic approach to chronic therapy.[225]

It is believed that the attenuation of responsiveness to endogenous ANPs with endopeptidase inhibition is due to activation of the RAAS. This has prompted the development of agents that both augment the action of ANP and block the RAAS, the dual NEP-ACE inhibitor drugs (e.g., omapatrilat, sampatrilat), which are now being examined in patients with systemic hypertension and CHF.[226]

In patients with heart failure, omapatrilat has been shown to be more effective in improving symptoms and reducing the combined risk of death and hospitalization than is the ACE inhibitor lisinopril (IMPRESS trial). In addition, fewer omapatrilat-treated patients exhibited signs of renal dysfunction. Results from a substudy showed that omapatrilat caused a greater improvement in arterial compliance.[227] Omapatrilat is being compared to enalapril in a long-term survival study (OVERTURE Study).

Another naturally occurring natriuretic peptide being evaluated for the treatment of patients with heart failure is adrenomedullin,[223,228] a hypotensive peptide originally isolated from human pheochromocytoma.

Endothelin Inhibitors

Endothelin-1 exhibits potent inotropic activity in isolated hearts, cardiac muscle strips, isolated cells, and instrumented intact animals.[229] High-affinity receptors for endothelin have been demonstrated in both the atria and the ventricles.[230,232] Intravenous endothelin-1 produces a delayed prolonged augmentation of LV performance in addition to its biphasic vasoactive effects of transient vasodilation followed by sustained vasoconstriction.[229]

Endothelin is also a potent secretagogue of atrial natriuretic factor, which is a naturally occurring antagonist of endothelin that acts by inhibiting its release.[233] The endothelin-A receptor appears to mediate endothelin's actions of vasoconstriction and the stimulation of the ANP secretion, and the endothelin-B receptor mediates endothelin-induced vasodilatation and activation of the RAAS. Urinary water excretion is mediated through both receptors, but sodium excretion is mediated through the endothelin-A receptor.

Increased endothelin levels have been described in patients with CHF[234-239] that are predictive of increased mortality risk.[235] It also has been suggested that increased endothelin levels may play an important role in the increased systemic vascular resistance observed in CHF.[234,240,241] Endothelin-1 levels decrease with therapy and have been found to correlate significantly with symptomatic improvement. It therefore appears that endothelin-1 is an independent, noninvasive predictor of functional and hemodynamic response to therapy in patients with CHF.[242] Increased endothelin levels also have been observed in the plasma and hearts of cardiomyopathic Syrian hamsters[243] and in the cells of endothelial cells infected with *Trypanosoma cruzi* in experimental Chagas' cardiomyopathy.[244]

There is early clinical evidence that treatment with endothelin-A receptor antagonists and endothelin-converting enzyme inhibitors can influence the course of human heart failure favorably.[245] Some of these agents are being investigated in clinical heart failure trials (bosentan, BMS193884, LU135252).[246,247] ACE inhibitors also may benefit patients with heart failure because of their antiendothelin actions.[248,249]

Vasopressin Antagonists

Vasopressin, which usually is elevated in patients with heart failure, correlates with the severity of disease and the incidence of hyponatremia. In human beings, this aquaretic hormone is released in response to the level of plasma osmotic pressure or osmolality. Its release also is influenced by hemodynamics in the setting of heart failure, a decrease in mean arterial pressure, a decrease in cardiac output, a decrease in atrial pressure, hormones such as angiotensin II, increased sympathetic nervous system activation, and a variety of less common stimuli.[250]

Two physiologically important subtypes of vasopressin receptors are the V1 and V2 receptors. V1 is found primarily in vascular smooth muscle and promotes vasoconstriction. The V2 receptor is found in renal collecting duct cells and promotes reabsorption of free water in the kidney. Vasopressin elevations in heart failure could induce vasoconstriction and increase renal water retention and thirst.

The first peptide vasopressin antagonists (V2 receptor specific) were developed in the 1980s.[251] More recently, combined V1A/V2 receptor antagonists have become available. In human studies vasopressin antagonists have been shown to reverse the impaired urinary diluting capacity seen in chronic heart failure, increase sodium free water excretion, correct dilutional hyponatremia, decrease urinary aquaporin-2 (AQP-2) excretion, promote peripheral vasodilation, and improve cardiac output.

Two orally active V2 receptor antagonists (WAY-VPA985 and SR49-059) and a combined V1A/V2 receptor antagonist YM087 are being evaluated in clinical trials in patients with class III and IV heart failure who are currently on standard treatment that includes continuous inotropic drug infusion.

Adenosine Receptor Antagonism

Blockade of adenosine (A1) receptors in animals can induce a brisk natriuresis without a kaliuretic effect,[252] an observation that has been confirmed in humans in short-term studies using FK 4531, a selective A1 receptor antagonist.[253-255] The mechanism for this lack of kaliuretic action has not been elucidated; neither has the safety and efficacy of this drug class in long-term clinical trials.

Oral Dopamine Receptor Agonists

The unique, selective vasodilatory and inotropic actions of intravenous dopamine are limited by the lack of an oral formulation. This has led investigators to develop newer dopamine agonists that are orally effective. Unlike L-dopa, which has been used in heart failure, these new drugs do not cross the blood-brain barrier but maintain most of the pharmacologic activity of dopamine.[256]

Ibopamine, which is an orally active derivative of dopamine, has dopaminergic D_1 and D_2 activity with alpha- and beta-adrenergic actions. In therapeutic doses, it is a peripheral vasodilator and appears to have favorable cardiovascular and renovascular actions in patients with heart failure. The results of the Prospective Randomized Study of Ibopamine on Mortality and Efficacy in Heart Failure (PRIME-2), however, raised serious questions about the safety of ibopamine and agents of this class[257] in patients with heart failure. Fenoldopam is a selective D_1 agonist that has been used to treat patients with CHF and hypertension. Because of bioavailability problems with the oral formulation, only the intravenous form is used in patients with severe hypertension.[258] Dopexamine is an intravenous D_1 and $beta_2$-receptor agonist that is being studied in patients with CHF and low cardiac output states.

Inhibition of Immune Activation

Cytokines are a group of small pleiotropic endogenous peptides produced by a variety of cell types in response to a variety of different stimuli. Tumor necrosis factor-alpha (TNFα), interleukin-1α and -1β, and interleukin-6 are classified as "proinflammatory" cytokines. These substances are responsible for initiating the primary host response to bacterial infections as well as initiating the repair of injured tissues.[259]

Cytokines are involved in augmenting the expression of adhesion molecules and the enhanced cell-to-cell

interactions involved in inflammation. In addition, the proinflammatory cytokines are able to affect cardiovascular functioning by promoting LV remodeling, causing ventricular dysfunction, and uncoupling myocardial beta receptors.[259] They are elevated in the serum in various cardiovascular disorders and are often a marker of the severity of disease.[260]

TNFα was originally discovered in 1975 as a protein with necrotizing effects in certain transplantable mouse tumors.[261] More recently, this cytokine has been shown to exert a spectrum of pleiotropic effects in many different cell types.[262] The major biological role of TNFα is thought to be a host response to systemic infections, most notably gram-negative sepsis.[263] In fact, TNFα levels are elevated considerably in patients with septic shock, and TNFα has been implicated as an important mediator in the lethal effect of endotoxin, possibly causing the symptoms characteristic of the "shock state."

Many experimental and clinical studies have shown an association between depressed myocardial function and elevated levels of TNFα.[264] The basis of this association is not clear; however, there are studies suggesting that elevated levels of TNFα play a major role in causing myocardial depression, whereas other studies have concluded that TNFα is likely to play a role in the alleviation of this condition.[265] A third school of thought suggests that the elevated levels of TNFα are merely a marker that may indicate the stage of progression of the disease. Thus, although it is clear that there are elevated levels of TNFα in various cardiac diseases, the reasons for these increased levels and the mechanisms of their effects are not agreed on. Since there is a strong association and possibly a causative relationship between TNFα and CHF, various drug trials are looking at TNFα and its possible metabolic pathways as a therapeutic target in the treatment of heart disease.[266]

The drugs thalidomide and pentoxifylline have been shown in small studies to suppress the production of TNFα in patients with heart failure, with favorable effects on hemodynamics being reported.

A study is in progress evaluating the effects of a soluble recombinant human TNF-R fusion protein (etanercept) on the clinical course of patients with advanced heart failure.[267-269] Preliminary results suggest that etanercept will suppress the cardioinflammatory cytokines IL-1β and IL-6 while increasing the anti-inflammatory cytokine IL-10. These effects appeared to be associated with impaired clinical functioning and regression of ventricular remodeling. Other inflammatory cytokines may be therapeutic targets in the future.

A recent clinical trial evaluated the use of the intravenous immunoglobulin IgG in patients with a new onset of dilated cardiomyopathy, with no apparent benefit compared to placebo. In experimental studies, the cytokine interleukin-10 has been used successfully to treat viral myocarditis.[270]

Studies with prednisone and cyclosporine have shown no clinical benefit in the treatment of patients with dilated cardiomyopathy and myocarditis.[271-273]

Other approaches under consideration for attenuating the heightened inflammatory responses observed in patients with heart failure include monoclonal antibodies that interfere with complement activation and those which interfere with neutrophil adhesion and migration.

Nitric Oxide

Preliminary work is being done investigating inhaled nitric oxide, a vasodilator substance produced by the endothelium, as a possible treatment for CHF.[274-277] Arginine, a nitric oxide precursor, and agents that potentiate nitric oxide synthesis, are now potential directions for new heart failure therapies. To date, results with L-arginine use in patients with heart failure have been inconclusive. Nitric oxide donor substances are also being evaluated.[277]

Imidazoline Receptor Agonists

The drugs rilmenidine and moxonidine are centrally acting antihypertensive agents that decrease sympathetic outflow by stimulating nonadrenergic imidazole-l receptors in the brain. These drugs are similar to clonidine in their pharmacologic activities but cause less sedation. Modulation of the sympathetic

nervous system by decreasing central catecholamine release has been proposed as a therapeutic approach to prolonging life in patients with CHF. However, the results of a recent study using moxonidine in heart failure patients did not show any benefit on survival.[278]

Matrix Metalloproteinase Inhibitors

Matrix metalloproteinases and their inhibitors are biological proteins that are involved with the formation and breakdown of collagen and interstitial tissue. Matrix metalloproteinase activity is elevated in patients with heart failure, suggesting that these proteins may be contributors to myocardial remodeling and the worsening of symptoms. Matrix metalloproteinase inhibitors are being considered as treatments for heart failure.[279]

Supplementary Hormones and Antioxidants

Increasing experimental evidence and preliminary clinical data suggest that growth hormones may have beneficial effects in the treatment of heart failure. However, the mechanisms behind these favorable actions are not well understood.[280,281] Growth hormone exerts its effects either directly or indirectly through insulin growth factors.

In experimental studies, growth hormone has been shown to increase the force of contraction by increasing the number of myocardial cross-bridges and the amount of available calcium. Growth hormone also can enhance peripheral blood flow and increase skeletal muscle mass. Growth hormone has been shown to attenuate pathologic remodeling without inducing LV hypertrophy.

In patients with heart failure, growth hormone has been shown to improve LV systolic function and exercise tolerance while normalizing plasma levels of BNP. Long-term morbidity and mortality studies in patients with heart failure remain to be done.

Anabolic steroids have been evaluated in patients with heart failure. They have been shown to improve left myocardial performance, increase skeletal muscle, and improve the patient's sense of well being. However, there is little long-term morbidity and mortality experience with this treatment.

Metabolic Enhancers and Antimetabolites

Abnormalities of energy metabolism often are cited as key elements in the progression of the worsening LV dysfunction that characterizes heart failure. Ranolazine is one of a class of partial inhibitors of fatty oxidation (pFOX inhibitors). By shifting adenosine triphosphate production away from fatty acid oxidation and toward carbohydrate oxidation, ranolazine reduces oxygen demand without decreasing cardiac work and maintaining coupling of glycolysis to pyruvate oxidation, which minimizes lactate accumulation. Ranolazine may be useful as an antianginal drug, and in experimental heart failure studies it has been shown to improve LV performance.

Carnitine is a biological substance that plays an important role in the oxidation of long-chain fatty acids. It also allows for the removal of short- and medium-chain fatty acids from the cell. Carnitine also has been shown to facilitate the aerobic metabolism of carbohydrates.[282]

It has been demonstrated by investigators that myocardial carnitine levels are decreased in many pediatric and adult cardiomyopathies in which myocardial fatty acid metabolism is impaired. It has been proposed that the restoration of normal carnitine levels through the administration of exogenous L-carnitine would be of therapeutic value in heart failure through its ability to stimulate fatty acid metabolism.

The usefulness of oral L-carnitine for the treatment of pediatric cardiomyopathy is well established.[283] A few small studies in patients with heart failure have examined the effects of L-carnitine and have demonstrated improvements in hemodynamics, functional capacity, and survival.[282] A large randomized, placebo-controlled trial is still required to adequately assess the usefulness of L-carnitine in heart failure.

Coenzyme Q10(CoQ10), or ubiquinone, is an endogenous cellular membrane constituent that has been

shown to have antioxidant properties. Its central physiologic role is in mediating electron transport between nicotinamide adenine dinucleotide and succinate dehydrogenases and the cytochrome system.

CoQ10 has been suggested as a treatment for CHF in which low levels of the substance in the myocardium have been observed. Despite a theoretical benefit in patients with heart failure, trials with CoQ10 supplementation have not demonstrated any effectiveness.

Heart failure also has been associated with the accumulation of oxygen free radicals, which can cause cellular damage in the heart. At this juncture, treatments with various nutritive antioxidants (vitamins and minerals) and naturally occurring enzymatic free radical scavengers have not been associated with efficacy in patients with heart failure.

Antiapoptosis Therapy

An innovative approach to preserving myocardial function involves interventions that can interfere with programmed myocardial cell death (apoptosis), a natural process that is accelerated by aging, myocardial ischemia, hypertension, diabetes mellitus, and myocardial cell stretch (LV dilation). Utilization of AII receptor blockers and the infusion of insulin growth factor in rats can inhibit the amount of myocardial apoptosis by 50 percent and suggests future therapeutic approaches in human beings. Caspase, an enzyme essential to the apoptotic process, can be inhibited pharmacologically, with evidence of enhanced myocardial preservation in experimental animals.

Gene Therapy

In experimental studies, gene therapy has been shown to improve failing human cardiac myocyte function.[284,285] It was demonstrated that the abnormal contraction, relaxation, and contraction amplitude-frequency relationship of isolated myocytes obtained from patients with dilated cardiomyopathy could be normalized by transfection of the myocytes in vitro with an adenovirus expressing the sarcoplasmic reticulum Ca^{2+}-ATPase, SERCA2a; transfection increased Ca^{2+}-ATPase activity 80 percent. The enhanced function of the myocytes was associated with corresponding improvements in the kinetics of the Ca^{2+} transient. The isolated myocyte results confirm previous in vitro findings by Meyer and associates in normal rabbit myocytes that indicated that adenoviral transfection of SERCA2a can improve contraction and relaxation.[286]

Nonpharmacologic Aspects of Treatment

Nonpharmacologic factors contribute to the overall efficacy of care. Weight reduction by dieting is generally advisable when obesity is present. Often, however, nutritional status is compromised and cachexia is present.[287] Limitation of salt intake is important and may delay the time when diuretics may be necessary as well as reduce the amount required. In advanced heart failure, strict salt limitation is essential, although it is difficult to maintain. A diet containing less than 20 g/day of salt is desirable. Intake of fluids should be reduced to 1 to 1.5 L every 24 h in patients with advanced heart failure, with or without hyponatremia, except in warm climates. As will be stressed in relation to the use of diuretics, a readable weight scale is essential, and daily weights are of great value in judging therapy.

Smoking should be discouraged strongly in all patients, especially in the presence of obstructive vascular disease. Alcohol is a cardiac depressant in general and should be forbidden if an alcoholic cardiomyopathy is suspected. In all other cases, daily intake of alcohol probably should not exceed 40 g/day in men and 30 g/day in women, although there are insufficient data on the effects of alcohol in patients with mild heart failure to support these recommendations.[288]

Patients should routinely receive vaccinations against influenza and pneumococcal pneumonia.

Deconditioning related to muscular inactivity in association with muscular atrophy and decreased metabolic vascular dilatation is a major factor in reducing exercise performance as heart failure progresses.[289] The 6-min walk test is a semiquantitative assessment tool for assessing functional capacity before and after treatment.[290] Low-level exercise, such as walking, should be encouraged, whereas strenuous isometric

activities should be discouraged. Specific exercise training needs to be tailored to the appropriate level of the patient's disease and always should be performed under medical guidance. Isometric exercise should be avoided. In patients with stable heart failure, there is evidence that appropriate physical exercise and exercise training can lead to improvements in both exercise capacity and the quality of life of the patient, although the effect of this intervention on the prognosis is unknown.[291-293] Specific recommendations include dynamic aerobic exercise (walking) three to five times a week for 20 to 30 min and cycling for 20 min at 70 to 80 percent of the peak heart rate five times a week.[291,292]

In patients with acute heart failure and in those with exacerbations of chronic heart failure, rest is advisable. Prolonged rest, however, should not be encouraged in patients with stable chronic heart failure.

Surgical Treatment

BIVENTRICULAR CARDIAC PACING

The use of dual-chamber pacemaker technology to treat patients with chronic heart failure remains controversial.[294-300] It has been proposed that by altering the timing, sequence, and site of cardiac electrical activation in patients with heart failure, hemodynamic abnormalities may be favorably altered.

The subgroups of patients with heart failure who might benefit include (1) those with an atrial contraction too early in relation to the onset of ventricular contraction during native conduction, (2) patients with long atrioventricular (AV) conduction and significant shortening of the diastolic filling period because of presystolic mitral or tricuspid regurgitation or both, and (3) certain patients with ECG PR intervals >200 ms in whom dual-chamber pacing at an optimal AV delay eliminates diastolic mitral regurgitation and improves cardiac output.[294]

In patients with heart failure, it was shown that single-site pacing at the site of greatest intraventricular conduction delay was as beneficial in improving hemodynamics as was biventricular pacing[300]

A blinded randomized clinical trial is in progress [The Multicenter InSync Randomized Clinical Evaluation (MIRACLE)] evaluating a new biventricular myocardial conduction resynchronization device (InSync) in 300 patients with class III and IV heart failure. End points include measures of functional status, quality of life, and effects on peak oxygen consumption and echocardiographic indices of both systolic and diastolic function.

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

In patients with documented sustained ventricular tachycardia or ventricular fibrillation, an implantable cardioverter defibrillator is highly effective in treating recurrences of these arrhythmias by antitachycardia pacing or cardioversion-defibrillation, reducing morbidity and the need for rehospitalization. There is some evidence that the efficacy of this device in terminating ventricular tachycardia or ventricular fibrillation may translate into improved survival[3,301] in patients with heart failure, but no definite proof exists. Studies are in progress that are designed to address this issue.[302,303]

The benefit of implantable cardioverter defibrillation therapy may decrease with increasing degrees of heart failure.[304] Preliminary data suggest improved survival compared with conventional antiarrhythmic therapy, including amiodarone, in patients with asymptomatic LV dysfunction or mild to moderate heart failure.[305,306] For patients with severe heart failure and documented sustained ventricular tachyarrhythmias, implantable cardioverter defibrillators at present should be considered a bridge to transplantation, but their effectiveness in this setting has not been proved.

LEFT VENTRICULAR ASSIST DEVICES

In a patient who cannot be sustained with medical therapy and for whom ultimate cardiac transplantation is anticipated, an LV mechanical support device (LVAD) has been successful in serving to maintain ventricular function as a bridge to transplantation. With two portable devices now approved by the FDA, the question remains whether they eventually can be used as long-term destination therapy for patients with

end-stage heart disease. Preliminary results from randomized studies have demonstrated a 100 percent increase in survival at 2 years in patients with class IV heart failure who are ineligible for heart transplantation and are maintained on standard medical therapy. However, recent data have shown that LVAD implantation in heart failure patients is associated with activation-induced T-cell death and immune dysfunction, putting recipients at risk of serious infection.[307]

HEART TRANSPLANTATION

Heart transplantation is now an accepted mode of treatment for end-stage CHF. Transplantation significantly increases survival, exercise capacity, return to work, and quality of life compared with conventional treatment provided that proper selection criteria are applied. Recent results in patients on triple immunosuppressive therapy have shown a 5-year survival of approximately 70 to 80 percent[308] and a return to full- or part-time work or seeking employment after 1 year in about two-thirds of the patients in the best series.[309]

Patients who should be considered for transplantation are those with severe CHF with no alternative form of treatment. Predictors of poor survival are taken into account. The patient must be willing and able to undergo intensive medical treatment and be emotionally stable to withstand the many uncertainties that are likely to occur both before and after transplantation.

Besides a shortage of donor hearts, the main problem in heart transplantation is rejection of the allograft, which is responsible for a considerable percentage of deaths in the first postoperative year. The long-term outcome is limited predominantly by the consequences of immunosuppression (infection, hypertension, renal failure, malignancy, accelerated progression of atherosclerotic vascular disease) and by transplant coronary artery disease.

Experimental work is under way looking at xenotransplantation of myocardial cells and entire organs (pig hearts) as potential heart failure treatment. The humoral immune response of the recipient against the graft remains a preeminent hurdle. There is also limited information regarding the physiology of the pig heart as a replacement for the human heart.

CORONARY REVASCULARIZATION SURGERY

A major and important surgical approach to ischemic cardiomyopathies is reperfusion of ischemic tissue by coronary bypass surgery.[310] This is based on the concept that transiently ischemic myocardium (stunning) and myocardium with reduced flow (hibernating) have reduced contractility, which may return to normal with restoration of adequate coronary blood flow. Moreover, revascularization of ischemic regions of the ventricle may prevent recurrent infarction in this area and thus help prevent further deterioration of ventricular function. In such patients, it is necessary to establish that significant amounts of viable tissue remain in an akinetic or hypokinetic zone; this can be accomplished with nuclear techniques such as a 24-h thallium perfusion study and positron emission tomographic scanning.[311] If contractile activity also can be elicited, as shown in echo studies with low-dose dobutamine stimulation[22] or postextrasystolic potentiation, coronary bypass surgery provides a good chance to stabilize or improve ventricular function[310,312,313] and enhance survival.[314] In this era, every patient with ischemic cardiomyopathy should be evaluated for possible revascularization and assumed to be a candidate until proved otherwise.

OTHER PROCEDURES

Other surgical approaches to the dilated heart have included the recent concept of removing a segment of the left ventricular wall, the "Battista operation," to reduce LV volume and thus wall stress. The surgical risk is immense, and specific benefits have not been established.[315]

Enhanced external counterpulsation is a noninvasive therapy consisting of gated diastolic sequential leg compression, producing hemodynamic effects similar to those from an intraaortic balloon pump. The procedure has been shown to improve exercise capacity and LV failure in patients with heart failure who already are receiving medical therapy.[316]

Immunoabsorption procedures have been directed against $beta_1$-adrenergic receptor antibodies, with clinical improvement found in patients with heart failure.[317]

The General Approach to Therapy in Congestive Heart Failure

Appropriate therapy in CHF depends on the stage of the disease process (Table 21-6 and Figs. 21-11 and 21-12). While one seeks to define and treat the factors that initiated the process, one also attempts to reduce symptoms and prolong life. Thus, with initial damage, e.g., after a large myocardial infarction, ACE inhibition or angiotensin II receptor blockade is indicated. Beta-adrenergic receptor blockers also are indicated at this stage because of mortality reduction. As failure progresses to more symptomatic phases, beta blockers also appear to be indicated, along with ACE inhibition. Once symptoms increase and edema and central congestion occur, loop diuretics and spironolactone become useful to maintain dry weight. To prevent further ischemic tissue loss, other measures, such as cessation of smoking and appropriate lipid control, are essential. Digitalis glycosides, especially in modest doses, are indicated when class II to III symptoms occur.

Table 21-6: Chronic Heart Failure-Choice of Pharmacologic Therapy

	ACE Inhibitor	Diuretic	Potassium-Sparing Diuretic	Cardiac-glycosides	Vasodilator (Hydralazine/ISDN)	Beta Blocker
Systolic dysfunction						
Asymptomatic LV dysfunction	Indicated in some	Not indicated (unless ↑ BP)	Not indicated	Only with atrial fibrillation	Not indicated	After MI
Symptomatic HF (NYHA-II)	Indicated			(a) When atrial fibrillation is present or (b) when improved from more severe HF in sinus rhythm	If ACE inhibitors are not tolerated	Indicated (under specialist care)
- Fluid retention		Indicated in some	Not indicated			
+ Fluid retention		Indicated	Persisting hypokalemia			
Worsening/severe HF (NYHA III-IV)	Indicated	Indicated, combinations of diuretics	Persisting hypokalemia; spironolactone for efficacy	Indicated	If ACE inhibitors are not tolerated or insufficient	Indicated (under specialist care)
End-stage HF (persisting NHYA IV)	Indicated	Indicated, combinations of diuretics	Persisting hypokalemia; spironolactone for efficacy	Indicated	If ACE inhibitors are not tolerated or insufficient	Indicated (under specialist care)

[a]Preliminary data from the DIG (Digitalis Investigation Group) trial suggest that digoxin also may be indicated in NYHA II heart failure and sinus rhythm.
NOTE: ACE, angiotensin-converting enzyme; BP, blood pressure; HF, heart failure; ISDN, isosorbide dinitrate; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association.
SOURCE: From Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. *Eur Heart J* 1997; 18:748. Reproduced with permission from the publisher and authors.

In acute decompensation, as may occur after a massive myocardial infarction or intermittently in class III to IV chronic heart failure, more aggressive therapy may be required, along with hospitalization for Swan-Ganz catheter monitoring. In this circumstance, short-term stimulation of the myocardium with dobutamine and/or milrinone, along with increasing amounts of intravenous diuretics, may be required for short periods to regain a stable state. At present there are no oral agents of this nature available to extend this care to outpatients, and if dobutamine cannot be withdrawn, occasional administration by an external pump is required. Such therapy presents a short outcome of days or months.

In summary, therapy for heart failure seeks the reversal or attenuation of the processes that initiated the syndrome while treating the patient to relieve symptoms and prolong life. The latter end is best achieved early in the disease process through prevention of further loss of myocardium (e.g., reperfusion) or reduction of loading (e.g., appropriate valve surgery or treatment of hypertension). In very late stages of the disease, relief of symptoms can now be accomplished with modest gains in life expectancy.

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Figure 21-1: The pathophysiology of heart failure progressing with time from the initial event, related to a loss of myocardium and/or a persistent overload, to the adaptive responses, including myocardial hypertrophy, and ultimately ventricular dilatation. Left ventricular (LV) dilatation augments diastolic wall stress that produces deformations of the ventricular wall and functional mitral regurgitation (MR) as well as further myocyte loss (apoptosis). Neurohumoral responses become activated with increased sympathetic tone, reduced parasympathetic tone, and activation of the renin-angiotensin system. These structural alterations constitute what is termed *ventricular remodeling*. With progression of these latter processes and with decreased ventricular capacity to augment cardiac output as required along with renal retention of sodium, central and peripheral edema ensue, with limitation of exercise performance. Thus, the syndrome of congestive heart failure (CHF) finally becomes manifest. Shown at the bottom of the figure are various studies addressing these phases of heart failure in terms of morbidity and mortality. GISSI, Gruppo Italiano per lo Studio dell a Sopravivenza nell'Infarcto Miocardio; CONSENSUS, Cooperative North Scandinavian Enalapril Study; SMILE, Survival of Myocardial Infarction; ISIS, International Study of Infarct Survival; SAVE, Survival and Ventricular Enlargement Trial; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation: V-HeFT, Veterans Administration Cooperative Vasodilator Heart Failure Trial; AIRE, Acute Infarction Ramipril Efficacy Study.

Figure 21-2: Ventricular remodeling and progression of ventricular dysfunction. Myocardial cell loss leads to ventricular remodeling, characterized by myocyte hypertrophy and elongation. An increase in ventricular volume (the Starling effect) helps maintain cardiac output (CO), but at the cost of increasing ventricular filling pressures. The increase in diastolic stretch and pressure produces further damage, including stretch-induced myocyte death (apoptosis), which amplifies the process of remodeling. With inadequate pump function, neurohumoral activation occurs with decreased vagal tone and enhanced sympathetic tone. With activation of the renin-angiotensin system and increased sympathetic tone, arterial vasoconstriction occurs with resultant maldistribution of blood flow. Decreased vagal and increased sympathetic stimulation induce tachycardia, and the latter system, along with the activated renin-angiotensin system, via angiotensin II can produce further myocyte death. In this manner, the process is self-perpetuating in that ventricular damage leads to remodeling, which in turn leads to further damage. These interrelated cycles thus provide therapeutic opportunities.

Figure 21-3: Progression of initial ventricular damage to sympathetic congestive heart failure. Data from the SOLVD trial of enalapril therapy, plotted in terms of LV ejection fraction and exercise capacity measured in terms of peak oxygen consumption (VO_2). Also shown are median plasma norepinephrine and plasma renin activity. The latter is shown in terms of patients who did or did not receive diuretics.

Figure 21-4: Evaluation of patients with congestive heart failure. Transthoracic Doppler and two-dimensional echocardiography provide a central modality to evaluate ventricular function and valvular abnormalities. Ventricular wall thickness and both end-diastolic and end-systolic volumes can be determined. With an ejection fraction (EF) more than 40 percent, coronary angiography is indicated in the presence of angina pectoris or evidence of significant ischemia. With an EF less than 40 percent, coronary arteriography is indicated since the underlying ischemic depression may be amenable to reperfusion by angioplasty or coronary bypass surgery. Nuclear imaging techniques are used to define viable ischemic myocardium, while stimulation of such myocardium with dobutamine or extrasystolic potentiation may indicate recoverable hibernating myocardium. Right ventricular biopsy may be indicated in the absence of coronary artery disease to rule out processes such as amyloid or sarcoid.

Figure 21-5: figuremeasure taged use of therapeutic agents in heart failure. Initial approaches include control of factors that may cause progression of heart failure and/or augment its manifestations. Hypertension requires control. Unanticipated tachycardia may augment oxygen needs while reducing the time in diastole for coronary flow to take place. The reduction in the diastolic time can lead to marked elevations of left ventricular (LV) diastolic pressure as well as increased ischemia. Moreover, atrial fibrillation will deprive ventricular filling of the "atrial kick" and lead to further elimination of diastolic pressures. These considerations are of special importance with ventricular hypertrophy and resultant diastolic dysfunction. During the "remodeling" phase of ventricular failure, the patient may be asymptomatic. Nevertheless, inhibition of the renin-angiotensin system is indicated to reduce the rate of ventricular remodeling and slow ventricular dilation. Beta-adrenergic blockade reverses ventricular remodeling and improves survival in patients with class II to III symptoms. * Reflects the inconsistent effects of beta-adrenergic blockade in patients with class IV symptoms. In the Copernicus trial, carvedilol was beneficial, while in the BEST trial, bucindolol appears to be detrimental. Once symptoms ensue, loop diuretics generally are needed for fluid control. Digitalis glycosides also are indicated for neurohumoral benefits in reducing sympathetic tone and enhancing parasympathetic tone while providing modest inotropic support. These actions appear to improve morbidity without necessarily altering mortality.

Figure 21-6: The classification and characteristics of angiotensin II receptors. DTT, dithiothreitol. (From Kang PM, Landau AJ, Eberhardt RT, Frishman WH. Angiotensin II receptor antagonists: A new approach to blockade of the renin-angiotensin system. *Am Heart J* 1994; 127:1388-1401.)

Figure 21-7: Treatment of congestive heart failure is directed toward controlling salt and water retention (central or peripheral edema) and/or relieving a low-flow state by increasing cardiac output while reducing very increased filling pressures. Dobutamine is useful to augment cardiac output except when $beta_1$-adrenergic blockade is present. Milrinone, which stimulates the adenyl cyclase system beyond the beta receptor, acts well in this circumstance to augment the effects of dobutamine while serving as an arterial and venous dilator. When inadequate cardiac output can no longer be maintained, surgical implantation of a left ventricular assist device (LVAD) may be used to pump blood from the left ventricle to the aorta as a temporary support or bridge to transplantation.

Figure 21-8: Structure of digitalis molecule. * Digitoxin becomes digoxin with OH placement at C_{12}. (From Sonnenblick EH, LeJemtel TH, Frishman WH. Digitalis preparations and other inotropic agents. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics*. New York, McGraw-Hill; 1997:241. Reproduced with permission from the publisher and authors.)

Figure 21-9: Diagram of various inotropic sites of action on and within the cardiac cell. While catecholamines act at cell surface receptors, agents such as amrinone and milrinone (PDE III inhibitors) act within the cell to augment adenylate cyclase. Calcium sensitizers increase Ca2+ sensitivity of troponin (Tn) in the contractile system itself. (From Varro A, Papp JG. Classification of positive inotropic actions based on electrophysiologic characteristics: Where should calcium sensitizers be placed? *J Cardiovasc Pharmacol* 1995; 26(suppl 1):S32. Reproduced with permission from the publisher and authors.)

Figure 21-10: Structure of catecholamines.

Figure 21-11: Flowchart of pharmacologic treatment of mild symptomatic systolic left ventricular (LV) dysfunction, NYHA II, and signs of fluid retention. ∗ Data available only for carvedilol. (From Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. *Eur Heart J* 1997; 18:746. Reproduced with permission from the publisher and authors.)

Figure 21-12: Flowchart of pharmacologic treatment of symptomatic left ventricular dysfunction and worsening heart failure (NYHA III to IV). (From Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. *Eur Heart J* 1997; 18:747. Reproduced with permission from the publisher and authors.)

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Part 3: HEART FAILURE
Chapter 22:

CARDIAC TRANSPLANTATION, MECHANICAL VENTRICULAR SUPPORT, AND ENDOMYOCARDIAL BIOPSY

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HISTORY AND OVERVIEW

Although a number of advances in therapy for failing myocardium have saved or at least prolonged the lives of many patients with previously terminal myocardial dysfunction, a sizable number of young patients are fated to die or be severely disabled because of irreversible myocardial disease. In patients with such end-stage disease, biological replacement of the heart has come to be a standard therapy and is currently widely accepted as a modality for prolonging life and improving its quality in carefully selected patients. As technological and engineering advances occur, mechanical replacement of the heart and xenotransplantation (transplantation of animal organs) may become very competitive or complementary modalities for the treatment of such patients, but biological replacement with human donor hearts is the current standard of therapy.

Interest in developing surgical techniques to interpose a functioning heart into a recipient's circulation dates back at least to the early part of the 20th century. In 1905, Carrel and Guthrie[1] described the heterotopic transplantation of a functioning donor heart into the neck of a dog. The heart in that model functioned in sequence with the recipient's heart in the circulation and was not actually capable of supporting the circulation. Although the exact anatomic connections were not described in detail, this apparently nonworking model of heterotopic transplantation beat regularly for approximately 2 h before the blood clotted in all the chambers. Carrel's initial interest was in the concept of performing vascular anastomoses, an interest reportedly stimulated by his distress at the inability of the best French surgeons of that time to avert the death by exsanguination from a severed portal vein of the president of the French republic.[2] Carrel and his colleague Guthrie developed innovative surgical techniques for vascular anastomoses at the University of Chicago, and those advances set the stage for anastomoses leading to organ transplantation. This work was a major part of the body of work for which Carrel was awarded the Nobel Prize for Medicine and Physiology in 1912.

Work in the field lay dormant until Mann and coworkers from the Mayo Clinic published their seminal report in 1933 of a technique for heterotopic heart transplantation with circulatory loading of the right ventricle.[3] Presumably because this was a working model, the chambers did not clot immediately, and the hearts in their dogs beat for a mean of 4 days. Mann perceived several important surgical points, including the importance of avoiding ventricular distention and air embolism and the prevention of thrombosis by heparin, but his most incisive and critical observation was that failure of a transplanted heart was in fact due not always to faulty surgical technique "but to some biologic factor which is probably identical to that which prevents survival of other homotransplanted tissues and organs." In what was undoubtedly the first description of acute allograft rejection, Mann recounts: "When the heart was removed just before it became quiescent . . . the surface of the heart was covered with mottled areas of ecchymoses . . . histologically the heart was completely infiltrated by large mononuclears and polymorphonuclears." Although various other animal models for surgical techniques for heterotopic heart transplantation were described in subsequent years,[4-7] it took another 30 years to

better understand and manipulate the "biologic factor" Mann described as limiting the survival of allografted organs. In 1960, Shumway and Lower performed orthotopic heart transplants in dogs using cardiopulmonary bypass and topical hypothermia for donor heart preservation.[8] The dogs survived between 6 and 21 days and died of rejection. Shumway and Lower also recognized the limiting "biologic factor" and stated that "if the immunologic mechanisms of the host were prevented from destroying the graft, in all likelihood it would continue to function adequately for the normal lifespan of the animal." Their technique, involving anastomoses at the midatrial level and the supravalvular level in the great vessels, remained the basis of cardiac transplant technique in the 1990s.

In the early 1960s, the concept of pharmacologic immunosuppression was introduced; it ushered in the marriage of surgical and medical technology that is known today as the field of organ transplantation. Immunosuppression was, of course, seen as a means to mitigate the "biologic factor" that otherwise limited organ graft survival. The first clinical transplants were of the kidney, a logical choice since hemodialysis was then available as a backup system if the graft failed, and the field has flourished since the early 1960s.[9]

The first human heart allograft procedure was performed in South Africa in 1967,[10] followed shortly by the first U.S. transplant by Shumway at Stanford in 1968 and then by a flurry of transplant activity in many centers. This initial enthusiasm subsided as it became evident that postoperative survival was limited by a variety of complex medical problems, including opportunistic infections and graft rejection. Most major centers discontinued performing heart transplantation in the early 1970s, and it was not until the introduction of cyclosporine-based immunosuppression at Stanford in 1980 and the demonstration of the attendant improvement in survival rates[11] that the procedure reemerged as a widely accepted therapy for end-stage heart disease. In the 1990s, many tertiary care centers provided programs for heart transplantation, and most medical care payers in the United States, including the federal government, provided coverage for such care.

Cardiopulmonary transplantation was introduced at Stanford in 1981,[12] and subsequent experience with heart and lung and with both single- and double-lung transplantation in many centers has proved that these procedures are valid therapies for a wide variety of primary lung diseases and end-stage cardiopulmonary disorders.[13]

Current Status

The most accurate data on volume and outcomes of thoracic organ transplantation are provided by the Registry of the International Society for Heart and Lung Transplantation and are updated yearly and published in the journal of that society. Since 1994, the Registry has been administered by the U.S. donor allocation organization, the United Network for Organ Sharing (UNOS), but it includes data on the vast majority of non-U.S. programs as well as all U.S. programs. As of the most recent Registry report,[13] there has been a plateau of heart transplant operations at approximately 3500 procedures worldwide on an annual basis since the late 1980s, a level generally accepted to be due to limitations of donor availability (Fig. 22-1). This most recent report includes data on 48,541 transplant procedures reported since the Registry's inception in 1982 and documents overall patient survival rates of 79, 71, and 63 percent, at 1, 3, and 5 years, respectively (Fig. 22-2). After the first year, there is a linear attrition rate of 4 percent per year to a survival of about 40 percent at 10 years.

According to this Registry, there are currently 304 programs in clinical heart transplantation, of which 165 are in the United States. According to data published in 1994, a large number of these U.S. programs have very low volume, and low volume is associated with inferior survival rates.[14,15] Thus, the survival rates to be expected at major, high-volume programs should be somewhat in excess of the overall reported rates.

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Chapter 22: CARDIAC TRANSPLANTATION, MECHANICAL VENTRICULAR SUPPORT, AND ENDOMYOCARDIAL BIOPSY

RECIPIENT SELECTION AND MANAGEMENT

As is the case with any surgical procedure, careful selection of patients for heart transplantation results in optimum postoperative survival rates. In contrast, however, to the quality-of-life or prolongation-of-life issues involved in decisions regarding more conventional heart surgery, decisions regarding candidacy for heart transplantation must take into consideration a limited donor supply and the necessity of following a highly complex medical regimen for the rest of the patient's posttransplant life. These considerations can make selecting recipients most difficult. Major guidelines for recipient selection have been developed and are intended to provide the maximum benefit from the limited resource of donor organs.[16] Selection criteria are in a state of change worldwide, and criteria for acceptance at one center may not match exactly those at another center. The criteria generally reflect experience with the selection of patients who are most likely to survive and benefit, with a return to a normal life after the transplant.

Some basic or general criteria can be described that are universally accepted; these criteria are summarized in Table 22-1. They include the most basic criterion: the existence of end-stage cardiac disease irremediable by other, more conventional forms of medical or surgical therapy. The term *end stage* is, of course, difficult to define exactly, but in general it refers to cardiac disease associated with New York Heart Association (NYHA) functional class IV symptomatic status despite optimum medical management. In the past, one criterion was an estimated life expectancy of 6 months or less; however, the increasingly long waiting times for a suitable donor caused by increased patient numbers on the transplant waiting list now require the much more difficult task of estimating 1- to 2-year mortality in potential candidates. *With the recent major advances in heart failure therapy has come the realization that many transplant operations in patients referred for transplantation can be avoided by utilizing aggressive medical therapies*. Many transplant centers have found that as many as 30 to 50 percent of patients referred for heart transplants can be stabilized or even have their heart failure reversed by an aggressive, well-organized medical approach using angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockade, combination diuretics, beta blockers, and meticulous monitoring of the patient's weight, general status, electrolytes, and renal function.[17,18] Thus, most heart transplant centers have evolved into centers for heart failure management as well as transplantation. Table 22-2 lists a typical drug regimen for a patient with advanced heart failure who is waiting for a donor. The frequency of clinic visits for monitoring ranges from every week to every 4 weeks, depending on the status of the patient. Furthermore, the introduction of transvenously placed antitachycardia/defibrillation devices and the increasing use of new beta blockers have contributed to this ability to stabilize patients in order to avoid or delay heart transplantation. It also has been realized that a small percentage of patients may have their left ventricular dysfunction reversed by high-risk percutaneous interventional procedures or coronary bypass surgery in order to restore blood flow to areas of "hibernating myocardium." Positron emission tomography (see Chap. 19) or 24-h thallium scanning (see Chap. 16) is utilized to identify potential candidates for such procedures. It is also important to identify potentially reversible causes of cardiomyopathy as summarized in Table 22-3 (see Chaps. 66 and 69). Cessation of excessive alcohol intake or slowing of the ventricular rate with drugs or atrioventricular (AV) nodal ablation in patients with rapid heart rates occasionally results in a dramatic reversal of the heart failure.[19] Although it is more controversial, some centers continue to treat biopsy-proven acute lymphocytic myocarditis with high-dose steroids. This approach also is used for sarcoid cardiomyopathy. Finally, the introduction of beta blockers has resulted in dramatic improvement in survival statistics. Their use is associated with improved left ventricular ejection fraction over time as well[20-25] (see Chap. 21).

Table 22-1: Criteria for Acceptance of Cardiac Transplant Recipients

- Unacceptable heart failure that has not responded to an aggressive medical or surgical regimen
- Unacceptable prognosis for survival of 1-2 years
- Biological age less than 55-60 years
- Absence of irreversible pulmonary hypertension
- Absence of other systemic diseases that would limit long-term survival
- Medically compliant, with the ability to follow a complex medical regimen
- Adequate psychosocial support to assure compliance with medical directions and office visits
- Absence of self-abusive behavior that would interfere with postoperative course

Table 22-2: Typical Pharmacologic Regimen for Advanced Heart Failure Patients

ACE inhibitor/angiotensin II blocker
Loop diuretic
Triamterene/hydrochlorothiazide
Digoxin (low dose)
Coumadin
Enteric-coated aspirin if CAD
HMG-CoA reductase inhibitor if CAD
Beta-blocker trial

ABBREVIATIONS: ACE = angiotensin-converting enzyme; CAD = coronary artery disease.

Table 22-3: Identification of Potentially Reversible Causes of Congestive Heart Failure

Ischemic left ventricular dysfunction reversible with interventional or surgical reperfusion
Cardiomyopathy secondary to
Lymphocytic myocarditis
Sarcoidosis
Tachycardia
Ethanol

Age limits for cardiac transplant recipients are a second criterion for acceptance, and those limits have been expanded considerably in both directions over the past several years. In the early years of experience with cardiac transplantation, older patients experienced very inferior survival rates and the upper limit of eligibility was set at age 50. Since the advent of cyclosporine-based immunosuppression in 1980, it has become apparent that survival rates are no longer inferior in older age groups.[24] In the most recent year in

which such data were analyzed in the Registry of the International Society for Heart Transplantation, the 30-day mortality rates according to age were identical (at 10 percent) for all ages between 10 and 69,[25] and in the current Registry data, 1- and 5-year mortality risk increases only slightly over age 65. Reports from several individual centers also have attested to the excellence of both early and late postoperative survival rates in older patients.[26-29] On the basis of those data, most centers have now advanced the official age of acceptability to 60 and may accept patients up to age 65 as well as highly selected patients over age 65. The lower age limits for transplantation eligibility also have been expanded recently, with a number of major centers embarking on programs involving neonates and young children.

Potential cardiac transplant recipients also are screened for the existence of any other systemic disease that independently is likely to limit their survival. The coexistence of an active malignancy and the potentially increased tendency for its advancement in the presence of immunosuppression are an obvious problem, and such patients are routinely excluded. How to deal with a patient with end-stage heart disease and a remote history of malignancy is a more difficult problem. Edwards and associates[30] reported a small group of patients with a prior history of malignancy who were considered to have been cured of their malignant disease and were otherwise candidates for cardiac transplantation. Seven such patients underwent transplantation; six had a remote history of lymphoproliferative disease, and one had had adenocarcinoma of the colon. Only the patient with colon cancer has had recurrence of malignancy during follow-up averaging over 2 years. Thus, cautious acceptance of such patients may be justified.

The coexistence of one other major systemic disease-insulin-requiring diabetes-had been considered a contraindication to cardiac transplantation in otherwise acceptable patients. The rationale for this was the well-known increase in the incidence of early peripheral and cerebrovascular disease and nephropathy in these patients as well as their generally poor ability for wound healing and the difficulty of diabetic control during the period of constantly varying steroid doses in the early postoperative period. As steroid requirements have become lower, this requirement generally has been relaxed to allow the inclusion of stable (as opposed to "brittle") insulin-requiring diabetic patients, and in recent years several reports have attested to the safety and efficacy of heart transplantation in very carefully selected diabetic patients.[31-33]

Human immunodeficiency virus (HIV) positivity generally is considered an absolute contraindication to heart transplantation. Other comorbid conditions must be considered on an individual basis, but irreversible organ dysfunction such as emphysema, severe peripheral vascular disease, and hepatic or renal dysfunction out of proportion to that predictable as a consequence of severe congestive heart failure are strong relative contraindications. The presence of an active infection is an often temporary absolute contraindication to transplantation because of the mandatory posttransplant institution of immunosuppression. Early in the years of clinical experience with heart transplantation, it was found that a normal donor right ventricle is unable to increase its external workload acutely to overcome elevated **pulmonary vascular resistance (PVR)**. Because of this, patients who have end-stage heart disease with an elevated **PVR** often experience acute right-sided heart failure and cardiogenic shock after the transplantation of a normal heart with a right ventricle that has not been conditioned to pump against high resistance. This problem was a major cause of intraoperative deaths in the early years of transplantation and led to the setting of an upper limit of 4 Wood units of **PVR** (approximately 320 dynes·s/cm^5) as the cutoff point or fourth criterion for suitability for cardiac transplantation. In recent years, the concept of reactivity of the pulmonary vasculature and the potential reversibility of elevated **PVR** has gained acceptance. Because of this, potential candidates with **PVR** greater than 4 Wood units (320 dynes·s/cm^5) at baseline usually are subjected to pharmacologic maneuvers during hemodynamic monitoring, using nitroprusside and/or prostaglandin E_1 or inhaled nitric oxide to determine whether the elevated **PVR** is reversible; such patients are accepted as candidates for transplantation if the **PVR** can be reduced to acceptable levels while systemic arterial pressure remains adequate.

The last criterion that is accepted by most centers is the absence of unresolved pulmonary infarction. In spite of systemic anticoagulation, pulmonary infarcts that are due to emboli from the dilated right ventricle or the leg or pelvic veins are common complications in patients with biventricular congestive heart failure who are awaiting transplantation. *Experience has shown that pulmonary infarcts have a high probability of becoming pulmonary abscesses after the institution of immunosuppression*. For this reason, waiting recipients who sustain a pulmonary infarction usually are removed temporarily from the waiting list until the infarct resolves radiographically. Unfortunately, such resolution can be quite slow in this severely ill group of patients, and many never survive to return to the waiting list.

On the basis of these criteria, a group of patients is selected who are believed to have the best chance of benefiting from the operation and the attendant substantial commitment of medical resources. The type of underlying heart disease in the adult population selected for the procedure is nearly evenly split between idiopathic cardiomyopathy and ischemic disease; in the pediatric population, predictably, there is a higher percentage with congenital heart disease.

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Chapter 22: CARDIAC TRANSPLANTATION, MECHANICAL VENTRICULAR SUPPORT, AND ENDOMYOCARDIAL BIOPSY

DONOR SELECTION AND MANAGEMENT

Acceptance of the concept of brain death, both legally and medically, has been central to the emergence of organ transplantation (particularly transplantation of unpaired organs such as the heart) in the modern era. The mandatory warm ischemic time that would be involved if cardiopulmonary death were the only accepted criterion of death would make heart transplantation impossible. Acceptance of the concept of irreversible brain death has been a perhaps surprisingly recent phenomenon. In 1970, Kansas became the first state in the United States to pass legislation recognizing the legal concept of brain death. Several states followed suit, and the medical and legal criteria for brain death have been refined over the years. The most recent and widely accepted set of guidelines was set out in the President's Commission Report in 1980.[34] It has been estimated that only 15 to 20 percent of persons who qualify as brain-dead and have usable or transplantable organs become organ donors in the United States.[35] The reasons for this are complex and include a lack of public awareness of the potential to donate organs as well as reticence among medical staff to make a request for donation. Efforts are being made in many areas to improve the percentage of organs recovered for transplantation from potential donors, but even with much higher recovery rates, heart transplantation probably will be a donor-limited field for the foreseeable future.

To be considered suitable donors for cardiac transplantation, brain-dead individuals must meet certain minimum criteria. Age criteria vary in different programs, but most cardiac donors have been under age 40. The donor obviously should not have had any significant cardiac disease, malignant disease, or acute or chronic infection. Risk factors for cardiovascular disease such as diabetes and severe hypertension or hypercholesterolemia are relative exclusion factors. Donors routinely are screened serologically for HIV and hepatitis B and C. Baseline serology for a number of other infectious diseases, such as cytomegalovirus (CMV), is obtained in many programs but usually is not used prospectively in donor-recipient matching. If there is any suspicion of cardiac disease in the donor, appropriate diagnostic studies (including echocardiography, cardiac catheterization, and coronary angiography) to assure the normality of the potential cardiac graft are pursued.

Once a potential donor is identified, the procurement process is initiated by contacting and referring to the local organ procurement organization (OPO), which maintains a registry of waiting recipients and coordinates equitable distribution of donor organs within a geographic area. Donor-recipient matching is fairly straightforward and requires ABO blood group compatibility as well as overall body size comparability, with ±20 percent body weight considered an acceptable discrepancy. Human leukocyte antigen (HLA) matching is not attempted prospectively because of the difficulty of obtaining HLA typing promptly as well as the relatively small numbers of donors and recipients, which severely limits choices.

Most donor hearts currently are "harvested," or removed, from the donor by a transplant donor team from a transplantation center and transported back to the center for implantation. A cold ischemic time of 4 h in adults generally is considered safe; this requirement limits the distance from which hearts can be transported and leads to the rationale for geographic subdivision into OPOs for cardiac allografts despite the drive for a "national" list for other organs.

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Chapter 22: CARDIAC TRANSPLANTATION, MECHANICAL VENTRICULAR SUPPORT, AND ENDOMYOCARDIAL BIOPSY

SURGICAL TECHNIQUE

As was noted above, the surgical technique used in most centers today differs little from that described by Lower and Shumway in 1960.[8] With this procedure, both the donor and recipient hearts are removed by transecting the atria at the midatrial level, leaving the multiple pulmonary venous connections to the left atrium intact in the posterior wall of the left atrium, and then transecting the aorta and pulmonary artery just above their respective semilunar valves (Fig. 22-3).

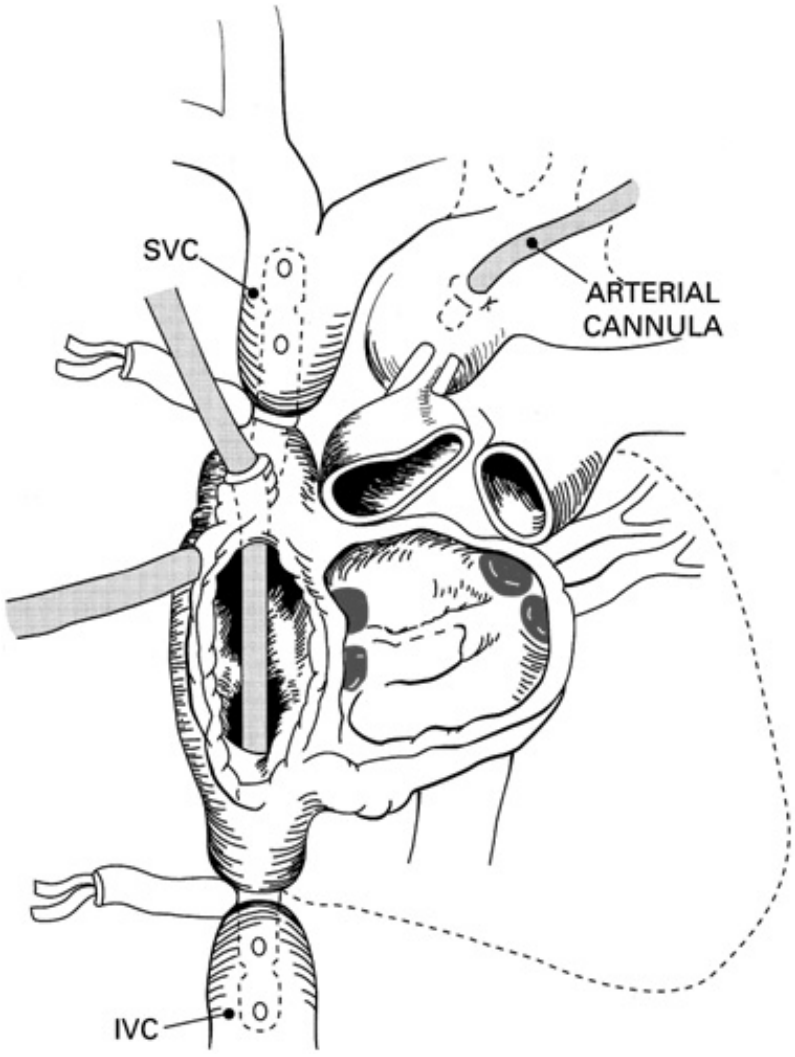

Figure 22-3: Diagram of recipient's mediastinum with heart resected and arterial and venous cannulas in place.

As was noted above, the donor heart usually is explanted, or harvested, by a surgical team at a hospital remote from the transplant center, and this surgery most often needs to be coordinated

with the requirements of other surgical teams procuring nonthoracic organs for transplantation at other centers. The donor heart is arrested with cold crystalloid or blood cardioplegic solution, and the explanted heart then is cooled topically by being placed in an iced preservation solution; it then is placed in a secure container and transported expeditiously to the transplant center. Ischemic times average 3 to 4 h. Implantation of the heart in the orthotopic position begins with reanastomosis at the midatrial level, beginning with the atrial septum (Fig. 22-4). Efforts are made to include a generous cuff of donor right atrium so that the sinoatrial node will be included. The great vessels are reanastomosed just above the semilunar valves.

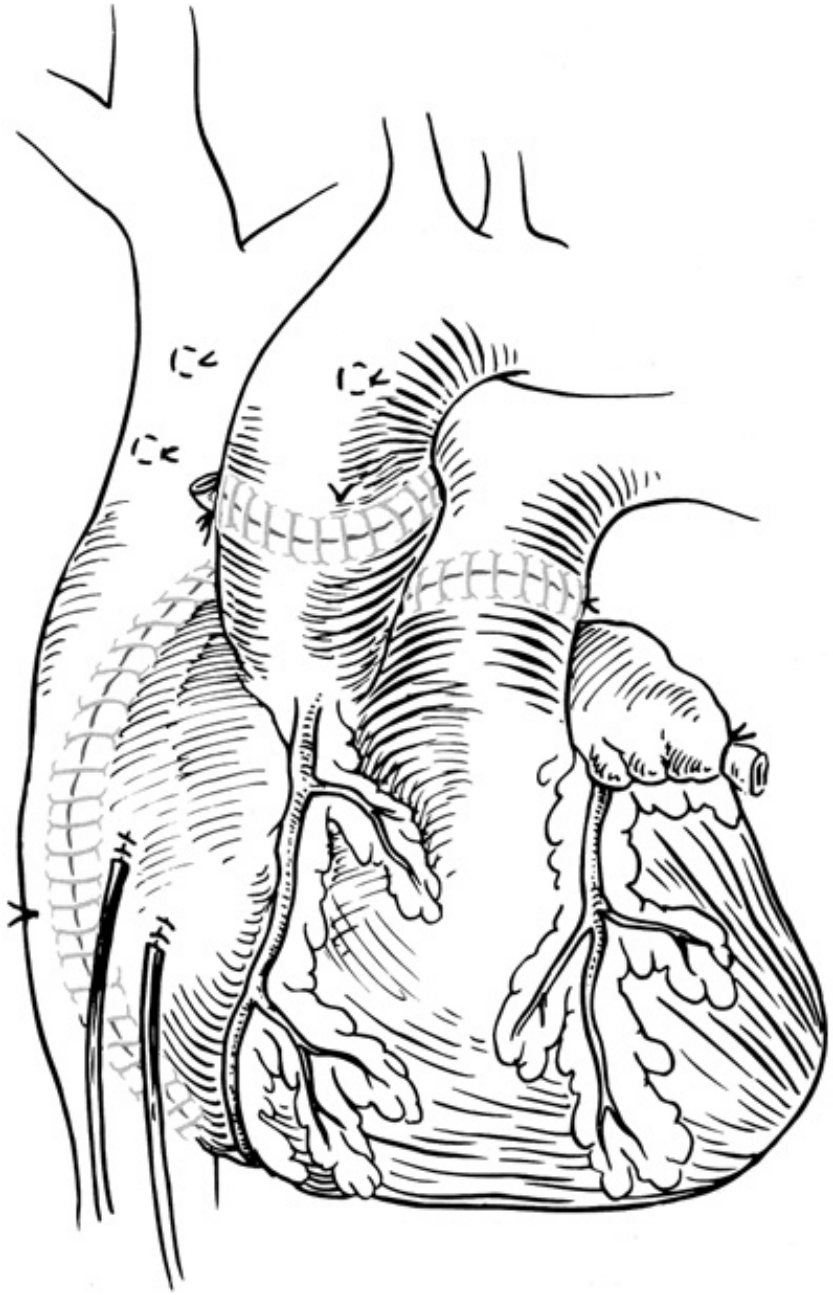

Figure 22-4: Diagram of donor heart anastomosed in the orthotopic position. Suture lines at the midatrial level and the aorta and pulmonary artery above semilunar valves.

In recent years, there has been a move to alter the surgical technique by leaving the donor atria intact and making anastomoses at the level of the superior and inferior venae cavae and pulmonary veins[36]; this is known as the *technique of bicaval anastomosis.*[37,38] There is evidence

that this modified technique is associated with a decreased requirement for pacemaker placement for donor sinus node malfunction and with less AV valve regurgitation,[39,40] most likely as a result of preservation of the geometric configuration and anatomic size of the atria and the preserved integrity of the sinoatrial node.

Immediate postoperative care differs little from that after more routine heart surgery except for the institution of immunosuppression (described below) and the need for chronotropic support of the donor sinoatrial node for the first 2 to 3 postoperative days, usually with temporary pacemaker support but occasionally with infusion of isoproterenol. Uncomplicated patients may be discharged from the hospital 7 to 10 days postoperatively.

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Chapter 22: CARDIAC TRANSPLANTATION, MECHANICAL VENTRICULAR SUPPORT, AND ENDOMYOCARDIAL BIOPSY

POSTOPERATIVE MANAGEMENT

Immunosuppression

GENERAL

The need to suppress the normal immune response in the presence of a solid organ allograft begins immediately at the time of surgery and continues for the life of the graft, which is generally concurrent with the life of the patient in the field of cardiac transplantation. Historically, most clinically used immunosuppressive regimens have consisted of a combination of several agents used concurrently and sequentially. This multiple-drug approach continues to be considered the state of the art. The number of drugs and the timing of their administration vary from institution to institution, but several general principles are commonly adhered to.

The first general principle is that immune reactivity and the tendency toward graft rejection are highest early after graft implantation and decrease with time, although they probably never disappear entirely. Thus, most regimens employ the highest levels of immunosuppression immediately after surgery and decrease those levels later, eventually settling on the lowest maintenance levels of suppression that are compatible with preventing recurrent graft rejection. The second general principle is reminiscent of that originated in oncology chemotherapy regimens, using low doses of several drugs without overlapping toxicities in preference to higher (and more toxic) doses of fewer drugs whenever feasible. The third general principle is that too much or too intense immunosuppression is undesirable because it leads to myriad undesirable effects, such as susceptibility to infection and malignancy, but too little is equally undesirable because it permits graft rejection. Finding the right balance between over- and underimmunosuppression in an individual patient is truly an art that utilizes science. As newer immunosuppressive agents and modalities are developed, the possible array of drug regimens can be expected to multiply accordingly, but these principles probably will remain, and the process of tailoring an individual patient's immunosuppressive regimen probably will continue to be an art as well as a science.

There is currently a relatively limited repertoire of approved agents for immunosuppression after organ transplantation, but their numbers can be expected to increase. Most programs employ a long-term two- or three-drug regimen, and roughly half additionally use a brief early postoperative course of "induction" cytolytic therapy. Most programs employ glucocorticoids as one of the agents, usually in relatively high doses early postoperatively and then tapering to low doses or discontinuing the drug during the first postoperative year. The commonly used drugs and their toxicities are outlined in Table 22-4.

Table 22-4: Currently Available Immunosuppressive Agents

Agent	Toxicities	Avoid Toxicity
Cyclosporine	Renal dysfunction	Follow blood levels
	Hypertension	Antihypertensive medication
	Neurotoxicity	?
Tacrolimus (FK506)	Renal dysfunction	Follow blood levels
	Neurotoxicity	?
Mycophenolate mofetil	Gastrointestinal disturbances	Reduce dose

	Marrow toxicity (mild)	Follow CBC
Azathioprine	Marrow toxicity	Follow CBC
	Hepatotoxicity	Discontinue drug
Glucocorticoids	Cushingoid habitus	Minimize dose
	Glucose intolerance	
	Osteoporosis	
Methotrexate	Marrow toxicity	Follow CBC

ABBREVIATIONS: CBC = complete blood count.

In managing patients on these drugs, it is most important to be aware of the potential for drug interactions when other agents are added to or deleted from the patient's regimen. A list of the most common and clinically important drug interactions is shown in Table 22-5. It is also important to keep in mind the potential for changing drug concentrations in the face of intercurrent hepatic or renal dysfunction.

SURVEILLANCE AND THERAPY FOR REJECTION

There are rarely any striking physical signs or symptoms of rejection until it is far advanced. Cardiac allograft rejection is diagnosed almost exclusively by examining histologic findings in surveillance right ventricular endomyocardial biopsies. The technique used and the pathologic criteria for diagnosis are described below. A wide variety of noninvasive methods to diagnose rejection have been investigated, but none has been determined to have sufficient sensitivity and specificity to replace the biopsy. Protocols for the timing of surveillance endomyocardial biopsies generally are chosen to match the observed frequency of rejection episodes, which is clearly highest in the early postoperative period. Most programs perform surveillance biopsies on a weekly basis for the first 4 to 6 postoperative weeks and then with diminishing frequency in a stable patient but at a minimum every 3 months for the first postoperative year. The need for continued surveillance biopsies after the first year in clinically stable patients has been questioned,[41,42] but most centers continue to do them every 4 to 6 months.

Rejection episodes are treated with augmented immunosuppression, the intensity of which is matched to the histologic, or occasionally clinical, severity of the episode. Early or first rejection episodes usually are treated with methylprednisolone given intravenously in a dose of 1 g daily for 3 days followed by a repeat biopsy in 7 to 10 days. Episodes after 3 months that are not clinically severe can be treated safely with an increase in the oral steroid dose.[43] More severe rejection is treated with glucocorticoids and the addition of cytolytic therapy with either polyclonal antithymocyte globulin (commonly of rabbit or equine origin) or the murine monoclonal anti-CD3 preparation OKT3. Such treatment is highly effective,[44] but sensitization can limit its use.[45]

Several strategies are employed as adjunctive therapy for repetitive or recalcitrant rejection episodes. They include the use of two modalities with proven efficacy in therapy for autoimmune disease: total lymphoid irradiation[46] and low-dose methotrexate.[47] Both have been shown to be of benefit in patients with frequent or difficult-to-treat cardiac allograft rejection.[48-51] An analysis from 1997 suggests that the two modalities are both reasonably effective in this setting.[52] Tacrolimus (FK506), when substituted for cyclosporine, has been reported to benefit several heart transplant recipients with resistant rejection[53] as well as to be safe and effective as a primary agent in a cohort of patients[54]; there is a larger body of experience with its use in resistant renal graft rejection.[55] Similar success has been reported with the use of mycophenolate mofetil in therapy for recalcitrant rejection.[56] Studies are under way to evaluate several other drugs, modalities, and immunologic manipulations in the setting of resistant graft rejection.

If all these strategies fail and severe graft dysfunction supervenes, retransplantation is the only remaining

option and is offered in many centers. The results of retransplantation in this setting are, however, disappointing, with only 33 percent 1-year survival in one registry[57] and consistently inferior survival in the international registry.[13]

Infectious Complications

Although their incidence has decreased in the cyclosporine "era," infections, often with unusual and opportunistic organisms, are the major cause of death during the first postoperative year and remain a threat throughout the life of a chronically immunosuppressed patient. Effective therapy demands an extremely aggressive approach to obtaining a specific diagnosis and a background of experience in recognizing the more common clinical presentations of CMV, *Aspergillus*, and other opportunistic infectious agents. Transplant cardiologists generally have expertise in infectious disease management but usually require the availability of both infectious disease consultation for the more unusual problems and a high-quality infectious disease laboratory. Several well-proven regimens for infection prophylaxis are commonly used and are outlined in Table 22-6. Infection surveillance is mainly clinical, but routine chest radiography often detects infections, especially fungal and mycobacterial ones, at an early and asymptomatic stage.

Table 22-6: Infection Prophylaxis Regimens

Pathogen/Disease	Strategy
Aspergillus	? Air filtration
	? Prophylactic antifungals
Bacterial endocarditis	Standard subacute bacterial endocarditis prophylaxis
Cytomegalovirus	Blood product selection
	Prophylactic ganciclovir
	Prophylactic immunoglobulin
Influenza	None recommended
Pneumococcus	Preoperative vaccine
Pneumocystis	Sulfamethoxazole/trimethoprim
	Inhaled pentaminide
Toxoplasma	Pyrimethamine if donor seropositive

Posttransplant Malignancy

Any program of chronic immunosuppression is associated with a subsequent increased risk of lymphoproliferative malignancy; the earliest cases were noted after a period of immunosuppressive therapy for chronic hepatitis.[58] Organ transplantation has proved to be no exception, and the incidence of posttransplant lymphoproliferative disease (PTLD) has been documented in a registry based at the University of Cincinnati. The incidence of PTLD in heart transplant recipients is somewhat higher than that in kidney transplant recipients but not as high as that in liver recipients (Table 22-7); this probably is related to the intensity of immunosuppression required after the various allograft procedures.[59] According to the most recent registry report, malignancy accounts for 18.6 percent of deaths 4 years after heart transplantation.[13]

Table 22-7: Posttransplant Lymphoproliferative Disorder Incidence in Organ Transplantation

Organ	Incidence, %
Kidney	1.0
Heart	1.8
Liver	3.0
Heart/lung	4.6

SOURCE: Reproduced from Penn I. Roundtable report: Immunosuppression and lymphoproliferative disorders, 1992. (With permission of the author and Pro/Com International, Parsippany, NJ.)

There is convincing evidence that most PTLDs are related to infection (either primary or reactivation) with the Epstein-Barr virus (EBV).[60-62] They frequently occur in unusual, extranodal locations and may respond to reduction in immunosuppression,[63] although such reduction is clearly a "double-edged sword" with a cardiac allograft for which there is no alternative system, such as dialysis in renal transplantation, if the graft is rejected. PTLDs are usually quite radiosensitive, and both radiotherapy and surgical resection can play a major role in therapy when there is a single lesion.

There is anecdotal evidence that the use of the antiviral agent acyclovir may be useful in therapy for PTLD,[64] and most centers employ it as an adjunctive therapy. In recent years, there has been interest in the use of interferon for these malignancies,[65] and a multicenter oncology group protocol is under way to evaluate its efficacy. Recently, there has been interest in the use of infusions of donor leukocytes[66] and donor-derived EBV-specific cytotoxic lymphocytes for this disease in bone marrow transplant recipients.[67] The technology may well be transferred to organ transplant recipients but would require the maintenance of donor tissue lines prospectively.

Allograft Vasculopathy

INCIDENCE

When clinical heart transplantation was introduced, the complications discussed above were all anticipated problems in light of the nonspecific nature of available immunosuppression, but the frequent development of diffuse and often rapidly progressive obliterative coronary artery disease in young donor hearts was not expected. It occurs angiographically in approximately 10 percent of cardiac transplant recipients by the first postoperative year and in 50 percent by 5 years postoperatively,[68,69] and its incidence did not decrease after the introduction of cyclosporine-based immunosuppression in the early 1980s.[70] *The ischemic sequelae of this vasculopathy account for the vast majority of late posttransplant deaths, and it is currently the main factor limiting truly long-term survival*.[13]

MORPHOLOGY

The angiographic morphology of cardiac allograft vasculopathy has been well described,[71,72] and its main features are summarized in Table 22-8. The very diffuseness of the disease makes it easy to underestimate angiographically even when, as is usually recommended, similar angiographic views from serial angiograms are reviewed simultaneously with side-by-side projectors.

Table 22-8: Angiographic Features of Cardiac Allograft Coronary Artery Disease

Distribution: diffuse, distal, concentric, longitudinal obliterative lesions
May coexist with focal proximal lesions
Collateral vessel formation uncommon

In recent years, the use of intravascular ultrasound has gained acceptance as a sensitive and early detector of the intimal thickening that characterizes graft vasculopathy.[73-75] Intravascular ultrasound measurements of the extent of coronary intimal thickening currently serve as surrogate end points for the prevention of vasculopathy in several trials of new immunosuppressive agents that have shown promise of lessening the incidence of vasculopathy in animal models.

PATHOLOGY

The morphologic features of accelerated transplant vasculopathy and the principal differences from conventional atherosclerosis have been described.[76-78] In transplant arteriopathy, the major epicardial vessels, their branches, and often the intramyocardial divisions display uniform, diffuse involvement extending along their entire length. The arteries are cordlike in texture, and cross sections show uniform, concentric luminal narrowing (Fig. 22-5). The asymmetric and calcified plaques or lesions composed of cholesterol that are characteristic of conventional atherosclerosis are not found in uncomplicated lesions of vessels affected by transplant vasculopathy. Histopathologic sections show a thickened intimal layer composed of modified smooth muscle cells, foamy macrophages, and variable numbers of histiocytes and lymphocytes within a connective tissue matrix that ranges from loose, edematous, and myxoid in early lesions to densely hyalinized and fibrotic in older lesions (Fig. 22-6). The internal elastic membrane is usually preserved, with only focal interruptions and reduplications. The medial layer is generally intact but may show atrophy in advanced lesions. Intraluminal thrombosis is uncommon. While these changes rarely are seen on endomyocardial biopsy samples, signs of ischemia or infarction seen in the endomyocardial biopsy should alert the pathologist and the clinician to the possibility of the insidious presence of graft coronary disease.[79]

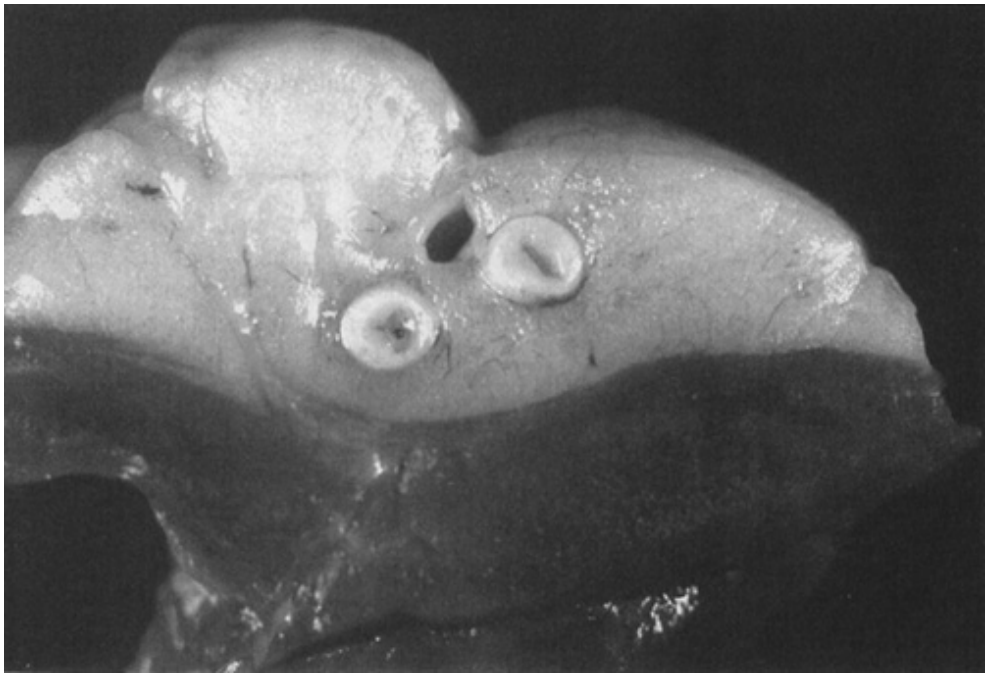

Figure 22-5: The mid-left anterior descending artery at autopsy in a 63-year-old man with advanced graft coronary disease.

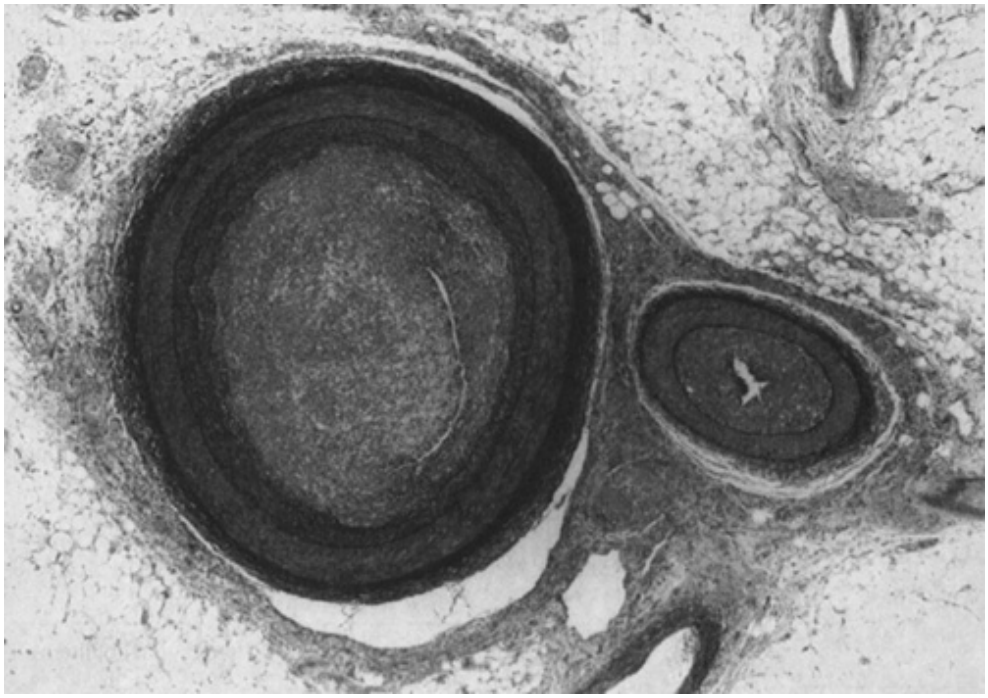

Figure 22-6: A main epicardial artery and division vessel showing occlusive graft coronary disease. Note the concentric intimal proliferation with a slitlike lumen. The internal elastica of both vessels is intact. (EUG ×10)

CLINICAL PRESENTATION, SCREENING, AND PROGNOSIS

Because most cardiac transplant recipients have a persistent state of both afferent and efferent cardiac denervation, most are incapable of experiencing the subjective sensation of angina pectoris. Clinical presentations of ischemia in this patient population usually are related to sequelae of the ischemia, such as arrhythmias or left ventricular dysfunction. In recent years, it has been convincingly shown that some cardiac transplant recipients do have physiologic evidence of reinnervation[80-83] and may experience angina pectoris.[84]

The usual lack of angina and the diffuseness of the disease have made standard clinical and noninvasive screening for native coronary artery disease fairly insensitive in detecting this form of coronary vasculopathy.[85] Most of this technology is designed to detect uneven myocardial perfusion caused by focal lesions and is less effective in detecting the global ischemia of diffuse obliterative disease. Several reports have suggested that dobutamine stress echocardiography may in fact be the one noninvasive technique that offers reasonable sensitivity and specificity as well as prognostic value in screening for this disease,[86-88] and it offers an attractive alternative to the usual annual coronary angiography performed in these patients.

The prognosis for survival once significant graft vasculopathy is detected angiographically is generally poor. In one study, the 1- and 2-year survival rates after the detection of any 40 percent coronary artery stenosis were 67 and 44 percent, respectively.[89] After an ischemic event such as congestive heart failure or myocardial infarction, 1-year survival was only 18 to 20 percent in this study.

APPROACHES TO PREVENTION

A number of approaches to the prevention of allograft vasculopathy have been proposed, and several show promise. As was noted above, a decreased incidence of vasculopathy is one of the desired end points in all preclinical and clinical trials of new immunosuppressive agents, and several such trials are in progress. In addition, two studies have shown some decrease in the incidence and sequelae of vasculopathy with the use of other agents: one with a calcium channel blocker added to the patient regimen early after surgery and another with the lipid-lowering agent pravastatin added. In the former study, diltiazem was used in a

randomized study involving a total of 106 patients, and those taking diltiazem had little change in overall coronary diameter on quantitative angiography over a 3-year follow-up period and displayed a trend toward a decreased incidence of angiographic coronary stenosis and clinical events resulting from ischemia.[90] In the other study,[91] also randomized and involving a total of 97 patients, the use of pravastatin (regardless of lipid levels) was associated with improved survival and a markedly decreased incidence of allograft vasculopathy seen both at angiography and at autopsy. A more recent study[92] documented similar results with simvastatin, and this benefit is probably a class effect.

The mechanism of action for either of these agents remains speculative. It is to be hoped that since, as described below, the etiology of allograft vasculopathy is most likely immunologic, improved methods of inducing specific graft tolerance in the future may lead to the disappearance of this disease and permit truly long-term survival rates after heart and other organ transplantation.

APPROACHES TO THERAPY

The choice of treatment for established cardiac allograft vasculopathy is often difficult and controversial. No agent or modality has been shown to reverse the process. Its very diffuseness makes the disease only infrequently amenable to otherwise standard revascularization procedures such as angioplasty and surgical bypass grafting. A registry of revascularization procedures performed on heart transplant recipients in 13 large transplant centers in the United States documented 97 balloon angioplasty procedures in 66 patients before November 1991.[93] There was an angiographic 94 percent success rate and an acceptable complication rate. There was, however, a 55 percent restenosis rate at a mean of 8 months after angioplasty, and 19 patients underwent 31 repeat angioplasty procedures for 24 restenoses and 30 new lesions. Only 61 percent of these patients were alive without retransplantation at a mean of 19 months after coronary angioplasty. In the same registry, 12 surgical coronary bypass procedures were reported; 4 of these patients died in the hospital, a fifth died suddenly 2 months postoperatively, and a sixth has required further palliative angioplasty. Revascularization is clearly, at best, short-term palliation for this highly lethal disease.

The most definitive form of therapy for graft failure resulting from severe vasculopathy is obviously retransplantation, and this procedure has been offered in many centers to highly selected patients with advanced allograft vasculopathy. Survival rates after retransplantation, however, are clearly inferior to those after primary transplants, averaging only 52 percent at 1 year in the most recent registry data.[13] In data analyzed from a group of the highest-volume U.S. centers, even the most ideal retransplant candidates had only 68 percent 1-year postoperative survival.[57] While this clearly represents an improvement in the individual patient's prognosis, these lower survival rates, along with the increased costs involved,[94] have led some to question the ethics of performing retransplantation.[95] Nevertheless, most large programs continue to offer the option to highly selected patients.

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ALTERNATIVES TO TRANSPLANTATION

Mechanical Support

TEMPORARY: PERCUTANEOUS INTRAAORTIC BALLOON PUMP

When aggressive medical therapy for severe heart failure no longer provides adequate organ perfusion in either the acute or the chronic setting, several mechanical devices are available to support the failing circulation on a temporary basis until myocardial recovery ensues or an appropriate cardiac donor for transplantation is procured. The intraaortic balloon pump (IABP), which first was described by Mouloupoulos in 1962,[96] is the most widely used device for such mechanical circulatory assistance. The device consists of a nonocclusive balloon catheter positioned in the descending aorta, with the balloon cyclically inflated during diastole (to provide diastolic pressure augmentation and increase coronary blood flow) and deflated during systole (to provide reduced arterial impedance or afterload reduction during ejection), a rhythmic sequence termed *counterpulsation.* These devices are widely used for circulatory support in acute situations, such as cardiogenic shock and refractory ischemia after myocardial infarction or cardiac surgery, as well as to support patients awaiting cardiac transplantation who become refractory to pharmacologic therapy.

Technique

A number of IABP systems are commercially available for surgical or percutaneous insertion. Most have a second lumen that permits balloon insertion over a guidewire and later provides monitoring of central aortic pressure. Percutaneous insertion systems generally require 9F femoral introducer sheaths. Retrograde insertion of the IABP system through a sheath in the femoral artery is the most commonly used method of insertion and can be accomplished under local anesthesia in the intensive care unit. When femoral pulses are absent or when percutaneous femoral cannulation is considered hazardous, surgical exposure of the common femoral artery enables the operator to cannulate the artery under direct vision. The existence of severe aortoiliac occlusive disease occasionally mandates insertion of the IABP from the upper extremities or from a graft attached to the ascending aorta.

Timing

Proper timing of inflation and deflation is necessary for IABP counterpulsation to provide effective ventricular assistance. Ideally, the balloon should inflate immediately after aortic valve closure and deflate at the onset of the subsequent systole. When initiating support, it is often helpful to begin with the balloon augmenting every other beat (the 2:1 mode) to be able to compare an unaugmented beat with an augmented beat as one adjusts the timing of the balloon. The aim here is to maximize the height of the augmented diastolic peak and minimize the height of the systolic peak after the augmented diastole.

Weaning

The balloon generally is used for augmentation of all beats (1:1 mode) until the patient's

ventricular function improves and allows stepwise reduction of the assist mode to the 2:1 and later the 3:1 mode over a period of 6 to 12 h.[97] When hemodynamic independence from the IABP is established, the balloon may be removed.

Complications

Complications have been reported to occur in 5 to 35 percent of IABP insertions.[98,99] Ischemia of the extremity distal to the femoral insertion site is the most common complication and may be more common when the percutaneous technique is used.[100] Severe ischemia requiring amputation of the toes, foot, or lower leg has been reported in 1 to 2 percent of cases.[97-99] Wound infection at the groin insertion site is the second most common complication, occurring in 3 to 4 percent of patients and usually presenting several days after catheter removal. Most of these complications resolve with topical care and systemic antibiotics. Other reported complications of IABP use include dissection or perforation of the distal aorta or its branches and peripheral or visceral embolization caused by thrombus formation. The incidence of the latter is decreased by the routine use of therapeutic doses of heparin.

TEMPORARY: VENTRICULAR ASSIST DEVICES

Mechanical support for a failing heart that becomes refractory even to IABP support is available in the form of ventricular assist devices (VADs) or replacement artificial ventricles. Since the first report of successful use of a VAD in 1965,[101] the technology has progressed a great deal. Most of these assist devices function by diverting blood out of the left ventricle through a large inflow conduit inserted into the left ventricular apex, into a pump-drive system, and back through a large outflow conduit into the ascending aorta. Figure 22-7 shows a typical VAD system in situ.

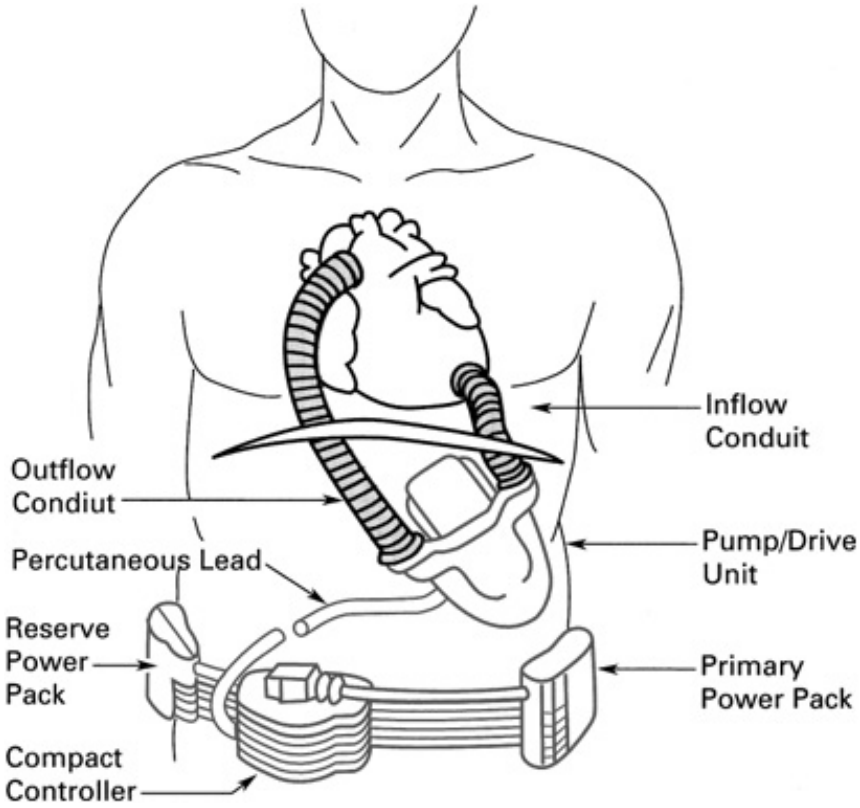

Figure 22-7: Diagram of a wearable Novacor left ventricular assist device in situ, showing inflow conduit inserted in apex of left ventricle leading to body of electrically driven pump, with outflow

conduit returning blood to the ascending aorta. (Courtesy of Novacor Division, Baxter Healthcare Corporation, Oakland, CA.)

In the United States, VADs are currently approved for two indications. The first is temporary support of potentially reversible cardiac dysfunction, and substantial myocardial salvage has been achieved in postcardiotomy[102,103] and, less frequently, postinfarction[104] cardiogenic shock. The second approved indication for VAD support is as a "bridge" to transplantation in waiting transplant recipients (who, by definition, have irreversible myocardial dysfunction) who deteriorate severely before a donor becomes available. Successful bridging with a VAD was first reported in 1984, using the Novacor implantable electrical VAD (Novacor Division, Baxter Healthcare Corporation, Oakland, CA) in a patient with end-stage ischemic heart disease.[105] Success with replacement artificial ventricles (an orthotopic artificial heart) was reported a year later in a patient with cardiomyopathy.[106] The artificial heart technology, however, was fraught with high complication rates and has not been used for a number of years. There has been some resurgence of interest in the use of total artificial hearts as bridges to transplantation[107] and their future is uncertain.

Because of the progressive "mismatch" between the increasing demand for donor hearts and the stable donor supply rate, increasing numbers of patients on transplant waiting lists are deteriorating and requiring the use of such bridge devices to survive until a donor becomes available. The use of mechanical technology in this situation is associated with excellent posttransplant survival rates for supported patients,[108,109] but it does add a substantial level of pretransplant expense and of course does not increase the overall size of the donor pool.

The Future: Permanent Ventricular Assist Devices

With the growing shortage of donor organs, there is an increasing need for a mechanical device as an alternative to the biological transplantation of a failing heart. The ultimate goal of the evolving technology first used for temporary ventricular assistance has been to develop a completely implantable electrical system with rechargeable batteries (allowing the patient freedom from tethering to a power supply) to serve as a permanent assist to left ventricular function. The first clinical trials of such devices have commenced and involve patients with end-stage heart disease who, for reasons of age or other comorbid conditions, are not considered transplant candidates.[110] If their safety and efficacy are established in this patient population, clinical trials comparing VAD support directly with transplantation can proceed and address many end points, such as quality of life, in addition to survival.

The Future: Xenotransplantation

Work on the development of a mechanical alternative to biological cardiac transplantation has proceeded simultaneously with immunologic research aimed at making it possible to use animal organs in humans, a field known as *xenotransplantation*. Formidable anatomic, physiologic, and immunologic barriers must be overcome before xenotransplantation can become a solution to the shortage of donor organs.[111] Anatomically, transplanted organs must be of the appropriate size and structure to replace the native organ. Physiologically, the transplanted organ must perform a complex set of tasks that require it to receive and often send appropriate hormonal and metabolic signals. Such needs require reasonable homology of both the involved hormones and the cell surface receptors between the human and donor species. Technically and biologically, primates are the obvious choice for a donor species. However, the supply of primates is much too small to fill the potential demand; ethical considerations also are a drawback to the use of primates as organ donors. The pig has emerged as the most likely species to provide the appropriate size, anatomic structure, and available numbers for human organ transplantation. Unfortunately, swine are quite phylogenetically distant from humans, and this distance is associated with a formidable

immunologic barrier. Humans universally possess so-called natural antibodies directed against swine antigens, primarily against carbohydrate moieties that are present on endothelial and other cells. These antibodies lead to hyperacute rejection of a swine organ through activation of the complement system initiated by the antibodies binding to donor endothelial cells, a process that occurs within an hour after implantation and leads to rapid destruction of the graft.[112,113]

Several means have been investigated to prevent hyperacute rejection. Depletion of xenogeneic natural antibodies against the donor organ as a way of modifying the host's humoral immunity is one approach.[114,115] Transient inhibition of complement activity with cobra venom factor or a soluble complement receptor delays hyperacute rejection and attests to the central role of the complement system in this process.[116] The activation and activity of complement are ordinarily regulated and limited by several endothelial cell-associated proteins. These proteins may function less effectively against heterologous than against native complement, making xenografts potentially more susceptible to complement-mediated injury. The production of transgenic swine bred to express human complement regulatory proteins to decrease the xenograft's susceptibility to complement-mediated injury has been an area of active research.[117,118] Such genetic alterations of the donor species hold some promise, at least for overcoming this first immunologic barrier to xenotransplantation. The later occurrences of acute and chronic rejection, however, are problems that remain to be solved. With current technology, the prevention of acute rejection of xenografts would require unacceptably intense regimens of immunosuppression, and prevention of chronic rejection, as was noted earlier, is inadequate with current technology, even in allografts.

The prospect of using animal tissues in transplantation has raised concern about the potential for the transmission of zoonotic pathogens from animal to human.[119] Since the likelihood of an organism causing disease in humans may be independent of its disease-causing potential in the donor species, the issue becomes a major one for the individual recipient and potentially has wide public health implications. When clinical trials begin, it will be extremely important to monitor recipients of xenogeneic tissue for the occurrence of unexplained illness; it has been suggested that the creation of a national or international registry of exposure to xenogeneic tissue would facilitate identification of clusters of events or illness.[119,120]

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ENDOMYOCARDIAL BIOPSY

The Instrument

A percutaneous transvascular approach to biopsy of the beating heart was first described by Sakakibara and Konno in Japan in 1962,[121] and modifications of their instrument are still widely used. They generally are introduced from a femoral or brachial vein. This technology to permit nonsurgical biopsy of the myocardium was further developed in response to the need to obtain tissue from a transplanted heart to assess the presence and severity of graft rejection and monitor the response to antirejection therapy. Cardiac allograft rejection initially had been recognized by means of clinical observation of phenomena such as the emergence of heart failure, a gallop rhythm, or declining electrocardiographic voltage. Such phenomena often did not occur, however, until rejection was quite severe, and biopsy offered a means of early and objective assessment of rejection. In 1973, Caves and associates at Stanford introduced a new, shorter (and therefore more controllable) bioptome, which was introduced from the jugular rather than the femoral vein and allowed easy and repeated serial biopsy procedures under fluoroscopic guidance.[122] The Caves-Schultz-Scholten instrument was improved by Mason[123] and for years was the most commonly used bioptome in the United States. This bioptome is reusable, but its cleaning procedure is costly and labor-intensive, and several disposable instruments have been developed and have gained widespread use in recent years. An example of one of the most widely used is shown in Fig. 22-8 with the standard percutaneous approach from the right internal jugular vein. Longer bioptomes are also available for use from the femoral approach (usually through a long guiding sheath) in patients without internal jugular access.

The Technique

The right ventricle is usually the ventricle of choice for obtaining biopsy material because of the relative convenience and safety of approach to the right, as opposed to the left, ventricle as well as the usually homogeneous distribution of myocardial inflammatory and rejection processes. The procedure is performed with the patient supine, usually in a cardiac catheterization laboratory or in a procedure room or in the operating room if facilities are available. For the internal jugular approach, positioning with the feet elevated increases central venous pressure and facilitates cannulation of the vein. After the introduction of an intravascular sheath with the standard percutaneous technique, the bioptome can be advanced through it down to the right atrium, across the tricuspid valve, and into the right ventricle, pointed toward the septal wall. The stimulation of premature ventricular contractions by the instrument serves as confirmation of its presence in the ventricular chambers. Once it is safely within the ventricle and directed toward the septum, the jaws of the bioptome are opened, the instrument is advanced gently against the wall, and the jaws are closed, "biting off" a piece of septal myocardium 1 to 3 mm in diameter. The bioptome is then withdrawn, and the specimen is retrieved and placed in an appropriate medium for pathologic examination. The process is repeated until three to five adequate specimens are obtained.

Endomyocardial biopsy procedures generally are performed on an outpatient basis without the requirement for sedation or concomitant measurement of right-sided heart pressures unless they are clinically indicated. The procedure usually is done under fluoroscopic guidance,[124] but many centers perform it safely[125] and potentially with less cost[126] under echocardiographic guidance.

Complications

Large series have documented the low morbidity and mortality of endomyocardial biopsy, with major complications such as cardiac perforation and tamponade occurring in <0.5 percent of procedures.[127,128] More minor and generally transient complications include bundle branch block and arrhythmias. Fistulas between the coronary artery and the right ventricle have been described in a number of transplant patients

who have had multiple biopsy procedures but generally seem to have no hemodynamic consequence.[129,130] With increasing lengths of survival of cardiac transplant recipients and the continued use of surveillance myocardial biopsies, complications related to the sheer numbers of biopsies performed are becoming more apparent. Chief among these complications is damage to the tricuspid valve and its subvalvular structures. This complication was first reported in 1990,[131] when a series of five patients with tricuspid valve chordal rupture as a complication of endomyocardial biopsy was reported. None of those patients had hemodynamically significant tricuspid regurgitation. Subsequently, there have been reports suggesting that signs of right-sided heart failure eventually appear in some patients, and several patients are known to have required tricuspid valve replacement because of intractable right heart failure. The incidence of tricuspid valve injury may be decreased with the use of a sheath across the valve during biopsy.[132]

Role in the Evaluation and Diagnosis of Cardiac Disease

TISSUE HANDLING AND PROCESSING

Correct handling of retrieved biopsy specimens is essential for obtaining accurate histopathologic results and interpretability. To limit crush distortion of the tissue, the biopsy specimenshould be teased gently from the bioptome with a needle and immediately placed in an appropriate fixative. Neutral buffered 10% formalin is the standard fixative for light microscopy, and gluteraldehyde-based solutions are used for transmission electron microscopy (TEM). The specific clinical circumstances usually determine how the specimen will be fixed and processed and which histochemical stains will be selected. For the evaluation of myocarditis, cardiomyopathy, and specific heart muscle diseases, at least four biopsy pieces are recommended for light microscopy; one piece may be retained for TEM, and an unfixed piece may be frozen for immunofluorescence or immunohistochemical studies (optional). At least four pieces are required for light microscopy for adequate sampling in the grading of acute rejection; one piece may be frozen for immunofluorescence studies if acute vascular rejection is suspected. All the tissue samples (four to five pieces) should be placed in gluteraldehyde when grading of anthracycline cardiotoxicity is the clinical issue.

INDICATIONS FOR ENDOMYOCARDIAL BIOPSY

Since the successful application of an endomyocardial biopsy for the diagnosis and monitoring of acute rejection in the early 1970s, the indications for the procedure have expanded. The right ventricle usually is selected for technical reasons, including safety, although left ventricular biopsy occasionally is performed for the diagnosis of endomyocardial fibrosis, infantile fibroelastosis, left-sided irradiation effects, and cardiac involvement by scleroderma. The current indications for endomyocardial biopsy are listed in Table 22-9.

Table 22-9: Possible Indications for Endomyocardial Biopsy

Diagnosis and grading of acute rejection
Diagnosis of myocarditis
Evaluation of idiopathic cardiomyopathy
Diagnosis of specific heart muscle diseases
Distinguish restrictive versus constrictive heart disease
Evaluation and grading of anthracycline cardiotoxicity
Diagnosis of primary and secondary cardiac neoplasms
Evaluation of idiopathic arrhythmias
Evaluation of atypical chest pain

Myocarditis

As an inflammatory or immunologic process, myocarditis is defined by the presence of an inflammatory infiltrate in association with nonischemic damage or necrosis of the adjacent myocytes;[133] these features are termed *the Dallas criteria* (see Chap. 69). The different types of inflammatory cells help define possible etiologies in myocarditis. Lymphocytes are the predominant cell type seen in idiopathic (postviral) myocarditis (Fig. 22-9), sarcoidosis, Lyme disease, Kawasaki's disease, polymyositis, and AIDS myocarditis (see Chap. 70). Eosinophils are commonly found in drug hypersensitivity but also may indicate parasitic infection or a hyper-eosinophilic syndrome. Myocyte necrosis associated with multinucleated giant cells is characteristic of giant-cell myocarditis[134] (Fig. 22-10). Epithelioid histiocytes forming granulomas are seen in cardiac sarcoidosis.[135]

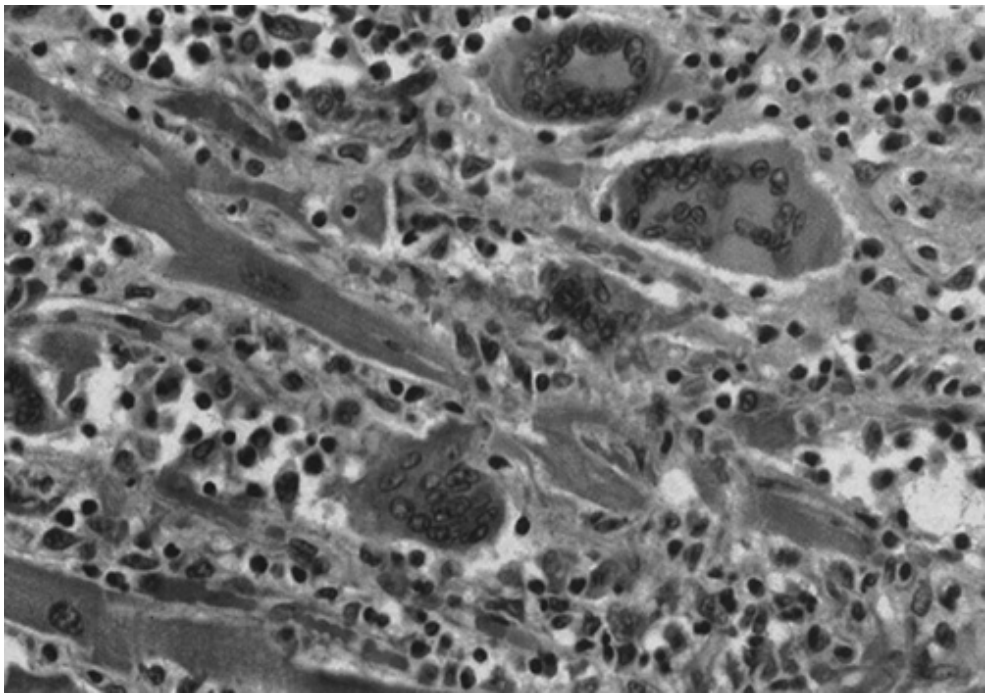

Figure 22-10: Giant-cell myocarditis showing an inflammatory infiltrate composed of lymphocytes, histiocytes, and eosinophils admixed with multinucleated giant cells. Myocyte damage is conspicuous in this case. (H&E ×400)

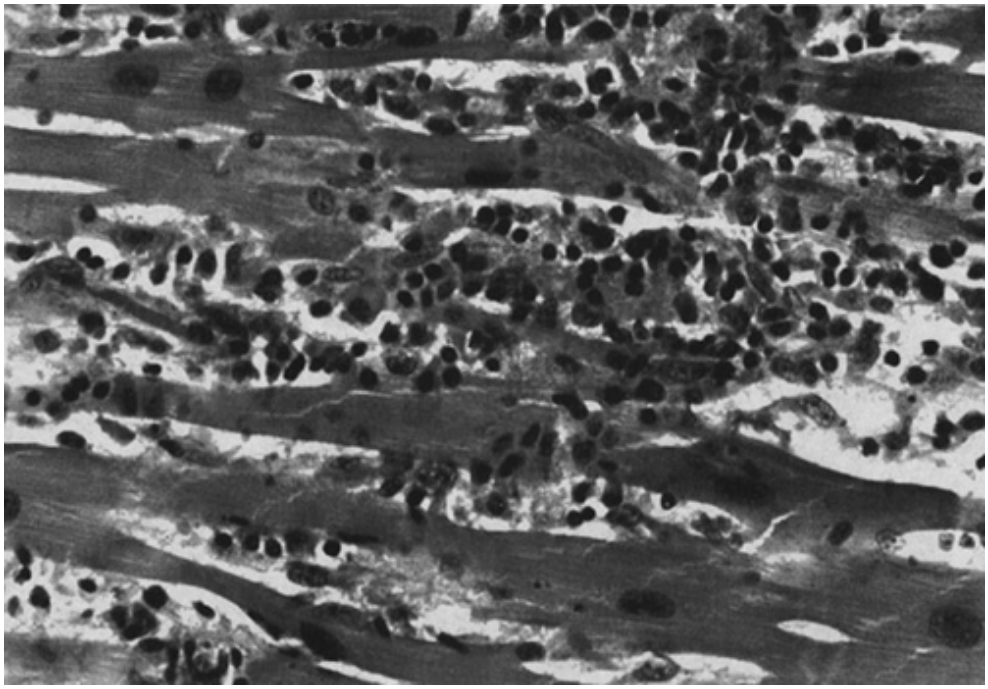

Figure 22-9: Lymphocytic myocarditis in a young man presenting with sudden-onset congestive heart failure. Dense interstitial infiltrates of lymphocytes are seen in association with myocyte damage. (H&E ×400)

Idiopathic Cardiomyopathy

The morphologic diagnosis of idiopathic dilated cardiomyopathy, including familial and postpartum types, is primarily one of exclusion, as a variety of storage and infiltrative heart muscle diseases and myocarditis may mimic dilated cardiomyopathy (see Chaps. 62, 66-69, and 82). Hypertensive, ischemic, and valvular heart disease also must be excluded. Endomyocardial biopsy is used routinely in some institutions in evaluating dilated cardiomyopathy of unknown causes. The morphologic features of idiopathic cardiomyopathy are nonspecific and include myocyte hypertrophy and interstitial fibrosis (Fig. 22-11). Hypertrophic cardiomyopathy is the second most common type of cardiomyopathy. It cannot be diagnosed reliably by endomyocardial biopsy since the characteristic histologic features are found mainly in the midportion of the ventricular septum.[136] Mimics of hypertrophic cardiomyopathy such as amyloidosis can be delineated by biopsy.

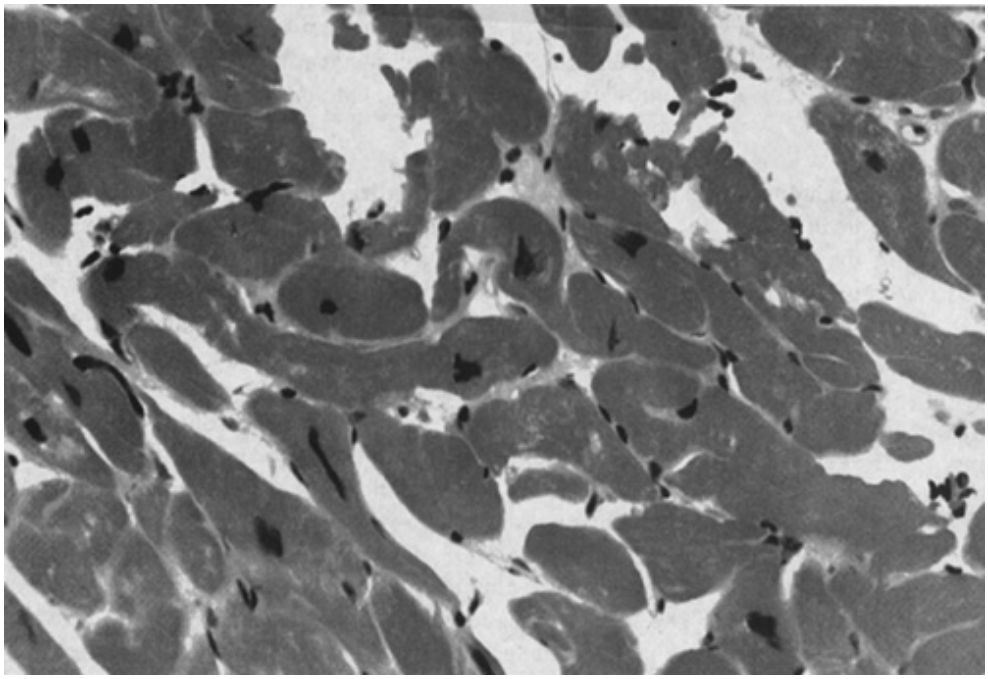

Figure 22-11: A young woman presenting with congestive heart failure. Myocyte hypertrophy characterized by large, irregular nuclei is seen. The findings are compatible with dilated cardiomyopathy. (H&E ×400)

Specific Heart Muscle Diseases

A variety of infiltrative diseases and storage disorders of the myocardium can be readily diagnosed by endomyocardial biopsy (see Chap. 68). Cardiac amyloidosis may be seen with primary amyloidosis, plasma cell dyscrasias, and chronic inflammatory conditions and in elderly patients (senile amyloid). The histologic appearance includes interstitial, subendocardial, or vascular deposits of finely fibrillar, eosinophilic material (Fig. 22-12). Senile amyloid often is characterized by nodular deposits of transthyretin. Histochemical stains such as Congo red and trichrome are useful in distinguishing amyloid from collagen.[137]

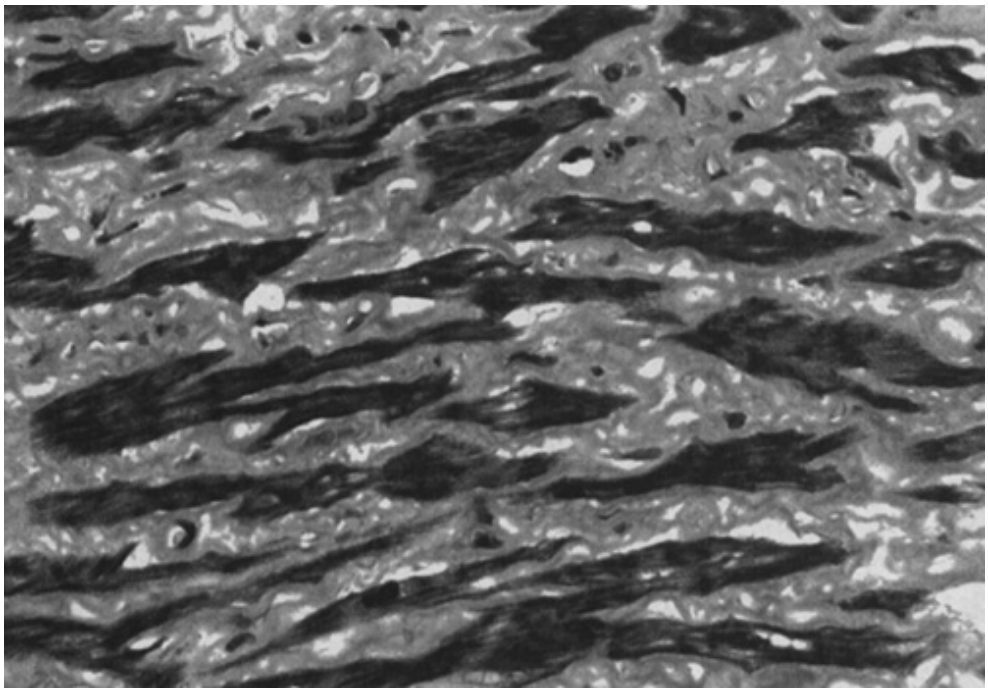

Figure 22-12: Severe interstitial amyloidosis showing fibrillar deposits along the sarcolemma with constriction of the myocytes. (H&E ×400)

Disorders of iron metabolism (hemochromatosis) and iron overload states (hemosiderosis) result in perinuclear accumulations of iron pigment within the myocytes. Special stains such as Prussian blue highlight the pigment (Fig. 22-13). In advanced disease, marked myocyte hypertrophy and interstitial fibrosis are found. The diagnosis of metabolic enzyme deficiencies, including glycogen storage diseases, Gaucher's disease, and Fabry's disease (see Chap. 62), also may be established by endomyocardial biopsy.

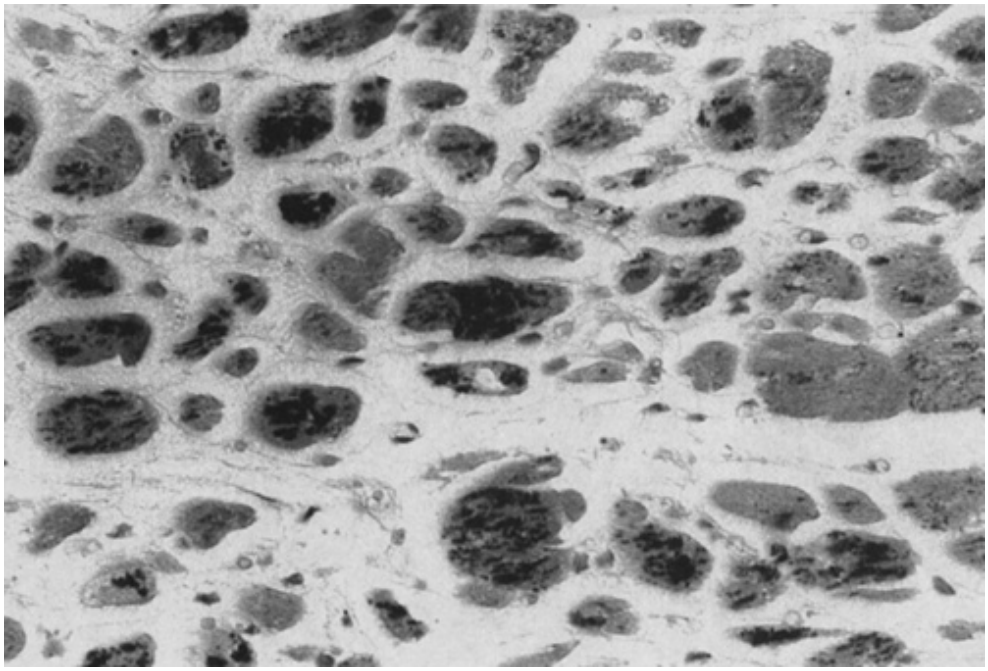

Figure 22-13: Cardiac hemochromatosis in a young man. Dense accumulations of iron pigment are seen in a perinuclear location. (Prussian blue ×400)

Restrictive versus Constrictive Heart Disease

The clinical distinction of restrictive heart disease from constrictive pericardial disease can be difficult, and the therapeutic implications are significant. In some cases, imaging and hemodynamic studies may not provide a definitive diagnosis. Specific heart muscle diseases resulting in restrictive physiologic profiles, including amyloidosis, carcinoid heart disease, endocardial fibrosis, and radiation-induced interstitial fibrosis, can be diagnosed by biopsy[138] (see Chaps. 68 and 72).

Anthracycline Cardiotoxicity

Anthracyclines such as doxorubicin are used commonly in the treatment of solid tumors and hematologic malignancies. Cardiac toxicity in the form of congestive heart failure is the most significant side effect of these agents and may develop months to years after the completion of therapy. The condition is dose-related and generally occurs after a cumulative dose of 550 mg/m^2. Individual patient variation and factors such as prior mediastinal irradiation, hypertension, and increased age may potentiate cardiotoxicity at lower cumulative doses.[139] TEM of heart biopsies remains the "gold standard" for the diagnosis and grading of doxorubicin toxicity.[140]

The Billingham grading scheme for doxorubicin toxicity is based on the percentage of myocytes that demonstrate doxorubicin effect. Grades 0 through 3 are used and are associated with specific therapeutic recommendations.[141] The characteristic changes include myofibrillar loss with Z-band remnants and sarcotubular dilatation within the myocytes (Fig. 22-14). This approach to drug toxicity has provided a

valuable method of monitoring patients and preventing irreversible cardiac failure.[142]

Figure 22-14: Transmission electron micrograph of adriamycin cardiotoxicity. Note the atrophic myocyte with myofibrillar loss surrounded by normal myocytes. (TEM ×3200)

Primary and Metastatic Neoplasms

Endomyocardial biopsy has been used to provide morphologic confirmation and classification of benign and malignant primary cardiac tumors and to document the presence of metastatic malignancies[143] (see Chap. 77). Cardiac myxomas, fibromas, and rhabdomyomas as well as sarcoma, lymphoma, leukemia, and malignant mesothelioma have been diagnosed. Secondary neoplasms such as metastatic carcinoma and melanoma also may be found in right ventricular specimens (Fig. 22-15).

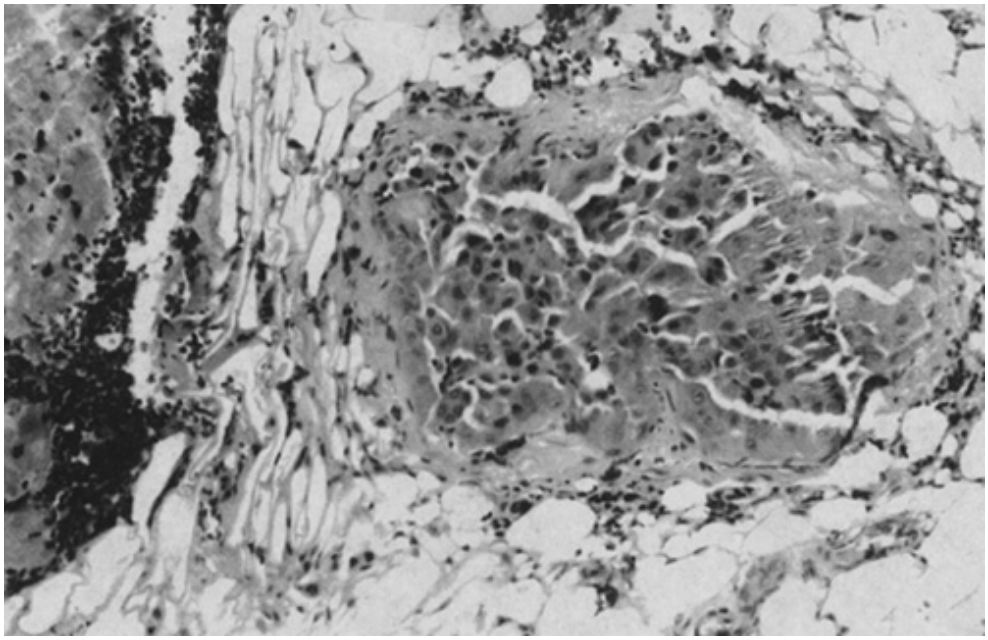

Figure 22-15: Metastatic adenocarcinoma in a 51-year-old woman with sudden-onset congestive heart failure and tamponade. (H&E ×400)

Idiopathic Arrhythmias

In the absence of a documented anatomic abnormality such as ischemic heart disease, cardiomyopathy, or mitral valve prolapse as an explanation for ventricular or supraventricular rhythm disturbances, an endomyocardial biopsy may be helpful. Lesions of the conduction system can result in nonspecific myocyte hypertrophy and interstitial fibrosis. Lymphocytic myocarditis, sarcoidosis, and giant-cell myocarditis all may present with arrhythmias. In a recent study of 80 patients with unexplained arrhythmias 88 percent of the biopsies revealed pathologic changes. Among these patients, 56 percent of the biopsies showed features of cardiomyopathy, 19 percent had clinically unsuspected myocarditis, 10 percent had small vessel disease, 3 percent had amyloidosis, and 1 percent showed an intravascular organizing thrombus.[144] An uncommon cause of arrhythmia is arrhythmogenic right ventricular dysplasia (see Chap. 33). It should be suspected in biopsy specimens showing hypertrophy and fibrosis in association with abundant myocardial deposits of adipose tissue. Clinicopathologic correlation is required for the diagnosis, as myocardial accumulations of fat normally are found in the right ventricle.

Pathology of Acute Rejection

MACROSCOPIC PATHOLOGY

In advanced cardiac rejection, the heart is larger than normal, stiff, and noncompliant. In the early posttransplant period, a fibrinous pericarditis may be seen. The heart appears edematous and hemorrhagic with a dark plum color. Along the atrial sutures a sharp tinctorial delineation between the hemorrhagic myocardium of the donor heart and the pale tan myocardium of the recipient heart is a characteristic of severe rejection. Less commonly, the valves may be swollen and turgid. The trabecular muscles are prominent and often demonstrate subendocardial hemorrhages.

MICROSCOPIC PATHOLOGY

Hyperacute Rejection

This rare pattern of allograft rejection occurs in the setting of preformed circulating antibodies such as ABO blood group incompatibility or, rarely, antibodies against specific endothelial antigens or HLA.[145] The myocardium is globally edematous and hemorrhagic as a result of diffuse interstitial hemorrhages. Neutrophils and fibrin thrombi may be seen within the microvasculature (Fig. 22-16). Hyperacute rejection

manifests as severe graft failure immediately or within the first few hours after transplantation. Without mechanical cardiopulmonary support, plasmapheresis, and emergent retransplantation, the recipient usually does not survive.

Figure 22-16: Hyperacute rejection is characterized by diffuse interstitial hemorrhage. (H&E ×400)

Acute Cellular Rejection

The principal histopathologic features of acute cellular rejection are the distribution and extent of inflammation and the presence or absence of myocyte damage. The severity of the rejection process reflects these features along a morphologic continuum. In 1973, the Stanford grading scheme of mild-moderate-severe rejection was introduced,[146] and modifications were developed by other programs.[147-149] As a result, comparisons of results between institutions and in multicenter clinical trials were not feasible. In 1990, a consensus was reached establishing a uniform and standardized grading system.[150] Currently, a numerical and descriptive grade is assigned to each biopsy sample. This scheme requires at least four pieces of myocardium using a standard bioptome, 50 percent of which must be evaluable myocardium, i.e., not a biopsy site or scar. If a smaller bioptome (7F or smaller) is used, at least six pieces of myocardium are required.

Six patterns of acute cellular rejection have been described (Table 22-10). Mild acute rejection is divided into two patterns on the basis of the cytoarchitectural features. Focal mild rejection (grade IA) represents a circumscribed, usually perivascular arrangement of lymphocytes in one or more sites that is not associated with myocyte damage. In diffuse mild rejection (grade IB), the infiltrates are arranged in a more diffusely interstitial architectural pattern; myocyte damage is not found. Focal moderate rejection (grade II) is characterized by a solitary, sharply circumscribed inflammatory focus that is associated with myocyte damage. The other biopsy pieces may be free of rejection or have a lower grade. In multifocal moderate rejection (grade IIIA), at least two foci of inflammatory infiltrate display myocyte damage. These foci are often in different pieces of myocardium. Diffuse moderate rejection (grade IIIB) is represented by diffuse interstitial infiltrates in most or all of the biopsy pieces. Myocyte damage is significant, and the findings may be classified as borderline severe rejection (Fig. 22-17). In severe rejection (grade IV), a dense polymorphous infiltrate that includes lymphocytes, neutrophils, and eosinophils is present diffusely in the interstitium. Myocyte damage, edema, and hemorrhage are conspicuous as a result of injury of the microvasculature. Resolving or resolved acute rejection is denoted by a lower grade on the biopsy than was denoted on the previous biopsy.

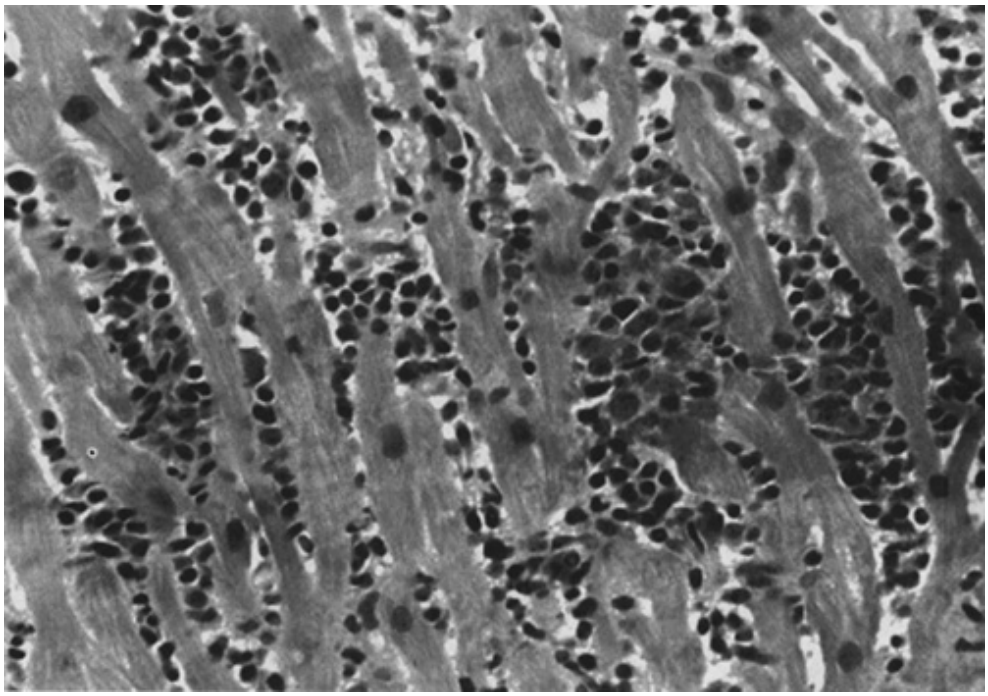

Figure 22-17: Diffuse moderate acute rejection (grade IIIB) showing activated lymphocytes within the interstitium and myocyte damage. (H&E ×400)

Table 22-10: Standardized Cardiac Biopsy Grading (Modified)

'Old' Nomenclature	Grade	'New' Nomenclature
No rejection	0	No rejection
Mild rejection	I	A = Focal (perivascular or focal interstitial infiltrate without myocyte damage)
		B = Sparse focal interstitial infiltrate without myocyte damage
'Focal' moderate rejection	II	One focus only with activated lymphocytes and myocyte damage
'Low' moderate rejection	III	A = Multifocal lymphocytic infiltrates with myocyte damage
'Borderline/severe' rejection		B = Diffuse (sometimes polymorphous) inflammatory process
'Severe/acute' rejection	IV	Diffuse, polymorphous infiltrate with myocyte necrosis ± edema ± hemorrhage ± vasculitis
'Resolving' rejection	Denoted by a lower grade	Healing tissue with fibroblasts and pigmented macrophages
'Resolved' rejection	0	Mature scar tissue

SOURCE: From Billingham ME, Carey NRB, Hammond EH, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart rejection study group. *J Heart Transplant* 1990; 9:587-592, with permission.

Morphologic Mimics of Acute Rejection

Inflammatory infiltrates and myocyte damage of the allograft may be found in conditions other than cardiac rejection. The diagnosis of acute rejection should be made after the careful exclusion of these histologic mimics (Table 22-11). Within the first 3 weeks after transplantation, biopsies often show evidence of ischemia or preservation injury. Reperfusion of the allograft contributes to myocyte damage. Likewise, the use of pressor agents for hemodynamic support either before or after transplantation may result in small circumscribed foci of myocyte damage. The infiltrates are composed of neutrophils in the initial stages and are replaced by granulation tissue. Sharply delineated endocardial infiltrates composed of lymphocytes and a delicate vascular stroma have been designated the "Quilty effect" and may be confused with rejection when the infiltrate extends into the subadjacent myocardium. Infectious myocarditis, particularly toxoplasmic and CMV myocarditis, can resemble acute rejection. The infiltrates are usually polymorphous (lymphocytes, neutrophils, and eosinophils), and the organisms may be found. Immunohistochemical or molecular techniques are useful in difficult cases.[151] The granulation tissue and inflammation associated with previous biopsy sites may be confused with acute rejection. PTLDs uncommonly involve a cardiac allograft. Both polyclonal and monoclonal lesions have been reported, and histopathologic analysis and clonality studies are essential for classification and prognosis.[152] The presence of atypical lymphocytes, plasmacytoid or immunoblastic cell infiltrates, abundant tissue necrosis, and frequent mitotic figures should suggest the possibility of PTLD.[153]

Table 22-11: Histopathologic Mimics of Acute Rejection

Reperfusion/ischemic injury
Quilty effect
Infectious myocarditis (cytomegalovirus/toxoplasmic)
Previous biopsy site
Posttransplant lymphoproliferative disorder

Acute Vascular (Humoral) Rejection

Most episodes of rejection in the posttransplant period are mediated by lymphocytes and histiocytes and are examples of "cellular" rejection. Hammond and colleagues found cases of allograft dysfunction occurring in the first 6 weeks after transplantation in which the classic features of cellular rejection were absent.[154] Immunofluorescence studies on fresh-frozen myocardial samples demonstrate the presence of immunoglobulin, complement, and fibrinogen, suggesting a humoral immune response mediated by endothelial and B cells. The myocardium displays large prominent endothelial cells in venules and capillaries, perivascular and interstitial edema. Currently, the diagnosis requires both the histologic and immunofluorescence findings. Infection and ischemic changes also must be excluded. A number of studies have suggested that these patients are at higher risk for developing accelerated graft coronary disease.[155] The etiology, incidence, optimum treatment strategies, and natural history of this form of rejection warrant further clinical studies.

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Chapter 22: CARDIAC TRANSPLANTATION, MECHANICAL VENTRICULAR SUPPORT, AND ENDOMYOCARDIAL BIOPSY

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Chapter 22: CARDIAC TRANSPLANTATION, MECHANICAL VENTRICULAR SUPPORT, AND ENDOMYOCARDIAL BIOPSY

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 23:

MECHANISMS OF CARDIAC ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Authors: Albert L. Waldo, Andrew L. Wit

OVERVIEW OF MECHANISMS OF CARDIAC ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Introduction

Because of the increasing availability of sophisticated electrophysiologic techniques for the study of cardiac tissues both in vivo and in vitro and the ability to study arrhythmias and conduction disturbances both in experimental models and in patients, knowledge about the mechanisms of arrhythmias and conduction disturbances has increased greatly. Although much is now known, much remains to be understood. Arrhythmias are due to normal or abnormal impulse generation, abnormal impulse conduction, or a combination of simultaneous abnormalities of impulse generation and conduction.[1] This chapter first provides an overview of these mechanisms and identifies the clinical arrhythmias with which they are thought to be associated. This is followed by a much more detailed discussion of these mechanisms as they are currently understood. The detailed discussion requires that the reader have a rudimentary knowledge of the basic cellular electrophysiology of the heart, including the ionic channels and membrane currents causing the resting potential and the cardiac action potential, as well as the mechanisms for automaticity and conduction. However, much of this material is included in a detailed discussion of the mechanisms of arrhythmias, since the chapter considers how alterations in normal electrophysiology lead to abnormal cardiac rhythms.

Causes of Arrhythmias

NORMAL OR ABNORMAL IMPULSE INITIATION

Automatic Rhythms

NORMAL MECHANISM

Cardiac cells that normally are capable of developing spontaneous diastolic (phase 4) depolarization are called *pacemaker cells*. When pacemaker cells manifest spontaneous diastolic depolarization (Fig. 23-1) and thus are responsible for generating the cardiac rhythm, the rhythm is classified as an *automatic rhythm*. Normally, the dominant pacemaker of the heart is in the sinus node, which in adults fires at a rate of 60 to 100 beats per minute. Cells capable of developing spontaneous diastolic depolarization (i.e., of manifesting automaticity) also are normally found in the specialized fibers in the atria, the atrioventricular (AV) junction, and the His-Purkinje system. The normal rate of impulse formation in adults by these ectopic pacemakers is 40 to 60 beats per minute in the AV junction (the AV node and His bundle). Normal rates of more distally located ectopic pacemakers are probably 20 to 40 beats per minute in the bundle branches. These ectopic (i.e., nonsinus) pacemakers also are called *latent* or *escape* pacemakers for two related reasons: (1) The normal intrinsic rate of these pacemakers is lower than that of the dominant pacemaker, the sinus node, and (2) spontaneous diastolic depolarization of these latent or escape pacemakers normally is suppressed by the more rapid rate of the sinus node pacemaker through the active process of overdrive suppression. Only when the sinus rate slows below the intrinsic rate of these ectopic pacemakers does "the next one in line" warm up and fire (see also "Automaticity," below).

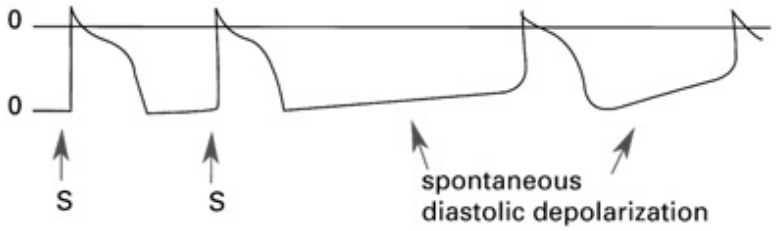

Figure 23-1: Arrhythmias may be caused by normal automaticity. Transmembrane potential recorded from a Purkinje fiber stimulated (S) at a regular rate is shown. When the stimulus is turned off, spontaneous diastolic depolarization develops to cause automatic firing by a normal mechanism.

Arrhythmias of the Sinus Node

An arrhythmia occurs when the sinus node pacemaker fires at a rate above 100 beats per minute (sinus tachycardia) (Table 23-1) or at a rate below 60 beats per minute (sinus bradycardia) and is still the dominant pacemaker of the heart. These are called *arrhythmias resulting from normal automaticity*, since the ionic mechanism causing the pacemaker depolarization is unchanged from the normal sinus rhythm. A sinus tachycardia is usually an appropriate response to a precipitating factor (e.g., exercise, fever, hypotension), although on occasion it may be inappropriate, as in the presence of a sympathetic dysautonomia (inappropriate sinus tachycardia). By contrast, sinus bradycardia often reflects an abnormality not only of the sinus node pacemakers (they are too slow) but also of the latent or escape pacemakers (when the sinus rate slows abnormally, they do not escape). Sinus bradycardia may be due to an intrinsic abnormality of pacemaker cells, a parasympathetic dysautonomia (inappropriate sinus bradycardia), or an extrinsic factor such as suppression of automaticity by drug therapy (e.g., a beta blocker, a Ca^{2+} channel blocker, or an antiarrhythmic agent). For some patients, sinus bradycardia, particularly when it is present only at rest, may simply reflect a normal response to increased vagal tone, as in a well-trained athlete. Marked beat-to-beat variations in cycle length of the sinus rhythm, which are due virtually always to the influence of vagal tone on the pacemaker cells of the sinus node, also is considered an arrhythmia (sinus arrhythmia) even if the overall sinus rate is normal.

Table 23-1: Types of Tachycardias and Their Selected Characteristics and Documented or Presumed Mechanism

Tachycardia	Mechanism	Origin	Rate Range, bpm	AV or VA Conduction
Sinus tachycardia	Automatic (normal)	Sinus node	≥100	1:1
Sinus nod reentry	Reentry	Sinus node and right atrium	?110-180	1:1 or variable
Atrial fibrillation	Reentry	Atria	260-450	Variable
	Fibrillatory conduction	Pulmonary veins, SVC	?	Variable
Atrial flutter	Reentry	Right atrium, left atrium (infrequent)	240-350, usually 300 ± 20	2:1 or variable
Atrial tachycardia	Reentry	Atria	150-240	1:1, 2:1, or variable
	Automatic (normal or abnormal)	Atria	?	?
	Triggered (DADs) 2° to digitalis toxicity	Atria	150-240	1:1, 2:1, or variable

AV nodal reentry tachycardia	Reentry	AV node with an atrial component	120-250, usually 150-220	1:1
AV reentry (WPW or concealed accessory AV connection)	Reentry	Circuit includes accessory AV connection, atria, AV node, His, Purkinje system, ventricles	140-250, usually 150-220	1:1
Accelerated AV junctional tachycardia	Automatic or ? triggered (? digitalis toxicity)	AV junction (AV node and His bundle)	61-200, usually 80-130	1:1 or variable
Accelerated idioventricular rhythm	Abnormal automaticity	Purkinje fibers	>60-?	Variable, 1:1, or AV dissociation
Ventricular tachycardia	Reentry	Ventricles	120-300, usually 140-240	AV dissociation, variable, or dissociation
	Automatic (rare) (normal or abnormal)	Ventricles	?	Variable, 1:1, or AV dissociation
Bundle branch reentrant tachycardia	Reentry	Bundle branches and ventricular septum	160-250, usually 195-240	AV dissociation, variable, or 1:1
Right ventricular outflow tract	? Triggered (DADs)	Right ventricular outflow tract	120-220	AV dissociation, variable, or 1:1
Torsades de pointes tachycardia	? Triggered (EADs) (with reentry)	Ventricles	>200	AV dissociation

ABBREVIATIONS: DAD = delayed afterdepolarization; WPW = Wolff-Parkinson-White syndrome; EAD = early afterdepolarization; bpm = beats per minute; SVC = superior vena cava.

ECTOPIC AUTOMATIC RHYTHMS

Arrhythmias occur when the site of the dominant pacemaker shifts to a site other than the sinus node (Table 23-1). The site of impulse initiation may shift from the sinus node to an ectopic (latent or escape) pacemaker if any of the following occur: (1) The intrinsic rate of the sinus node decreases, e.g., when pacemaker dysfunction is limited to the sinus node. (2) The intrinsic rate of the ectopic (latent or escape) pacemaker increases, e.g., as a result of enhanced automaticity of latent pacemakers. During such rhythms, the sinus node is normally automatic, but overdrive suppression of the sinus node pacemaker usually occurs because the ectopic pacemaker fires at a more rapid rate. Alternatively, if the rate of the ectopic pacemaker is very fast, there may be entrance block into the sinus node, in which case exit block of the sinus impulses rather than overdrive suppression occurs. (3) The normal sinus impulse is prevented from being the dominant pacemaker of the heart because of sinus node exit block or sinoatrial block (i.e., the impulse cannot exit from the sinus node to excite the atria and subsequently the ventricles) or AV block (the impulse cannot excite the ventricles because of conduction block in the specialized AV conduction system, i.e., the AV node, His bundle, or both bundle branches) (see Chaps. 12 and 27). The automaticity at the ectopic pacemaker site is a result of the normal automatic mechanism; hence, these are arrhythmias caused by normal automaticity.

ABNORMAL MECHANISM

Typically, normal working atrial and ventricular myocardial cells do not develop automaticity. Thus, when they manifest normal transmembrane potentials, no evidence of spontaneous diastolic (phase 4) depolarization is present. Under certain conditions, however, these cardiac muscle fibers, as well as specialized atrial and ventricular fibers, can develop an abnormal type of automatic firing. This occurs when the cell is relatively depolarized so that maximum diastolic potential is reduced to levels much lower than normal, usually by intrinsic cardiac disease. When this occurs, spontaneous diastolic (phase 4) depolarization may occur (Fig. 23-2). Such abnormal automaticity is caused by a pacemaker current that is different from the pacemaker current of normally automatic cells. The transmembrane action potentials associated with abnormal automaticity may be of the slow-response type; i.e., the transmembrane action potential upstroke may depend on the slow inward (L-type) Ca^{2+} current because of inactivation of Na^{+} channels at the reduced level of membrane potential. Arrhythmias caused by abnormal automaticity will not be evident unless the rate of the abnormal focus is greater than that of the dominant automatic pacemaker (usually the sinus node) of the heart. They therefore also appear as ectopic automatic rhythms. Accelerated idioventricular rhythms after myocardial infarction sometimes may be caused by abnormal automaticity in Purkinje's cells in the ischemic region (Table 23-1) (see Chap. 47).

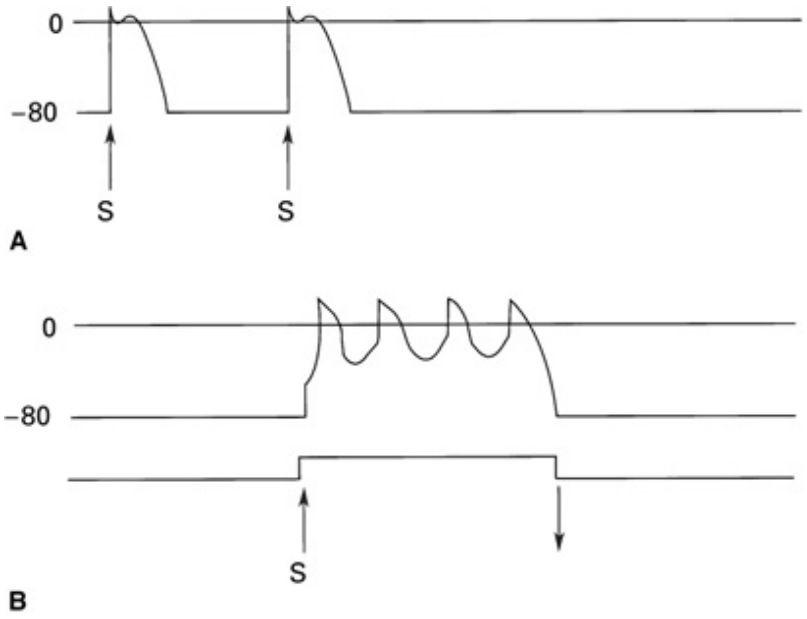

Figure 23-2: Arrhythmias may be caused by abnormal automaticity. The figure shows how abnormal automaticity may develop in a ventricular muscle fiber. *A*. Transmembrane potentials recorded from a muscle fiber with a normal resting potential are shown. When the fiber is not stimulated, phase 4 depolarization and automatic firing do not occur (compare with Fig. 23-1). *B*. At the arrow S, the membrane potential is reduced to -50 mV by a current pulse passed through a microelectrode. Automatic firing occurs at this low level of membrane potential. In the heart, certain abnormal states may cause a similar decrease in membrane potential.

Triggered Rhythms

These arrhythmias are caused by afterdepolarizations (Table 23-1).

Early afterdepolarizations (*EADs*) are associated with a prolongation of the duration of the action potential and occur during repolarization of a transmembrane action potential that has been initiated from a normal level of membrane potential. They appear as a shift in membrane potential in a positive direction relative to the membrane potential expected during normal repolarization (Fig. 23-3*A* and *B*). Repetitive depolarizations may originate from the low level of membrane potential that occurs during the afterdepolarization (Fig. 23-3*B*). A clinical example of a rhythm thought to be initiated by EADs is torsades de pointes. This is a polymorphic ventricular tachycardia that is associated with abnormal QT-interval prolongation (and therefore prolongation of the Purkinje fiber and ventricular muscle action potentials)

caused by any of a variety of factors. This includes a toxic response to class IA or III antiarrhythmic agents or any other agents that prolong the duration of the ventricular action potential, hypokalemia, and hypomagnesemia. It also includes torsades de pointes associated with syndromes characterized by an intrinsic prolongation of the QT interval (and therefore of the Purkinje fiber and ventricular muscle action potentials), such as the congenital long QT syndromes, which also are thought to be initiated by EADs (Table 23-1).

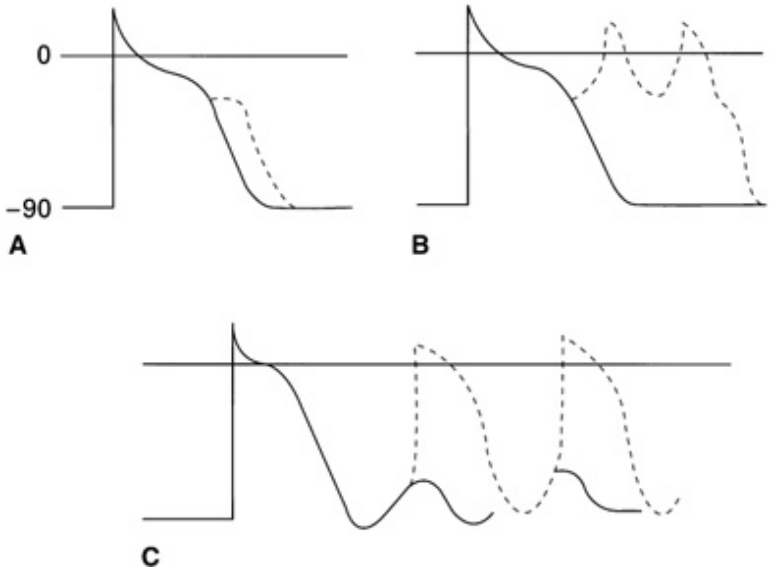

Figure 23-3: Triggered activity is caused by afterdepolarizations. *A.* A solid trace shows the normal transmembrane potential from a Purkinje fiber. The dashed trace shows an EAD that is subthreshold. *B.* Early afterdepolarization reached the threshold for the slow inward current, causing repetitive firing during the plateau of the Purkinje fiber action potential (*dashed trace*). *C.* Solid trace shows a transmembrane action potential followed by a subthreshold DAD. The dashed trace shows the triggered action potentials that occur when the afterdepolarization reaches threshold potential.

Delayed afterdepolarizations (*DADs*) are transient depolarizations that occur after repolarization of the transmembrane action potential (Fig. 23-3*C*). Triggered impulses occur when DADs reach the threshold potential for activation of the inward current responsible for the upstroke of the transmembrane action potential. Delayed afterdepolarizations have been recorded from atrial, ventricular, and Purkinje's cells exposed to catecholamines, digitalis, or abnormally high levels of Ca^{2+} and are caused by abnormally high intracellular Ca^{2+}. The ionic mechanism causing DADs is the transient inward current, a current caused by oscillatory changes in intracellular Ca^{2+} concentrations. Some digitalis toxic rhythms are thought to be due to delayed afterdepolarizations as well as some idiopathic ventricular tachycardias originating in the right ventricular outflow tract (Table 23-1).

ABNORMAL IMPULSE CONDUCTION

Prolongation of Conduction Time

Prolongation of the conduction time of the cardiac impulse may occur anywhere in the heart. It may result from slow conduction and be generalized, as in response to a class IC antiarrhythmic agent, or the slow conduction may be localized to a portion of the heart, e.g., in a portion of the specialized AV conduction system or in ventricular myocardium injured by a myocardial infarction or by other kinds of cardiac disease. Prolongation of conduction time resulting from slow conduction also may occur as a normal response of cardiac tissue, as in prolongation of AV nodal conduction time associated with a propagated premature beat. In addition to slow conduction, prolongation of conduction time may occur when the cardiac impulse takes longer than normal to get from one place to another even though the conduction velocity of the impulse along the route is normal. An example of this is found in patients with an endocardial cushion defect in which the sinus impulse takes an abnormally long time to reach the AV node.

This occurs because the location of the ostium primum defect forces the activation wavefront generated by the sinus impulse to take a longer route to reach the AV node.[2] As is shown below, however, perhaps the most important role of prolongation of conduction time is in the genesis and maintenance of most tachycardias resulting from circus movement or reentrant excitation.

Block of Conduction

Block of the propagating impulse may occur for any number of reasons. It may block because the impulse arrives at tissue that is inexcitable either because the tissue is still in its effective refractory period after a recent depolarization or because it has an abnormally low resting potential caused by disease. Block also may occur because the strength of the propagating wavefront is insufficient to excite the tissue ahead of it despite the fact that that tissue is fully excitable (decremental conduction and block). Block also may occur because the propagating impulse encounters tissue that is intrinsically unable to conduct the cardiac impulse, e.g., scar tissue associated with a prior myocardial infarction or surgical incision. If there is conduction block of the cardiac impulse, disturbances of cardiac rhythm may occur in several different ways. If the sinus impulse fails to propagate to the right atrium (sinus node exit block or sinoatrial block), normally an ectopic (latent or escape) pacemaker will emerge and assume the role of cardiac pacemaker. If propagation of the cardiac impulse is impaired in the specialized AV conduction system so that the ventricles are not activated at a sufficiently rapid rate, an ectopic pacemaker (latent or escape) distal to the site of block often will emerge and assume the role of cardiac pacemaker. When either sinoatrial or AV block occurs, however, an ectopic pacemaker may not emerge quickly enough and/or at a clinically adequate rate under some circumstances. Thus, a period of asystole, marked bradycardia, or both may occur. If either or both happen, the clinical problem may be quite serious and even life-threatening. Block also may occur in one of the bundle branches, causing either left or right bundle branch block. Bundle branch block per se is rarely a clinical problem of consequence except when the block occurs simultaneously in both bundle branches.

Unidirectional Block and Reentry

During normal sinus rhythm, the conducted impulse from the sinus node pacemaker dies out after orderly and sequential activation of the atria, the specialized AV conduction system, and the ventricles because the impulse is prevented from reactivating the myocardium by the refractoriness of the tissue that has just been activated. The heart then must wait for a new impulse from the sinus node pacemaker for each subsequent activation. The phenomenon of reentry occurs when the propagating impulse does not die out but rather continues to propagate and reactivate the heart, because the activation wavefront continuously encounters excitable cardiac tissue. Most clinically important tachyarrhythmias are due to reentry (Table 23-1). For reentry to occur, several conditions must be met. First, there must be a substrate in the cardiac tissue capable of supporting reentry, i.e., a region in the heart with the appropriate electrical properties in which reentry can occur. Second, the excitation wavefront must encounter unidirectional block. Third, the activation wavefront must be able to circulate around a central area of block.

Figure 23-4*A*, *B*, and *C* illustrates a simple model of reentry in a loop of excitable tissue, as was demonstrated first by Mayer in 1906 in the excitable ring of a jellyfish[3] and later by Mines in rings of cardiac tissue cuts from a tortoise heart.[4] The center of the loop is a hole, and this serves as a central area of block around which the reentrant wavefront can circulate. If the loop of excitable tissue is stimulated at a single point, two wavefronts of excitation circulate in the ring in opposite directions from this point (Fig. 23-4*A*). Since the wavefronts collide, they die out. If block of one of the circulating wavefronts occurs (e.g., in the shaded area), however, an excitation wavefront can circulate in only one direction around the loop; i.e., unidirectional block of the stimulated wavefront has occurred (Fig. 23-4*B*). If either conduction of the nonblocked impulse around the loop is slow enough (e.g., because of a region or regions of slow conduction) or, in the presence of normal conduction, the loop is long enough so that by the time the circulating wavefront has returned to its site of origin, this latter region has recovered excitability, the wavefront can then reexcite (i.e., reenter) tissue it has previously excited and continue to circulate (Fig. 23-4*C*). For this to occur, however, the region of block must manifest unidirectional block, i.e., block in the right-to-left direction but conduction in the left-to-right direction (Fig. 23-4*C*). If the region of previous block remains unexcitable, bidirectional block at this site has prevented reentry. Since the block is unidirectional, reentry occurs. In the presence of myocardium manifesting unidirectional block and a

central inexcitable area around which an excitation wavefront can circulate, as long as the wavelength (the product of the conduction velocity of the circulating wavefront and the effective refractory period of the tissue of the potentially reentrant circuit) of the circulating wavefront is shorter than the length of the pathway in which it is traveling, the wavefront will continue to circulate. In other words, as long as myocardium in the reentrant circuit ahead of the propagating reentrant excitation wave has sufficient time to recover excitability after its prior excitation, reentry can continue. The result is classical circus movement or reentrant excitation. Thus, an area of slow conduction is not an absolute requisite for reentrant excitation to occur.

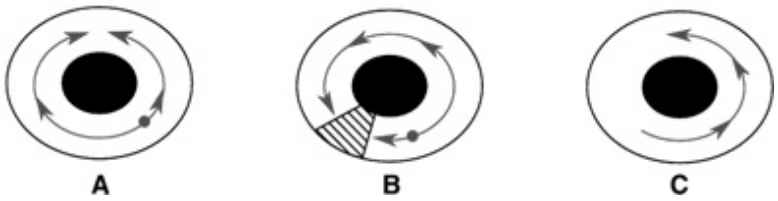

Figure 23-4: Schematic representation of reentry in a ring of excitable tissue. *A*. Ring was stimulated in the area indicated by the black dot. Impulses propagated away from the point of stimulation in both directions (*arrows*) and collided; no reentry occurred. *B*. The striped area was compressed while the ring was stimulated, again at the black dot. The impulse propagated around the ring in only one direction, having been blocked in the other direction by the area of compression. Then, immediately after stimulation, the compression was relieved. *C*. Circulating impulse is shown returning to its point of origin and then continuing around the ring. Identical reentry would occur if the striped area in *B* were a region of permanent unidirectional conduction block with block in the right-to-left direction.

Reentry can occur at normal conduction velocities if the path length is sufficiently long. Most reentrant circuits, however, require the presence of an area of slow conduction. This is the case because in most circumstances, despite the presence of unidirectional block, the length of the potential reentrant circuit is too short, so that without the presence of an area or areas of slow conduction, the nonblocked wavefront would otherwise travel around the circuit so quickly that it would arrive at the point of origin of the wavefront (the stimulus site in Fig. 23-4) before that site had recovered sufficiently to become excitable again. In fact, presumably for this very reason, an area or areas of slow conduction is part of the reentrant circuit for virtually all clinical reentrant rhythms. Reentrant circuits may be located almost anywhere in the heart, and they can assume many sizes and shapes.

Reentry in which the circulating wavefront continuously reenters over the same stable pathway to generate the reentrant rhythm is called *ordered reentry*.[1] The circuit may constitute a well-defined anatomic pathway, an anatomic circuit. One example is the reentrant circuit in AV reentrant tachycardia (atrium, AV node, His-Purkinje system, ventricle, accessory AV connection). Functional circuits, which depend on cellular electrophysiologic properties rather than anatomy, also can be associated with ordered reentry if the electrophysiologic properties crucial for reentry are confined to a specific location and reentry occurs only in that location. Ordered reentry also can involve a combination of anatomic and functional pathways. Examples of arrhythmias caused by ordered reentry include atrial flutter, most monomorphic ventricular tachycardias, AV nodal reentrant tachycardia, AV reentrant tachycardia involving an accessory AV connection, and sinus node reentrant tachycardia (Table 23-1) (see Chap. 27). During random reentry,[1] propagation occurs in reentrant pathways that continuously change their size and location with time. For this to occur, circuits must, at least to a significant degree, be functional. Random reentry need not depend on any special electrophysiologic abnormality in the heart, although electrophysiologic abnormalities also may lead to random reentry. Examples of random reentry include some forms of atrial and ventricular fibrillation (Table 23-1).

Reflection

The term *reflection* has been used to describe a form of reentry in a linear bundle in which two excitable regions are separated by an area of depressed conduction.[5] During reflection, excitation occurs slowly in one direction along the bundle and is followed by continued propagation and excitation occurring in the

opposite direction. One form of reflection may in fact be microreentry based on functional longitudinal dissociation within the depressed segment.[6-8] How this may occur is diagrammed in Fig. 23-5. The diagram at the top of the figure depicts two adjacent fibers in a bundle. The entire shaded area is depressed (reduced membrane potential and slow action potential upstrokes), with the darker area in the upper fiber indicating more severe depression than the lighter area in the lower fiber. Unidirectional conduction block occurs in the more severely depressed region. Arrows labeled I show the impulse entering the two fibers from the left end. Conduction of the impulse (I) blocks in the fiber at the top, in the severely depressed region, but continues in the fiber at the bottom, which is not as depressed. The impulse conducts transversely from the bottom fiber to the top fiber once it is past the region of severe depression. It then conducts retrogradely through this severely depressed region in the top bundle. Arrows labeled II show the reflected impulse returning to reexcite the left end of the bundle. Action potentials that were recorded from sites a, b, and c in the bottom fiber are shown below: action potentials labeled I were recorded as the impulse conducted from left to right; action potentials labeled II were recorded as the impulse conducted from right to left, returning to its origin. It is thought that such reentry may occur in the His bundle, one of the bundle branches or peripheral branches of Purkinje fiber bundles.

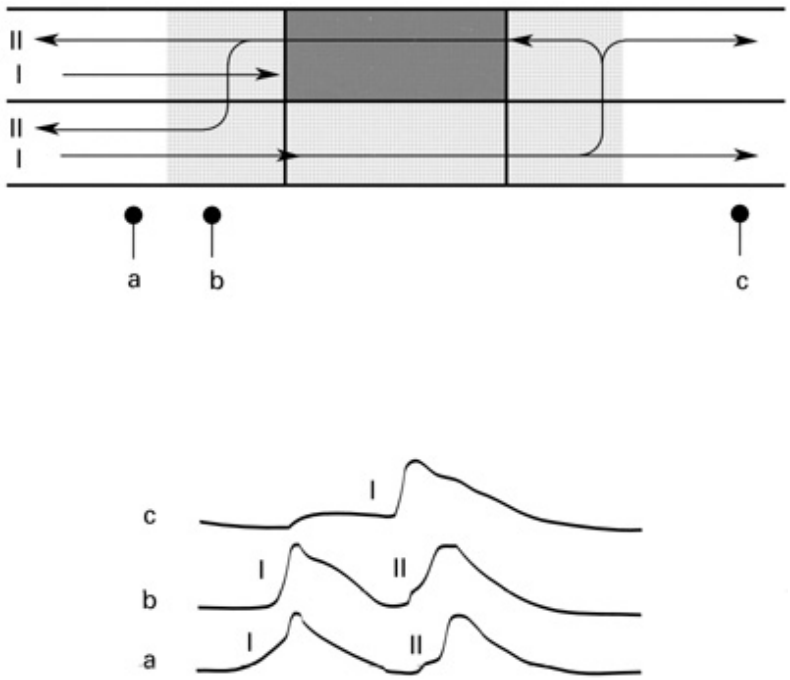

Figure 23-5: Diagram of reflection based on microeentry. *Top*: Schematic representation of two adjacent myocardial fibers. The shaded region indicates an area of depressed conduction. Arrows show the pattern of activation: Arrow I is a wavefront conducting in an antegrade direction, and arrow II is a reflected wavefront conducting in a retrograde direction. The action potentials shown below were recorded at sites a, b, and c on the diagram. (Modified from Wit AL, Bigger JT Jr. Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. *Circulation* 1975; 52(suppl):III96-III115. Reproduced with permission from the publisher and authors.)

SIMULTANEOUS ABNORMALITIES OF IMPULSE GENERATION AND CONDUCTION

Parasystole

At times, an ectopic pacemaker may be connected to the remainder of the heart through tissue or tissues in which there is unidirectional block. The unidirectional block prevents the dominant rhythm, usually a sinus rhythm, from entering the region where the ectopic pacemaker is located. As a result, the ectopic pacemaker is not suppressed by the dominant rhythm of the heart. At the same time, because the block is unidirectional, impulses generated by the ectopic pacemaker can be conducted out to other regions of the heart as long as they are not refractory, causing premature beats or even a tachycardia. This kind of rhythm is called *parasystole*. Thus, parasystole is a rhythm that is due to impulse generation (presumed to be due to

an ectopic pacemaker, but it could be due to any mechanism) in a protected focus. The focus is protected because there is entrance block into the focus (owing to unidirectional block). An impulse may exit the focus and excite the heart if the impulse generated by the parasystolic focus finds tissue that is excitable, i.e., not in the effective refractory period.

Phase 4 Block

Block of an impulse may occur if the impulse arrives at a site-e.g., in the His bundle or one of the bundle branches-that is partially depolarized during spontaneous phase 4 depolarization but has not yet reached threshold. This spontaneous diastolic depolarization can depolarize the tissue sufficiently that the fast Na^+ channels are inactivated enough to cause failure of propagation.[9]

NEXT

Chapter 23: MECHANISMS OF CARDIAC ARRHYTHMIAS AND CONDUCTION DISTURBANCES

DETAILED DISCUSSION OF MECHANISMS OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Arrhythmias Caused by Impulse Initiation

INTRODUCTION

The term *impulse initiation* is used to indicate that an electrical impulse can arise in a single cell or a group of closely coupled cells through depolarization of the cell membrane and, once initiated, can spread through the rest of the heart. Impulse initiation occurs because of localized changes in ionic currents that flow across the membranes of single cells. There are two major causes for the impulse initiation that may result in arrhythmias: automaticity and triggered activity. Each has its own unique cellular mechanism that results in membrane depolarization.

AUTOMATICITY

It is convenient to subdivide automaticity into two kinds: normal and abnormal. Normal automaticity is found in the primary pacemaker of the heart, the sinus node, as well as in certain subsidiary or latent pacemakers that can become the pacemaker under the conditions described below. Impulse initiation is a normal property of these latent pacemakers. By contrast, abnormal automaticity, whether the result of experimental interventions or of disease, occurs in cardiac cells only when there are major abnormal changes in their transmembrane potentials, in particular in steady-state depolarization of the membrane potential. This property of abnormal automaticity is not confined to any specific latent pacemaker cell type but may occur almost anywhere in the heart.

Normal Automaticity: Pacemaker Mechanisms

The normal site of impulse initiation is the sinus node. The cause of normal automaticity in the sinus node is a spontaneous decline in the transmembrane potential during diastole, referred to as the *pacemaker potential*, *phase 4*, or *diastolic depolarization* (the terms are interchangeable). Diastolic depolarization is the part of the sinus node membrane potential labeled dd in the top panel (*A*) of Fig. 23-6. When the depolarization reaches the threshold potential (dashed line labeled TP), the upstroke of the spontaneous action potential is initiated. In the case of the sinus node this upstroke is caused mainly by an inward-directed calcium current through L-type calcium channels. This fall in membrane potential during phase 4 reflects a gradual shift in the balance between inward and outward membrane currents in the direction of net inward (depolarizing) current.

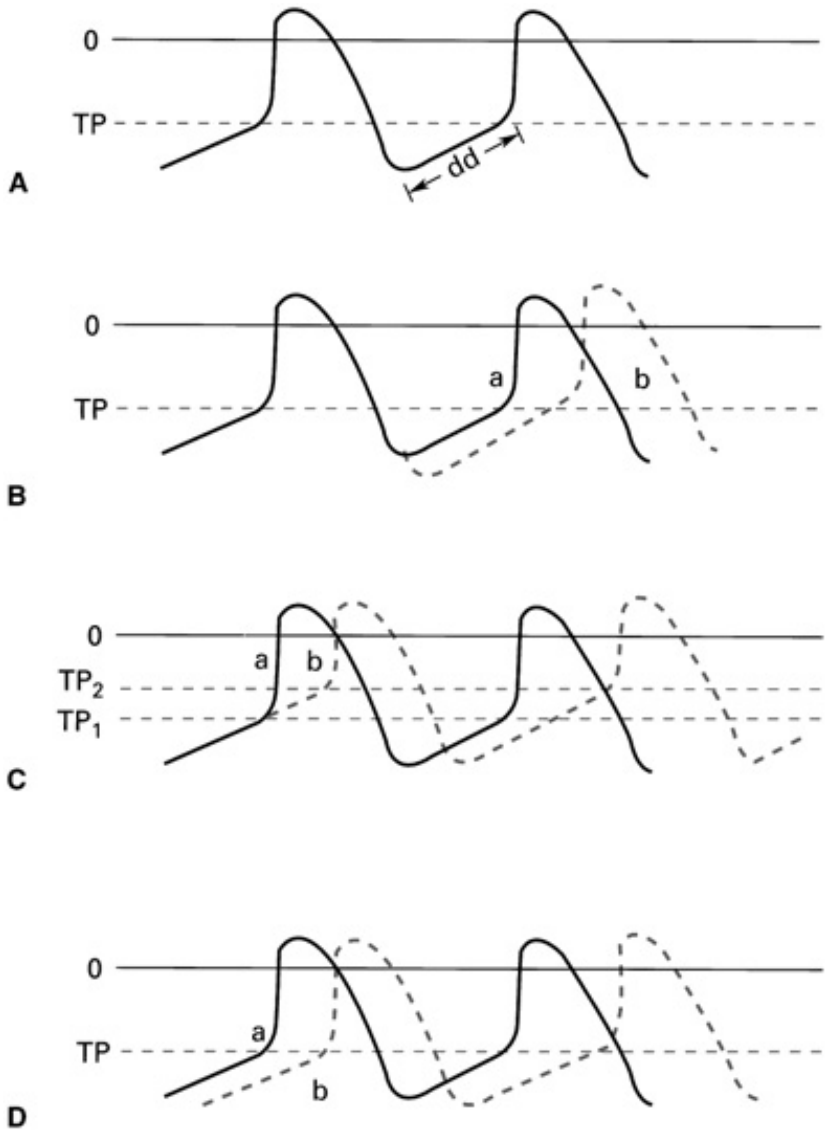

Figure 23-6: Diagrams of sinus node action potentials illustrating normal automaticity caused by spontaneous diastolic depolarization and the factors that change the rate of impulse initiation. *A.* Typial sinus node action potential with spontaneous diastolic depolarization (dd). *B.* Change in the rate when the maximum diastolic potential is shifted to a more negative level (from a to b). *C.* Change in rate caused by change in threshold potential to a less negative level (from TP1 to TP2). *D.* Change in rate that occurs when the slope of phase 4 depolarization is decreased (from a to b). (Modified after Wit AL, Janse MJ. *The Ventricular Arrhythmias of Ischemia and Infarction: The Electrophysiological Mechanisms*. Mount Kisco, NY: Futura; 1992:3. Reproduced with permission from the publisher and authors.)

Studies have been done to elucidate and characterize the membrane currents that cause diastolic (phase 4) depolarization in the sinus node, using voltage clamp techniques in small tissue preparations and in single dissociated sinus node cells. The cause of the pacemaker potential is still controversial. There is some evidence that diastolic depolarization results from the turning on of an inward current, called i_f, which is activated after repolarization of the sinus node action potential. The net inward i_f current is carried largely by Na^+.[10] From the voltage clamp studies, it is known that the i_f channels are inactivated at positive membrane potentials, begin to activate after hyperpolarization to around -40 mV, and are fully activated after hyperpolarization to around -100 mV.[11-13] Since the maximum diastolic potential of the sinus node pacemaker cells is between -60 and -70 mV, the i_f current is turned on during repolarization to this level, although it is not fully activated at the maximum diastolic potential. Activation of the i_f conductance also has

a time dependency; therefore, the inward current continues to increase after complete repolarization, causing the progressive fall in the membrane potential during phase 4. Important roles for other membrane currents, including the potassium current i_K and the T and L Ca^{2+} currents that cause spontaneous diastolic depolarization, also have been proposed.[14-22] Therefore, there may be no single pacemaker current in the sinus node; rather, a number of currents may contribute to the occurrence of automaticity.[18]

The intrinsic rate at which sinus node pacemaker cells initiate impulses is determined by the interplay of three factors:[23] (1) the maximum diastolic potential, (2) the threshold potential, and (3) the rate or slope of phase 4 depolarization. The third factor is related to the properties of the pacemaker current or currents. A change in any one of these factors will alter the time required for phase 4 depolarization to carry the membrane potential from its maximum diastolic level to threshold and thus alter the rate of impulse initiation. For example, if the maximum diastolic potential increases (becomes more negative) going from the solid trace to the dashed trace in Fig. 23-6*B*, spontaneous depolarization to the threshold potential will take longer and the rate of impulse initiation will fall. Conversely, a decrease in the maximum diastolic potential will tend to increase the rate of impulse initiation (going from dashed trace to solid trace). Similarly, changes in threshold potential or changes in the slope of phase 4 depolarization will alter the rate of impulse initiation. In Fig. 23-6*C*, a change in threshold potential from TP1 to the less negative TP2 causes spontaneous diastolic depolarization to proceed for a longer time (dashed action potential trace) before an impulse is initiated, slowing the rate. In Fig. 23-6*D*, a decrease in the slope of spontaneous diastolic depolarization from a to b also results in a longer interval between action potentials (dashed trace) because of the longer time required for membrane potential to reach the threshold potential. In Fig. 23-6*C* and *D*, changes in the threshold potential or slope of diastolic depolarization in the opposite direction would speed up the rate.

The alterations in the rate of impulse initiation in the sinus node resulting from the factors discussed above may lead to arrhythmias. These arrhythmias are often a result of the actions of the autonomic nervous system on the sinus node. Parasympathetic stimulation and the resultant release of acetylcholine hyperpolarize the membrane potential through stimulation of muscarinic receptors and the activation of a K current (Fig. 23-6*B*).[24,25] Acetylcholine also decreases the inward Ca^{2+} current and the i_f pacemaker current.[26] A combination of these effects slows the rate. Sympathetic stimulation and norepinephrine release increase the slope of diastolic depolarization and therefore sinus rate by increasing L-type Ca^{2+} current[27] and increasing activation of the inward i_f current at the completion of action potential repolarization.[12,13,28] These effects are mediated through $beta_1$-receptor stimulation.

In addition to the sinus node, cells with pacemaking capability in the normal heart are located in some parts of the atria and ventricles, although they are not pacemakers while the sinus node is functioning normally. These are latent or subsidiary pacemakers. Since spontaneous diastolic depolarization is a normal property, the automaticity generated by these cells is classified as normal. In the atria, cells with well-polarized membrane potentials (resting potentials of around -80 mV) and action potentials characterized by fast upstrokes, a plateau phase of repolarization, and spontaneous diastolic depolarization are located along the crista terminalis (Fig. 23-7*A*).[29] Subsidiary atrial pacemakers with somewhat lower maximum diastolic potentials (-75 to -70 mV) and prominent phase 4 depolarization are located at the junction of the inferior right atrium and the inferior vena cava, near or on the eustachian ridge (a remnant of the eustachian valve of the inferior vena cava) (Fig. 23-7*B*).[30-32] Other potential atrial pacemakers are at the orifice of the coronary sinus (Fig. 23-7*C*)[33] and in the atrial muscle that extends into the tricuspid and mitral valves (Fig. 23-7*D*).[34-36] Action potentials of cells in the valves have slow upstrokes that probably are caused to a significant extent by L-type Ca^{2+} current. In the AV junction, AV nodal cells possess the intrinsic property of automaticity (Fig. 23-7*E*),[37] although there is still some

uncertainty about the exact location of these pacemakers in the node.[38] The intrinsic rate of the atrial pacemakers is greater than that of AV junctional pacemakers.[39] Both atrial and AV junctional subsidiary pacemakers are under autonomic control, with the sympathetics enhancing pacemaker activity through $beta_1$-adrenergic stimulation and the parasympathetics inhibiting pacemaker activity through muscarinic receptor stimulation.[40-43] In the ventricles, latent or subsidiary pacemakers are found in the His-Purkinje system, where Purkinje fibers have the property of spontaneous diastolic depolarization (Fig. 23-8).[23,44] The intrinsic Purkinje fiber pacemaker rate in general is lower than the rate of atrial and AV junctional pacemakers and decreases from the His bundle to the distal Purkinje branches.[45] The spontaneous diastolic depolarization in this region is also under similar autonomic control. As in the atria, sympathetic activation enhances automaticity,[46] while parasympathetic activation can reduce it, mostly through inhibition of sympathetic influences.[47,48]

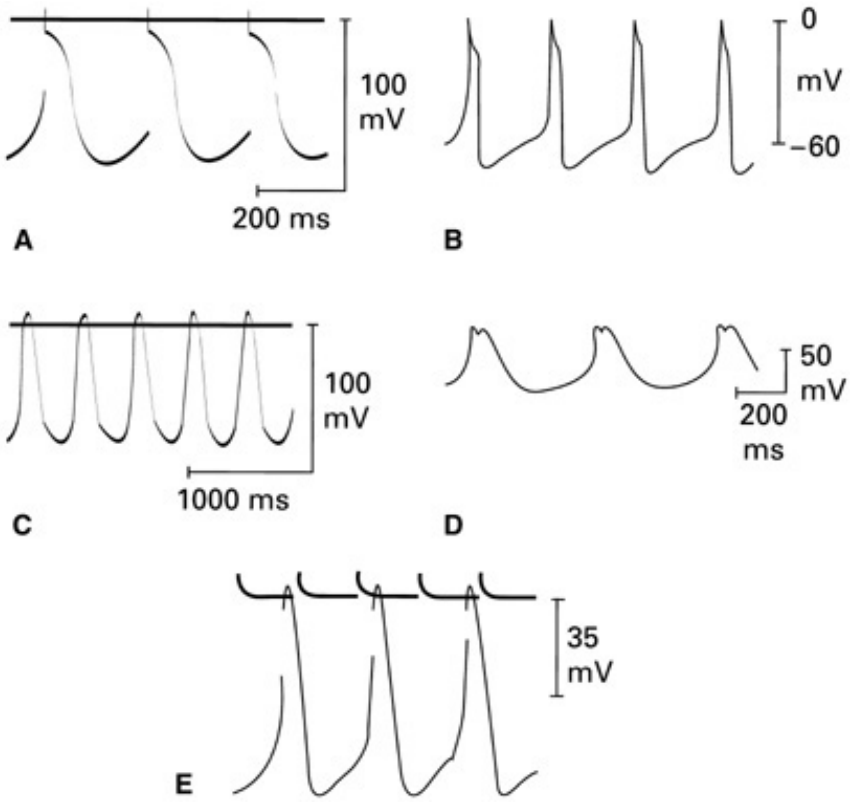

Figure 23-7: Transmembrane potentials recorded in isolated superfused preparations from some subsidiary pacemaker cells with the property of normal automaticity. Spontaneous diastolic depolarization that developed in the absence of overdrive suppression is shown in each panel. *A.* Atrial fiber in the crista terminalis in the presence of isoproterenol. *B.* Atrial fiber in the inferior right atrium. *C.* Atrial fiber in the ostium of the coronary sinus in the presence of norepinephrine. *D.* Atrial fiber in stretched mitral valve leaflet. *E.* Atrioventricular nodal fiber of the rabbit heart after the AV node was separated from the atrium. (From Wit AL, Janse MJ. *The Ventricular Arrhythmias of Ischemia and Infarction: The Electrophysiological Mechanisms*. Mount Kisco, NY: Futura; 1992:7. Reproduced with permission from the publisher and authors.)

The membrane currents that cause the normal spontaneous diastolic depolarization at ectopic sites also have been studied. The most thorough analyses have been done on the pacemaker current in Purkinje's cells, using voltage clamp techniques. These studies have shown the presence of an i_f pacemaker current, as in the sinus node.[28,49,50] The i_f channels are deactivated during the action potential upstroke and the initial plateau phase of repolarization but begin to activate as

repolarization brings the membrane potential to levels more negative than about -60 mV. Since the activation kinetics are slow, the channels continue to activate throughout diastole, leading to an increasing net inward current carried mostly by Na^+ and diastolic depolarization.[49,50] Other currents are also likely to contribute to the pacemaker potential in Purkinje's cells.[28,51-53] It is likely that the net increase in inward current during diastole that causes spontaneous diastolic depolarization in Purkinje fibers is a result of an increase in an inward current i_f and a decrease in outward current (i_{K_1} and i_K).[52]

Abnormal Automaticity: Pacemaker Mechanisms

Working atrial and ventricular myocardial cells do not normally have spontaneous diastolic depolarization and do not initiate spontaneous impulses even when they are not excited for long periods of time by propagating impulses. When the resting potentials of working atrial or ventricular myocardial cells are reduced sufficiently, however, spontaneous diastolic depolarization may occur and cause repetitive impulse initiation, a phenomenon called *depolarization-induced automaticity* or *abnormal automaticity*. The level of membrane potential at which abnormal automaticity occurs is often in a range between -70 and -30 mV (see Fig. 23-2).[54] Likewise, cells in the Purkinje system, which are normally automatic at high levels of membrane potential, also show abnormal automaticity when the membrane potential is reduced.[55] As was discussed before, the i_f channels that participate in normal pacemaker activity in Purkinje fibers have a gating mechanism controlling channel opening and closing that is dependent on the transmembrane voltage. At membrane potentials that are positive to about -60 mV, as occurs after the upstroke and during the early phases of repolarization, the channels are closed. In response to the negative potentials that occur after complete repolarization, the channels reopen, gener ating the inward pacemaker current.[49,50] For this reason, when the steady-state membrane potential of Purkinje fibers is reduced to around -60 mV or less, as sometimes may occur in ischemic regions of the heart, these normal pacemaker channels are not functional and automaticity is not caused by the normal pacemaker mechanism. It can, however, be caused by an "abnormal" mechanism (described below).

In Fig. 23-9, the transmembrane potential recorded from a spontaneously firing Purkinje fiber with normal automaticity is shown in panel *A*, and abnormal automatic activity occurring while the membrane potential is depolarized to progressively lower membrane potentials is shown in panel *B*, 1, 2, and 3. The abnormal automatic rate increased as membrane potential became more positive. This is a general characteristic of abnormal automaticity in atrial and ventricular cells as well. A low level of membrane potential is not the only criterion for defining abnormal automaticity. If this were so, the automaticity of the sinus node would have to be considered abnormal. Therefore, an important distinction between abnormal and normal automaticity is that the membrane potentials of fibers showing the abnormal type of activity are reduced from their own normal level. For this reason, automaticity in the AV node or valves, where membrane potential is normally low, is not classified as abnormal automaticity. A likely cause of automaticity at depolarized membrane potentials in ventricular muscle is activation and deactivation of the delayed rectifier K current.[56,57] The conductance of this K channel is activated during the normal action potential plateau, and the outward current that flows through it normally contributes to repolarization. The channel then deactivates during diastole. No significant outward current flows through this channel at normal diastolic potentials, since the resting potential lies near the reversal potential and the driving force is negligible.[57] When the membrane potential is depolarized, however, an outward current flows through this channel, which is activated at the depolarized membrane potentials. This current hyperpolarizes the membrane potential. As the channel then deactivates at the hyperpolarized potentials, spontaneous diastolic depolarization occurs. If either Na or Ca channels have been reactivated since the preceding action potential, the spontaneous depolarization caused by K-channel deactivation may lead to an upstroke caused by current flowing through one of these channels (depending on the level of the membrane

potential).[57] A similar mechanism may cause abnormal automaticity in partially depolarized Purkinje fibers.

Experiments on depolarized human atrial myocardium from dilated atria indicate that Ca^{2+}-dependent processes also may contribute to abnormal pacemaker activity at low membrane potentials.[58,59] It was proposed that intracellular Ca^{2+} released from the sarcoplasmic reticulum controls membrane permeability to an inward current during diastole, leading to spontaneous diastolic depolarization and abnormal automaticity. The mechanism may be similar to the one that causes the transient inward current responsible for DADs (see "Triggered Rhythms," above). An increase in intracellular Ca^{2+} also is expected to cause an inward Na^+ current through Na^+-Ca^{2+} exchange. In summary, therefore, several different mechanisms probably cause abnormal automaticity, including activation and deactivation of K^+ currents, Ca^{2+}-dependent activation of an inward current, inward Ca^{2+} currents, and even some contribution by the pacemaker current i_f.

It has not been determined which of these mechanisms are operative in the different pathologic conditions in which abnormal automaticity may occur. The upstrokes of the spontaneously occurring action potentials generated by abnormal automaticity may be caused by either Na^+ or Ca^{2+} inward currents or possibly a mixture of the two. In the range of diastolic potentials between approximately -70 and -50 mV, repetitive activity is dependent on extracellular Na^+ concentration and can be decreased or abolished by the Na^+ channel blockers lidocaine and tetrodotoxin, indicating that the Na^+ inward current is involved. In a diastolic potential range of approximately -50 to -30 mV, repetitive activity depends on extracellular Ca^{2+} concentration and is reduced by Ca^{2+} channel blockers, Mn^{2+}, and verapamil, indicating a role for the L-type Ca^{2+} inward current.[5,60] The decrease in the membrane potential of cardiac cells required for abnormal automaticity to occur may be induced by a variety of factors related to cardiac disease. Although an increase in the extracellular potassium concentration can reduce membrane potential, normal or abnormal automaticity in working atrial, ventricular, and Purkinje fibers usually does not occur when $[K]_o$ is elevated because of the increase in K^+ conductance (and hence net outward current) that results from an increase in $[K]_o$.[61,62] This argues against abnormal automaticity being responsible for arrhythmias arising in acutely ischemic myocardium, where cells are partially depolarized by increased extracellular K^+.[63-65] A decrease in $[K]_i$, which also causes a decreased membrane potential, has been shown to occur in the Purkinje fibers that survive on the endocardial surface of infarcts, and this decrease persists for at least 24 h after the coronary occlusion.[66] The reduction in $[K]_i$ contributes to the low membrane potential[67] and the accompanying abnormal automaticity.[68,69] Isolated preparations of diseased atrial and ventricular myocardium from human hearts superfused with Tyrode's solution show phase 4 depolarization and abnormal automaticity at membrane potentials in the range of -50 to -60 mV.[70-72] It has been proposed that a decrease in membrane potassium conductance is an important cause of the low membrane potentials in the atrial fibers.[71]

Suppression of Normal and Abnormal Automatic Subsidiary Pacemakers

During sinus rhythm in a normal heart, the intrinsic rate of impulse initiation resulting from automaticity of cells in the sinus node is higher than that of the other potentially automatic cells, and the latent pacemakers are excited by propagated impulses from the sinus node before they can depolarize spontaneously to threshold potential. Not only are latent pacemakers prevented from initiating an impulse because they are depolarized before they have a chance to fire, but the diastolic (phase 4) depolarization of the latent pacemaker cells with the property of normal automaticity is actually inhibited because they are repeatedly depolarized by the impulses from the sinus node.[73,74] This inhibition can be demonstrated by suddenly stopping the sinus node, e.g., by vagal stimulation (vagal stimulation also inhibits subsidiary pacemakers in the atria and AV junction) or in the tissue bath after termination of overdrive pacing (Fig. 23-8). Impulses

then usually arise from a subsidiary pacemaker in the ventricular Purkinje system, but that impulse initiation generally is preceded by a long period of quiescence.[75,76] Impulse initiation by the Purkinje fiber pacemaker then begins at a low rate and only gradually speeds up to a final steady rate that is, however, still slower than the original sinus rhythm. The quiescent period after abolition of the sinus rhythm reflects the inhibitory influence exerted on the subsidiary pacemaker by the dominant sinus node pacemaker. This inhibition is called *overdrive suppression*. Similarly, the sinus node also overdrive-suppresses subsidiary atrial pacemakers.[77]

The mechanism of overdrive suppression has been characterized in microelectrode studies of isolated Purkinje fiber bundles exhibiting pacemaker activity.[73] It is mediated mostly by enhanced activity of the Na^+-K^+ exchange pump that results from driving a pacemaker cell faster than its intrinsic spontaneous rate. During normal cardiac rhythm, the sinus node drives the latent pacemakers at a faster rate than their normal (intrinsic) automatic rate. As a result, the intracellular Na^+ of the latent pacemakers is increased to a higher level than would be the case if the pacemakers were firing at their own intrinsic rate. This is the result of Na^+ entering the cells during each action potential upstroke. The rate of activity of the Na^+ pump is determined largely by the level of intracellular Na^+ concentration,[78] so that pump activity is enhanced during high rates of stimulation.[73] The increased pump activity prevents intracellular Na^+ from rising to very high levels, although there is some increase in the steady-state Na^+ concentration at high rates of firing. Since the Na^+ pump moves more Na^+ outward than K^+ inward, it generates a net outward (hyperpolarizing) current across the cell membrane.[79] When subsidiary pacemaker cells are driven faster than their intrinsic rate by the sinus node, the enhanced outward pump current hyperpolarizes the membrane potential and suppresses spontaneous impulse initiation in these cells, which, as was described before, is dependent on the net inward current. When the dominant (overdrive) pacemaker is stopped, this suppression continues because the Na^+ pump continues to generate the outward current as it reduces the intracellular Na^+ levels toward normal. The continued Na^+ pump-generated outward current is responsible for the period of quiescence, which lasts until the intracellular Na^+ concentration, and hence the pump current, becomes small enough to allow subsidiary pacemaker cells to depolarize spontaneously to threshold. Intracellular Na^+ concentration decreases during the quiescent period because Na^+ is constantly being pumped out of the cell and little is entering.[60] Intracellular Na^+ and pump current continue to decline even after spontaneous firing begins because of the slow rate, causing a gradual increase in the discharge rate of the subsidiary pacemaker.

The higher the overdrive rate or the longer the duration of overdrive, the greater the enhancement of pump activity, so that the period of quiescence after the cessation of overdrive is directly related to the rate and duration of overdrive.[73] The sinus node itself also can be overdrive-suppressed if it is driven at a rate more rapid than its intrinsic rate. Thus, there may be a quiescent period after termination of either overdrive pacing or a rapid ectopic arrhythmia before the sinus rhythm resumes.[80-83] When overdrive suppression of the normal sinus node occurs, however, it is of lesser magnitude than that of subsidiary pacemakers overdriven at comparable rates.[30,80] The sinus node action potential upstroke is largely dependent on slow inward current carried by Ca^{2+} through the L-type Ca^{2+} channels, and far less Na^+ enters the fiber during the upstroke than occurs in latent pacemaker cells such as Purkinje fibers. As a result, the activity of the Na^+ pump probably is not increased to the same extent in sinus node cells after a period of overdrive; therefore, there is less overdrive suppression caused by enhanced Na^+ pump current. The relative resistance of the normal sinus node to overdrive suppression may be important in enabling it to remain the dominant pacemaker even when its rhythm is perturbed transiently by external influences such as transient shifts of the pacemaker to an ectopic site. The diseased sinus node, however, may be much more easily overdrive-suppressed.[84]

There is an important distinction between the effects of the dominant sinus pacemaker on the two kinds of automaticity, as abnormal automaticity at reduced levels of membrane potential is not

overdrive-suppressed to the same extent as is the normal automaticity that occurs at high levels of membrane potential.[85-87] The amount of suppression of spontaneous diastolic depolarization that causes abnormal automaticity by overdrive is directly related to the level of membrane potential at which the automatic rhythm occurs.[86,87] For example, Purkinje fibers that show automaticity at moderately depolarized membrane potentials of -60 to -70 mV still manifest some overdrive suppression, although less than do fibers with automaticity at -90 mV. Automaticity in Purkinje fibers with membrane potentials less than -60 mV is suppressed only slightly by overdrive, if it is suppressed at all. These differences in the effects of overdrive may be related to the reduction in the amount of Na^+ entering the cell as the membrane potential decreases, as was described for overdrive of the sinus node. At low levels of membrane potential, Na^+ channels are inactivated, decreasing the fast inward Na^+ current; therefore, there is a reduction in the amount of Na^+ entering the cells during overdrive and the degree of stimulation of the sodium-potassium pump.[88]

In addition to overdrive suppression being of paramount importance for maintenance of normal rhythm, the characteristic response of automatic pacemakers to overdrive, as was discussed in the previous paragraphs, is often useful for identifying mechanisms of arrhythmias in the in situ heart, where arrhythmia mechanisms cannot be identified by recording transmembrane potentials because of the technical difficulties. Not all mechanisms of arrhythmogenesis respond in the same way to overdrive that automatic pacemakers do, and the differences in response sometimes can be used to distinguish among mechanisms. These differences are described in detail later in this chapter. In addition to overdrive suppression, a mechanism that may suppress subsidiary pacemakers is the electrotonic interaction between the pacemaker cells and the nonpacemaker cells in the surrounding myocardium.[89] This mechanism may be particularly important in preventing AV nodal automaticity[90,91] or automaticity in the distal Purkinje system, where the pacemaking Purkinje fibers are in contact with nonpacemaking working ventricular muscle.[89,92-93]

Arrhythmias Caused by Automaticity

Arrhythmias caused by normal or abnormal automaticity of cardiac fibers may occur for several different reasons. Such arrhythmias may result simply from an alteration in the rate of impulse initiation by the normal sinus node pacemaker without a shift of impulse origin to a subsidiary pacemaker at an ectopic site. Sinus bradycardia and tachycardia are examples of these arrhythmias. The cellular mechanisms that can change the rate of impulse initiation in the sinus node are described in Fig. 23-6. During alterations in sinus rate, there may be shifts of the pacemaker site within the sinus node.[23,94] A shift in the site of impulse initiation to one of the regions where normal or abnormal subsidiary pacemakers are located also results in arrhythmias. This would be expected to happen when any of the following occurs: (1) The rate at which the sinus node activates subsidiary pacemaker falls considerably below the intrinsic rate of the subsidiary pacemakers, (2) inhibitory electrotonic influences between nonpacemaker cells and pacemaker cells are interrupted, or (3) impulse initiation in subsidiary pacemakers is enhanced.

The rate at which the sinus node activates subsidiary pacemakers may be decreased in a number of situations. Impulse initiation by the sinus node may be slowed or inhibited altogether by heightened activity in the parasympathetic nervous system[95] or as a result of sinus node disease.[96] Alternatively, there may be block of impulse conduction from the sinus node to the atria or block of conduction from the atria to the ventricles. A latent pacemaker also may be protected from being overdriven by the sinus node if it is surrounded by a region in which impulses of sinus origin block (entrance block) before reaching the pacemaker cells. Such block, however, must be unidirectional, so that activity from the pacemaker can propagate into surrounding myocardium whenever the surrounding regions are excitable. Some possible mechanisms for unidirectional block are discussed later in this chapter.

The protected pacemaker is said to be a *parasystolic focus*.[97] In general, under these conditions, a

protected focus of automaticity of this type can fire at its own intrinsic frequency. Electronic current flow from surrounding regions also may influence the cycle length of a protected focus, either prolonging or abbreviating it, depending on whether the surrounding activity occurs during the early or late stage of diastolic depolarization.[98-100] Under any of the above conditions (sinus slowing, sinoatrial or AV block, parasystolic focus), there may be "escape" of a subsidiary pacemaker. There is a natural hierarchy of intrinsic rates of subsidiary pacemakers that have normal automaticity, with atrial pacemakers having faster intrinsic rates than do AV junctional pacemakers and AV junctional pacemakers having faster rates than do ventricular pacemakers.[45,74] Once overdrive suppression is removed by sinus node inhibition, the pacemaker with the fastest rate becomes the site of impulse origin.[74] Sometimes mechanisms responsible for the suppression of impulse initiation in the sinus node also suppress pacemaker activity in the atria. In experimental studies in which the sinus node is damaged or removed, the most prevalent atrial pacemaker site is at the junction of the inferior vena cava and the posterior wall of the right atrium.[30,101-103] These atrial pacemakers may cause atrial arrhythmias if the sinus node or its arterial supply is damaged.[104]

Ectopic impulse initiation may occur in the AV junction. In fact, an AV junctional pacemaker may become the dominant rhythm in the absence of normal sinus node function. Atrioventricular junctional pacemakers may be located either in the AV node or in the His bundle. These different sites have somewhat different properties, including their intrinsic rates (faster in the AV node than in the His bundle) and responses to autonomic nerve activity (parasympathetic activity suppresses AV nodal pacemakers to a greater extent than it does His bundle pacemakers). Atrioventricular junctional rhythms may occur during AV block, since the site of block is often proximal to the AV junctional pacemaker location.[38] If AV junctional pacemakers also are suppressed or if the site of disease causing AV block is in the His bundle or bundle branches, the subsidiary pacemaker location is in the His-Purkinje system. The His bundle at the proximal end of the specialized AV conduction system has a faster intrinsic rate than do the more distally located Purkinje fibers.[45] The electrocardiogram (ECG) during idioventricular rhythm in patients with complete heart block often is characterized by a wide, aberrant QRS complex, suggesting impulse initiation in the distal Purkinje system.[105] In acute myocardial ischemia, particularly when it occurs in the inferior wall, parasympathetic activity may be enhanced, depressing the sinus rate, AV conduction, or both.[106] Ectopic impulse initiation then may arise in the ventricular specialized conduction system.[107]

Any event that decreases intercellular coupling between latent subsidiary pacemaker cells and surrounding nonpacemaker cells may remove the inhibitory influence of electrotonic current flow on the latent pacemakers and allow them to fire at their intrinsic rate.[89] Coupling may be reduced by fibrosis, which can separate myocardial fibers. For example, fibrosis in the atrial aspect of the AV junctional region that results in heart block may release nodal pacemakers from electrotonic suppression by surrounding atrial cells and permit them to become the dominant pacemakers driving the ventricles. Uncoupling also may be caused by factors that increase intracellular Ca^{2+},[108] since elevated intracellular Ca^{2+} levels decrease coupling between myocardial cells by decreasing the conductance of gap junction channels (*connexons*). This may result, for example, from treatment with digitalis,[109] which inhibits Na^{+} extrusion and thus increases Ca^{2+} levels in the cell.[110] In myocardial infarction, Purkinje fiber pacemakers may be uncoupled from damaged ventricular muscle cells, allowing the Purkinje fibers to fire at their intrinsic rates.

Some inhibition of the sinus node is still necessary for the site of impulse initiation to shift to an ectopic site that is no longer inhibited because of uncoupling from surrounding cells, since, as was explained above, the intrinsic firing rate of subsidiary pacemakers is still slower than that of the sinus node. Subsidiary pacemaker activity also may be enhanced, causing impulse initiation to shift to ectopic sites even when sinus node function is normal. One cause may be enhanced sympathetic nerve activity. Norepinephrine released locally from sympathetic nerves steepens the slope of diastolic depolarization of latent pacemaker cells.[23,33,34,111,112] and diminishes the inhibitory effects of overdrive.[113] The increase in slope of spontaneous diastolic depolarization

may result from effects of norepinephrine on the i_f current, as was described above, as well as from an increase in inward Ca^{2+} current in those cells in which this current participates in pacemaker activity. Localized effects on subsidiary pacemakers may occur in the absence of sinus node stimulation.[114] Therefore, sympathetic stimulation may enable the membrane potential of ectopic pacemakers to reach threshold before they are activated by an impulse from the sinus node, resulting in ectopic premature impulses or automatic rhythms. There is evidence that in the subacute phase of myocardial ischemia, increased activity of the sympathetic nervous system may enhance automaticity of Purkinje fibers, enabling them to escape from sinus node domination. Enhanced subsidiary pacemaker activity also may not require sympathetic stimulation. The flow of current between partially depolarized myocardium and normally polarized latent pacemaker cells may enhance automaticity.[115] This mechanism has been proposed to be a cause of some of the ectopic beats that arise at the borders of ischemic areas in the ventricle.[93]

Inhibition of the electrogenic sodium-potassium pump results in a net increase in inward current during diastole because of the decrease in outward current normally generated by the pump and therefore may increase automaticity in subsidiary pacemakers sufficiently to cause arrhythmias. This may occur after adenosine triphosphate (ATP) is depleted during prolonged hypoxia or ischemia or in the presence of toxic amounts of digitalis.[116,117] A decease in the extracellular potassium level also enhances normal automaticity,[75] as does acute stretch.[118] Stretch can induce rapid automatic rates in Purkinje fibers with normal maximum diastolic potentials.[119,120] Stretch of the ventricles also can induce arrhythmias in an intact heart,[121] although the site of origin of the ectopic impulses has not been localized. Stretch of the Purkinje system may occur in akinetic areas after acute ischemia or in ventricular aneurysms in hearts with healed infarcts. At normal sinus rates, there may be little overdrive suppression of pacemakers with abnormal automaticity. As a result of the lack of overdrive suppression, even transient sinus pauses or occasional long sinus cycle lengths may permit an ectopic focus with a slower rate than the sinus node to capture the heart for one or more beats. In contrast, ectopic pacemakers with normal automaticity probably would be quiescent during relatively short, transient sinus pauses because they are overdrive-suppressed.

It is also possible that the depolarized level of membrane potential at which abnormal automaticity occurs may cause entrance block into the focus and prevent it from being overdriven by the sinus node even when impulses initiated in the focus could leave it (unidirectional block).[122] This would lead to parasystole, an example of an arrhythmia caused by a combination of an abnormality of impulse conduction and initiation. All these features of abnormal automaticity are evident in the Purkinje fibers that survive in regions of transmural myocardial infarction and cause ventricular arrhythmias during the subacute phase.[68] The firing rate of an abnormally automatic focus also might be enhanced above that of the sinus node, leading to arrhythmias in the absence of sinus node suppression or conduction block between the focus and the surrounding myocardium. The automatic rate is a direct function of the level of membrane potential: The greater the depolarization, the faster the rate.[5,55,57,123,124] Experimental studies have shown firing rates in muscle and Purkinje fibers of 150 to 200/min at membrane potentials less than -50 mV, and these rates should be sufficiently rapid to enable these pacemakers sometimes to control the rhythm of the heart. Catecholamines also increase the rate of firing caused by abnormal automaticity[125] and therefore may contribute to a shift in the pacemaker site from the sinus node to a region with abnormal automaticity. Among the clinical arrhythmias that are likely to be caused by abnormal automaticity is accelerated idioventricular rhythm after myocardial infarction (see Chap. 47).

TRIGGERED ACTIVITY

Triggered activity is a term used to describe impulse initiation in cardiac fibers that is dependent on afterdepolarizations.[126-128] Afterdepolarizations are oscillations in membrane potential that

follow the upstroke of an action potential. Two kinds of afterdepolarizations may cause triggered activity. One occurs early, i.e., during repolarization of the action potential (EADs), and the other is delayed until repolarization is complete or nearly complete (DADs). When either kind of afterdepolarization is large enough to reach the threshold potential for activation of a regenerative inward current, action potentials result that are referred to as "triggered." Therefore, a key characteristic of triggered activity, discriminating it from automaticity, is that for triggered activity to occur, at least one action potential must precede it (the trigger). Automatic rhythms can arise de novo in the absence of any prior electrical activity, such as after long periods of quiescence, whereas triggered activity cannot.[5,128] Triggered activity will cause arrhythmias when the site of impulse initiation shifts from the sinus node to the triggered focus. For this to occur, the rate of triggered impulses should be faster than the sinus rate either transiently or persistently. This may result when firing of the sinus node is slowed or inhibited, when there is block of sinus impulses, or when the rate of triggered activity is faster than normal sinus node impulse initiation. The factors causing the shift in the site of impulse initiation should be very similar to those described in the discussion of automaticity.

Delayed Afterdepolarizations and Triggered Activity

Figure 23-10 shows an example of a DAD recorded with a microelectrode in a superfused preparation of atrial muscle exposed to catecholamines. The DAD is an oscillation in membrane potential that occurs after repolarization of the action potential (indicated in the figure by the unfilled arrow). The DAD is caused by events occurring during the action potential that will be described below. Figure 23-10*A* also shows that a DAD may be preceded by an afterhyperpolarization (red arrow), in which case the membrane potential transiently becomes more negative after the action potential than it was just before it. Afterhyperpolarizations, however, do not always precede DADs. The transient nature of the DAD clearly distinguishes it from normal spontaneous diastolic (pacemaker) depolarization, during which the membrane potential declines almost monotonically until the next action potential occurs (compare Fig. 23-10*A* with Fig. 23-6). In addition to microelectrode recordings such as the one shown in Fig. 23-10*A*, DADs can be identified by using techniques for recording extracellular potentials.[129,130] A major problem that exists when this technique is used in situ to locate DADs in the heart, however, is discriminating the extracellular voltage deflections caused by afterdepolarizations from deflections that result from the motion of the heart, since movement alone can mimic DADs in extracellular recordings.[131] A second important problem is a possible difficulty in locating focal sites at which afterdepolarizations and triggered activity may be originating. Nevertheless, extracellular electrodes have been used to demonstrate what appear to be DADs occurring in the in situ heart.[132,133]

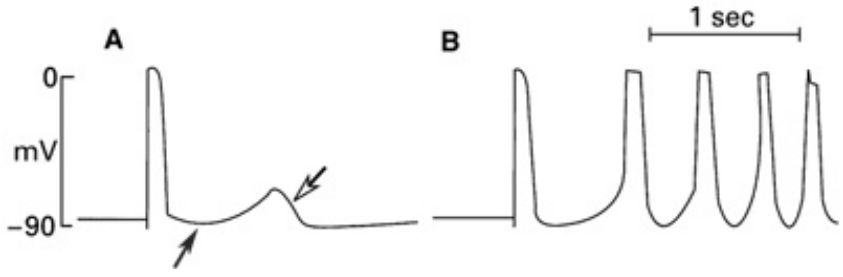

Figure 23-10: An example of a DAD (*white arrow*) recorded with a microelectrode from an atrial fiber in the canine coronary sinus. The red arrow indicates an afterhyperpolarization. *B*. The onset of triggered activity is shown. (From Wit AL, Rosen MR. After depolarizations and triggered activity: Distinction from automaticity as an arrhythmogenic mechanism. In: Fozzard HA, Haber E, Jennings RB, et al., eds. *The Heart and Cardiovascular System*. Scientific Foundations, 2d ed.

New York, Raven Press; 1991:2113. Reproduced with permission from the publisher and author.)

A triggered impulse is initiated when a DAD depolarizes the membrane potential to the threshold potential for activation of the inward current responsible for the upstroke of the action potential. Triggered impulses are shown in Fig. 23-10*B*. Afterdepolarizations do not always reach threshold, so that triggerable fibers sometimes may be stimulated at a regular rate without becoming rhythmically active, e.g., the stimulated action potential in Fig. 23-10*A*. Probably the most important influence that causes subthreshold DADs to reach threshold is a decrease in the cycle length (an increase in the rate) at which action potentials occur. Therefore, arrhythmias triggered by DADs can be expected to be initiated by either a spontaneous or a pacing-induced increase in the heart rate. A triggered action potential also is followed by an afterdepolarization that may or may not reach threshold. When it does not reach threshold, only one triggered action impulse occurs. Quite often, the first triggered action potential is followed by a short or long "train" of additional triggered action potentials, each arising from the afterdepolarization caused by the previous action potential (Fig. 23-10*B*). The merging of the rising phase of the afterdepolarization with the upstroke of the action potential during triggered activity may be smooth, and as a result, the fiber may show phase 4 depolarization that is indistinguishable from the phase 4 depolarization seen during automatic activity.

CAUSES OF DELAYED AFTERDEPOLARIZATIONS AND TRIGGERED ACTIVITY

Delayed afterdepolarizations usually occur under a variety of conditions in which there is an increase in Ca^{2+} in the myoplasm and the sarcoplasmic reticulum above normal levels (sometimes referred to as *Ca overload*). Abnormalities in the sequestration and release of Ca^{2+} by the sarcoplasmic reticulum also may contribute to their occurrence. On depolarization of the membrane during an action potential, the intracellular free Ca^{2+} normally increases, primarily by Ca^{2+} influx through the L-type Ca^{2+} channels. Initially, this rapid rate of change of intracellular Ca^{2+} triggers Ca^{2+} release from the sarcoplasmic reticulum, causing a further rise in intracellular free Ca^{2+} and contraction[134] (see Chap. 3). Repolarization then induces synchronous Ca^{2+} uptake by the sarcoplasmic reticulum in the cell and relaxation. If intracellular Ca^{2+} is very high or if catecholamines or cyclic adenosine monophosphate (AMP) is present, both of which enhance Ca^{2+} uptake by the sarcoplasmic reticulum, the Ca^{2+} in the sarcoplasmic reticulum may rise during repolarization to a critical level, at which time a secondary spontaneous release of Ca^{2+} from the sarcoplasmic reticulum occurs after the action potential and relaxation of contraction.[134] This secondary release of Ca^{2+} generates an aftercontraction as well as the transient inward (TI) current and the afterdepolarization. The TI current is an oscillatory membrane current that is distinct from the pacemaker currents.[135-142] After one or several afterdepolarizations, myoplasmic Ca^{2+} may decrease because Na^+-Ca^{2+} exchange extrudes Ca^{2+} from the cell, and the membrane potential stops oscillating.

The exact mechanism by which the secondary rise in myoplasmic Ca^{2+} after repolarization causes the TI current is unclear. Two possibilities have been considered. The first is that the Ca^{2+} released from the sarcoplasmic reticulum after repolarization acts on the sarcolemma to increase its conductance to ions (mainly Na^+) that flow into the cell down a concentration gradient through membrane channels. The second mechanism proposed for the origin of the TI current is that the rise in Ca^{2+} causes the TI current through an electrogenic (rheogenic) exchange of Ca^{2+} for Na^+. According to this hypothesis, the transient rise in myoplasmic Ca^{2+} released from the sarcoplasmic reticulum after the action potential is expected to result in "transport" of Ca^{2+} out of the cell across the sarcolemma by the Na^+-Ca^{2+} exchanger. Such an efflux is coupled to an Na^+ influx. If more than two Na^+ ions are exchanged for each Ca^{2+} ion, a net inward current occurs.[143-145]

The most widely recognized cause of DAD-dependent triggered activity is digitalis

toxicity.[116,117,145-151] Afterdepolarizations caused by digitalis sometimes may reach threshold to cause triggered action potentials, particularly if the rate of stimulation is sufficiently rapid. Ventricular arrhythmias (repetitive responses) caused by digitalis in the heart in situ also can be initiated by pacing at rapid rates.[152] As toxicity progresses, the duration of the trains of repetitive responses induced by pacing increases.[153-155] It is assumed that these arrhythmias are caused by DADs. In addition, spontaneously occurring accelerated ventricular rhythms and ventricular tachycardia that occur during digitalis toxicity are likely to be caused by DADs.

Cardiac glycosides cause DADs by inhibiting the Na^+-K^+ pump. In toxic amounts, this effect results in a measurable increase in intracellular Na^+.[156,157] An increase in intracellular Na^+ in turn causes an increase in intracellular Ca^{2+}.[158] When intracellular Na^+ is increased, the concentration-dependent driving force for Na^+ across the sarcolemma is decreased, and this in turn diminishes Ca^{2+} extrusion from the cell by Na^+-Ca^{2+} exchange. Hence, there is a net inward Ca^{2+} movement.[44,159-160]

Catecholamines are probably the next most widely recognized cause of DADs. Delayed afterdepolarizations and triggered activity caused by catecholamines have been recorded with microelectrodes in atrial fibers of the mitral valve,[161] atrial fibers lining the coronary sinus,[33] atrial fibers in the inferior right atrium,[31] and atrial fibers from hearts with cardiomyopathy.[162] The DADs in Fig. 23-10 were caused by catecholamines in atrial fibers of the canine coronary sinus. Infusion of catecholamines through a catheter into the coronary sinus in the dog causes atrial tachycardia that has all the characteristics of triggered activity;[163] therefore, some naturally occurring atrial tachycardias caused by triggered activity probably are induced by the sympathetic nervous system. Ventricular muscle and Purkinje fibers also can develop DADs in the presence of catecholamines.[164,165] Sympathetic stimulation therefore may also cause triggered ventricular arrhythmias, possibly some of the ventricular arrhythmias that accompany exercise[166] and some ventricular arrhythmias that occur during ischemia and infarction.[167,168]

Catecholamines may cause DADs by increasing the slow inward L-type Ca^{2+} current through stimulation of beta-adrenergic receptors.[169,170] The net effect is an increase in transsarcolemmal Ca^{2+} entry into cardiac cells. In addition to increasing the inward Ca^{2+} current, catecholamines enhance the uptake of Ca^{2+} by the sarcoplasmic reticulum, leading to increased Ca^{2+} stored in the sarcoplasmic reticulum and the subsequent release of an increased amount of Ca^{2+} from the sarcoplasmic reticulum during contraction.[134,171,172] The increased Ca^{2+} in the sarcoplasmic reticulum induced by catecholamines also may lead to the occurrence of DADs. Delayed afterdepolarizations and triggered activity also may occur in the absence of pharmacologic agents, catecholamines, or an increase in extracellular Ca^{2+}. Triggerable fibers have been found in the upper pectinate muscles bordering the crista terminalis in the rabbit heart, branches of the sinoatrial ring bundle or transitional fibers between the ring bundle and ordinary pectinate muscle,[173] apparently normal fibers in human atrial myocardium,[174] human atrial fibers with very low membrane potentials (below -60 mV) and slow response action potentials,[70,71,174] rat ventricular muscle that is hypertrophic secondary to renovascular hypertension,[175] and ventricular myocardium from diabetic rats.[176]

PROPERTIES OF DELAYED AFTERDEPOLARIZATIONS

The TI current that causes DADs is maximal at around -60 mV and diminishes at more positive and more negative membrane potentials.[138,140,177] As a result of the dependence of the TI current on the level of membrane potential, the amplitude of DADs and therefore the possibility of triggered activity are influenced by the level of membrane potential at which the action potentials occur. In the digitalis-toxic Purkinje system, there is a "window" of membrane voltage for maximum diastolic potential, which is approximately between -75 and -80 mV, at which the

amplitude of DADs tend to be greatest.[178,179] When DADs occur at the membrane potentials that favor a maximum amplitude, any intervention that hyperpolarizes or depolarizes the membrane tends to reduce their magnitude and suppress any rhythms the afterdepolarizations might induce. Similarly, when there are no DADs in the presence of digitalis and the membrane potential is at a voltage less than or greater than the window, interventions that bring membrane potential into this voltage range often induce DADs. A similar dependence on membrane potential has been shown for DADs in atrial fibers of the coronary sinus[180] and in Purkinje fibers from infarcts.[181,182]

Delayed afterdepolarizations are influenced by the action potential duration, with longer action potential durations favoring the occurrence of DADs.[180] When the action potential duration is longer, more Ca^{2+} is able to enter the cell. Drugs such as quinidine, which prolong action potential duration, may increase DAD amplitude,[183] while drugs such as lidocaine, which shorten action potential duration, may decrease DAD amplitude.[184] The amplitude of DADs is dependent on the number of action potentials that precede them; i.e., after a period of quiescence, the initiation of a single action potential may be followed by either no afterdepolarization or only a small one. With continued stimulation, the afterdepolarizations increase in amplitude, and triggered activity eventually may occur.[33,117,147,161,185] The amplitude of DADs and their coupling interval to the previous action potentials also are dependent on the cycle length at which action potentials are occurring, and triggered activity can be induced by a critical decrease in the drive cycle length.[117,147,161,168,173,175,176] This is illustrated by the effects of the stimulus cycle length on the amplitude of DADs recorded from an atrial fiber in the canine coronary sinus (Fig. 23-11). The transmembrane potentials at the left were recorded when the stimulus cycle length was 2000 ms; the afterdepolarization amplitude after the last stimulated impulse is 5 mV. In the center, the stimulus cycle length was 1500 ms, and the afterdepolarization amplitude after the last stimulated impulse is 15 mV. At the right, at a stimulus cycle length of 1200 ms, afterdepolarization amplitude reached 20 mV after the third stimulated action potential before triggered activity was initiated. Digitalis-induced DADs occur either singly or as two or more "damped" oscillations after the action potential.[117,147] When two or more afterdepolarizations are present, their relation to the drive cycle length is complex. As drive cycle length decreases, the amplitude of the first afterdepolarization increases, reaching a peak at a cycle length of about 500 ms, and triggered activity may occur. If it does not, at shorter drive cycle lengths the magnitude of this first afterdepolarization decreases. The second DAD, however, continues to increase in magnitude as drive cycle length shortens further and eventually may reach threshold and induce triggered activity. A decrease in the length of even a single drive cycle (i.e., a premature impulse) also results in an increase in the amplitude of the DAD that follows the premature cycle.

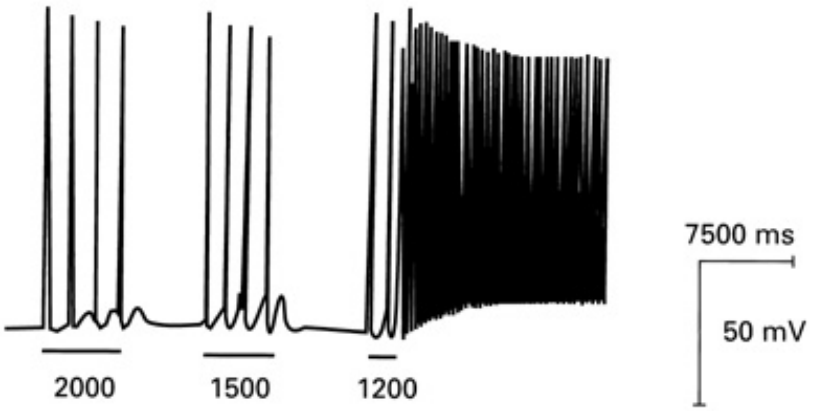

Figure 23-11: Effects of stimulation rate on DADs and triggered activity. Transmembrane action potentials were recorded from an atrial fiber in the canine coronary sinus superfused with Tyrode's solution containing norepinephrine. The stimulus cycle lengths and the periods of stimulation are

indicated by the black bars. Sustained triggered activity occurred after stimulation at a cycle length of 1200 ms. The rate of triggered activity is so rapid that the individual action potentials cannot be seen at the slow oscilloscopic sweep speed. (From Wit AL, Cranefield PF. Triggered and automatic activity in the canine coronary sinus. *Circ Res* 1977; 41:435. Reproduced with permission from the publisher and author.)

The premature coupling interval at which triggered activity occurs is also dependent on the basic drive cycle length. As the basic drive cycle length decreases, the premature coupling interval needed to induce triggered activity increases.[186] Decreasing the drive cycle length, in addition to increasing amplitude, tends to decrease the coupling interval of DADs to the action potential upstroke or terminal phase of repolarization by increasing the rate of depolarization of the afterdepolarization.[33,117,147,173] As a result, there is a direct relation between the drive cycle length at which triggered impulses are initiated and the coupling interval between the first triggered impulse and the last stimulated impulse that induced them; i.e., as the drive cycle length is reduced, the first triggered impulse occurs earlier with respect to the last driven action potential. This characteristic property forms the basis for one of the indirect ways in which triggered activity induced by a decrease in the drive cycle length in the whole heart sometimes is distinguishable from reentrant activity induced by a decrease in the drive cycle length, since the relationship for reentrant impulses initiated by rapid stimulation is often the opposite; i.e., as drive cycle length is reduced, the first reentrant impulse occurs later with respect to the last driven action potential because of rate-dependent conduction slowing in the reentrant pathway (described in more detail later in this chapter). The increased time during which the membrane is in the depolarized state at shorter stimulation cycle lengths or after premature impulses increases Ca^{2+} in the myoplasm and the sarcoplasmic reticulum, thus increasing the TI current responsible for the increased afterdepolarization amplitude and causing the current to reach its maximum amplitude more rapidly, decreasing the coupling interval of triggered impulses. The repetitive depolarizations can increase intracellular Ca^{2+} because of repeated activation of the inward Ca^{2+} current that flows through L-type Ca^{2+} channels.

This chapter has discussed how triggered activity caused by DADs is initiated by stimulation. These characteristics may be of use in identifying triggered activity in the in situ heart (described below). Also of importance in identifying triggered arrhythmias in situ are the effects of electrical stimulation on established triggered activity. In general, triggered activity is influenced markedly by overdrive pacing (i.e., pacing at a rate faster than the rate of the triggered rhythm). The effects of overdrive pacing on triggered activity have been studied only in several experimental situations: in atrial fibers in which triggered activity is caused by catecholamines and in Purkinje fibers in which triggered activity is caused by digitalis or myocardial infarction. These effects are dependent on both the rate and the duration of overdrive pacing.[187,188] When overdrive pacing is done for a critical duration of time and at a critical rate during a catecholamine-dependent triggered rhythm, the maximum diastolic potential after the overdrive pacing increases to levels more negative than before; during the increase in membrane potential, the rate of triggered activity slows until the triggered rhythm stops. When triggered activity stops after a period of overdrive pacing at a moderate rate, some 10 to 50 impulses may occur after termination of the overdrive pacing before termination of the triggered activity occurs. The increase in maximum diastolic potential and the slowing and termination of triggered activity after a period of overdrive pacing are caused by enhanced activity of the electrogenic Na^+ pump.[187] During a period of overdrive pacing, there is a transient increase in intracellular Na^+ because the increased number of action potentials stimulates the pump to generate increased outward current.[73,189]

In digitalis-toxic Purkinje fibers, overdrive pacing also can terminate triggered activity, and this effect is dependent on the overdrive pacing cycle length but not on the overdrive pacing duration.[186,190] Termination occurs more frequently at more rapid overdrive pacing rates and may not be immediate; i.e., several triggered impulses may continue to occur after stimulation is stopped before triggered activity stops.[186] When overdrive pacing is not rapid enough to terminate

the triggered rhythm, it can cause overdrive acceleration. Termination by overdrive pacing is not accompanied by hyperpolarization of the maximum diastolic potential and probably is not caused by increased Na^+-K^+ pump activity, since the pump is partially inhibited by digitalis. The exact mechanism for termination has not been elucidated. Premature stimuli also may terminate triggered rhythms, as shown in digitalis-toxic Purkinje fibers,[186] Purkinje fibers in myocardial infarcts,[191] and atrial fibers exposed to catecholamines,[161,188] although termination is much less common than it is by overdrive pacing.[190] It has not been demonstrated that the premature impulse must occur at a critical point in the cycle length of triggered activity.

Early Afterdepolarizations and Triggered Activity

Early afterdepolarizations are manifest as a sudden change in the time course of repolarization of an action potential such that the membrane potential does not follow the trajectory characteristic of normal repolarization but suddenly shifts in a depolarizing direction. This is illustrated in the example of an EAD recorded with an intracellular microelectrode in a superfused Purkinje fiber shown in Fig. 23-12. The normal time course of repolarization of the action potential is shown in panel *A*. The arrow in panel *B* shows the deviation in membrane potential that constitutes the EAD. Early afterdepolarizations may appear at the plateau level of membrane potential, which is usually more positive than -60 mV, as in Fig. 23-12*B*, or they may appear later, during phase 3 of repolarization. In Fig. 23-13*B*, trace 1 shows the normal time course of repolarization of a Purkinje fiber action potential, while trace 2 shows a deviation from this normal time course late during phase 3, which is the EAD. Early afterdepolarizations occurring late in repolarization occur at membrane potentials more negative than -60 mV in atrial, ventricular, or Purkinje cells that have normal resting potentials. Normally, a net outward membrane current shifts the membrane potential progressively in a negative direction during repolarization of the action potential. An EAD occurs when for some reason the current-voltage relation is altered to cause outward current during repolarization to approach or attain 0, at least transiently. Such a shift can be caused by any factors that either decrease outward current, mostly carried by K^+, or increase inward current, carried by Na^+ or Ca^{2+}. If the change in the current-voltage relation results in a region of net inward current during the plateau range of membrane potentials,[192] it can lead to a secondary depolarization (a triggered action potential) during the plateau or phase 3 by activating a regenerative inward current.

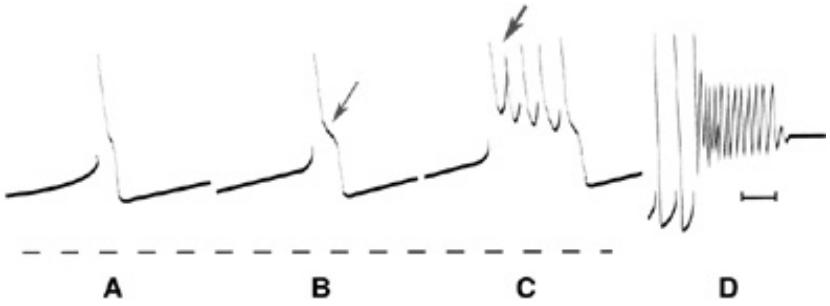

Figure 23-12: Early afterdepolarizations and triggered activity during repolarization in a Purkinje fiber. *A*. Transmembrane potential with normal repolarization of a spontaneously active Purkinje fiber. *B*. Early afterdepolarization (*arrow*) occurring during the plateau phase of the action potential. *C*. Triggered action potentials (*arrow*) during the plateau. *D*. Arrest of repolarization at a low level of membrane potential after a period of triggered activity. (From Cranefield PF. Action potentials, afterpotentials and arrhythmias. *Circ Res* 1977; 41:415-425. Reproduced with permission from the publisher and author.)

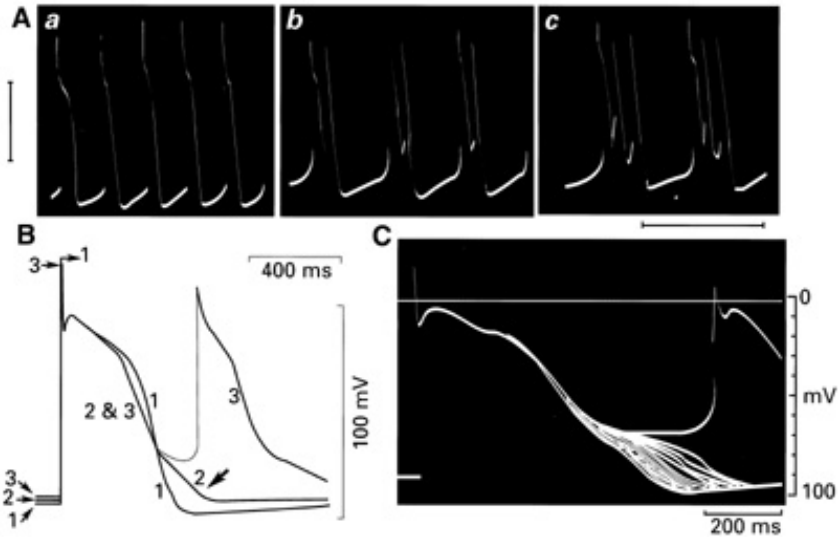

Figure 23-13: Early afterdepolarizations and triggered activity during late repolarization in a Purkinje fiber. *A*. Three panels are shown: (*a*) a spontaneously firing Purkinje fiber with prominent phase 4 depolarization, (*b*) occurrence of a single triggered action potential caused by an EAD, occurring during repolarization of each spontaneous action potential, (*c*) two triggered action potentials caused by an EAD occurring during repolarization of each spontaneous action potential. *B*. Development of an EAD and a triggered action potential in three superimposed traces: (1) normal Purkinje fiber action potential, (2) alteration in the time course of late repolarization leading to the occurrence of an EAD (*arrow*), (3) further alteration in late repolarization, leading to a triggered action potential. *C*. Superimposed traces recorded from a Purkinje fiber in the course of developing EADs and a triggered action potential. (From Coulombe A et al. Role of the "Na window" current and other ionic currents in triggering early after-depolarizations and re-exitation in Purkinje fibers. In: Zipes DP, Jalife J, ed. *Cardiac Electrophysiology and Arrhythmias*. New York: Grune & Stratton; 1985:43. Reproduced with permission from the publisher and author.)

Under certain conditions, EADs can lead to "second upstrokes"[5,127] or action potentials; when an EAD is large enough, the decrease in membrane potential leads to an increase in net inward (depolarizing) current, and a second action potential occurs before complete repolarization of the first, as shown in panel *C* (arrow) of Fig. 23-12 and trace 3 in panel *B* of Fig. 23-13. The second action potential occurring during repolarization is triggered in the sense that it is evoked by an EAD, which in turn is induced by the preceding action potential. The second action potential also may be followed by other action potentials, all occurring at the low level of membrane potential characteristic of the plateau (Fig. 23-12*C*) or at the higher level of membrane potential of later phase 3 (Fig. 23-13, panels *Ab*, *Ac*, and *B*). Without the initiating action potential, there could be no triggered action potentials. The sustained rhythmic activity may continue for a variable number of impulses and terminates when repolarization of the initiating action potential returns membrane potential to a high level (Fig. 23-12*C*). As repolarization occurs, the rate of the triggered rhythm slows because the rate is dependent on the level of membrane potential in the same way that abnormal automaticity is. Sometimes repolarization to the high level of membrane potential may not occur, and membrane potential may remain at the plateau level or at a level intermediate between the plateau level and the resting potential[62] (Fig. 23-12*D*). The sustained rhythmic activity then may continue at the reduced level of membrane potential and assumes the characteristics of abnormal automaticity.[127]

The level of membrane potential at which the triggered action potentials occur determines both the rate of triggered activity and whether the triggered action potentials can propagate and excite adjacent normal regions.[193] At the more positive membrane potentials of the plateau, the rate of

triggered activity is more rapid than it is late during phase 3. Triggered action potentials occurring at the plateau level have slow upstrokes; therefore, conduction of these action potentials sometimes may block,[194,195] while the faster upstrokes of triggered action potentials occurring later during phase 3 enable them to propagate more easily. The ionic current responsible for the upstrokes of the action potentials during triggered activity caused by EADs is determined by the level of membrane potential at which the action potentials occur. Triggered action potentials occurring during the plateau phase and early during phase 3, at a time when most fast Na^+ channels are still inactivated, most likely have upstrokes caused by the inward L-type Ca^{2+} current.[5,196] At higher membrane potentials during late phase 3 of repolarization, where there is partial reactivation of the Na^+ channels, the upstrokes are caused by the fast inward Na^+ current. Current flowing through both L-type Ca^{2+} channels and partially reactivated fast Na^+ channels may be involved over intermediate ranges of membrane potential.

CAUSES OF EARLY AFTERDEPOLARIZATIONS AND TRIGGERED ACTIVITY

Early afterdepolarizations and triggered activity have been produced in experimental studies under a variety of conditions, some of which would never be expected to be associated with naturally occurring arrhythmias in the in situ heart. Most of these conditions somehow delay repolarization of the action potential by increasing inward current or decreasing outward current during the plateau and repolarization phases. Most often, EADs occur more readily in Purkinje fibers than in ventricular or atrial muscle, although EADs can readily occur in the so-called M cells, which are ventricular muscle cells with a prominent plateau phase.[197] Early afterdepolarizations may occur when the rate of stimulation is markedly slowed, reducing the outward current generated by the Na^+-K^+ pump, especially when K^+ in the extracellular environment is lower than normal, also reducing outward current.[128]

At a "physiologic range" of cycle lengths (a range that encompasses the normal sinus rhythm of the adult human heart: 1000 to 700 ms), EADs have rarely occurred in studies of isolated preparations of cardiac fibers. As cycle length is increased and repolarization is prolonged, EADs and triggered activity are more likely to occur.[198] The result is a bradycardia-induced tachycardia during which there may be very slow conduction. Another important characteristic is that the longer the basic drive cycle length, the greater the number of impulses that are triggered by EADs.[198] Once EADs have achieved a steady-state magnitude at a constant drive cycle length, any event that shortens drive cycle length tends to reduce their amplitude.[198] Hence, the initiation of a single premature depolarization, which is associated with an acceleration of repolarization, will reduce the magnitude of the EADs that accompany the premature action potential; as a result, triggered activity is not expected to follow premature stimulation. Polymorphic ventricular tachycardias that sometimes resemble torsades de pointes have been induced in dogs by the infusion of cesium, which blocks i_{K_i} to cause EADs.[199] Occurrence of tachycardia is preceded by QT-interval prolongation, a consequence of delayed repolarization, as is characteristically seen in patients with torsades de pointes.[200] The initial beat of the tachycardia caused by cesium often occurs during repolarization, i.e., during the T wave.

Early depolarizations and triggered activity have been seen in monophasic action potentials recorded from the ventricles in dogs with cesium-induced ventricular tachycardia.[201,202] Because the experimental arrhythmias caused by agents such as cesium, which are known to induce EADs, resemble torsades de pointes, it has been proposed that clinically occurring torsades de pointes sometimes may be caused by EADs. Other agents that can cause EADs and triggered activity are used therapeutically, and therefore, arrhythmias associated with their use may result from triggered activity. Antiarrhythmic drugs that prolong the duration of the action potential of Purkinje fibers or ventricular muscle (e.g., sotalol,[203,204] *N*-acetylprocainamide,[205] and quinidine[206,207]) can cause EADs and triggered activity when administered to isolated preparations, particularly when the rate of stimulation is low and the extracellular K^+

concentration is lower than normal, e.g., <4 m*M*/L.

The mechanisms by which these effects are exerted have been studied in detail for only some of these drugs. Both the d (no beta receptor blockade) and the I (beta-blocking) forms of sotalol prolong the action potential duration by inhibiting the repolarizing K current, i_{K_i}.[204] Similarly, the prolongation of the action potential by quinidine, which may lead to EADs, is related to the blocking effect of quinidine on the outward membrane repolarizing K^+ current, not to that drug's well-known blocking effect on the Na^+ channel.[208] It is known that quinidine may cause ventricular tachyarrhythmias in patients undergoing antiarrhythmic therapy with that drug. Interestingly, the arrhythmias may occur at low plasma quinidine concentrations that do not cause widening of the QRS complex in the ECG,[209] consistent with observations in superfused Purkinje fibers that afterdepolarizations caused by quinidine occur without depression of the action potential upstroke. Hypokalemia and bradycardia both predispose to the occurrence of quinidine-induced torsades de pointes,[200,210] and both have been shown to potentiate the induction of EADs in vitro by quinidine.[206,207] Torsades de pointes also has been associated with the administration to patients of *N*-acetylprocainamide[211] and sotalol.[212] Magnesium has been shown to abolish EAD-dependent triggered activity in experimental studies.[207,213] Magnesium also has been shown to provide effective therapy when used to treat some clinical cases of drug-induced torsades de pointes,[214,215] providing further evidence that this clinical arrhythmia may be a manifestation of triggered activity (see Chap. 27).

Arrhythmias Caused by Reentry

INTRODUCTION

As was discussed previously, the excitation wavefront originating in the sinus node normally activates the cardiac tissues in an orderly sequence and then dies out. Thus, during normal sinus rhythm, each heartbeat is generated by a new pacemaker impulse in the sinus node. There are, however, arrhythmias in which, in the presence of a requisite set of circumstances, an excitation wavefront does not die out but rather can propagate continuously and thus continue to excite the heart because it always encounters excitable tissue. Such an arrhythmia is called reentrant.

REQUISITES FOR REENTRANT EXCITATION

Perhaps the easiest way to illustrate this is to discuss again, but in more detail, the earliest description of reentrant excitation by Mayer[3] in 1906 in the excitable subumbrella ring of tissue of the scyphomedusae (jellyfish), as is shown in Fig. 23-4. This example well illustrates the requisites for reentrant excitation. First, a substrate must be present that will support reentrant excitation, in this case the subumbrella ring of excitable tissue of the jellyfish. Second, the excitation wavefront propagating in this substrate must encounter unidirectional block (Fig. 23-4*B*). Unidirectional block must be present or the excitation wavefronts traveling around the ring will collide and extinguish each other (Fig. 23-4*A*). If the site of unidirectional block instead manifests bidirectional block, reentrant excitation will not occur because the circulating excitation wavefront will be unable to propagate through the area of block to reexcite the tissue that initially was excited. Third, there must be a central area of block around which the reentrant excitation wavefront can circulate. In this example, it is the hole in the center of the ring that clearly is inexcitable. Without a central area of block, the excitation wavefront will not necessarily be conducted around the ring of excitable tissue. Rather, it could take a shortcut, permitting the circulating excitation wavefront to arrive quite early at the site where it originated. If it arrives sufficiently early, the latter tissue will still be refractory, and reentrant excitation will not be possible. But even with the presence of a central area of block and without the presence of a shortcut, the circulating wavefront will manifest reentrant excitation only if the tissue it initially activated has had sufficient time to recover its excitability by the time the reentrant wavefront

returns. Thus, conduction of the circulating excitation wavefront in the rest of the circuit must take long enough for this to happen, and there must always be a gap of excitable tissue (either fully or partially excitable) ahead of the circulating wavefront (the so-called excitable gap). In the case of the experiment by Mayer on the subumbrella ring of excitable tissue of the jellyfish, conduction velocity was constant and the length of the ring was long enough that conduction time around the ring was longer than the effective refractory period of the excitable tissue constituting the ring, permitting reentry. If the length of the ring had been critically shorter or if the conduction velocity had been critically faster, the circulating excitation wavefront would have arrived at the site of initial excitation before sufficient recovery of excitability had occurred, preventing reexcitation.

From these sorts of observations grew the concept of the wavelength of the circulating impulse.[4,216,217] The wavelength is the product of the conduction velocity of the circulating excitation wavefront and the effective refractory period of the tissue in which the excitation wavefront is propagating. It quantifies how far the impulse travels relative to the duration of the refractory period. Thus, the wavelength of the reentrant excitation wavefront must be shorter than the length of the pathway of the potential reentrant circuit for reentrant excitation to occur; i.e., the impulse must travel a distance during the refractory period that is less than the complete reentrant path length to give myocardium ahead of it sufficient time to recover excitability.

For virtually all clinically important reentrant arrhythmias resulting from ordered reentry, however, in the presence of uniform, normal conduction velocity along the reentrant pathway, the wavelength would be too long to permit reentrant excitation. Thus, virtually all these arrhythmias must have, and in fact do have, one or more areas of slow conduction as a part of the reentrant circuit. The associated changes in conduction velocity (as well as associated changes in refractory periods) actually cause the wavelength to change in different parts of the circuit. However, the presence of one or more areas of slow conduction permits the average wavelength of reentrant activation to be shorter than the path length.

The fact that the reentrant circuit of virtually all clinically important reentrant arrhythmias has one or more areas of slow conduction serves to emphasize the fact that the electrophysiologic properties of the cardiac tissue making up the reentrant circuit are not uniform. In fact, there may be, and usually are, variations of conduction velocity and refractoriness along the course of the reentrant circuit. An additional requisite for random reentry is the necessity of a critical mass of tissue to sustain the one or usually more simultaneously circulating reentrant excitation wavefronts.[218] Thus, it is essentially not possible to achieve sustained fibrillation of ventricles of very small normal mammalian hearts and equally difficult to achieve sustained fibrillation of the normal atria of humans or smaller mammals.

Finally, another prerequisite for reentrant excitation to occur is often (but not always) the presence of an initiating trigger. The trigger, usually the occurrence of one or more premature beats, frequently is required because it elicits or brings to a critical state one or more of the conditions necessary to achieve reentrant excitation. Thus, a premature impulse initiating reentry may arrive at one site in the potential reentrant circuit sufficiently early that it encounters unidirectional block because that tissue has had insufficient time to recover excitability after excitation by the prior beat (Fig. 23-4). Furthermore, in the other limb of the potential reentrant circuit, the premature arrival of the excitation wavefront either causes slow conduction or results in further slowing of conduction of the excitation wavefront through an area of already slow conduction. The resulting increase in conduction time around this limb of the potential reentrant circuit serves to allow the region of unidirectional block in the tissue in the other limb activated initially by the premature beat to recover excitability. Thus, when the circulating excitation wavefront of the premature beat arrives at these tissue sites, the excitation wavefront can reexcite the tissue, thus manifesting reentrant excitation (Fig. 23-4).

It should be noted that the mechanism causing the premature beat may be different from the

reentrant mechanism causing the tachycardia. Thus, the premature beat may be caused by automaticity or triggered activity. An example of the latter may be torsade de pointes, in which the initiating beat (or beats) is the result of triggered activity caused by early afterdepolarization, but the remainder of the beats in this rhythm (it is frequently nonsustained) are now thought to be due to reentry.[219] Another example may occur during cardiac catheterization, in which the premature beat may be due to the catheter forcefully hitting the heart wall, i.e., a mechanical cause. However, the trigger to initiate reentrant excitation need not be a premature beat. The trigger to initiate reentrant excitation may be the normal sinus beat. One example is the rhythm known as permanent nonparoxysmal AV junctional reentrant tachycardia.[220,221] In this example, the potential reentrant circuit contains an area of permanent unidirectional block in an antegrade direction. Moreover, the potential reentrant circuit also has a relatively stable area of very slow conduction, causing the wavelength of the propagating excitation wavefront to be shorter than the path length of the potential reentrant circuit. In this circumstance, the normal sinus beat propagates around the reentrant circuit with sufficient delay that when it arrives in a retrograde direction at the area of permanent antegrade unidirectional block, the tissue at that site has recovered excitability. Furthermore, the conduction time around the reentrant circuit is such that the excitation wavefront continually encounters excitable tissue in the direction in which it is propagating, resulting in continuous reentrant excitation and an incessant tachycardia. Another example where a premature beat is not necessary is reentrant premature ventricular beats, as in ventricular bigeminy (see Chap. 24).

COMPONENTS OF THE REENTRANT CIRCUIT

The Substrate

The cardiac tissue that constitutes the substrate for reentrant excitation can be located almost anywhere in the heart. Furthermore, the reentrant circuit may be a variety of sizes and shapes and may include a number of different kinds of myocardial cells, e.g., atrial, ventricular, nodal, and Purkinje. The reentrant circuit may be an anatomic structure such as a loop of fiber bundles in the Purkinje system.[222] The reentrant circuit may be a functionally rather than an anatomically defined pathway, with its existence, size, and shape determined by the electrophysiologic properties of cardiac tissues in which the reentrant wavefront circulates, as has been shown in some patients with atypical atrial flutter.[223,224] Or it may be an anatomic-functional combination, as has been suggested for some intraatrial reentrant rhythms, such as atrial flutter.[224]

The Area(s) of Slow Conduction

As has been discussed, a condition necessary for reentry is that the impulse be delayed sufficiently in the alternative pathway(s) to allow elements proximal to the site of unidirectional block to recover excitability. If reentry is to succeed, the impulse traveling around the reentrant circuit in one direction as a result of the unidirectional block must not return to this site of block before it and regions around it recover excitability. In the presence of normal conduction, sufficient time to allow recovery of excitability may occur if the alternative pathway is sufficiently long. Reentry is facilitated when conduction in all or a part of the alternative pathway is slow, since long pathways that are often not present in the heart are then not necessary. The area(s) of slow conduction may be an anatomic structure normally expected to manifest slow conduction, such as the AV node. Thus, the AV node is the area of slow conduction in AV reentrant tachycardia (a reentrant tachycardia in which the circuit involves the atria, the AV node, the His-Purkinje system, the ventricles, and an accessory AV connection). The area of slow conduction may be in cardiac tissue that normally does not manifest slow conduction. Such an area is not present during sinus rhythm (in contrast to the AV node) but is functionally present during the tachycardia. These areas may develop as a result of premature excitation or may evolve during a rapid transitional rhythm as occurs during atrial flutter.[224,225] An example of a functionally determined area of slow conduction is found in the posterior-inferior right atrium during atrial flutter in patients[226] or in

the free wall of the right atrium of the canine sterile pericarditis mode of atrial flutter.[224] Yet another example may be found in tissue that has been damaged, as after a myocardial infarct. Such tissue normally would not manifest slow conduction but after the injury may become an area of slow conduction even during sinus rhythm.[227] Slow conduction can be a consequence of active membrane properties determining the characteristics of inward currents depolarizing the membrane during the action potential, or it can be a consequence of passive properties governing the flow of current between cardiac cells.

DEPRESSION OF RESTING MEMBRANE POTENTIAL

An important feature of the transmembrane action potential of atrial, ventricular, and Purkinje fibers that governs the speed of propagation is the magnitude of the inward Na^+ current flowing through the fast Na^+ channels in the sarcolemma during the upstroke. The magnitude of this current flow is reflected in the rate at which the cell depolarizes ($V(r)_{max}$ of phase 0)[228] and the overshoot of the upstroke (the positive level of depolarization). The depolarization phase or upstroke of the action potential results from the opening of specific membrane channels (fast Na^+ channels) through which Na^+ ions rapidly pass from the extracellular fluid into the cell.

During conduction of the impulse, the inward transmembrane Na^+ current flowing during the depolarization phase (phase 0) of the action potential results in the flow of axial current along the cardiac fiber through the cytoplasm and the gap junctions of the intercalated disks that connect the cardiac cells. The current flows out of the cells through the membrane ahead as resistive and capacitive current. The conduction velocity depends on both how much capacitive current flows out of the cell at unexcited sites ahead of the propagating wavefront and the distance at which the capacitive current can bring membrane potential to threshold. One important factor that influences the amount of current flowing through the sarcoplasm of a muscle fiber (axial current), and therefore capacitive current, is the amount of fast inward current causing the propagating action potential. A reduction in this inward current, leading to a reduction in the rate or amplitude of depolarization during phase 0, may decrease axial current flow, slow conduction, and lead to conduction block. Such a reduction may result from inactivation of Na^+ channels. The intensity of the inward Na^+ current depends on the fraction of Na^+ channels that open when the cell is excited and the size of the Na^+ electrochemical potential gradient (relative concentration of Na^+ in the extracellular space compared with Na^+ concentration inside the cell[229]). The fraction of Na^+ channels available for opening is determined largely by the level of membrane potential at which an action potential is initiated.[229] The Na^+ channels are inactivated either after the upstroke of an action potential or if the steady-state resting membrane potential is reduced. Immediately after the upstroke, cardiac fibers are inexcitable because of Na^+ channel inactivation at the positive level of membrane potential.

During repolarization, progressive removal of inactivation allows increasingly large Na^+ currents to flow through the still partially inactivated Na^+ channels when the cells are excited. The inward Na^+ current, amplitude, and rate of rise of premature action potentials initiated during this relative refractory period are reduced because the Na^+ channels are only partly reactivated.[229] In Fig. 23-14*B*, premature action potentials *a*, *b*, and *c* have low amplitudes and slow rates of depolarization because they were initiated before full repolarization of the action potential. Hence, the conduction velocity of these premature action potentials is low. Premature activation of the heart therefore may induce reentry because premature impulses conduct slowly in regions of the heart where the cardiac fibers are not completely repolarized (where Na^+ channels are to some extent still inactivated).

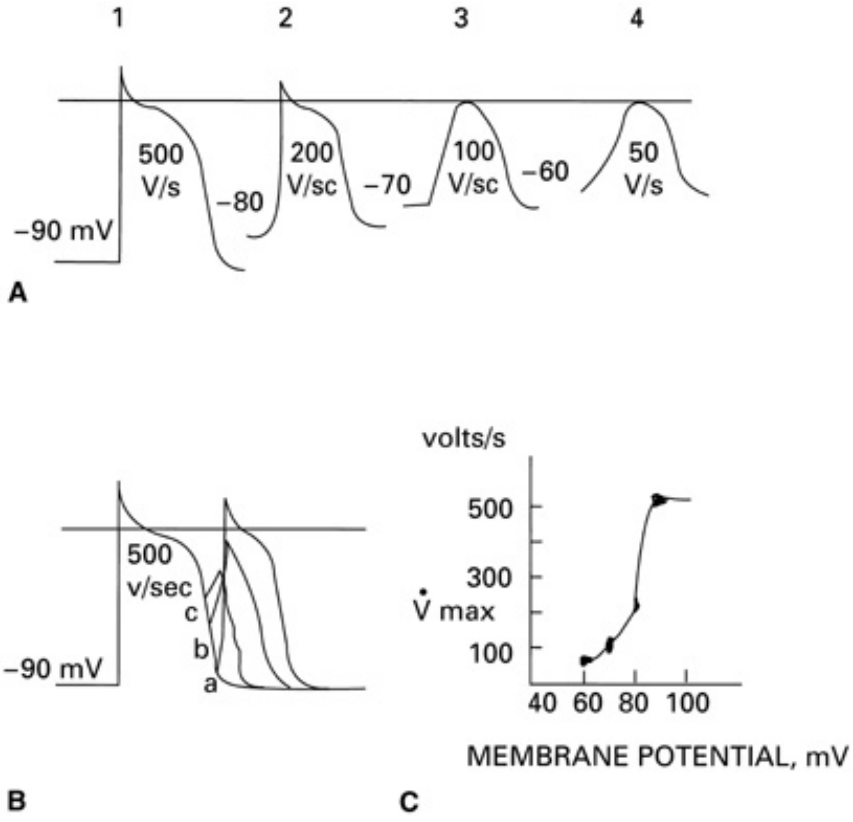

Figure 23-14: Diagrammatic representation of the relation between the level of membrane potential at the onset of phase 0 and the maximum rate of depolarization during phase 0 (dv/dt_{max} or $V(r)_{max}$). *A*. Fiber has been depolarized by progressively increasing the extracellular potassium concentration. As resting membrane potential decreases, the rate of depolarization of the action potential upstroke decreases. *B*. Fiber is activated by premature stimuli that occur at different times during phase 3 (*a*, *b*, and *c*). The premature action potentials have reduced rates of depolarization because they arise at reduced membrane potentials. *C*. For both types of experiments, the general relationship between $V(r)_{max}$ and membrane potential is shown. As the membrane potential becomes smaller (less negative), the rate of phase 0 depolarization ($V(r)_{max}$) decreases and therefore conduction velocity decreases.

Conduction slow enough to facilitate reentry also may occur in cardiac cells with persistently low levels of resting potential (which may be between -60 and -70 mV) caused by disease. At these resting potentials, a significant percentage of the Na^+ channels are inactivated;[229] therefore, they are unavailable for activation by a depolarizing stimulus. Also, at these resting membrane potentials, recovery from inactivation is markedly prolonged and extends beyond complete repolarization.[230] The magnitude of the inward current during phase 0 of the action potential is reduced; consequently, both the speed and the amplitude of the upstroke are diminished (Fig. 23-14*A*, action potentials 2, 3, and 4), decreasing axial current flow and slowing conduction significantly. Such action potentials with upstrokes dependent on inward current flowing via partially inactivated Na^+ channels sometimes are referred to as *depressed fast responses*. Further depolarization of the resting membrane potential and further inactivation of the Na^+ channel may decrease the excitability of cardiac fibers to such an extent that they may become a site of unidirectional conduction block.[231] Thus, in a diseased region with partially depolarized fibers, there may be some areas of slow conduction and some areas of conduction block, depending on the level of resting potential and the amount of Na^+ channels that are inactivated. This combination may cause reentry. The chance for reentry in such fibers is even greater during premature activation or during rhythms at a rapid rate because slow conduction or the possibility of block is increased even further owing to the prolonged time for the Na^+ channels to recover

from inactivation when the resting potential is partially depolarized.

After the upstroke of the normal action potential of atrial, ventricular, or Purkinje cells, membrane potential begins to return to the resting level because the Na^+ channels are inactivated and the fast (depolarizing) Na^+ current ceases to flow. This return, however, is slowed by a second inward current that is smaller and slower than the fast Na^+ current and probably is carried by both Na^+ and Ca^{2+} ions.[232] This secondary inward current flows through L-type Ca^{2+} channels that are distinct from the fast Na^+ channels.[20] The threshold for activation of the L-type Ca^{2+} current is in the range of -30 to -40 mV, compared with about -70 mV for the fast Na^+ current. This current inactivates much more slowly than does the fast Na^+ current and gradually diminishes as the cell repolarizes. It causes much of the plateau phase of the action potential. Under special conditions, this Ca^{2+} current also may underlie the occurrence of the slow conduction that causes reentrant arrhythmias.[5] Although the fast Na^+ channel may be largely inactivated at membrane potentials near -50 mV, the L-type Ca^{2+} channel is not inactivated and is still available for activation.[5,232]

Under certain conditions, when the resting potential is reduced to levels lower than -60 mV (as occurs when membrane conductance is very low or when catecholamines are present), this normally weak inward Ca^{2+} current may give rise to regenerative action potentials that propagate very slowly and are prone to block. The propagated action potential, which is dependent on inward Ca^{2+} current, is referred to as the *slow response*.[5] Slow-response action potentials can occur in diseased cardiac fibers with low resting potentials, but they also occur in some normal tissue of the heart, such as cells of the sinus and AV nodes, where the maximum diastolic potential is normally about -60 mV or less.[5,233] In fact, slow conduction is a normal property of both the sinus and the AV nodes. Thus, it should be of no surprise that either of these nodes may be a critical area of slow conduction in some reentrant circuits, e.g., the AV node in AV reentrant tachycardia involving an accessory AV connection.

ANISOTROPY

The slow conduction that facilitates the occurrence of reentry also can be caused by factors other than a decrease in inward current during the upstroke of the transmembrane action potential. An increased resistance to axial current flow, which can be expressed as *effective axial resistance* (defined as resistance to current flow in the direction of propagation[234,235]) decreases the magnitude and spread of axial current of the propagating impulse among the myocardial fibers and may decrease conduction velocity. During conduction of the impulse, axial current flows from one myocardial cell to the adjacent cell through the gap junctions of the intercalated disks, which form a major source of intercellular resistance to current flow between fiber bundles.[228] Therefore, the structure of the myocardium that governs the extent and distribution of these gap junctions has a profound influence on axial resistance and conduction. This influence can be seen in normal atrial or ventricular myocardium, although the structure is different in different regions.

The atria (crista terminalis) and certain regions of the ventricles (except for the subepicardial muscle) are composed of bundles of myocardial cells that have been called *unit bundles* by Sommer and Dolber.[236] Such bundles are made up of 2 to 30 cells surrounded by a connective tissue sheath. Within a unit bundle, cells are tightly connected or coupled to each other through intercalated disks that contain the gap junctions. All the cells of a unit bundle are connected to each other within the space of 30 to 50 μm down the length of a strand.[236] An individual cardiac myocyte may be connected to as many as nine other myocytes through one or more intercalated disks.[237] These connections are mainly at the ends of the myocytes rather than along their sides, but the overlapping nature of the junctions effectively connects myocytes within a bundle in the transverse direction as well as the longitudinal direction. Therefore, as a consequence of the many intercellular connections, the myocytes in a unit bundle are activated uniformly and synchronously as an impulse propagates along the bundle. The unit bundles also are connected to

each other. Unit bundles lying parallel to each other in normal atrial and ventricular muscle are connected in a lateral (transverse) direction at intervals in the range of 100 to 150 μm.[236] As a consequence of this structure, the myocardium in regions in which unit bundles occur is better coupled in the direction of the long axis of its cells and bundles (because of the high frequency of the gap junctions within a unit bundle) than in the direction transverse to the long axis (because of the low frequency of interconnections between the unit bundles). This is reflected in a lower axial resistivity in the longitudinal direction than in the transverse direction in cardiac tissues that are composed of many unit bundles.[238,239]

The structure of the interconnections between muscle fibers is somewhat different in the subepicardial regions of the ventricles (and possibly other regions as well) but is still a cause of lower longitudinal axial resistance rather than transverse axial resistance. The subepicardial region is not made up of unit bundles.[240] Each ventricular muscle cell is connected to approxi mately 11 to 12 other muscle cells in three dimensions. The junctions that connect the cells occur at both the ends and the sides of cells in roughly equivalent numbers; approximately half of all connections are side to side, and half are end to end. Therefore, activation wavefronts can conduct equally well between individual cells in both the longitudinal and transverse directions because there are equal numbers of gap junctions. In the transverse direction, however, a wavefront encounters more gap junctions than it does over an equivalent distance in the longitudinal direction because cell diameter is much smaller than cell length; therefore, the wavefront must traverse more cells transversely. Thus, there is a greater resistance transversely than longitudinally because of the increased number of gap junctions per unit distance traveled.[238]

As was stated above, the effective axial resistivity is an important determinant of the conduction velocity; therefore, conduction through atrial and ventricular myocardium is much more rapid in the longitudinal direction, owing to the lower resistivity, than it is in the transverse direction. Thus, cardiac muscle is anisotropic; its conduction properties vary depending on the direction in which they are measured.

Spach and associates.[234,235,241,242] classified anisotropy into two major subdivisions: uniform and nonuniform. Uniform anisotropy is characterized by an advancing wavefront that is smooth in all directions (longitudinal and transverse to fiber orientation), indicating relatively tight coupling between groups of fibers in all directions. Uniform anisotropy is exemplified by the conduction properties of normal septal ventricular muscle, as shown in Fig. 23-15*A*. The muscle in the diagram was stimulated in the center (pulse symbol), and activation spread away from this site in all directions. In the direction of the longitudinal axis of the fibers (from top to bottom), the activation isochrones are widely spaced, indicating rapid conduction-in this case, 0.51 m/s. There is a relatively broad area of fast conduction with an elliptic shape of the isochrones that is characteristic of uniform anisotropy.[241] In the direction transverse to the long axis (to the right and to the left), the isochrones are spaced close together, indicating slower conduction: 0.17 m/s in this example. As the direction of propagation changes between these two axes, the apparent conduction velocity changes monotonically from fast to slow, another characteristic of uniform anisotropy.[234]

The slow conduction in the direction transverse to the longitudinal fiber axis occurs despite action potentials with normal resting potentials and upstroke velocities and is caused by the higher transverse axial resistance. Associated with the differences in conduction velocity that are based on the direction of propagation, however, are unexpected changes in the action potentials. Thus, when going from fast longitudinal conduction to slow transverse conduction, the rate of depolarization during the upstroke of the action potential ($V(r)_{max}$) increases and the time constant of the foot of the upstroke decreases without any change in the resting potential, as shown in Fig. 23-15*C*; the upstroke that is dashed was recorded from a cell during longitudinal propagation, while the upstroke indicated by the solid line was recorded from the same cell during transverse propagation.[234] These characteristics are opposite to the changes in the action

potentials associated with slowing of conduction when the membrane currents are altered (e.g., by membrane depolarization).[243,244] Despite the increase in $V(r)_{max}$, when conduction is slowed in the transverse direction, the slowing of conduction is associated with a decrease in the amplitude of the extracellular electrogram, showing that there is a decrease in the extracellular current flow as a result of the increased axial resistivity.

In uniformly anisotropic tissue, the extracellular unipolar waveform has a large-amplitude, smooth biphasic, positivenegative morphology during propagation in the fast longitudinal direction (Fig. 23-15*B*, dashed line) and a low-amplitude, smooth triphasic (negative-positive-negative) morphology in the transverse direction (Fig. 23-15*B*, solid line). The initial negativity of the electrogram in the transverse direction is a reflection of distant activity rapidly propagating along the longitudinal axis.[245]

Nonuniform anisotropy has been defined[235] as tight electrical coupling between cells in the longitudinal direction but recurrent areas in the transverse direction in which side-to-side electrical coupling of adjacent groups of parallel fibers is absent. Therefore, propagation of normal action potentials transverse to the long axis is interrupted so that adjacent bundles are excited in a markedly irregular sequence (*zigzag conduction*).[235,241] In nonuniformly anisotropic muscle, there also may be an abrupt transition in conduction velocity from the fast longitudinal direction to the slow transverse direction, unlike the case with uniform anisotropic muscle, in which intermediate velocities occur between the two directions. This pattern of excitation in nonuniform anisotropic atrial pectinate bundles from older patients is diagrammed in Fig. 23-16*A*. The white arrow on the outline of the preparation indicates the narrow region of fast conduction down the long axis of the fibers when the bundle was excited at the asterisk. The zigzag arrow indicates the irregular course of excitation across the fibers, which occurred all along the length of the zone of fast conduction. Conduction in the transverse direction in these nonuniformly anisotropic bundles was nearly as slow at the slowest conduction associated with membrane depolarization and slow-response action potentials.[5] In pectinate muscles from older patients, mean fast velocity was 0.69 m/s and slow velocity was 0.07 m/s, a ratio of almost 10,[241] despite the normal resting potential and the fast action potential upstroke of the atrial cells. As in uniform anisotropy, the upstroke velocity of the action potential is more rapid in the slow direction transverse to the long axis of the fibers than in the fast direction parallel to the long axis.

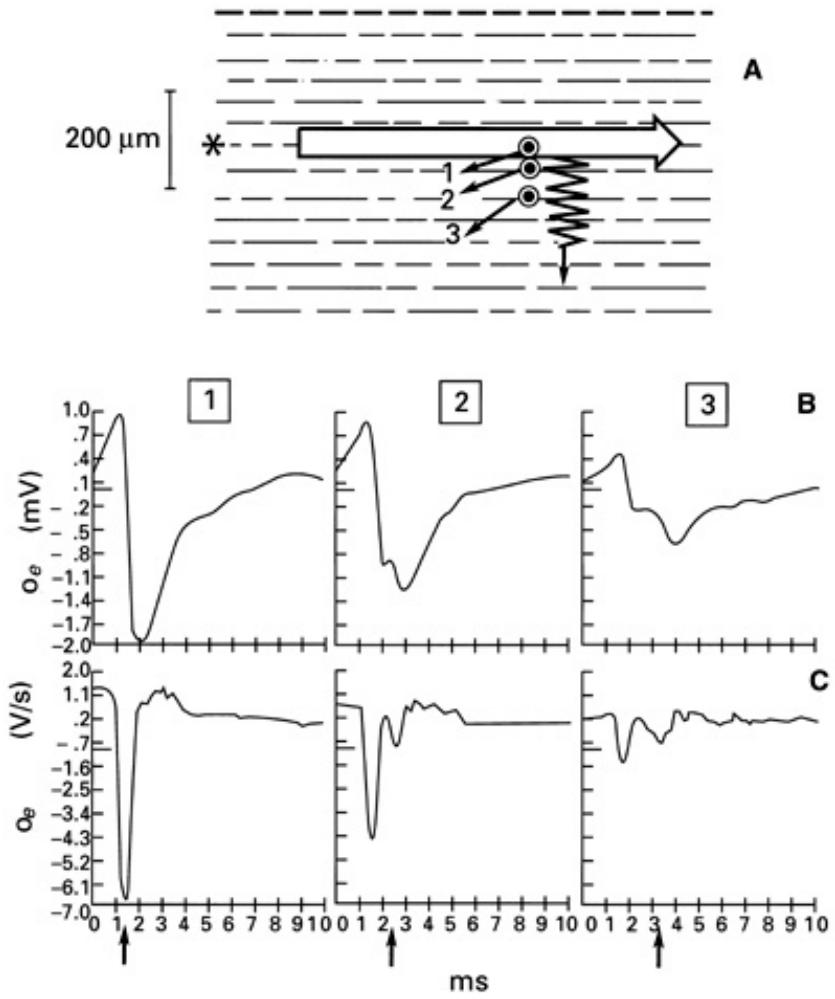

Figure 23-16: *A.* Diagram of a nonuniform anisotropic atrial muscle bundle with the long axis of the myocardial fibers indicated by the dashed lines. The bundle was stimulated at the asterisk. Propagation of the longitudinal wavefront is shown by the large white arrow. Transverse propagation occurred as diagrammed by the zigzag arrow. *B.* Electrograms recorded from sites 1, 2, and 3 on the diagram. *C.* The first derivative of these electrograms is shown. (From Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle: Evidence for uncoupling of side-to-side fiber connections with increasing age. *Circ Res* 1986; 58:356. Reproduced with permission from the publisher and author.)

The morphologic basis for the nonuniform anisotropic properties in human atrial muscle is that the fascicles of muscle bundles are separated in the transverse direction by fibrous tissue that proliferates with aging to form longitudinally oriented insulating boundaries. Intercellular connections cannot occur where the cardiac fibers are separated by connective tissue septa and there is uncoupling between parallel-oriented groups of fibers.[235,241] Part of the reduction of the conduction velocity in this transverse direction may be a result of the tortuous path length necessary for the wavefront to propagate transversely from one bundle to another because of these septa, accounting for the zigzag activation pattern. Similar connective tissue septa cause nonuniform anisotropy in other normal cardiac tissues, such as the crista terminalis and the interatrial band in adult atria or ventricular papillary muscle, as well as pathologic situations such as chronic ischemia or a healing myocardial infarction, in which fibrosis in the myocardium occurs.

The irregular activation transversely is evident in the extracellular electrogram, which is characterized by a sequence of multiple deflections, each representing activation of a separate

bundle of fibers, with the largest, most rapid intrinsic deflection produced by local excitation and less rapid and lower-amplitude deflections produced by excitation of adjacent fascicles.[235] In Fig. 23-16*B*, the multiple deflections can be seen in electrograms recorded from sites 2 and 3 in the atrial pectinate muscle and are even more prominent in the derivatives of these electrograms (Fig. 23-16*C*). A similarly fractionated electrogram also can be recorded from diseased regions of the ventricles. During longitudinal propagation, large biphasic electrograms are still evident (electrogram at site 1).

Anisotropy on a macroscopic scale also can influence conduction at sites where a bundle of cardiac fibers branches or where separate bundles coalesce. Marked slowing can occur when there is a sudden change in the fiber direction, causing an abrupt increase in the effective axial resistivity.[235] Figure 23-17 illustrates this point. The drawings show a small branch of an atrial pectinate muscle from the crista terminalis. The general direction of the fiber orientation is indicated by the thin broken lines, and the pattern of propagation is illustrated by the thick solid lines with arrows. In *A* (1) at the left, wavefronts initiated by stimulation at the top propagate throughout the crista and its branch along the longitudinal axis of the fibers throughout so that there is no conduction delay entering the branch. At the right in *A* (2), wavefronts initiated by stimulation at the bottom propagate up the crista and into the branch, but they encounter a marked change in the direction of the fibers from longitudinal to transverse while entering the branch, resulting in a slowing of conduction because of the sudden increase in axial resistance. Conduction block, which sometimes may be unidirectional, may occur at such junction sites, particularly when the inward current is decreased, as will be described later.

In addition to the structural features of the cellular interconnections influencing axial current flow and conduction as expressed in the anisotropic properties of cardiac muscle, the intercellular resistance may increase because of an increase in gap junctional resistance that results from a decrease in the conductance of the junctions, i.e., a decrease in the ease with which the ions that carry axial current move through the junctions. In a computer model, conduction velocity can be reduced by a factor of 20 by increasing disk resistance, and decremental conduction and block will result.[246,247]

Perhaps the most important influence on gap junctional resistance in pathologic situations is the level of intracellular Ca^{2+}. A significant rise increases resistance to current flow through the junctions and eventually leads to physiologic uncoupling of the cells.[248,249] Intracellular Ca^{2+} increases during ischemia and may be a factor causing slow conduction and reentry. Thus, there are several causes for slow conduction that may lead to reentry: (1) slow responses that are a normal property of some regions of the heart, such as the sinus and AV node, (2) depressed fast responses or slow responses caused by pathology-induced partial depolarization of the membrane potential, (3) anisotropy, and (4) changes in gap junctional resistance.

Unidirectional Block

Unidirectional block occurs when an impulse cannot conduct in one direction along a bundle of cardiac fibers but can conduct in the opposite direction. This condition is necessary for the occurrence of classical reentrant rhythms. Thus, unidirectional block in part of the circuit leaves a return pathway through which the impulse conducts to reenter previously excited areas. A number of mechanisms, involving both active and passive electrical properties of cardiac cells, may cause unidirectional block.

REGIONAL DIFFERENCES IN RECOVERY OF EXCITABILITY

One cause of unidirectional block that allows the initiation of reentry is regional differences in recovery of excitability. When differences in the duration of the effective refractory period occur in adjacent areas, conduction of an appropriately timed premature impulse may be blocked in the

region with the longest refractory period, which then becomes a site of unidirectional block, while conduction continues through regions with a shorter refractory period. Figure 23-18 is a schematic representation of the initiation and continuation of circus movement in an anatomically defined circuit, with differences in effective refractory period duration resulting from differences in the time course of action potential repolarization being the cause of unidirectional block in one of the pathways. The action potentials in various parts of the circuit are shown. In the upper panel (*A*), conduction of a premature impulse (extrasystole), which either can be induced by electrical stimulation or may occur "spontaneously," is blocked in the pathway with the long action potential duration and therefore long effective refractory period (to the left), referred to as the *blocked pathway*. The premature impulse, however, conducts in the other pathway with shorter action potential durations and refractory periods (to the right). This pattern of activation is indicated by the arrows. For block to occur, the premature impulse also must arise in a region with a short effective refractory period so that it occurs before repolarization of the action potentials in the left pathway occurs. In the lower panel (*B*), which shows the continuation of these events, the blocked pathway is invaded retrogradely by the impulse conducting from the right, thus causing the second action potential (arrow at the left). The proximal region where the premature impulse originated is then reexcited (reentry) as the impulse once again enters the right pathway and continues around the reentrant circuit, causing another action potential in the right pathway (large arrow). For successful reexcitation to occur in the region where the premature impulse was initiated, elements in the circuit at the region of block and proximal to it (toward the site of origin) must have regained their excitability by the time the cardiac impulse arrives there. Continuation of reentry induced by a premature impulse also is facilitated because the duration of the effective refractory period associated with conduction of the premature impulse is shortened. Therefore, on the next excursion of the reentrant impulse around the circuit, conduction occurs in a circuit with a shorter effective refractory period. Finally, the conduction velocity of premature impulses may be decreased, shortening the wavelength[250,251] and facilitating successful excitation of the region proximal to the unidirectional block.

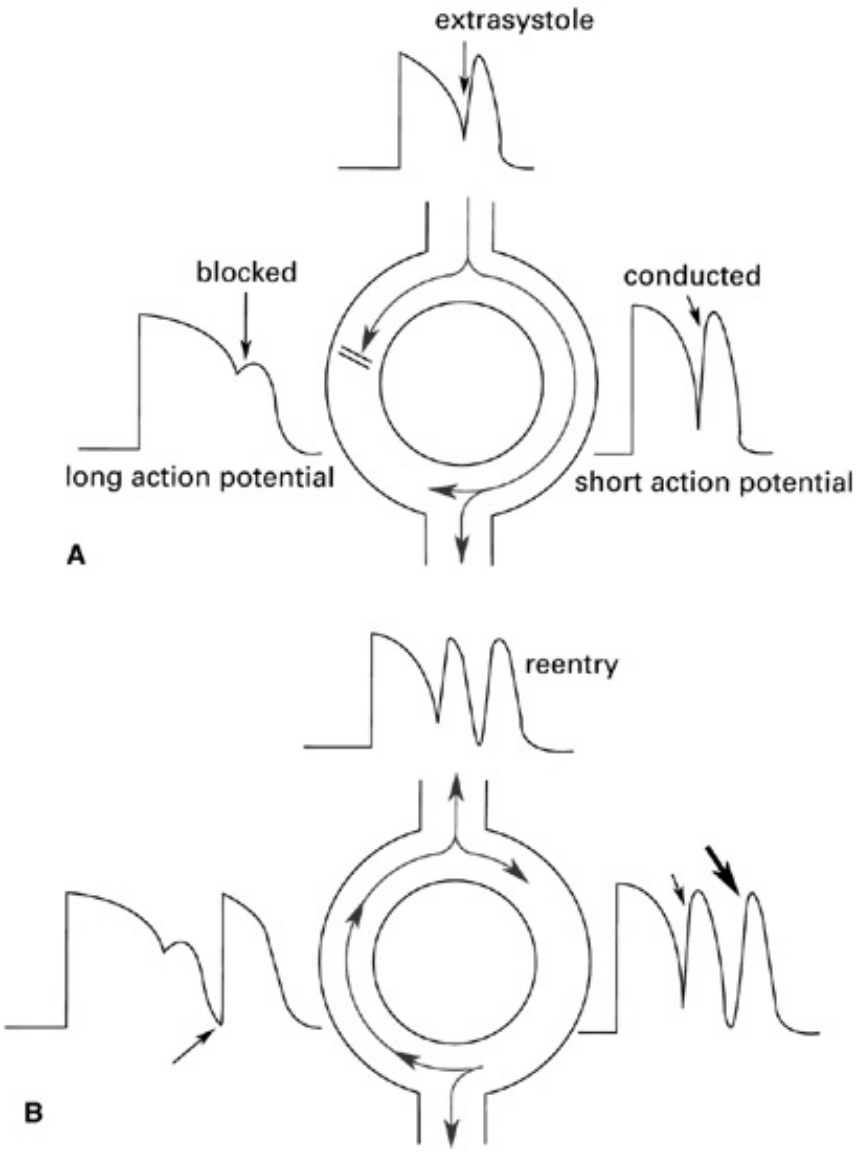

Figure 23-18: Diagram of reentry caused by dispersion in refractory periods. A ring of cardiac tissue is shown, and the pattern of conduction is indicated by the arrows. Action potentials with different durations located in different regions of the ring are diagrammed. (From Wit AL, Janse MJ. *The Ventricular Arrhythmia of Ischemia and Infarction: The Electrophysiological Mechanisms.* Mount Kisco, NY: Futura; 1992:86. Reproduced with permission from the publisher and authors.)

Therefore, unidirectional block caused by regional differences in excitability is actually a result of transient block. Block occurs in the antegrade direction in the left pathway while conduction is successful in the retrograde direction. This kind of unidirectional block can cause the initiation of reentry not only in anatomic circuits, as shown in Fig. 23-18, but also in functional circuits. For reentrant arrhythmias to arise because of regional differences in effective refractory periods, a premature impulse that initiates reentry is as necessary a requirement as are the conditions allowing the perpetuation of reentrant activation. Thus, both a "trigger" (the premature impulse) and a "substrate" (the reentrant circuit) are needed. The mechanism causing the premature impulse may be quite different from the arrhythmia it initiates. It may arise spontaneously by automaticity or result from triggered activity. The premature impulse also may be induced by an electrical stimulus during a programmed stimulation protocol. The degree of nonuniformity in effective refractory period duration necessary for a properly timed premature stimulus to cause unidirectional block may be quite small. This degree of nonuniformity often is referred to as the *dispersion in the refractory periods* or *dispersion in recovery of excitability*, meaning the

difference between the shortest and longest refractory periods.

When stimuli were delivered in the region with the shortest refractory period at the border of two areas with different refractory periods in atrial tissue in the experiments of Allessie and coworkers,[252] the minimal difference in effective refractory period needed to cause block of an appropriately timed stimulated premature impulse was between 11 and 16 ms, well within the normal physiologic range of variation of effective refractory period durations. A properly timed single premature stimulus can initiate reentry in the atria because the differences in refractory period may cause unidirectional block.[252] In the ventricles, where refractory periods are much longer than they are in the atria, the physiologic differences between the longest and shortest refractory period durations is on the order of 40 ms.[253,254] Unlike the case in the atria, dispersion of refractory periods in normal ventricles is not sufficiently large to allow initiation of reentry by premature impulses.

In experiments in which the dispersion of refractory periods was increased by local cooling of the ventricles and a critical difference between the shortest and longest effective refractory periods ranging from 95 to 145 ms was reached, premature stimuli delivered at the site with the shortest effective refractory period induced repetitive activity in the canine left ventricle, presumably because block of the premature impulses in the regions with a long effective refractory period created unidirectional block and permitted reentry.[255,256] Similarly, critical increases in the dispersion of refractory periods that are caused by acute or prolonged ischemia result in reentrant arrhythmias. The difference between the longest and shortest refractory periods is not the only factor that determines whether premature stimuli will induce reentry.[252] If the regions of long and short refractory periods are separated by a large distance, an early premature impulse arising in a region of short refractoriness may not be able to arrive in the region of long refractoriness sufficiently early to cause block because conduction between the regions may be slow. Regions of long refractory periods therefore must be relatively close to a region of shorter refractory periods where the premature impulse arises for block to occur. In addition, if block does occur, the size of the area of unidirectional block is of crucial importance, particularly in a functionally determined reentrant circuit. Even in the presence of large differences in effective refractory period duration, reentry may not occur when the area with long effective refractory periods resulting in unidirectional block is small, because the impulse can travel around the area of unidirectional block along an alternative pathway or pathways and will not be delayed sufficiently to allow reexcitation of the point of origin at the end of the latter's effective refractory period. This cannot occur in an anatomic circuit such as the one shown in Fig. 23-18. Thus, *dispersion in recovery of excitability* is by itself not sufficient to describe the propensity for induction of reentrant arrhythmias. The regional differences in recovery of excitability that lead to unidirectional conduction block also may occur in the absence of regional differences in action potential duration. Computer models have shown that the activation sequence of a propagating impulse can lead to asynchronous repolarization and refractoriness even when membrane properties are homogeneous.[89,247] A stimulated premature impulse can block in a region that has been depolarized most recently by a prior wave of excitation and is therefore still refractory, but it may conduct into another region that was excited much earlier by the prior wave of excitation if it has had time to recover excitability. The conducting premature excitation wave then can later return to excite the area of block after it recovers, resulting in reentry.

ASYMMETRIC DEPRESSION OF EXCITABILITY

Unidirectional conduction block in a reentrant circuit also can be persistent and independent of premature activation. Persistent unidirectional block often is associated with depression of the transmembrane potentials and excitability of cardiac fibers.[257] There are several possible mechanisms for the persistent unidirectional block in a region where action potentials are depressed. One mechanism is asymmetric depression of excitability. This asymmetric depression may occur because of asymmetric distribution of a pathologic event. As a simple example, the

action potential upstrokes in a bundle of fibers may be diminished as a result of a reduction of perfusion after coronary occlusion, but the depression of the upstroke may be more severe toward one end of the bundle than toward the other. This situation is diagrammed in Fig. 23-19. A propagating impulse consisting of an action potential with a normal upstroke velocity (site 1) enters the poorly perfused region (stippled in the diagram) and propagates through this region with decrement (from left to right or from site 1 to 4); i.e., as it conducts from the less depressed end (1) to the more severely depressed end (4), the action potential upstroke velocity and amplitude progressively decrease, as does the axial current flowing toward cells that will be excited by the upstroke (as indicated by the decreasing size of the striped arrows). When the impulse arrives at the opposite end of the depressed segment of the bundle where there is suddenly a normally perfused bundle with normal action potentials (between action potentials 4 and 5), the action potential amplitude is markedly reduced and the weak axial current from site 4 is not sufficient to depolarize the normal membrane to threshold at site 5. Conduction therefore blocks in the left-to-right direction even though the normally perfused region is excitable. Conduction in the opposite direction (from right to left), however, still may succeed. The large axial current generated by the normal action potential at site 5 can flow for a considerable distance through the depressed region and may depolarize to threshold fibers at some distance from the most severely depressed region (perhaps as far as site 3). These cells in turn may be able to excite adjacent fibers in the direction of propagation (from right to left), and as a result, the impulse successfully propagates from site 3 to site 1, as indicated by the black arrows.

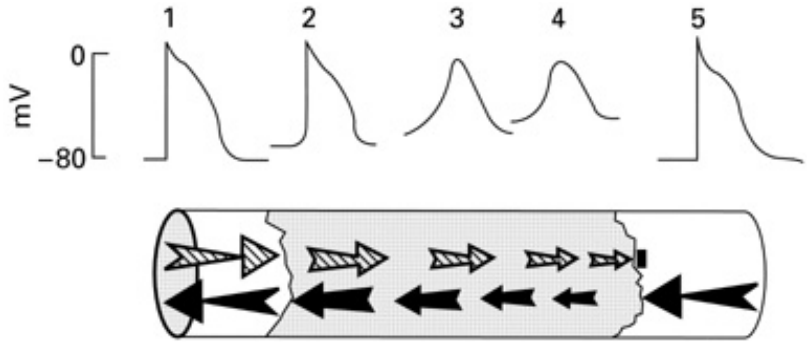

Figure 23-19: Asymmetric depression of excitability as a mechanism for unidirectional conduction block in a bundle of cardiac muscle fibers. The action potentials shown above were recorded from sites on the fiber bundle. The shaded part of the bundle is depressed. Conduction from left to right along the bundle is indicated by the striped arrows, conduction from right to left by the black arrows. (Modified from Wit AL, Rosen MR. Cellular electrophysiological mechanisms of cardiac arrhythmias. In: MacFarlane PW, Veitch Lawrie TD, eds. *Comprehensive Electrocardiology: Theory and Practice in Health and Disease*, vol. 2. New York: Pergamon Press; 1989:801. Reproduced with permission from the publisher and authors.)

GEOMETRIC FACTORS CAUSING UNIDIRECTIONAL BLOCK

Geometric factors related to tissue architecture also may influence impulse conduction and under certain conditions lead to unidirectional block. An impulse can conduct rapidly in either direction along the length of a bundle of atrial, ventricular, or Purkinje fibers with normal electrophysiologic properties. There is usually some asymmetry in the conduction velocity, however, meaning that conduction in one direction may take slightly longer than it does in the other direction.[5,228,231] This is usually of no physiologic significance. The asymmetry of conduction can result from several factors. Bundles of cardiac muscle are composed of interconnecting myocardial fibers with different diameters packed in a connective tissue matrix. These bundles branch frequently (although the individual myocardial fibers do not branch). An impulse conducting in one direction encounters a different sequence of changes in fiber diameter,

branching, and frequency and distribution of gap junctions than it does when traveling in the opposite direction. The configuration of pathways in each direction is not the same.[231] These structural features influence conduction by affecting the axial currents that flow ahead of the propagating wavefront.

The results of theoretical analyses indicate that the conduction velocity of an impulse passing abruptly from a fiber of small diameter to one of large diameter transiently slows at the junction because the larger cable results in a larger sink for the longitudinal axial current (there is more membrane for this current to depolarize to threshold if conduction of the impulse is to continue).[228,231,247,258,259] A similar slowing occurs when an impulse conducts into a region where there is an abrupt increase in branching of the myocardial syncytium; conduction transiently slows because of the larger current sink provided by the increased membrane area that must be depolarized.

In the opposite direction, it can be predicted that conduction will speed transiently as the impulse moves from a larger cable to a smaller cable because the small sink for axial current results in more rapid depolarization of the membrane to threshold.[228,258,259] Theoretically, if there is a large enough difference in the diameter of the two cables, an impulse conducting from the small cable to the large cable should block at the junction, while conduction in the opposite direction (from large cable to small cable) is maintained.

A probable example of unidirectional block based on this geometric factor in the normal heart occurs at the junctions between Purkinje's and muscle cells. At certain sites, propagation from muscle to Purkinje fibers is possible, while propagation from Purkinje fibers to muscle is not.[260] This asymmetry of conduction results from the difference in mass between the Purkinje and muscle layers. The smaller-mass Purkinje fiber bundle is the small-diameter cable, while the larger-mass muscle is the larger-diameter cable. It is unlikely that in normal circumstances these localized sites of unidirectional block predispose to reentry since the myocardium is quickly excited via the many other Purkinje-to-muscle junctions where the geometric differences are not sufficient to cause block. It is possible, however, when conduction in ischemic myocardium is slow and coupling resistance at the junction increases, that such sites of unidirectional block may become important in initiating reentry.[261-263]

It is doubtful that abrupt changes in geometric properties such as fiber diameter of the magnitude required to cause block of the *normal* action potential often exist (except at some Purkinje fiber-muscle junctions, as was described above) because the safety factor for conduction is large; i.e., there is a large excess of activating current over the amount required for propagation.[228] Dodge and Cranefield[231] pointed out that "only if an action potential is a relatively weak stimulus and the unexcited area is not easily excited will plausible changes in membrane resistance, cell diameter, or intercellular coupling produce block." There is a necessity for interaction of abnormal action potentials and decreased excitability with the preexisting anatomic impediments, as occurs in acute ischemia. When the resting potential of fibers in a muscle or Purkinje bundle is decreased, the reduced action potential upstroke results in a decreased axial current, and therefore, the action potential is a weak stimulus. The normal directional differences in conduction are then exaggerated.

At a critical degree of depression of the action potential upstroke, conduction may fail in one direction while being maintained in the other (although it may be slowed markedly). At this critical degree of depression, the reduced axial current may not be sufficient to depolarize the membrane to threshold where the current sink is increased because of the structural changes described above (increased fiber diameter), but the axial current is still more than adequate during conduction in the opposite direction.

The anisotropic properties of cardiac muscle also represent a geometric factor that sometimes may

contribute to the occurrence of unidirectional block. Spach and colleagues[234] indicated that in anisotropic muscle, the safety factor for conduction is lower in the longitudinal direction of rapid conduction than it is in the transverse direction of slow conduction (the opposite of that predicted on the basis of continuous cable theory). The low safety factor longitudinally is a result of a large current load on the membrane associated with the low axial resistivity and large membrane capacitance in the longitudinal direction. This low safety factor may result in a preferential conduction block of premature impulses in the longitudinal direction relative to the transverse direction under certain conditions. In uniformly anisotropic muscle, a decrease in inward current during the depolarization phase of an action potential, as may result from premature activation, results in slowing of conduction in the longitudinal direction more than in the transverse direction, but propagation still continues as a spatially smooth process. Conduction block of early premature impulses occurs in both longitudinal and transverse directions nearly simultaneously in uniformly anisotropic muscle.[242]

In nonuniformly anisotropic muscle, however, premature activation can result in conduction block in the longitudinal direction even when the impulse is conducting from a region with a long refractory period into a region with a shorter refractory period while conduction in the transverse direction continues.[242] The site of block in the longitudinal direction can become a site of unidirectional block that leads to reentry, much like the block of premature impulses caused by a sudden increase in action potential duration and effective refractory period. It can be excited by an impulse propagating in the opposite direction, i.e., by the wavefront initially launched successfully in the transverse direction that later propagates to the distal side of the region of the block. In contrast to the propensity of premature impulses to block in the longitudinal direction in nonuniformly anisotropic myocardium because of the decreased depolarizing current and low safety factor, when coupling resistance between cells is increased, conduction of all impulses will block first in the transverse direction. Preferential block in this direction occurs because an increase in coupling resistance will reduce the safety factor below the critical level needed to maintain transverse conduction before the safety factor for longitudinal conduction is reduced to this critical level.[264,265] Unlike longitudinal block of a premature impulse, which is transient block and may lead to reentry, block in the transverse direction caused by increased coupling resistance may be bidirectional and, if so, should not cause reentry.

Anisotropy also can result in unidirectional block at sites of muscle bundle branching or at the junction of muscle bundles.[235] It was shown in Fig. 23-17*A*(2) that when a wavefront propagating in a bundle of parallel fibers enters a branch formed at an acute angle, the direction of propagation is altered quickly from longitudinal to transverse, causing an abrupt increase in the effective axial resistance in the direction of propagation and a slowing of conduction velocity. If the inward current also is reduced by partial depolarization, as occurs after premature stimulation or elevation of extracellular K^+, conduction block may occur.[235] This is shown in Fig. 23-17*B*(2), where the extracellular K^+ concentration was increased from 4.6 to 9.0 meq/L. Failure of the stimulated impulse to enter the branch is shown by the absence of electrical activity at sites c and d. By contrast, as shown in Fig. 23-17*B*(1), propagation from the other direction into the branch does not involve a change in the direction of the wavefront relative to the fiber orientation since it continues in a parallel direction; therefore, there is no block in this direction.[235] These sites can become areas of unidirectional block that are instrumental in the occurrence of reentry.

Alterations in Refractory Period

Alterations in the effective refractory period may contribute to the occurrence of reentry. A decrease in the effective refractory period decreases the wavelength of the reentrant impulse and therefore the necessary size of the reentrant circuit. If the refractory period is decreased, the degree of slow conduction needed for successful reentry is diminished. The effective refractory period of cardiac fibers in a reentrant circuit may be decreased during rapid tachycardias because

of rate-dependent shortening of the action potential duration.[247,266] The computer model of Quan and Rudy[247] predicts that in circuits with a small or no excitable gap, electrotonic interaction between the head and the tail of the reentrant wavefront also can shorten action potential duration and the refractory period. If the effective refractory period is decreased sufficiently, more than one reentrant circuit can exist at a time in some regions.[267,268] The effective refractory period of atrial muscle, for example, is decreased by the acetylcholine released during vagal stimulation. As a result, reentry in atrial muscle causing atrial fibrillation is more easily induced during vagal stimulation.[269] Several reentrant circuits exist simultaneously during this arrhythmia.[268,270] Action potential duration and effective refractory period are decreased in the ventricle during reperfusion after brief periods of ischemia or in some of the ventricular muscle cells in chronically ischemic areas, probably contributing to the occurrence of reentry.

The Central Area of Block

The central area of block around which the reentrant wavefront circulates may be anatomic, functional, or a combination of the two. Anatomic block is the result of a nonconductive medium in the center of the circuit. An example of an anatomically determined central area of block is in the tricuspid ring reentrant circuit found in a canine model of atrial flutter[266] and perhaps present in a clinical counterpart, the atrial flutter found commonly in patients who have previously had a Mustard procedure to repair transposition of the great vessels.[271] The animal model depends critically on large incisions made in the right atrial free wall, which in fact are similar to those made by the surgeon during the Mustard procedure. Functional block at the center of a circuit occurs when there is block of impulses in otherwise excitable cardiac muscle. An example of a functional center of block was first described by Allessie and associates[272] in a model of reentrant excitation in the rabbit left atrium called the leading circle mechanism of reentry. Functional block subsequently has been described in several other models of atrial flutter.[223,224,273,274] The central area of functional block develops during the initiation of the reentrant circuit by the formation of a line of block that most likely is due to refractoriness. When the reentrant circuit forms, the line of block then is sustained by centripetal activation from the circulating reentrant wavefront, which by repeatedly bombarding the central area of block maintains the state of refractoriness of this region. A combination of an anatomic and a functional central area of block in the reentrant circuit has been described in some models of atrial flutter (e.g., the orifice of one or both of the cavae and an area of functional block continuous with or adjacent to either or both of the caval orifices).[224,275]

The Excitable Gap

The excitable gap in a reentrant circuit is the region of excitable myocardium that immediately precedes the head of the reentrant wavefront and moves around the circuit in advance of the reentrant wavefront. The occurrence of a gap is dependent on the recovery of excitability of the myocardium from its previous excitation by the reentrant wavefront. There are two different measurements of the excitable gap. One is the spatial gap, which is the distance in the circuit ahead of the wavefront that is excitable. The spatial gap may be composed of either partially excitable or fully excitable myocardium, depending on the time interval between successive excitations of the circuit. The size of the spatial gap changes in different parts of the circuit as the wavelength of the reentrant impulse changes because of changes in conduction velocity, refractory periods, or both, as was described previously.

The second measurement of the excitable gap is the temporal excitable gap. This is the time period during the cardiac cycle in which a stimulus can excite the region ahead of the reentrant wavefront. In regard to the spatial gap, the temporal gap in different parts of the reentrant circuit also can have both partially excitable and fully excitable components and varies in different parts of the circuit because of the changes in the wavelength. The characteristics of the excitable gap may be quite different in reentrant circuits caused by different mechanisms. For example, some anatomically determined circuits have been shown to have large excitable gaps with a fully

excitable component, although even in anatomically determined circuits, the gap may be only partially excitable.[276] By comparison, functional reentrant circuits caused by the leading circle mechanism have very small gaps that are only partially excitable,[273] although parts of some functionally determined reentrant circuits may have a small fully excitable gap during part of the reentrant cycle.

TYPES OF REENTRY

It was indicated previously that there are two types of reentry: ordered and random.[1] The reentrant circuits can be anatomically determined, functionally determined, or both. In anatomically determined circuits, the pathway is fixed and the characteristics of the reentrant circuit are determined by the characteristics of the anatomic components of the circuit. Anatomic circuits therefore are associated with ordered reentry. Perhaps the best example is AV reentrant tachycardia, in which the reentrant circuit is composed of atrium, the AV node, the His-Purkinje system, the ventricle, and an accessory AV connection.

In functionally determined circuits, the pathway is formed because of the electrophysiologic properties of the cardiac cells, not by a predetermined anatomic pathway. Functional circuits can be associated with ordered or random reentry. Mechanisms for functionally determined reentrant circuits include the leading circle type of reentry,[272] anisotropic reentry,[277] and spiral wave reentry. Allessie and coworkers[252,272,278] were able to induce stable reentrant tachycardia in small pieces of isolated rabbit left atrium by precisely timed premature impulses in regions that were activated normally at regular rates of stimulation. Initiation of reentry was made possible by the different refractory periods of atrial fibers in close proximity to one another. The premature impulse that initiated reentry blocked in fibers with long refractory periods and conducted in fibers with shorter refractory periods, eventually returning to the initial region of block after excitability recovered there. The impulse then continued to circulate around a central area that was kept refractory because it was bombarded constantly by impulses propagating toward it from all sides of the circuit. This central area provides a functional obstacle that prevents excitation from propagating across the fulcrum of the circuit. No anatomic obstacles or anatomically defined conducting pathways are present in the leading circle, and the reentrant circuit is completely defined by the electrophysiologic properties of the tissue involved. The circumference of the leading circle around a functional obstacle may be as little as 6 to 8 mm and represents a pathway in which the efficacy of stimulation of the circulating wavefront is just sufficient to excite the tissue ahead, which is still in its relative refractory phase. Conduction through the functional reentrant circuit is slowed, therefore, because impulses are propagating in partially refractory tissue (a partially excitable gap). Some of the reentrant excitation that has been mapped in the atria of canine models of atrial flutter may be caused by the leading circle mechanism.[273] The reentrant circuit remains in the same place during the flutter and therefore is ordered reentry. Functional reentrant circuits of the leading circle type also may change their size and location; if they do, they fall under the general category of random reentry. This may occur when leading circle reentry causes fibrillation.

Anisotropy can cause conduction slow enough to result in reentry in small anatomic circuits. Reentrant circuits caused by anisotropy also can occur without well-defined anatomic pathways and may be classified as functional. Unlike the functional characteristic that leads to the leading circle type of reentry (local differences in membrane properties causing a difference in effective refractory periods in adjacent areas), in functional reentry caused by anisotropy, the functional characteristic that is important is the difference in effective axial resistance to impulse propagation dependent on fiber direction. This mechanism has been classified as *anisotropic reentry*.[277] In its pure form, both the unidirectional conduction block and slow conduction in the reentrant circuit result from anisotropic, discontinuous propagation, and there is no need for variations in membrane properties such as regional differences in effective refractory periods or depression of the resting and action potentials.[242]

On the basis of the longitudinal and transverse conduction velocities of premature impulses in nonuniform anisotropic muscle and of measurements of refractory periods in these experiments, Spach and colleagues[242] calculated that circuits in nonuniform anisotropic bundles can be as small as 2 to 4 mm^2 (transverse velocity of 0.5 m/s, dissociated longitudinal velocity of 0.2 m/s) in the absence of nonuniformities in repolarization. Furthermore, anisotropic circuits are elliptical or rectangular because of the directional differences in conduction velocities with the long axis of the ellipse in the fast, longitudinal direction. Circuits with this shape can have a smaller dimension than do circular circuits such as the leading circle.[242] Anisotropic reentrant circuits usually remain in a fixed position to cause ordered reentry.[279] The degree of anisotropy (ratio of longitudinal to transverse conduction velocity) varies in different regions of the heart, and the circuit can reside only in a region where the conduction transverse to the longitudinal axis is sufficiently slow to allow reentry. Stability of anisotropic reentrant circuits also is assisted by the presence of an excitable gap that does not occur in the leading circle functional circuit. The excitable gap is caused by the sudden slowing of conduction velocity and a decrease in the wavelength of excitation as the reentrant impulse turns the corner from the fast longitudinal direction to the slow transverse direction and from the slow transverse direction to the fast longitudinal direction.[280,281]

Another type of functional reentrant excitation, called spiral waves, does not require any inhomogeneities of refractory periods as in leading circle reentry, inhomogeneities in conduction properties as in aniostropic reentry, or a central obstacle, whether functional or anatomic. Spiral waves originally were initiated in computer models of homogeneous elements or in various kinds of homogeneous excitable media (properties do not vary throughout the media), an example of which is molecular diffusion in a chemical system. Under appropriate circumstances, a pulse in two-dimensional, homogeneous, excitable media can be made to circulate as a rotor with a wavelength that is proportional to the square root of the diffusion coefficient of the media.[282-284]

Preexisting functional heterogeneities in conduction (or diffusion) properties or refractoriness (time course of recovery of excitability) are not prerequisites for the initiation of spiral waves in excitable media. The heterogeneity that allows initiation can result from a previous excitation wave and the pattern of recovery from that wave. When heterogeneities in recovery exist, the application of a second stimulus over a large geometric area to initiate a second excitation wave only excites a region where there has been sufficient time for recovery from the previous excitation, not regions that have not yet recovered. An excitation wave is elicited at the excitable site that is in the form of a rotor because the wave cannot move in the direction of the wake of the previous wave but only in the opposite direction, moving into adjacent regions as they in turn recover. The inner tip of the wavefront circulates around a disk of quiescent medium instead of a region of conduction block. The size of this disk expands as the medium is made less excitable.[282-284] The rotor, by definition, has a marked curvature, and this curvature slows down its propagation. A similar pattern of excitation can be induced in cardiac muscle.[285,286]

In the case of a curved depolarization wavefront (rotor) in excitable tissue such as cardiac muscle, slow conduction results from an increased electrical load; e.g., not only must a curved wavefront depolarize cells in front of it in the direction of propagation, but current also flows to cells on its sides. The slow activation by a rotor is not dependent on conduction in relatively refractory myocardium; therefore, there is an excitable gap despite the functional nature of reentry.[282] The location of the rotor can occur anywhere the second stimulated excitation encounters the wake of the first excitation with the appropriate characteristics.[287] Reentrant excitation that occurs during the initiation of ventricular fibrillation by strong electrical shocks[288,289] has characteristics consistent with spiral waves or rotors. These small circulating rotors are not stable and meet the criteria of random reentry. Spiral waves also may cause other kinds of arrhythmias. Even though nonuniform dispersions of refractoriness or anisotropy are not necessary for the initiation of reentrant excitation caused by rotors in excitable media, the myocardium, even when normal, is never homogeneous and the heterogeneities may modify the characteristics of the spiral waves.

Methods to Identify Mechanisms of Arrhythmias

INTRODUCTION

Since the early and classic experiments of Mayer[3,290] on reentry in the Medusa ring and later studies by Mines[4,291] on reentry in ring preparations cut from dogfish auricles or from canine right ventricles, it has been thought that mapping of the sequence of activation of the heart during tachycardia should provide the best evidence for the presence of a reentrant circuit. Even so, the admonition of Mines[291] that "the chief error to be guarded against is that of mistaking a series of automatic beats originating in one point of a ring [substitute "apparent reentrant circuit"] and traveling around it in one direction only owing to a complete block close to the point of origin of the rhythm on one side of this point" for reentrant beats must be kept in mind. The point, of course, is that even sequence of activation mapping may not provide definitive proof of the presence of reentry even though it provides evidence that is consistent with reentry. Mines suggested that severing the ring (again, substitute "the critical portion of the apparent reentrant circuit") and then demonstrating that no further reentrant excitation could occur were required for proof that reentrant excitation had been present. This, of course, has been accomplished in the example of AV reentrant tachycardia, with cure of the arrhythmia following catheter or surgical ablation of the accessory AV connection. Nevertheless, while "severing the ring" is both diagnostic and therapeutic when it can be accomplished to treat a tachyarrhythmia, it is virtually always clinically impractical as a diagnostic tool. Furthermore, until recently, precise sequence of activation cardiac mapping to identify reentry was quite difficult to perform, particularly in patients.

Although it is now possible to obtain remarkably precise maps of the sequence of cardiac activation in vivo by using simultaneous multisite mapping techniques, it is possible only with use of sophisticated recording techniques that require the chest to be open and the heart to be exposed. In fact, for the study of arrhythmias in the in situ heart, it is not routinely possible to obtain the direct electrical recordings (microelectrode studies, simultaneous multisite mapping, etc.) from the arrhythmogenic source that will enable one to determine the electrophysiologic mechanism causing the arrhythmias. A three-dimensional, sequential site-mapping system using a special endocardial catheter system has become available for use in mapping stable reentrant circuits. Indirect approaches have evolved that can provide information that suggests the mechanism of an arrhythmia. These approaches include (1) characterizing the arrhythmia from the ECG, (2) analyzing the response of the arrhythmia to selected forms of cardiac pacing, (3) analyzing the effects of selected pharmacologic agents on the arrhythmia, and (4) analyzing the results of radiofrequency ablation. Since cardiac pacing has long been an important tool in the study of mechanisms of both clinical and experimental arrhythmias and since it is also usually rather easy to apply, the following section presents a discussion of the use of this technique to identify the mechanism of an arrhythmia.

CARDIAC PACING TO DETERMINE ARRHYTHMOGENIC MECHANISMS

The mechanism of an arrhythmia in the in situ heart sometimes can be deduced from the response of the arrhythmia to cardiac pacing. Knowledge about the response of the different arrhythmogenic mechanisms to pacing is based largely on studies in which the effects of electrical stimulation were determined on transmembrane action potentials recorded with microelectrodes in isolated and superfused cardiac tissues. Critical to the ability to use the response to electrical stimulation to determine arrhythmia mechanisms is the requirement that the stimulated impulse(s) reach the site of origin of the arrhythmia. There are many reasons why this may not happen. The stimulated impulse(s) may not reach the site at which the arrhythmia arises because of the electrophysiologic properties of the intervening tissue between the stimulus site and the site of arrhythmia origin. An intervening region of prolonged refractoriness or depressed conduction may cause stimulated impulses to block before they reach the site of origin. If conduction time from

the stimulation site to the site of arrhythmia origin is prolonged for any reason, impulses generated in the arrhythmogenic focus also may be able to leave that focus and depolarize large regions of myocardium around it, preventing the stimulated impulse from reaching the site of arrhythmia origin. Even when the stimulation site is close to the site of arrhythmia origin, areas of depressed conduction may prevent the stimulated impulses from reaching the arrhythmogenic cells.

Two basic patterns of stimulation generally are used to study the mechanisms of arrhythmias: (1) overdrive pacing (pacing at a rate or rates faster than the spontaneous rate of the arrhythmia) and (2) introduction of a premature beat or beats by using programmed stimulation. With either technique, the effects of the stimulated impulses on the spontaneous rhythm are observed. Overdrive pacing generally is used during the arrhythmia to determine whether the overdrive can terminate it or, if it does not, to determine the effect of the overdrive on characteristics of the arrhythmia. Overdrive pacing sometimes is used during sinus rhythm to determine whether the period of stimulation can induce an arrhythmia that previously has occurred spontaneously.

The introduction of a premature beat or beats at selected intervals during electrical diastole by programmed stimulation of the heart can be performed either during the spontaneous arrhythmia to test the effects of the premature beats or during sinus rhythm or fixed-rate pacing to see if the arrhythmia can be induced.

EFFECTS OF ELECTRICAL STIMULATION ON ARRHYTHMIAS CAUSED BY AUTOMATICITY

The prior discussion of automaticity as an arrhythmogenic mechanism included a consideration of how the sinus node pacemaker and electrical stimulation (pacing) influence subsidiary pacemakers with different automatic mechanisms. Overdrive either by the sinus node or by electrical stimuli exerts an inhibitory effect on the normal automatic mechanism of subsidiary or latent pacemakers (overdrive suppression) that is primarily the result of enhanced Na^+-K^+ pump activity but has fewer inhibitory effects on the abnormal automatic mechanism of subsidiary pacemakers. These known effects of overdrive on pacemaker mechanisms are sometimes useful in distinguishing automatic arrhythmias from arrhythmias caused by reentry or triggered activity in the in situ heart. The effects of overdrive pacing also can be of use in distinguishing arrhythmias caused by normal automaticity from those caused by abnormal automaticity.[86] From the results of experimental studies, it can be assumed that arrhythmias caused by normal automaticity in the in situ heart cannot be initiated by overdrive pacing. Arrhythmias caused by normal automaticity can be suppressed transiently but cannot be terminated by overdrive pacing. Microelectrode studies on isolated superfused pacemaker tissues indicate that when overdrive pacing is applied during an ongoing arrhythmia caused by normal automaticity, the arrhythmia is expected to be suppressed transiently immediately after the overdrive pacing is stopped. This is manifest by a transient pause after overdrive and should be followed by a gradual speeding up of the rhythm (so-called warmup) until the original rate of the automatic rhythm is resumed. The duration of the transient pause and the time required for resumption of the original rate are expected to be directly related to the rate and duration of the overdrive. This behavior is mainly the result of the increased activity of the Na^+-K^+ pump, which is dependent both on the rate and on the duration of stimulation. This characteristic behavior of normally automatic pacemakers has been demonstrated in some clinical and experimental electrophysiologic studies of both atrial and ventricular tachycardias.[181,292,293]

Like normal automaticity, arrhythmias caused by abnormal automaticity can be neither initiated nor terminated by overdrive pacing. By contrast, arrhythmias caused by abnormal automaticity should not be suppressed by overdrive pacing unless the overdrive period is long and the rate of overdrive is fast.[86] The difficulty in suppressing such arrhythmias stems from the lesser amount of Na^+ entering the cells during the upstroke of the action potential and therefore less intense Na^+ pump stimulation by overdrive. Short periods of overdrive can even result in a transient speeding

of the rate of impulse generation (overdrive acceleration).[86] Accelerated idioventricular tachycardia in myocardial infarction is not easily overdrivesuppressed and therefore may be caused by abnormal automaticity.

The response of automatic arrhythmias to premature stimulation also is sometimes useful in distinguishing automaticity from other arrhythmogenic mechanisms. Of major importance, automatic rhythms caused by either normal or abnormal automaticity can be neither initiated nor terminated by premature stimuli, in contrast to reentry and triggered activity (discussed below). Other than that, premature impulses induced at different times during diastole may transiently perturb an automatic rhythm for a few cycles. The characteristics of the perturbation sometimes may distinguish automaticity from other arrhythmogenic mechanisms. The response of normal and abnormal automaticity to premature stimulation may be somewhat similar. The characteristic response of an automatic pacemaker to premature stimulation is best exemplified by the response of the sinus node to atrial premature stimulation.[294] Figure 23-20 plots the normalized return cycle (the cycle after the premature impulse) on the *y* axis versus the normalized premature cycle (test cycle) on the *x* axis for a study in which premature stimuli were applied to the atria of the human heart during sinus rhythm. The solid line (*A*) represents the line of identity; points falling on this line are compensatory (the sum of the premature cycle and the return cycle is equal to the sum of two spontaneous cycles). Premature impulses delivered late in the cycle length are followed by a compensatory pause and fall on this line (as the test cycle shortens, the return cycle lengthens in a reciprocal manner) because the premature impulses collide with the impulse emanating from the sinus node pacemaker without reaching and resetting the pacemaker. Therefore, the pacemaker discharge that follows the premature impulse occurs exactly on time. As the premature coupling interval is decreased, a point is reached in the basic cycle where the premature impulse reaches the pacemaker before it has depolarized spontaneously to threshold and depolarizes it early. The pacemaker is reset. When this occurs, the postextrasystolic cycle (which is a result of the stimulated or reset pacemaker cells spontaneously depolarizing to threshold) is less than compensatory and the points fall below the line of identity. For the most part, the postextrasystolic cycle length is expected to be equal to the unperturbed spontaneous cycle length. The dashed line (*B*) on the graph in Fig. 23-20 indicates the cycle length of the basic rhythm, and so the return cycle length relative to the basic cycle length can be seen to be somewhat longer in this study. The prolonged return cycle has been proposed to result from slowed conduction of both the premature impulse into the pacemaker site and the pacemaker impulse out of this site.[294] It also may result, at least partly, from depression of the rate of spontaneous diastolic depolarization. Further shortening of the premature coupling interval to midcycle results in points parallel to the dashed line and possibly slightly above it; this indicates no change in the postextrasystolic cycle length over a wide range of coupling intervals. Finally, conduction of very early premature impulses may block before reaching the pacemaker, and the next pacemaker discharge will again occur on time and be compensatory. Of course, this relationship might be upset by changes in conduction of impulses into and out of the pacemaker site. This relation between premature and return cycle length found in studies of sinus rhythm also has been shown in studies on some ectopic tachycardias and, when found, indicates that the tachycardias are likely to be caused by automaticity.[292,293,295]

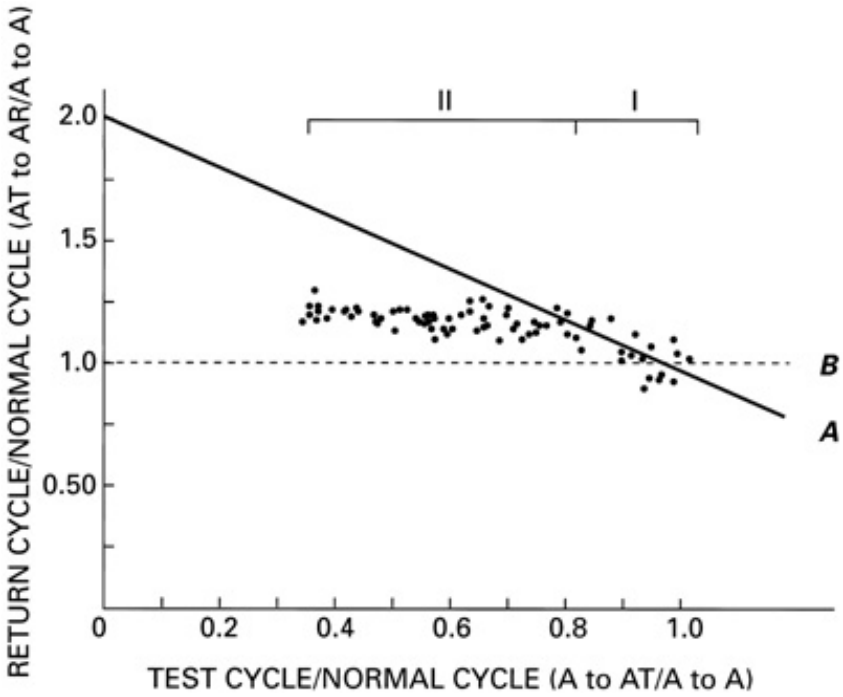

Figure 23-20: Return cycles as a function of premature stimulated cycles during premature atrial stimulation in a patient in sinus rhythm. The graph depicts the relation of the normalized return cycle to the degree of prematurity of the test cycle, which also is normalized. Points falling on line *A* represent nonreset of the sinus pacemaker (fully compensatory pause) and are in zone I. Premature stimulated atrial beats introduced earlier in atrial diastole fall in zone II. Line *B*, projected from the *y* axis, is a reference line indicating the spontaneous sinus cycle length. The distance the zone II points (reset points) are above line *B* is interpreted to indicate conduction time into and out of the sinus node, assuming the sinus node pacemaker cycle length immediately after the stimulated premature atrial beat is identical to the preceding sinus node pacemaker cycle length. (From Strauss HC et al. Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man: A presentation of data and critical review of the literature. *Circulation* 1973; 47:86. Reproduced with permission from the publisher and author.)

Ectopic pacemakers also may exist in an extensive region of slow conduction, much as the pacemaker in the sinus node does, and conduction delays into and out of the pacemaker site may influence to some extent the relationship between the return cycle and the premature cycle. Conduction delays may cause some prolongation of the return cycle. When this relationship is seen, however, it is probably indicative of automaticity (either normal or abnormal), since triggered activity and reentry are expected to show a different behavior. In addition to the atrial arrhythmias discussed here, some ventricular arrhythmias are likely to be caused by automaticity. Idioventricular rhythms in patients with complete heart block respond in the manner shown in microelectrode studies of slowly beating Purkinje fibers; the postextrasystolic cycle that follows late premature impulses is longer than the cycle length of the basic rhythm but less than compensatory, while it is shorter than the basic cycle length that follows early premature impulses (and obviously less than compensatory).[296] Some exercise-provoked ventricular tachycardias also may be caused by normal automaticity.[297,298] By contrast, there is some evidence that accelerated idioventricular rhythms in the clinical setting of myocardial infarction may be caused by abnormal automaticity.

EFFECTS OF ELECTRICAL STIMULATION OF REENTRANT EXCITATION

A hallmark feature of a reentrant rhythm is that it usually can be induced and terminated by electrical stimuli (overdrive pacing, introduction of premature stimuli, or both), unlike automaticity. Initially it was thought sufficient to show that an arrhythmia could be initiated or

terminated by overdrive pacing or programmed stimulation to demonstrate a reentrant mechanism.[299] That was the case because until the 1970s the only other mechanism that was widely considered a cause of arrhythmias was automaticity, and automatic rhythms can be neither initiated nor terminated by pacing. After the 1970s, when the concept of afterdepolarization-induced arrhythmias was revived and expanded, these criteria alone were no longer sufficient, because triggered activity caused by DADs also can be initiated and terminated by pacing.

The induction of arrhythmias by overdrive pacing or the introduction of a premature beat or beats can be used as an indicator of a reentrant mechanism if other characteristics are also present that eliminate the probability of triggered activity that is dependent on DADs. The ability to demonstrate directly that the induction of an arrhythmia is related to a critical amount of slow conduction in the region where the arrhythmia originates adds credence to the interpretation that the arrhythmia is caused by reentry. The sudden large increase in the A-H interval associated with pacing induction of AV nodal reentrant tachycardia is one example. The induction of triggered activity caused by DADs is not dependent on slowed conduction and should not show this relationship. Also, when a tachycardia is initiated by the introduction of a premature beat over a wide range of coupling intervals, there may be an inverse relation between the coupling interval of the premature impulse and the interval from the premature impulse to the first impulse of tachycardia.[300-302] As the premature impulse occurs earlier in the cycle, its conduction through the reentrant pathway is slower, causing the return cycle to prolong. This too is not found with the induction of triggered activity resulting from DADs. Failure to initiate an arrhythmia by stimulated impulses does not per se eliminate reentry as a mechanism for the arrhythmia.

Another feature of reentrant arrhythmias is that they can be terminated by overdrive pacing or premature stimulation. This is not specific for reentry, since triggered activity caused by DADs also can be terminated. As with initiation, termination by overdrive pacing requires a critical rate and duration of the stimulation train, while termination with stimulated premature impulses requires a critical coupling interval between the premature impulse and the previous impulse of the tachyarrhythmia. Failure to terminate an arrhythmia by stimulated impulses does not by itself eliminate reentry as a mechanism for the arrhythmia. Termination of reentry requires that the stimulated impulse enter the reentrant circuit to cause the block of the reentrant wavefront, and this usually requires that the circuit have a fairly large excitable gap. Some reentrant circuits, particularly if they are caused by the leading circle mechanism of reentry, may not have a gap of excitability large enough to allow a premature impulse to penetrate readily into the circuits. If a tachycardia is very rapid, the excitable gap also may be very small, again preventing ready entry into the circuit by stimulated impulses.

Entrainment

In this context, the demonstration of transient entrainment of a tachycardia with or without its subsequent interruption is a relatively easy and reliable way to identify reentry as the mechanism of a tachyarrhythmia. Transient entrainment of a tachycardia was first described in 1977 during rapid pacing to interrupt type I atrial flutter.[303] At that time, although transient entrainment was not well understood, it was recognized as representing an increase in the rate of the tachycardia to the faster pacing rate, with resumption of the intrinsic rate of the tachycardia occuring upon either abrupt cessation of pacing or slowing of the pacing rate below the intrinsic rate of the tachycardia.[303] On the basis of a series of clinical studies during rapid pacing of atrial flutter,[303-306] ventricular tachycardia,[307-309] AV reentrant tachycardia involving an accessory AV connection,[310,311] AV nodal reentrant tachycardia,[312] and intraatrial reentrant tachycardia,[313] it was proposed that transient entrainment represents capture of a reentrant circuit by wavefronts generated by the pacing impulse without causing interruption of the tachycardia. This was confirmed during studies of transient entrainment in animal models of ventricular tachycardia[314-316] and atrial flutter[317,318] that utilized multiplexing techniques to record simultaneously from large numbers of electrodes in direct contact with cardiac tissue. During transient entrainment of a

reentrant tachycardia, the wavefront from each pacing impulse enters into the excitable gap of the reentrant circuit. Once there, it travels in two directions: (1) antidromically, i.e., in the opposite direction of the circulating reentrant wavefront of the spontaneous tachycardia, where it collides with the orthodromic wavefront of the preceding beat, and (2) orthodromically, i.e., in the same direction as the circulating reentrant wavefront of the spontaneous tachycardia, thus both continuing the tachycardia and resetting it to the pacing rate. This explanation is universal for transient entrainment of any tachycardia resulting from reentry with an excitable gap and is diagrammatically illustrated in Fig. 23-21.

The left panel of the figure is a diagrammatic representation of the reentrant circuit during a ventricular tachycardia (VT) at an assumed rate of 145 beats per minute. The *X*s represent the orthodromic wavefronts of the reentrant rhythm. The arrows indicate the direction of spread of the impulse, the box represents an area of slow conduction in the reentrant circuit, the serpentine line indicates slow conduction of the impulse in this latter area, and the dots represent recording sites along the course of the double arc of reentry from which ventricular electrograms (VEGs) are recorded.

The middle panel is a diagrammatic representation of the introduction of the first pacing impulse ($X + 1$) during ventricular pacing at a rate of 150 beats per minute during the VT. The antidromic (anti) wavefronts ($X + 1$) collide with the orthodromic wavefronts from the previous reentrant beat (X), resulting in fusion of ventricular activation. The orthodromic wavefront (ortho) from the pacing impulse ($X + 1$) continues the VT, resetting it to the pacing rate.

The right panel of the figure shows a diagrammatic representation of the introduction of the second pacing impulse ($X + 2$) during ventricular pacing at a rate of 150 beats per minute during the VT. The antidromic wavefronts ($X + 2$) collide with the orthodromic wavefronts from the previous paced beat ($X + 1$), again resulting in ventricular fusion. Once again, the orthodromic wavefront ($X + 2$) from the pacing impulse continues the VT, resetting it to the pacing rate.

CRITERIA TO ESTABLISH TRANSIENT ENTRAINMENT

Four criteria have been established (Table 23-2), any one of which, if demonstrated, establishes the presence of transient entrainment and thus the presence of a reentrant rhythm with an excitable gap. Figures 23-22 to 23-24 demonstrate the four criteria in diagrammatic fashion for the same ventricular tachycardia illustrated in Fig. 23-21. In Fig. 23-22, which illustrates the first criterion (Table 23-2), the left panel is a diagrammatic representation of the termination of ventricular pacing illustrated in Fig. 23-21. In the left panel, the large arrow indicates the wavefront from the last pacing impulse delivered at a rate of 150 beats per minute entering into the reentrant circuit of the ventricular tachycardia, where it is conducted orthodromically and antidromically. The antidromic wavefronts (X_n[a]) collide with the orthodromic wavefronts (X_n[o]) of the previous beat (X_{n-1}), resulting in the fusion of ventricular activation, but the orthodromic wavefront from the last pacing impulse (X_n[o]) continues and resets the tachycardia. The right panel shows that the orthodromic wavefronts from the last pacing impulse are now unopposed by any antidromic wavefronts because there is no subsequent pacing impulse. Thus, no fusion of ventricular activation occurs despite the presence of transient entrainment. This last entrained beat travels around the reentrant circuit, continuing the tachycardia.

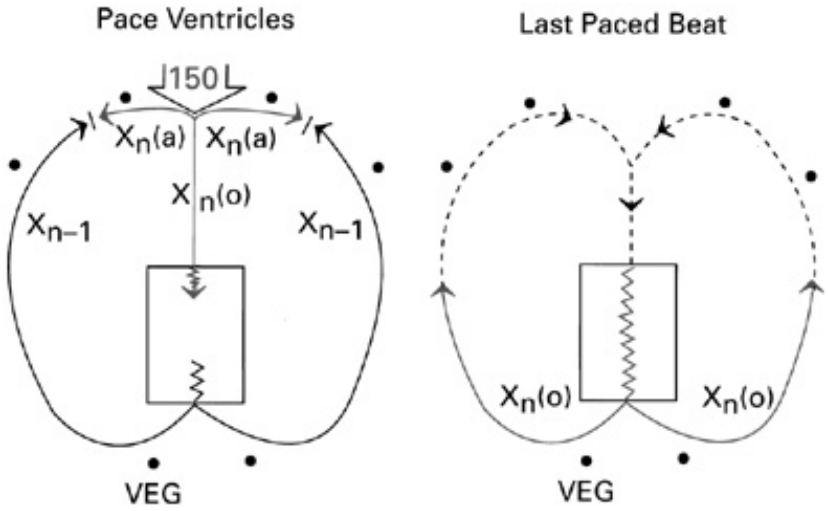

Figure 23-22: Diagrammatic representation of the first entrainment criterion during termination of ventricular pacing illustrated in Fig. 23-21. (From Waldo AL, Henthorn RW. Use of transient entrainment during ventricular tachycardia to localize a critical area in the reentry circuit for ablation. *PACE* 1989; 12:231. Reproduced with permission from the publisher and authors.)

Table 23-2: Criteria to Establish the Presence of Transient Entrainment

1. The demonstration of constant fusion beats in the ECG during the period of rapid pacing at a constant rate except for the last captured beat, which is entrained but not fused (i.e., the last entrained beat demonstrates the ECG morphology of the spontaneous tachycardia)
2. The demonstration of constant fusion beats in the ECG during rapid pacing at any constant rate but different degrees of constant fusion at different rapid rates, i.e., progressive fusion
3. Interruption of the tachycardia associated with localized conduction block to a site(s) for one beat, followed by subsequent activation of that site(s) from a different direction, which manifests itself by a change in morphology of the electrogram at the blocked site(s) and with a shorter conduction time
4. A change in conduction time to and electrogram morphology at one recording site when pacing from another site at two different constant pacing rates, each of which is faster than the spontaneous rate of the tachycardia but fails to interrupt it

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Figure 23-23 is a diagrammatic representation of entrainment in the same ventricular tachycardia during pacing from the same site proximal to the area of slow conduction of the reentrant circuit at rates of 150 (left panel), 155 (middle panel), and 160 beats per minute (right panel), demonstrating both the second and the fourth entrainment criteria. When pacing is at a rate of 155 beats per minute, the pacing cycle length is shorter than it is at 150 beats per minute, so that the antidromic wavefront from each pacing impulse will penetrate the excitable gap of the reentrant circuit to a further degree in an antidromic direction compared to 150 beats per minute, resulting in a degree of fusion of the QRS complex in the ECG different from that which occurs at a rate of 150 beats per minute. As a result, the QRS complex morphology in the ECG during pacing at 155 beats per minute will be different than it is at 150 beats per minute. This, then, is the demonstration of progressive fusion (Table 23-2). When pacing is at 160 beats per minute, once again the antidromic wavefront from each pacing impulse will collide with the orthodromic wavefront, but at yet a different site. This occurs because the pacing cycle length is shorter than pacing at the previous rates, permitting greater penetration of the excitable gap by the antidromic

wavefront of the pacing impulse, illustrating yet more progressive fusion.

These diagrams also illustrate the fourth criterion (Table 23-2): A site or sites activated by the orthodromic wavefront of each pacing impulse during entrainment at one pacing rate will be activated by the antidromic wavefront of each pacing impulse during entrainment at a faster pacing rate. This will be manifest by both a change in the morphology of the electrogram recorded at the site in question (it will have the same morphology during the tachycardia that it has during pacing at the rate that results in activation of the site by the orthodromic wavefront but a different morphology when activated by the antidromic wavefront of the pacing impulse at a faster pacing rate) and a change in conduction time to the recording site from the pacing site (the stimulus-to-recording site interval will be longer when activated by the orthodromic wavefront of each pacing impulse than when activated by the antidromic wavefront of each pacing impulse). Thus, note that the two middle recording sites denoted by black dots on each side of the reentrant circuit become activated in turn from a different direction and with a shorter conduction time when the pacing rate is increased from 150 to 155 beats per minute and then to 160 beats per minute.

Figure 23-24 is a diagrammatic representation of the third criterion and shows the events during interruption of the ventricular tachycardia by ventricular pacing at a rate of 165 beats per minute. In the left panel, the large arrow indicates the wavefront from the pacing impulse delivered at a rate of 165 beats per minute entering into the reentrant circuit of the ventricular tachycardia, where it is conducted orthodromically ($X + 1$[o]) and antidromically ($X + 1$[a]). The antidromic wavefronts collide with the orthodromic wavefronts from the previous beat (X), resulting in fusion of ventricular activation. Note that this fusion of ventricular activation is at still a site different from the site during pacing at the previous pacing rates (Fig. 23-23). Thus, initially there is still more progressive fusion of the QRS complex morphology in the ECG. This time, however, the orthodromic wavefront does not reset the tachycardia to the pacing rate. Rather, it too is blocked, presumably in the area of slow conduction, during the same beat. Note that each recording site on each of the two arcs of reentry immediately distal to the area of slow conduction is activated by the orthodromic wave front of the previous beat (X) but is not activated by $X + 1$ because the orthodromic wavefront ($X + 1$[o]) never reaches either site (there is localized conduction block for one beat). In the right panel, the large arrows indicate the next pacing impulse ($X + 2$) delivered at the same pacing rate (165 beats per minute) from the same pacing site described in the left diagram. The dashed lines indicate the reentrant circuit present during the previous periods of ventricular tachycardia and transient entrainment of the ventricular tachycardia. Because the ventricular tachycardia has been interrupted by the previous pacing impulse ($X + 1$), the sequence of ventricular activation of the next pacing impulse ($X + 2$) is as one would expect during overdrive pacing of sinus rhythm from that same ventricular pacing site. Therefore, the two electrogram recording sites immediately distal to the previous (but no longer present) area of slow conduction are now activated from a direction different from that during transient entrainment. In addition, because the presumed area of slow conduction is no longer functionally present, the stimulus-to-right-ventricular conduction time is shorter. Thus, the requirements for the third criterion of entrainment are fulfilled (Table 23-2).

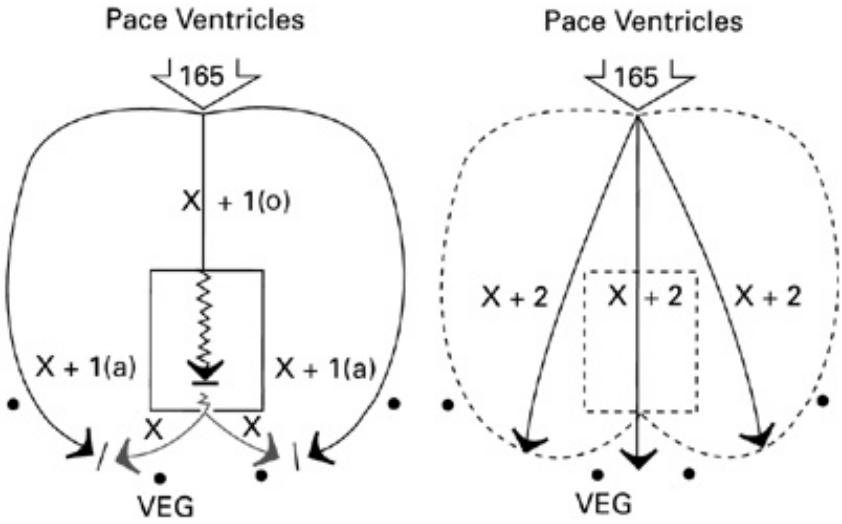

Figure 23-24: Diagrammatic representation of the third entrainment criterion during interruption of the ventricular tachycardia by ventricular pacing at a rate of 165 beats per minute. (From Waldo AL, Henthorn RW. Use of transient entrainment during ventricular tachycardia to localize a critical area in the reentry circuit for ablation. *PACE* 1989; 12:231. Reproduced with permission from the publisher and authors.)

Although these illustrative diagrams show the example of transient entrainment and interruption of ventricular tachycardia, the principles are the same for all the putative reentrant rhythms. For AV nodal reentrant tachycardia, however, only the third criterion has been demonstrated,[312] presumably because there is no ECG manifestation of AV nodal activation, and recording directly from the AV node using surface electrograms has not been reliably demonstrated. Although the phenomena associated with transient entrainment of a tachycardia with or without its subsequent interruption are best explained by reentry, it still must be asked whether any or all of the criteria for the demonstration of transient entrainment can be explained by another mechanism. Present understanding of the response of automatic and triggered rhythms to rapid pacing is not consistent with the phenomena observed during transient entrainment (Table 23-2). Automatic rhythms also should not be interrupted by pacing.

CONCEALED ENTRAINMENT

While the ability to demonstrate transient entrainment of a tachycardia provides an important and powerful tool for the identification and study of reentrant tachyarrhythmias, a limitation is that it is not always possible to demonstrate any of the transient entrainment criteria despite the fact that rapid pacing may indeed have entrained and even interrupted the tachycardia. This phenomenon, called *concealed entrainment*,[309,311] can result when pacing is performed from a site that is orthodromically distal to the area of slow conduction in the reentry circuit, when pacing is done from a site that is rather distant from the reentrant circuit, or when pacing is done from an area of slow conduction in the reentrant circuit.[309,311,319-321]

To label a response of a tachycardia to rapid pacing as concealed entrainment, except in the example of pacing from an area of slow conduction in the reentry circuit, one also must show that transient entrainment can be demonstrated when pacing is from another site. Thus, it is clear that unless one is able to pace from an appropriate site, a reentrant circuit with an excitable gap may be present, but entrainment, though present, will not be demonstrable.

Resetting

The response of an arrhythmia to a prematurely stimulated impulse that does not terminate the

arrhythmia still may provide information useful for determining the mechanism of the arrhythmia. Information on the effects of stimulated premature impulses on reentry comes from studies on experimental preparations of isolated tissues or hearts in which reentrant excitation has been mapped. Other predictions concerning the effects of premature impulses on reentry are based mainly on theoretical considerations using a model of a reentrant circuit with a fixed pathway in which the circuit cannot change its dimensions and in which there is an excitable gap. Such circuits may have a single entrance and exit pathway leading into and out of the circuit, as illustrated in Fig. 23-25, or the entrance and exit pathways may be separate. These characteristics will influence the characteristics of the resetting response as seen on the ECG.

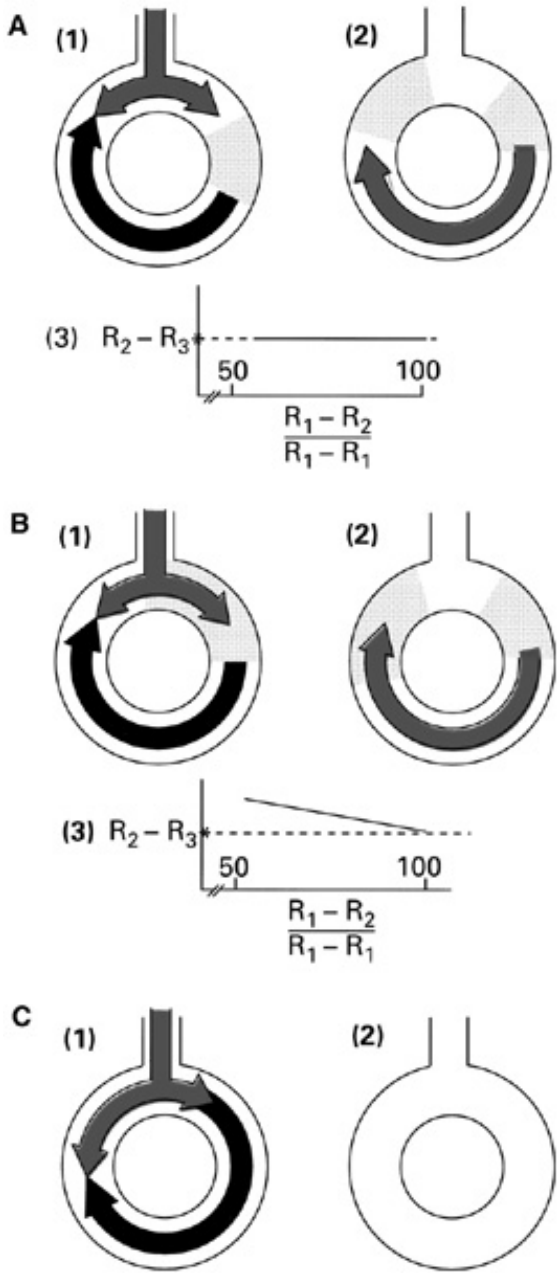

Figure 23-25: Effects of premature impulses on reentrant circuit with an excitable gap. In each panel, diagrams are shown of an anatomic circuit with a single entrance route from above. In *A*(1), *B*(1), and *C*(1), red arrows in the circuit represent the reentrant impulse causing tachycardia. The length of the arrow is the wavelength of the impulse and shows the part of the circuit that is completely refractory, The part of the circuit that is stippled is relatively refractory, and the part of the circuit that is clear is completely excitable (the fully excitable gap). Red arrows entering the

circuit from above represent a prematurely stimulated impulse initiated outside the circuit. *A*(2) and *B*(2) show conduction of the premature impulse in the circuit. Graphs show the expected relation between the return (premature impulse) cycle length (R_2-R_3) and the premature coupling interval (R_1-R_2/R_1-R_1) for premature impulses conducting in the fully excitable gap *A*(3) and in the relatively refractory tissue of a partially excitable gap *B*(3). (Modified after Wit AL, Janse MJ. *The Ventricular Arrhythmias of Ischemia and Infarction: The Electrophysiological Mechanisms*. Mount Kisco, NY: Futura; 1992:135. Reproduced with permission from the publisher and authors.)

The theoretically possible responses of a tachycardia caused by reentrant excitation to premature stimulation are explained in the diagram in Fig. 23-25. An anatomic circuit with fixed dimensions and a single entrance pathway is diagrammed. In this diagram, the entrance pathway also serves as an exit pathway for the reentrant wavefront to enter surrounding myocardium, but other models may have separate entrance and exit pathways. The black arrow in the reentrant circuit represents the reentrant impulse, with the arrow point being the crest of the depolarizing wave and the end of the arrow being the tail. The length of the arrow is the absolutely refractory part of the circuit, the dotted area that trails it is the relatively refractory part, and the clear region is the fully excitable gap (in some instances there may be no fully excitable gap in the reentrant circuit). The transit time of the reentrant impulse around the circuit determines one cycle length of the tachycardia (the R_1-R_1 interval).

In panel *A*(1), a stimulated premature impulse (R_2) (red arrow from above) is shown to reach the circuit and enter it in the region of the fully excitable gap. The stimulated premature wavefront may then propagate both in the orthodromic (to the right) and antidromic (to the left) directions in the reentrant pathway. In the antidromic direction, it collides with the oncoming reentrant wavefront, extinguishing both stimulated and reentrant impulses at the point of collision. In the orthodromic direction, the stimulated impulse becomes the reentrant impulse and propagates through the circuit in completely excitable tissue of the gap (which also moves around the circuit), as shown in panel *A*(2). This stimulated reentrant wavefront would leave the circuit through the normal exit route and become the next tachycardia impulse.

Since the stimulated impulse traveled through the circuit in completely excitable tissue at a normal conduction velocity, the interval between the stimulated impulse (R_2) and the next impulse of tachycardia (R_3) is equal to the normal transit time around the circuit or the normal tachycardia cycle length (R_1-R_1). The rhythm, however, is reset; i.e., the sum of the curtailed (premature) cycle length and the return cycle length (R_1-R_2 + R_2-R_3) (first poststimulus cycle) is less than two cycle lengths of the tachycardia [2(R_1-R_1)]. This holds throughout the range of premature coupling intervals at which the stimulated premature impulse is able to conduct around the circuit at a normal velocity in completely excitable tissue. Thus, a plot showing the relationship between the premature coupling intervals and the return (poststimulus) cycles over this range appears as a flat line. This plot is shown in Fig. 23-25*A*(3). The poststimulus cycle length is the R_2-R_3 interval on the *y* axis. The normalized premature coupling interval is represented by R_1-R_2/R_1-R_1 on the horizontal axis where R_1-R_1 is the basic cycle length of the tachycardia. In this graph, R_2-R_3 remains constant (and equal to R_1-R_1) over the entire range of premature coupling intervals, indicating conduction of the premature impulse in completely excitable tissue. Premature impulses entering the circuit in the relatively refractory part of the excitable gap (stippled region in the circuit) shown by the red arrow from above in Fig. 23-25*B*(1) also collide with the reentrant impulse in the antidromic direction, extinguishing it while conducting in the orthodromic direction. But conduction around the circuit is slower than normal because the impulse is activating relatively refractory tissue, as indicated by the stippled area in Fig. 23-25*B*(2). Therefore, the return (poststimulus) cycle, which is dependent on the conduction time of the stimulated impulse in the circuit, is longer than the tachycardia cycle.

As the coupling interval of the stimulated premature impulse is decreased and this impulse enters the circuit earlier and earlier in the relatively refractory period of the excitable gap, conduction time around the circuit and the return cycle progressively increase. Thus, a plot showing the relation between the premature coupling interval and the return cycle length appears as shown in Fig. 23-25*B*(3). The line representing the R_2-R_3 interval increases as the normalized premature coupling interval (R_1-R_2/R_1-R_1) decreases. It is also apparent on the graph that the conduction time of the premature impulse around the circuit as measured by the R_2-R_3 interval is greater than the conduction time of the normal tachycardia impulse around the circuit, which is indicated by the dashed line. The sum of the premature and return cycle may be less than or greater than compensatory, depending on how slow conduction of the premature is around the circuit. More often, despite slowing of the conduction of the premature impulse in the circuit, the prolonged return cycle does not compensate for the shortened premature cycle.[322-325]

Panel *C* shows what happens when an earlier premature impulse, indicated by the red arrow from above, reaches the circuit when it is even less excitable. It conducts antidromically into the circuit and collides with the wavefront of the reentrant impulse but cannot excite the orthodromic path because it blocks in refractory tissue (black tail of the reentrant impulse). Thus, reentry is terminated, as shown in *C*(2). The range of coupling intervals over which there is evidence that the premature impulse entered the reentrant circuit to reset the tachycardia before the termination of reentry is a rough measurement of the duration of the excitable gap at the entrance route into the circuit if the premature stimuli are applied close to the circuit.[325] Therefore, fixed reentrant circuits with excitable gaps have patterns of responses to premature stimulation that are characteristic of this mechanism.

In sum, the stable tachycardia cycle length (R_1-R_1) is determined by the time it takes the reentrant wavefront to travel one complete revolution around the circuit and reach an exit pathway to the ventricles. When such a circuit is the cause of a tachycardia, premature depolarizations delivered late in the cycle length often are followed by a postextrasystolic pause that is compensatory for the same reason described for automatic tachycardias; i.e., the stimulated impulse may not be able to reach the reentrant circuit, possibly as a result of collision between the stimulated impulse and the impulse coming from the circuit. The next tachycardia impulse then comes precisely on time. In this case, the tachycardia is not reset since the sum of the premature cycle length and the return cycle length is equal to two successive premature cycle lengths. Over the range of premature coupling intervals that do not reset the tachycardia, the relation between the premature coupling interval and the following (return) cycle falls along the line of identity (see Fig. 23-20).

Premature impulses delivered earlier in the tachycardia cycle may have several different effects that are dependent on some of the characteristics of the reentrant circuit. If there is virtually no excitable gap, as might be expected in some functional circuits, no resetting of the tachycardia will occur, since the stimulated impulse cannot enter the circuit and the return cycle will remain compensatory. If the excitable gap is partially excitable, e.g., composed of relatively refractory tissue, premature impulses that succeed in entering the circuit and traveling around it will do so at reduced conduction velocities, as diagrammed in Fig. 23-25*B*.[326] When they emerge from the circuit, they cause the first postextrasystolic (tachycardia) impulse. As a result of the slowing of conduction of the premature impulse around the circuit, the postextrasystolic cycle is longer than the basic cycle [represented by the dashed line in Fig. 23-25*B*(3)].

The conduction time of the premature impulse around the circuit should continue to increase as the premature impulse is delivered earlier and earlier in the cycle, since the premature impulse conducts in more refractory tissue, causing an inverse relation between the premature coupling interval and the postextrasystolic cycle [Fig 23-25*B*(3)]. In the study of Bigger and Goldreyer[301] on AV nodal reentrant tachycardia, the prolongation of the postextrasystolic cycle over the entire range of premature coupling intervals was sufficient to result in a greater than compensatory pause

after the premature impulse. However, the postextrasystolic cycle length can be less than compensatory. An inverse relation between the premature interval and the return cycle interval caused by slowing of the conduction of the premature impulse in the reentrant circuit, as shown in Fig. 23-25*B*(3), is indicative of reentry, since this type of response does not occur with automaticity or triggered activity. Recall that for automatic impulse initiation, the return cycle length is fairly constant over a wide range of premature coupling intervals. If there is a large fully excitable gap, premature impulses reaching the circuit are expected to conduct around the circuit with the same velocity as the reentrant wavefront that is causing the tachycardia, and the postextrasystolic cycle will be equal to the tachycardia cycle and less than compensatory [Fig. 23-25*A*(1) and *A*(2)]. This could occur over a relatively wide range of coupling intervals, resulting in a relationship similar to that expected from a pacemaker over the intermediate range of coupling intervals; the line describing the relationship of the return cycle to the premature cycle would be flat [Fig. 23-25*A*(3)]. Eventually, it is expected that stimulated extrasystoles that are sufficiently premature will invade the circuit when it is relatively refractory, resulting in prolonged return cycles that are inversely related to the premature coupling intervals.

The prolongation of the postextrasystolic cycle after early premature impulses is opposite to that which occurs during automaticity. Thus, a curve might be plotted that consists of a segment that is compensatory at long premature coupling intervals (because the stimulated impulse does not reach the circuit), a segment that is less than compensatory and flat at intermediate premature coupling intervals (when the stimulated impulse is conducting in completely excitable tissue in the circuit), and a segment that is ascending at short premature coupling intervals (when the stimulated impulse is conducting in relatively refractory tissue in the circuit). Still earlier premature impulses might block before reaching a circuit, resulting in interpolation, as described for an automatic focus. A sufficiently early premature impulse also could terminate the tachycardia by blocking in the circuit and causing block of the reentrant wavefront. This is not expected of automatic impulse initiation.

As was mentioned above, the entrance route a stimulated impulse takes into a reentrant circuit and the exit route from the circuit may be separate. When this occurs, the return cycle that follows a premature impulse may be less than the tachycardia cycle because the premature impulse, after entering the circuit, need not conduct around the entire circuit before exiting. The return cycle still may show any of the relationships to the premature cycle described in Fig. 23-25; i.e., it may be flat or show an inverse relationship to the premature coupling interval, depending on whether it is conducting in partially or fully excitable tissue. This expected effect of premature impulses on the cycle length of reentry also may be altered in a functional circuit if the premature impulse somehow can cause a change in the size or shape of the circuit. It is not possible to predict what the effects would be.

In summary, the relation between the postextrasystolic cycle and the curtailed cycle when premature impulses are introduced during a tachycardia caused by reentry may be different from that during automaticity. Therefore, premature stimulation during the study of a tachycardia may provide useful information that helps determine whether reentry is the mechanism. There are, however, a number of confounding influences that, if present, can upset the theoretically predicted relation. They include the absence of a fully excitable gap and properties of intervening tissue between the stimulus site and the site of the circuit that can slow or block conduction of premature impulses into and out of the circuit. Therefore, failure to find the relationships expected for a reentrant mechanism does not necessarily mean that the arrhythmia is caused by a mechanism other than reentry.

EFFECTS OF ELECTRICAL STIMULATION ON ARRHYTHMIAS CAUSED BY TRIGGERED ACTIVITY

Arrhythmias Caused by Delayed Afterdepolarizations

The amplitude of DADs increases with a decrease in the cycle length at which the action potentials occur until the afterdepolarizations reach threshold to cause the triggered activity. Therefore, triggered arrhythmias caused by DADs in the in situ heart should be initiated by either overdrive pacing or programmed premature stimulation. Since automatic arrhythmias are not initiated by pacing, they should be distinguished readily from triggered arrhythmias caused by DADs. Reentrant arrhythmias also can be induced by the same stimulation protocols, however, and so whether there are any other characteristics during arrhythmia induction by pacing that might distinguish between triggered activity and reentry is important. An attempt to distinguish between the two mechanisms is further complicated by the fact that triggered activity caused by DADs may be due to different causes, e.g., digitalis and catecholamines, each with somewhat different characteristics.

The following guidelines have been proposed to assist in distinguishing DAD-induced triggered activity from other causes of arrhythmias.[327,328] The guidelines are based on the characteristics of triggered activity determined from in vitro studies with microelectrodes. Triggered activity caused by DADs has been more easily induced by rapid pacing or by several successive premature stimuli than by a single premature stimulus in studies of isolated tissue preparations. This characteristic, which should be expected to occur in the in situ human heart, probably is explained by the fact that rapid pacing or the introduction of a number of premature stimuli is more effective than a single premature stimulus in increasing intracellular Ca^{+} levels. The Ca^{+} levels control the afterdepolarization amplitude. Also, arrhythmias caused by triggered activity should be more easily induced by premature stimuli superimposed on a rapid drive rate than on a slow one because during rapid pacing, the afterdepolarization amplitude is larger and the membrane potential at the peak of the afterpolarization is closer to threshold. In contrast, ordered reentrant rhythms in humans (with the exception of atrial flutter) seem to be more easily and reproducibly induced by premature impulses than by rapid pacing, although several premature impulses in succession sometimes are necessary. One reason for this may be that premature impulses block more effectively in areas with long refractory periods than do impulses during rapid pacing because rapid pacing can shorten refractory period duration. This, of course, is important because block is a prerequisite for the initiation of reentry.

Both extrasystoles and the first beat of a tachycardia, when caused by DAD-dependent triggered activity initiated by pacing, are predicted to occur late in the cardiac cycle.[327] This proposal is based on experimental data from studies of isolated tissue that show that DADs rarely reach their peak amplitude at less than 50 percent of the cardiac cycle when the drive cycle length is shorter than 1000 ms. In contrast, reentrant beats often occur early in the cycle. One would expect a direct relationship between the pacing cycle length that induces triggered activity resulting from DADs and the coupling interval from the last stimulated impulse to the first beat of the induced tachycardia. As the pacing cycle length decreases, the coupling interval from the last stimulated impulse to the first impulse of tachycardia should decrease because at short cycle lengths, the coupling interval of the afterdepolarizations to the proceeding action potential decreases.

A direct relationship between pacing cycle length and the coupling interval of the first impulse of the tachycardia has been shown to occur in arrhythmias caused by digitalis toxicity.[329] This relationship sometimes may be complicated by the presence of two afterdepolarizations and the possibility of a triggered impulse arising from either one.[330] No comparable data are available from pacing studies on digitalis-toxic human hearts. The direct relation also has been shown in some cases of idiopathic ventricular tachycardia believed to be caused by triggered activity.[166] A direct relation like this is not expected during the initiation of reentrant arrhythmias. Failure to show the direct relation, however, cannot be taken as proof that the arrhythmia is not caused by triggered activity, since slow conduction into or out of the triggerable focus can distort it. In microelectrode studies, during the initiation of triggered activity with premature stimuli, no significant effects of the premature stimulus coupling interval were observed on the relation (coupling interval) of the first triggered impulse to the premature stimulus.[188] On the basis of

these data, it is expected that during the initiation of arrhythmias caused by triggered activity in situ with programmed premature stimulation, the coupling interval of the first beat of tachycardia should remain relatively constant over a range of coupling intervals of introduced premature impulses. The response to premature stimulation is also contrary to that expected during the initiation of reentrant arrhythmias, where an inverse relation is expected between the premature stimulus coupling interval and the coupling interval between the premature impulse and the first impulse of tachycardia.

Triggered arrhythmias, unlike automatic arrhythmias but like reentrant arrhythmias, are predicted to be terminated by cardiac pacing. Single premature impulses may terminate triggered arrhythmias, but on the basis of the results of microelectrode studies, termination should be infrequent and not usually reproducible at the same critical premature cycle length. In contrast, single premature impulses often terminate reentrant arrhythmias in a reproducible manner and over a consistent range of premature cycle length in any single individual as long as the reentrant circuit has an excitable gap.[331,332] Therefore, an arrhythmia that is terminated readily by a single prematurely stimulated impulse is more likely to be caused by reentry than by triggered activity.

The effects of premature impulses that do not terminate sustained triggered activity also have been determined.[191] The response is almost identical to that of automaticity. The return cycle length remains fairly constant over a wide range of premature coupling intervals and is nearly the same as the cycle length of the basic triggered rhythm (less than compensatory). By contrast, overdrive pacing should terminate triggered arrhythmias caused by afterdepolarizations. This termination requires a critical rate and duration of overdrive,[186-188] just as it does with reentry.[302,303,307] Overdrive stimulation may cause acceleration of triggered arrhythmias followed by gradual slowing and termination, or rapid overdrive may cause abrupt termination. Although reentrant rhythms may be accelerated by overdrive pacing, a gradual slowing of the rate before termination is not expected. Overdrive pacing that does not terminate triggered activity, as occurs when the cycle length of the overdrive is too long or when the duration of trains of stimuli are too short, does not entrain the arrhythmia either.[333] In fact, none of the characteristics of entrainment are expected during overdrive pacing of triggered activity caused by DADs.

It therefore is apparent that although the response of triggered arrhythmias caused by DADs to stimulation can be predicted from experimental studies, there is no single feature that would positively allow a triggered rhythm to be distinguished from reentry except entrainment. Since the characteristics of initiation and termination of triggered rhythms by stimulation are very different from the characteristics of automatic rhythms, it should be easier to distinguish between these mechanisms by using pacing techniques. This differentiation may be made more difficult when an arrhythmia is persistent and the initiation cannot be studied. Also, entrance block of stimulated impulses into arrhythmogenic foci, whether automatic, triggered, or reentrant, may negate the use of pacing techniques to distinguish between these mechanisms.

The characteristics of some clinical arrhythmias occasionally conform to those expected of DAD-dependent triggered activity.[128,334] In addition to digitalis toxicity, an example is some cases of exercise-induced ventricular tachycardia in patients with no structural heart disease.[166,298] This tachycardia, which occurs spontaneously during exertion, sometimes can be initiated by overdrive pacing or programmed premature stimulation. An isoproterenol infusion during stimulation may be required for successful initiation. Lerman and coworkers[166] proposed that these tachycardias are caused by a catecholamine-induced increase in cyclic AMP, which is known to cause DADs. Evidence supporting this hypothesis is provided by the termination of tachycardias by intravenous injection of adenosine, which antagonizes the electrophysiologic effects of catecholamines mediated through the adenylate cyclase-cyclic AMP system. Jackman and associates[335] proposed that some forms of ventricular tachycardia associated with the congenital long QT syndrome and dependent on adrenergic stimulation result from triggered activity caused by DADs. Cranefield and Aronson[128] provided a detailed review of the clinical arrhythmias that may be caused by

triggered activity (see Chap. 27).

Arrhythmias Caused by Early Afterdepolarizations

Arrhythmias caused by EADs should not be inducible by overdrive pacing, similar to automatic arrhythmias and unlike arrhythmias caused by DADs or reentry. Similarly, triggered activity dependent on EADs is not expected immediately to follow the short cycle length of one or several prematurely stimulated impulses. As has been shown in experimental studies, the appearance of EAD-induced triggered activity is facilitated by long cycle lengths. Therefore, this kind of triggered activity should be initiated by slowing the basic heart rate. Of course, if an increase in heart rate caused by pacing resulted in entrance block into a focus where EADs occur, the block could cause a prolongation of the cycle length in that focus that might result in triggered activity.[128] Prematurely stimulated impulses also may initiate triggered activity if there is a long compensatory pause after the stimulated impulse. The long cycle might trigger an arrhythmia that would follow it.[128] In the absence of such entrance block, bursts of tachycardia caused by EADs should occur more frequently when the heart rate is slowed, and pacing the heart at rates faster than the basic underlying rhythm is predicted to cause disappearance of the period of tachycardia. Increasing the basic heart rate shortens action potential duration and thereby suppresses EADs. When the pacing is stopped, arrhythmias should reappear, as the action potential returns to its original duration. The reappearance of the arrhythmias may not be immediate, however, since it requires some time for the action potential duration to lengthen owing to the enhanced pump current that follows a period of rapid stimulation.

Many of these characteristics have been shown to apply to the experimental triggered arrhythmias caused by cesium in the in situ canine heart[199] and have been demonstrated in some cases of torsades de pointes in human patients. Acquired forms of the syndrome (e.g., prolonged QT and torsades de pointes by quinidine) exhibit all the features expected of triggered activity caused by EADs, whereas other forms (e.g., congenital) may not be due to this mechanism.[336] Torsades de pointes invariably occurs after a preceding long R-R interval,[200] is unlikely to be initiated by programmed stimulation,[337] and can be prevented from occurring by pacing the heart at a rapid rate.[200,337] Parenthetically, it has been suggested that such rhythms are initiated by EADs but maintained by reentrant excitation.[219] In contrast, triggered arrhythmias caused by DADs may become more frequent as heart rate increases,[327] and the effect of increasing the heart rate on extrasystoles caused by reentry is variable; i.e., reentry may be exacerbated or may stop.[222]

There may be some difficulty in distinguishing EAD-dependent triggered arrhythmias from automatic arrhythmias only on the basis of their response to electrical stimulation, however, since the occurrence of automatic arrhythmias is facilitated by slow heart rates and increasing the basic heart rate by overdrive pacing may cause disappearance of automatic arrhythmias during the periods of pacing. The ECG characteristics of arrhythmias caused by triggered activity resulting from EADs and by automaticity may be of additional help. The triggered rhythms are more likely to occur in bursts or salvos of different lengths, with the first few cycle lengths of a burst decreasing progressively and the last few cycle lengths increasing progressively.

Triggered arrhythmias caused by EADs not only may occur in bursts but also may be sustained. When sustained, their response to single premature stimuli or overdrive pacing can be predicted on the basis of the results of in vitro studies. Some arrhythmias may be terminated by premature stimuli, but this should be a relatively rare occurrence. The effects of premature stimulated impulses that do not terminate the arrhythmia are expected to be the same as their effects on automatic impulse initiation. Some arrhythmias also may be terminated by overdrive pacing, but termination should not be the usual effect. When termination occurs, it is expected to follow the overdrive immediately, whereas termination of triggered activity caused by DADs sometimes may be preceded by up to 10 triggered "afterbeats."[186,187] When termination does not occur, overdrive is not expected to cause any significant effect on the rhythm; the response should be more like that

of an arrhythmia caused by abnormal automaticity[191] than one caused by normal automaticity, which is readily overdrive-suppressed.[73] Because of this variability of response, stimulation during a sustained tachycardia caused by EADs is not much help in determining the mechanism.

Therefore, as in the triggered arrhythmias caused by DADs, there is no single feature in the response to cardiac pacing that would positively enable EAD-induced triggered rhythms to be distinguished from other arrhythmogenic mechanisms. Early afterdepolarization-induced nonsustained arrhythmias usually can be differentiated from rhythms induced by DADs or automaticity at high membrane potentials and sometimes from reentry by pacing, but the response of sustained triggered activity to pacing is often indistinguishable from abnormal automaticity at low membrane potentials.

SUMMARY OF EFFECTS OF ELECTRICAL STIMULATION

Despite the fact that there are exceptions and inconsistencies to virtually all the rules that can be proposed to distinguish among the different arrhythmogenic mechanisms using pacing techniques, determining the effects of electrical stimulation is quite useful. The following is a summary of the most important points: (1) Initiation of a tachycardia by stimulation indicates that the arrhythmia is caused by reentry or delayed afterdepolarization-induced triggered activity. Other characteristics of initiation are then useful in distinguishing between the two. Other mechanisms of arrhythmias-such as automaticity and triggered activity caused by early afterdepolarizations-are eliminated when a tachycardia is induced by cardiac pacing. (2) Termination of a tachycardia by overdrive pacing or premature stimulation is expected of reentry or triggered activity caused by delayed afterdepolarizations but not of automaticity and early afterdepolarization-dependent triggered activity. Overdrive suppression is expected of arrhythmias caused by normal automaticity, and overdrive acceleration may occur with arrhythmias caused by abnormal automaticity. (3) Demonstration of entrainment of a tachycardia during overdrive pacing is indicative of a reentrant mechanism and is not expected of other mechanisms. (4) The response to premature stimulation is different during arrhythmias caused by automaticity and those caused by reentry. During automatic arrhythmias, the return cycle length should not increase as the premature coupling interval decreases. The return cycle should be less than compensatory. During reentrant arrhythmias, the return cycle length should increase as the premature impulse occurs earlier in the dominant cycle. The increase sometimes may begin to occur with late coupled premature impulses or may not occur until premature impulses are early coupled. The return cycle length is often less than compensatory.

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Figure 23-6: Diagrams of sinus node action potentials illustrating normal automaticity caused by spontaneous diastolic depolarization and the factors that change the rate of impulse initiation. *A.* Typial sinus node action potential with spontaneous diastolic depolarization (dd). *B.* Change in the rate when the maximum diastolic potential is shifted to a more negative level (from a to b). *C.* Change in rate caused by change in threshold potential to a less negative level (from TP1 to TP2). *D.* Change in rate that occurs when the slope of phase 4 depolarization is decreased (from a to b). (Modified after Wit AL, Janse MJ. *The Ventricular Arrhythmias of Ischemia and Infarction: The Electrophysiological Mechanisms*. Mount Kisco, NY: Futura; 1992:3. Reproduced with permission from the publisher and authors.)

Figure 23-7: Transmembrane potentials recorded in isolated superfused preparations from some subsidiary pacemaker cells with the property of normal automaticity. Spontaneous diastolic depolarization that developed in the absence of overdrive suppression is shown in each panel. *A.* Atrial fiber in the crista terminalis in the presence of isoproterenol. *B.* Atrial fiber in the inferior right atrium. *C.* Atrial fiber in the ostium of the coronary sinus in the presence of norepinephrine. *D.* Atrial fiber in stretched mitral valve leaflet. *E.* Atrioventricular nodal fiber of the rabbit heart after the AV node was separated from the atrium. (From Wit AL, Janse MJ. *The Ventricular Arrhythmias of Ischemia and Infarction: The Electrophysiological Mechanisms*. Mount Kisco, NY: Futura; 1992:7. Reproduced with permission from the publisher and authors.)

Figure 23-8: Overdrive suppression of normal automaticity in a canine Purkinje fiber. The action potentials are displayed at a slow oscilloscopic sweep speed, and so the time course of repolarization cannot be seen. Note the warmup of the spontaneous pacemaker after the termination of pacing. (From Cranefield PF. *The Conduction of the Cardiac Impulse: The Slow Response and Cardiac Arrhythmia*. Mount Kisco, NY: Futura; 1975. Reproduced with permisson from the publisher and author.)

Figure 23-9: Normal and abnormal automaticity in a canine Purkinje fiber. *A.* Transmembrane potential recording from a Purkinje fiber with a normal maximum diastolic potential of -85 mV and spontaneous diastolic depolarization. *B.* Abnormal automaticity that occurred when membrane potential was decreased: (1) Fiber was depolarized (*at arrow*) to a membrane potential of -45 mV by the injection of a long-lasting current pulse through a microelectrode, (2) membrane potential was reduced to -40 mV (*at arrow*), (3) membrane potential was reduced to -30 mV (*at arrow*). (Reproduced from Wit AL, Friedman PF. Basis for ventricular arrhythmias accompanying myocardial infarction: Alterations in electrical activity of ventricular muscle and Purkinje fibers after coronary artery occlusion. *Arch Intern Med* 1975; 135:459. Reproduced with permission from the publisher and author.)

Figure 23-10: An example of a DAD (*white arrow*) recorded with a microelectrode from an atrial fiber in the canine coronary sinus. The red arrow indicates an afterhyperpolarization. *B.* The onset of triggered activity is shown. (From Wit AL, Rosen MR. After depolarizations and triggered activity: Distinction from automaticity as an arrhythmogenic mechanism. In: Fozzard HA, Haber E, Jennings RB, et al., eds. *The Heart and Cardiovascular System*. Scientific Foundations, 2d ed. New York, Raven Press; 1991:2113. Reproduced with permission from the publisher and author.)

Figure 23-11: Effects of stimulation rate on DADs and triggered activity. Transmembrane action potentials were recorded from an atrial fiber in the canine coronary sinus superfused with Tyrode's solution containing norepinephrine. The stimulus cycle lengths and the periods of stimulation are indicated by the black bars. Sustained triggered activity occurred after stimulation at a cycle length of 1200 ms. The rate of triggered activity is so rapid that the individual action potentials cannot be seen at the slow oscilloscopic sweep speed. (From Wit AL, Cranefield PF. Triggered and automatic activity in the canine coronary sinus. *Circ Res* 1977; 41:435. Reproduced with permission from the publisher and author.)

Figure 23-12: Early afterdepolarizations and triggered activity during repolarization in a Purkinje fiber. *A*. Transmembrane potential with normal repolarization of a spontaneously active Purkinje fiber. *B*. Early afterdepolarization (*arrow*) occurring during the plateau phase of the action potential. *C*. Triggered action potentials (*arrow*) during the plateau. *D*. Arrest of repolarization at a low level of membrane potential after a period of triggered activity. (From Cranefield PF. Action potentials, afterpotentials and arrhythmias. *Circ Res* 1977; 41:415-425. Reproduced with permission from the publisher and author.)

Figure 23-13: Early afterdepolarizations and triggered activity during late repolarization in a Purkinje fiber. *A*. Three panels are shown: (*a*) a spontaneously firing Purkinje fiber with prominent phase 4 depolarization, (*b*) occurrence of a single triggered action potential caused by an EAD, occurring during repolarization of each spontaneous action potential, (*c*) two triggered action potentials caused by an EAD occurring during repolarization of each spontaneous action potential. *B*. Development of an EAD and a triggered action potential in three superimposed traces: (1) normal Purkinje fiber action potential, (2) alteration in the time course of late repolarization leading to the occurrence of an EAD (*arrow*), (3) further alteration in late repolarization, leading to a triggered action potential. *C*. Superimposed traces recorded from a Purkinje fiber in the course of developing EADs and a triggered action potential. (From Coulombe A et al. Role of the "Na window" current and other ionic currents in triggering early after-depolarizations and re-exitation in Purkinje fibers. In: Zipes DP, Jalife J, ed. *Cardiac Electrophysiology and Arrhythmias*. New York: Grune & Stratton; 1985:43. Reproduced with permission from the publisher and author.)

Figure 23-14: Diagrammatic representation of the relation between the level of membrane potential at the onset of phase 0 and the maximum rate of depolarization during phase 0 (dv/dt_{max} or $V(r)_{max}$). *A*. Fiber has been depolarized by progressively increasing the extracellular potassium concentration. As resting membrane potential decreases, the rate of depolarization of the action potential upstroke decreases. *B*. Fiber is activated by premature stimuli that occur at different times during phase 3 (*a*, *b*, and *c*). The premature action potentials have reduced rates of depolarization because they arise at reduced membrane potentials. *C*. For both types of experiments, the general relationship between $V(r)_{max}$ and membrane potential is shown. As the membrane potential becomes smaller (less negative), the rate of phase 0 depolarization ($V(r)_{max}$) decreases and therefore conduction velocity decreases.

Figure 23-15: Relation between the spread of excitation in uniform anisotropic ventricular muscle (*A*) and extracellular (*B*) and transmembrane potential waveforms (*C*). The excitation sequence in *A* was constructed from the extracellular waveforms measured at 100 positions on the endocardial surface of the right ventricular septum. The extracellular waveforms in *B* were measured at the sites indicated by the solid dots superimposed on the isochrones of *A*. The direction of propagation at the single transmembrane recording site was altered by initiating propagation at different locations, one to produce propagation along the longitudinal axis of the impaled fiber and the other to produce propagation along the transverse axis. Panel *C* shows the effects of the different directions of propagation on the upstroke of the action potential. (From Spach MS, Dolber PC. The relation between discontinuous propagation in anisotropic cardiac muscle and the "vulnerable period" of reentry. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology and Arrhythmias*. New York: Grune & Stratton, 1985:241. Reproduced with permission from the publisher and author.)

Figure 23-16: *A*. Diagram of a nonuniform anisotropic atrial muscle bundle with the long axis of the myocardial fibers indicated by the dashed lines. The bundle was stimulated at the asterisk. Propagation of the longitudinal wavefront is shown by the large white arrow. Transverse propagation occurred as diagrammed by the zigzag arrow. *B*. Electrograms recorded from sites 1, 2, and 3 on the diagram. *C*. The first derivative of these electrograms is shown. (From Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle: Evidence for uncoupling of side-to-side fiber connections with increasing age. *Circ Res* 1986; 58:356. Reproduced with permission from the publisher and author.)

Figure 23-17: Conduction characteristics and unidirectional block at branch sites. The drawings represent a small branch formed by the origin of a pectinate muscle from the larger crista terminalis. The general direction of the fiber orientation is indicated by the broken lines. The patterns of propagation are shown by the solid arrows. Extracellular waveforms recorded at sites indicated by the dashed lines also are shown. (From Spach MS et al. The functional role of structural complexities in the propagation of depolarization in the atrium of the dog: Cardiac conduction disturbances due to discontinuities of effective axial resistivity. *Circ Res* 1982; 50:175. Reproduced with permission from the publisher and authors.)

Figure 23-18: Diagram of reentry caused by dispersion in refractory periods. A ring of cardiac tissue is shown, and the pattern of conduction is indicated by the arrows. Action potentials with different durations located in different regions of the ring are diagrammed. (From Wit AL, Janse MJ. *The Ventricular Arrhythmia of Ischemia and Infarction: The Electrophysiological Mechanisms.* Mount Kisco, NY: Futura; 1992:86. Reproduced with permission from the publisher and authors.)

Figure 23-19: Asymmetric depression of excitability as a mechanism for unidirectional conduction block in a bundle of cardiac muscle fibers. The action potentials shown above were recorded from sites on the fiber bundle. The shaded part of the bundle is depressed. Conduction from left to right along the bundle is indicated by the striped arrows, conduction from right to left by the black arrows. (Modified from Wit AL, Rosen MR. Cellular electrophysiological mechanisms of cardiac arrhythmias. In: MacFarlane PW, Veitch Lawrie TD, eds. *Comprehensive Electrocardiology: Theory and Practice in Health and Disease*, vol. 2. New York: Pergamon Press; 1989:801. Reproduced with permission from the publisher and authors.)

Figure 23-20: Return cycles as a function of premature stimulated cycles during premature atrial stimulation in a patient in sinus rhythm. The graph depicts the relation of the normalized return cycle to the degree of prematurity of the test cycle, which also is normalized. Points falling on line *A* represent nonreset of the sinus pacemaker (fully compensatory pause) and are in zone I. Premature stimulated atrial beats introduced earlier in atrial diastole fall in zone II. Line *B*, projected from the *y* axis, is a reference line indicating the spontaneous sinus cycle length. The distance the zone II points (reset points) are above line *B* is interpreted to indicate conduction time into and out of the sinus node, assuming the sinus node pacemaker cycle length immediately after the stimulated premature atrial beat is identical to the preceding sinus node pacemaker cycle length. (From Strauss HC et al. Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man: A presentation of data and critical review of the literature. *Circulation* 1973; 47:86. Reproduced with permission from the publisher and author.)

Figure 23-21: Diagrammatic representation of the reentrant circuit during spontaneous ventricular tachycardia (VT) and the first two beats of entrainment of the ventricular tachycardia at a rate of 150 beats per minute (*middle and right panels, respectively*). Each *X* represents the orthodromic wavefronts of the reentrant rhythm. In this and subsequent diagrams, the arrows indicate the direction of spread of the impulse, the box represents an area of slow conduction, the serpentine line indicates slow conduction of the impulse in the area of slow conduction, the dots represent recording sites along the course of the double arc of reentry from which ventricular electrograms (VEGs) are recorded, and the large arrow indicates the wavefront from the pacing impulse entering into the ventricular tachycardia reentry circuit, where it is conducted orthodromically (ortho) and antidromically (anti). (From Waldo AL, Henthorn RW. Use of transient entrainment during ventricular tachycardia to localize a critical area in the reentry circuit for ablation. *PACE* 1981; 12:231. Reproduced with permission from the publisher and authors.)

Figure 23-22: Diagrammatic representation of the first entrainment criterion during termination of ventricular pacing illustrated in Fig. 23-21. (From Waldo AL, Henthorn RW. Use of transient entrainment during ventricular tachycardia to localize a critical area in the reentry circuit for ablation. *PACE* 1989; 12:231. Reproduced with permission from the publisher and authors.)

Figure 23-23: Diagrammatic representation of the second and fourth entrainment criteria during entrainment of the same spontaneous ventricular tachycardia shown in Fig. 23-21 by ventricular pacing at rates of 150 (*left panel*), 155 (*middle panel*), and 160 (*right panel*) beats per minute. (From Waldo AL, Henthorn RW. Use of transient entrainment during ventricular tachycardia to localize a critical area in the reentry circuit for ablation. *PACE* 1989; 12:231. Reproduced with permission from the publisher and authors.)

Figure 23-24: Diagrammatic representation of the third entrainment criterion during interruption of the ventricular tachycardia by ventricular pacing at a rate of 165 beats per minute. (From Waldo AL, Henthorn RW. Use of transient entrainment during ventricular tachycardia to localize a critical area in the reentry circuit for ablation. *PACE* 1989; 12:231. Reproduced with permission from the publisher and authors.)

Figure 23-25: Effects of premature impulses on reentrant circuit with an excitable gap. In each panel, diagrams are shown of an anatomic circuit with a single entrance route from above. In *A*(1), *B*(1), and *C*(1), red arrows in the circuit represent the reentrant impulse causing tachycardia. The length of the arrow is the wavelength of the impulse and shows the part of the circuit that is completely refractory, The part of the circuit that is stippled is relatively refractory, and the part of the circuit that is clear is completely excitable (the fully excitable gap). Red arrows entering the circuit from above represent a prematurely stimulated impulse initiated outside the circuit. *A*(2) and *B*(2) show conduction of the premature impulse in the circuit. Graphs show the expected relation between the return (premature impulse) cycle length (R_2-R_3) and the premature coupling interval (R_1-R_2/R_1-R_1) for premature impulses conducting in the fully excitable gap *A*(3) and in the relatively refractory tissue of a partially excitable gap *B*(3). (Modified after Wit AL, Janse MJ. *The Ventricular Arrhythmias of Ischemia and Infarction: The Electrophysiological Mechanisms*. Mount Kisco, NY: Futura; 1992:135. Reproduced with permission from the publisher and authors.)

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Chapter 23: MECHANISMS OF CARDIAC ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 24:

RECOGNITION, CLINICAL ASSESSMENT, AND MANAGEMENT OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Authors: Robert J. Myerburg, E. Martín Kloosterman, Agustin Castellanos

The diagnosis and management of cardiac arrhythmias and conduction disturbances require the coordination of (1) electrocardiographic (ECG) analysis of the rhythm disturbance, (2) assessment of the clinical setting, and (3) identification of an end point and method of therapy.[1]

ECG recognition of arrhythmias requires an organized system of analysis of atrial and ventricular myocardial activation and deduction of atrioventricular (AV) conduction patterns. Forms of arrhythmias are separated into those that cause limited symptoms but may trigger symptomatic sustained arrhythmias under appropriate conditions (e.g., premature atrial or ventricular impulses) and those that are sustained symptomatic and/or potentially fatal arrhythmias [e.g., supraventricular tachycardias (SVTs), ventricular tachycardias (VTs), ventricular fibrillation (VF), or bradycardias] (Table 24-1).

Table 24-1: Assessment of Cardiac Arrhythmias

Forms of cardiac arrhythmias
Ambient or triggering arrhythmias (e.g., premature atrial or ventricular impulses)
Sustained or potentially lethal arrhythmias (e.g., supraventricular or ventricular tachycardias, ventricular fibrillation, sustained bradyarrhythmias)
Clinical settings in which arrhythmias occur
Acute, transient (e.g., acute ischemic events, metabolic disturbances)
Chronic, persistent, recurrent (e.g., chronic ischemic heart disease, cardiomyopathy, anatomic or physiologic substrate for paroxysmal supraventricular tachycardia, chronic conducting system disease)
End points of management
Antiarrhythmia (suppress ambient or triggering arrhythmias)
Antitachycardia or antifibrillatory (prevent or revert tachycardias or fibrillation)
Heart rate support (prevent symptomatic bradycardias)

SOURCE: Modified from Myerburg et al.,[1] with permission of the *American Heart Journal.*

Clinical settings are broadly divided into those that are acute or transient, such as acute ischemia, the acute phase of myocardial infarction, electrolyte disturbances, or proarrhythmic effects of antiarrhythmic drugs, and those that provide a persistent substrate for arrhythmias, such as chronic ischemic heart disease, cardiomyopathies, and anatomic and physiologic substrates for the various paroxysmal supraventricular tachyarrhythmias.[2,3] Analogous to the concept of "triggering" and "sustained" arrhythmias, transient ischemia and hemodynamic disturbances may be viewed as triggering events and chronic ischemic heart disease and the hypertrophied or myopathic heart as sustaining substrates.

The goals, or end points, of therapy of cardiac arrhythmias are dependent on the forms, clinical settings, and mechanisms of arrhythmia. Broadly, goals of treatment may be antiarrhythmic (targeted to the suppression of ambient or triggering arrhythmias or events) or antitachycardiac, antifibrillatory, or heart-rate supporting (in which the goal is prevention or reversion of sustained arrhythmias), whether the arrhythmias are well tolerated, symptomatic, or life-threatening.

PRINCIPLES OF CARDIAC RHYTHM ANALYSIS

The Standard Electrocardiogram

The standard 12-lead ECG and rhythm strips provide a direct and easily accessible method for diagnosing disturbances of cardiac rhythm. The simultaneous-lead rhythm strip accompanying the 12-lead ECG on many current ECG machines, plus the option of recording longer multilead rhythm strips, will yield sufficient information for a prompt and accurate diagnosis of most cardiac rhythm disturbances.

For many arrhythmias, analysis requires only the recognition of P-wave and QRS morphology, their relative timing, and their vectors. Simple inspection of the tracing, with caliper-assisted measurements, may be sufficient; but the analysis of more complex arrhythmias is facilitated by the use of ladder diagrams. First used extensively by Sir Thomas Lewis, they are also referred to as Lewis lines. The ladders are usually constructed with three tiers-A, AV, and V (Fig. 24-1*A*)-but additional tiers may be helpful in depicting events related to sinoatrial (SA) conduction (Fig. 24-1*B*) or ventricular ectopic rhythms (Fig. 24-1*C*). The A and V tiers are used to depict activation of atrial and ventricular muscle, respectively. The middle tier (AV) is used to infer conduction characteristics in the AV junction. Since atrial and ventricular activation are the only direct registrations of cardiac electrical activity on the standard ECG, they are diagrammed first. The A line is drawn from the beginning of the P wave and the V line from the beginning of the QRS. Time is indicated by the slope of the line, and the site within a tier in which impulse propagation begins (upper, middle, or lower) shows the direction the impulse is traveling. The site of origin may be represented by a black dot. A blocked impulse is indicated by a short bar at a right angle to the line indicating direction of conduction, and aberrant intraventricular conduction is shown as a pair of slightly divergent lines. A variety of such examples are shown in Fig. 24-1. In using the diagram, particularly for complex arrhythmias, the first caution is to draw only what can be seen or inferred with certainty. Subsequently, the AV tier can be used to diagram proposed mechanisms of conduction (Fig. 24-2).

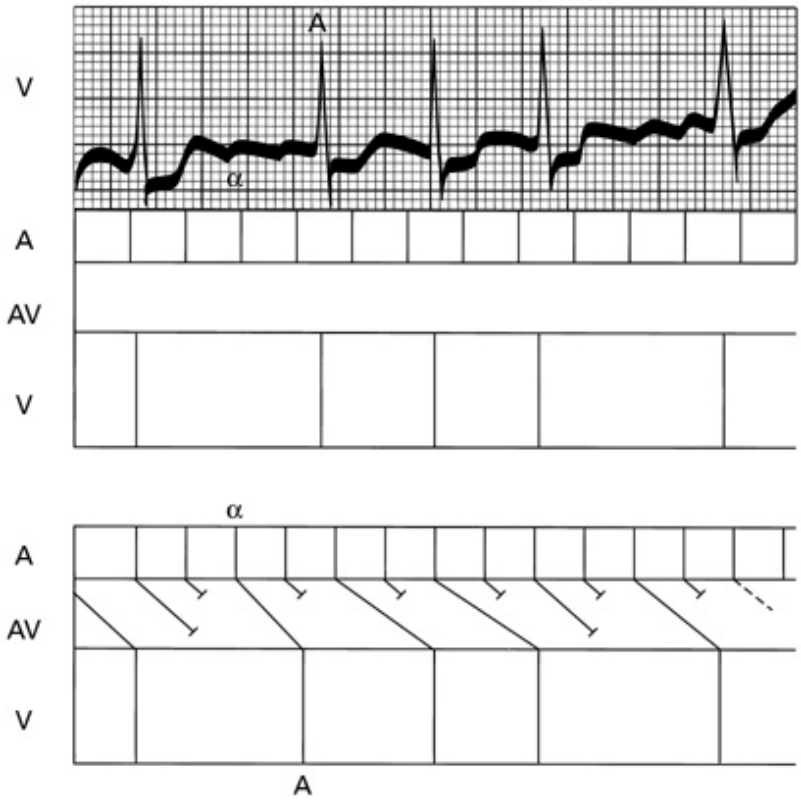

Figure 24-2: Construction of ladder diagrams for analyzing specific arrhythmias. *Stage 1:* Draw lines to represent atrial activity (seen and inferred by measurement) and ventricular complexes. *Stage 2:* Since the FR interval in flutter usually ranges between 0.26 and 0.45 s, start by connecting the F wave (α) to the QRS (A) in this example. As successive impulses are diagrammed, it becomes apparent that there is a basic 2:1 AV conduction with a Wenckebach period during the alternate cycles. (From Marriott HJL. *Armchair Arrhythmias.* Tampa, FL: Tampa Tracings; 1966. Reproduced with permission from the publisher and authors.)

Special Leads

When the standard ECG does not provide sufficient information to establish a diagnosis, usually due to inability to identify P waves, special lead systems may be used. The simplest is the Lewis lead configuration, in which the right and left arm electrodes are deployed as a bipolar lead to the right of the sternum in a superior-inferior orientation.

A bipolar esophageal lead can record left atrial activity, and an intraatrial electrode catheter can record atrial activity from within the right atrium. For both techniques, it is necessary to have at least one standard surface ECG lead recorded simultaneously with the special lead.

Continuous Monitor Recordings

Continuous monitoring of cardiac rhythm may be performed in hospital in special care units or in the ambulatory patient using various types of portable recording devices. Some systems provide the capability for simultaneous multilead recordings that improve diagnostic yield considerably. Long-term storage capabilities for inpatient monitoring permit off-line analysis of complex rhythm disturbances if the physician is not available at the time the arrhythmia occurs. The two most popular leads for use in bedside monitoring are lead II and MCL-I, the latter providing a pattern similar to V_1.

For infrequently occurring arrhythmias, a number of event recorders are now available. They allow the patient to activate the device when an event occurs, providing internal storage that can be transmitted by telephone to a central station for later review. Transtelephonic transmitters also can be used in real time for more persistent or frequent events. Finally, a small subcutaneous implantable recorder is available for patients with infrequent arrhythmias that warrant an aggressive documentation attempt.[4] The device may be

explanted after a diagnosis is established.

Exercise Testing for Cardiac Arrhythmias

Treadmill stress testing may be used to initiate an evanescent arrhythmia, document an exercise relationship to its onset, and evaluate both efficacy and adverse responses to therapy. The standard treadmill is used, and thallium or echocardiographic imaging is not necessary unless an ischemic basis correlating with the onset of arrhythmia is suspected. The procedure is especially useful for eliciting and evaluating therapy of exercise-induced ventricular arrhythmias, for distinguishing autonomic from structural disease mechanisms of sinus or AV node dysfunction, and for evaluating adverse effects of drug therapy, such as rate-dependent proarrhythmic effects, as may occur with strong Na^+-channel blockers, such as flecainide[5] (see below).

Exercise testing may also provide some general insights into the refractory period of an accessory pathway in Wolff-Parkinson-White (WPW) syndrome. Abrupt disappearance of the delta wave during exercise-induced increase in heart rate suggests encroachment on the refractory period, while gradual disappearance may simply be due to enhanced AV nodal conduction.[6]

Signal-Averaged Electrocardiography, Heart Rate Variability, and Baroreceptor Sensitivity

Signal-averaged electrocardiography, heart rate variability, and baroreceptor sensitivity provide information on mortality risk and the probability of life-threatening arrhythmias, whether used separately or combined with other estimates of risk [e.g., premature ventricular contractions (PVCs) and nonsustained VT on 24-h ambulatory monitoring and ejection fraction (EF) measurements]. They have been applied most intensively after myocardial infarction.

Signal-averaged electrocardiography employs amplification of low-amplitude signals occurring after the termination of the standard electrocardiographic QRS complex, as recorded by high-amplification techniques. The low-amplitude signals are repetitive electrical events caused by a delayed activation sequence of part or parts of the ventricular muscle mass. Their repetitive timing allows them to be amplified during signal averaging, while random noise is being canceled out. The resultant signal is a high-gain, high-frequency QRS complex, followed by low-amplitude signals representing the late potentials. The terminal delayed activation pattern represents a pathophysiologic marker for susceptibility to ventricular arrhythmias. It results from fragmented activation in an area of delayed conduction, which is a well-established substrate for reentrant arrhythmias. The characteristics of an abnormal signal-averaged ECG include (1) a prolonged filtered QRS complex (115 ms) with a normal duration of the standard QRS complex, (2) the terminal portion of the filtered QRS complex less than 40 μV for 39 ms, and (3) less than 20 μV of amplitude during the last 40 ms of the filtered QRS complex.[7] At least two of the three criteria must be abnormal to consider the tracing abnormal, and many would require all three to be abnormal (Fig. 24-3). Residual high-frequency noise content must be less than 1 μV with a 25-Hz high-pass cutoff (less than 0.7 μV with a 40-Hz high-pass cutoff).

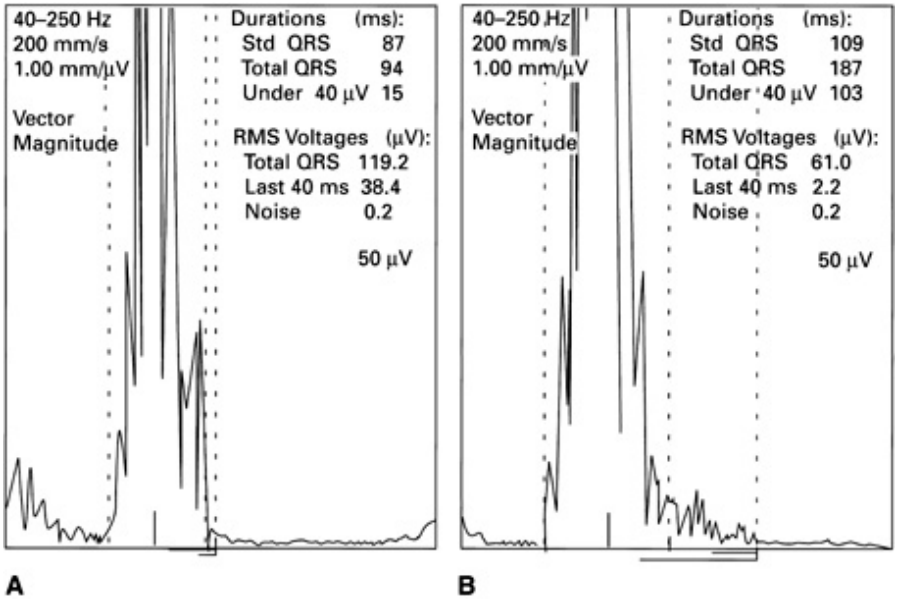

Figure 24-3: *A.* Normal signal-averaged vector complex. *B.* Abnormal signal-averaged vector complex. All three signal-averaged measurements are abnormal. The signal-averaged QRS duration is 187 ms, low-amplitude signals are 103 ms in duration, and the root-mean-square voltage is 2.2 μV. (Courtesy of Paul F. Walter, M.D.)

Signal-averaged electrocardiography is most useful for demonstrating presence and absence of risk for ventricular arrhythmias and sudden death after myocardial infarction.[8] It is most powerful as a negative predictor of risk, in that a normal signal-averaged ECG after healing of myocardial infarction identifies a greater than 97 percent probability of remaining free of ventricular arrhythmias. The positive predictive accuracy is less powerful and is heavily influenced by other variables, such as EF and ambient ventricular arrhythmias. Signal-averaged electrocardiography alone has a positive predictive value in the range of 20 percent, and combined with a low EF and ambient arrhythmias, the risk may be as high as 50 percent in some subgroups (see "Ventricular Arrhythmias," below).

Heart rate variability studies provide estimates of sympathetic and parasympathetic balance.[9] Blunting of the normal patterns of variability of sinus rate over time in subgroups of myocardial infarction and cardiac arrest survivors appears to increase the risk of life-threatening events.[9,10] As is the case for signal-averaged electrocardiography, the test is used primarily for prognostic information rather than as a therapeutic guide.

Baroreceptor sensitivity estimates the relationship between phenylephrine-induced blood pressure increase and concomitant fall in heart rate as an indication of parasympathetic responsiveness to the pure α-adrenergic stimulus.[11] Following a myocardial infarction, a blunted baroreceptor sensitivity predicts an increased risk of VT and death. A recent large study also demonstrated its power for predicting adverse outcome following a myocardial infarction, which was further enhanced when combined with other risk variables, such as low EF and ambient arrhythmias.[12]

Intracardiac Electrocardiography and Programmed Electrophysiologic Studies

Intracardiac electrocardiography and programmed electrophysiologic studies, which are described in detail in Chap. 26, can be used to diagnose many disturbances in rhythm and conduction for which surface electrocardiography is insufficient. Intracardiac electrophysiologic studies are also used to define appropriate therapy and to test the results of therapy for various forms of supraventricular and ventricular arrhythmias. The use of multicatheter electrode systems, providing simultaneous recordings from many intracardiac sites (Fig. 24-4), allows mapping of the sequence of excitation in the atria, AV junction, and ventricle. Intracardiac mapping procedures permit the identification of sites of accessory pathways, mechanisms of ventricular tachyarrhythmias, and the reentrant circuits or sites of origin of supraventricular tachyarrhythmias. Such techniques provide the basis for electrocardiographically guided therapy, such as radiofrequency (RF) ablation. In addition, the distinction between AV block above and below the level of the bundle of His and between true AV block and pseudo-AV block caused by concealed extrasystoles is

also possible. Specific clinical applications are provided in the appropriate sections below and in Chap. 26.

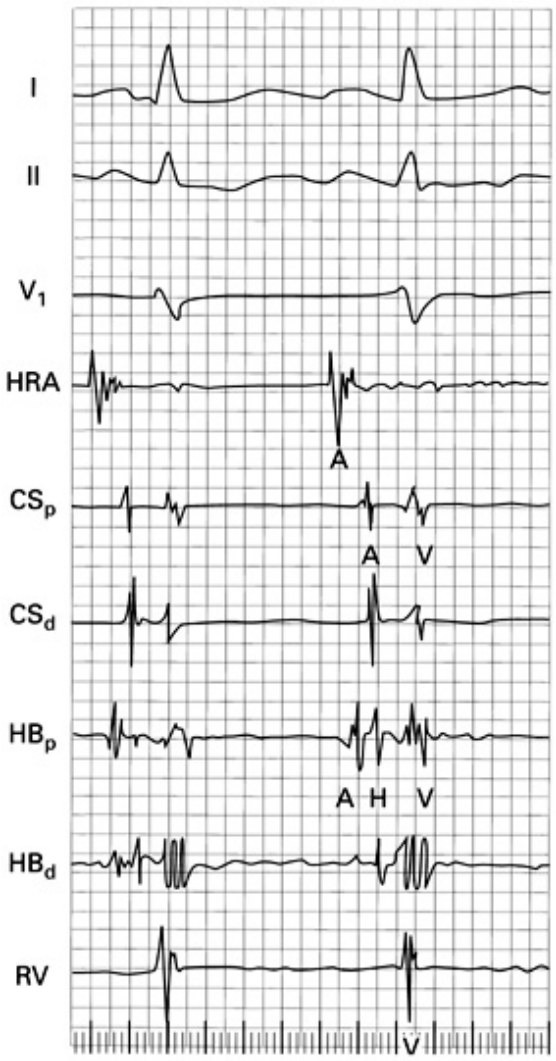

Figure 24-4: Intracardiac recordings during electrophysiologic testing. Recordings during sinus rhythm in a multicatheter study are illustrated. The intracardiac study includes the recording of atrial activity (A), the His bundle deflection (H), and ventricular activity (V) used to determine the timing and sequences of activation at various intracardiac sites. A activity is recorded from the high right atrium (HRA); and both A and V activity are recorded from a proximal (HBp) and distal (HBd) site in the His bundle region and from proximal (CSp) and distal (CSd) sites within the coronary sinus. The CS sites record atrial and ventricular activity from the posterior-posteroseptal and posterolateral-lateral areas, respectively. V activity is also recorded from the right ventricle (RV), either the apex or outflow tract, depending upon the positioning of the catheter in the right ventricle. For more detailed mapping procedures, more sites in the coronary sinus or sites around the tricuspid ring can be recorded, or the left ventricle can be mapped by a retrograde recording catheter from the femoral artery. Less extensive studies using fewer catheters and recording sites can be used for different clinical purposes. The configuration shown is standard for studies of supraventricular tachycardias. For ventricular tachycardia studies, three catheters can be used (HRA, HB, and RV) for the diagnostic study.

Endocardial Catheter Mapping and Intraoperative Multiarray Epicardial Mapping

Techniques for mapping pathways and sites of origin for both ventricular and supraventricular tachyarrhythmias, originally developed for intraoperative mapping during antiarrhythmic surgery, have found broad application in catheter-based procedures. Greatly improved catheter-ablation techniques for many arrhythmias, in conjunction with the development of sophisticated computer-based recording,

storage, and retrieval systems,[13,14] have limited the role of intraoperative mapping and interventions with the expansion of catheter techniques. The new mapping systems allow simultaneous recordings from many points, generating on-line maps of activation during a procedure. This technology allows the clinical electrophysiologist to identify target areas for delivery of RF energy during an ablation procedure. Figure 24-5 (Plate 74), provides an example of a computer-generated atrial endocardial activation map from such a system, demonstrating a focal atrial tachycardia. The technique of left ventricular (LV) endocardial catheter mapping for identification of sites appropriate for catheter ablation of VT is demonstrated in Fig. 24-6. Computer-generated maps are now also available for ventricular arrhythmias.

NEXT

Chapter 24: RECOGNITION, CLINICAL ASSESSMENT, AND MANAGEMENT OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

OVERVIEW OF MANAGEMENT STRATEGIES

Strategies for the prevention and management of cardiac arrhythmias are based on an understanding of the mechanisms of specific arrhythmias (Table 24-2), in conjunction with systemic and cardiac factors that can be modified to influence predisposition to arrhythmias, and the range of indications for pharmacologic therapy and nonpharmacologic interventions (Table 24-3). Many patients are managed with multiple interventions, one therapeutic mode being complementary to another.

Table 24-3: Summary of Approaches to Arrhythmia Management

General systemic interventions
Respiratory support
Hemodynamic support
Metabolic and electrolyte control
Neurophysiologic control
Electropharmacologic therapy
Control triggering events
Suppress triggering arrhythmias
Prevent or reverse arrhythmogenic factors (e.g., anti-ischemic therapy, or electrolyte replacement)
Control sustained arrhythmias
Acute interventions
Chronic prevention
Control ventricular rate
Catheter ablation procedures
Supraventricular tachycardias
AV nodal reentry
WPW syndrome
AV node ablation in atrial fibrillation
Atrial flutter
Atrial fibrillation, focal mechanisms[a]
Atrial, sinus node, and AV junctional tachycardias
Ventricular tachycardias

Surgical intervention
Antiarrhythmic surgery
Anomalous pathways[a]
Aneurysmectomy, endocardial resection[a]
Cryoablation[a]
Maze procedure for atrial fibrillation[a]
Anti-ischemic surgery
Structural heart disease surgery
Electronic device
Acute applications
Cardioversion
Defibrillation
Temporary pacemakers
Long-term applications
Permanent pacemakers
Implantable cardioverter defibrillators

[a]Limited clinical application at the time of this writing.

A complete management plan for any arrhythmia must coordinate three spheres of information: (1) the underlying structural etiology (coronary heart disease, cardiomyopathy, WPW syndrome, etc.); (2) transient triggering factors that interact with the underlying structural abnormality (e.g., transient ischemia and hemodynamic, electrolyte, metabolic, and respiratory abnormalities; see Table 24-4),[2,3] and (3) individual patients' preferences and decisions regarding pharmacologic versus interventional approaches. The identification of contributing factors, which interact with underlying etiology as the proximate causes of an arrhythmia, is inherent to any treatment plan. Contributing factors may be systemic or cardiac. The major systemic abnormalities include hemodynamic dysfunction, hypoxia, acidosis, electrolyte disturbances, toxic or proarrhythmic drug effects, and endocrine abnormalities. Central nervous system factors, including fluctuations in autonomic tone, may cause or aggravate specific arrhythmias. Prompt reversal of serious arrhythmias may follow control of these disturbances.

Table 24-4: Causes of Cardiac Arrhythmias: Structure and Function

Structural Abnormalities	Functional Factors
Coronary heart disease	Transient alterations of coronary blood flow
Acute myocardial infarction	Vasomotor dynamics
Chronic ischemic heart disease	Acute ischemia
	Reperfusion after ischemia
Ventricular hypertrophy	
Secondary left ventricular hyper-trophy	Systemic factors
Hypertrophic cardiomyopathy	Hemodynamic fluctuations
Obstructive	Hypoxia, acidosis
Nonobstructive	Electrolyte imbalance
Myopathic ventricles	Neurophysiologic alterations
Dilated cardiomyopathy	Central nervous system influences
Pericarditis, myocarditis	Receptor function
Noninfectious inflammatory diseases	Neurotransmitters
Infiltrative diseases	
	Toxic substances
Structural electrophysiology abnor-malities	Proarrhythmic drugs
Sinus node, AV node, and His-Purkinje disease	Idiosyncratic
Accessory pathways	Dose dependent
Abnormalities of molecular structure (ion channels)	Cardiotoxic substances

SOURCE: Modified from Myerburg et al.,[3] with permission of the *American Journal of Cardiology*.

Primary and secondary arrhythmias must be distinguished for both management and prognosis. Medical writings contain conflicting definitions of the term *primary arrhythmia*, which must be clarified for interpretation of investigative data. Historically, a primary arrhythmia was first described as one that resulted from an electrophysiologic disturbance caused by a disease process, in the absence of a significant change in hemodynamic function. An arrhythmia that resulted from an electrical disturbance caused or perpetuated by hemodynamic deterioration or metabolic abnormalities was defined as a secondary arrhythmia (Fig. 24-7). In the former, antiarrhythmic drugs alone may be useful, while a secondary arrhythmia requires the concomitant use of hemodynamically active drugs to support the failing circulation. In secondary arrhythmias, antiarrhythmic and hemodynamically active drugs have complementary roles. Subsequent uses of the term *primary arrhythmia* were an arrhythmia that was the first clinical manifestation of disease, such as cardiac arrest due to ventricular fibrillation in coronary heart disease, or an arrhythmia in the absence of structural disease. To avoid confusion, the term primary must be carefully defined with each use.

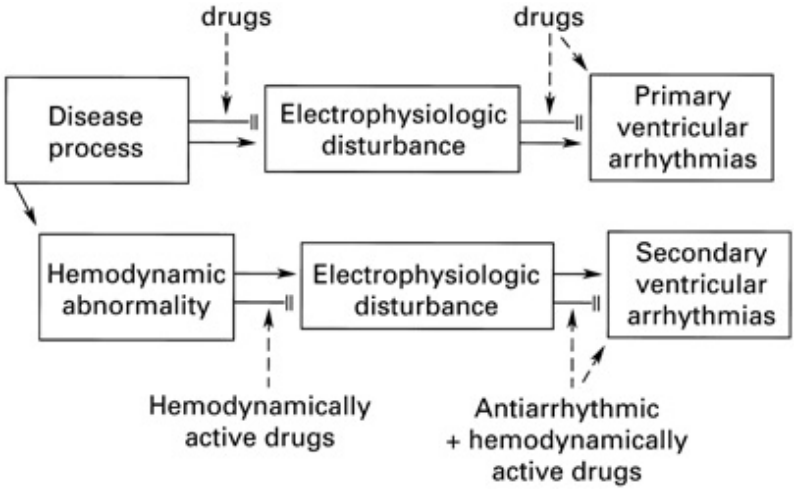

Figure 24-7: Primary and secondary arrhythmias. When a disease process directly initiates an electrophysiologic disturbance, the resulting arrhythmia is referred to as primary. In contrast, when the disease process produces a hemodynamic abnormality that in turn initiates the electrophysiologic disturbance, a resulting arrhythmia is referred to as secondary. Antiarrhythmic drugs may be used to prevent the electrophysiologic disturbance, prevent the electrophysiologically unstable heart from developing a manifest arrhythmia, or reverse a primary arrhythmia. In secondary arrhythmias, hemodynamically active drugs are used to prevent or reverse secondary electrophysiologic disturbances, usually in conjunction with antiarrhythmic drugs. Antiarrhythmic drugs alone are less likely to be effective for secondary arrhythmias. (Modified from Myerburg et al.[1] Reproduced with permission from the publisher and authors.)

Direct cardiac interventions for control of arrhythmias include pharmacologic approaches, ablation of specific foci involved in arrhythmogenesis, antiarrhythmic surgical approaches, and implantable devices designed to control tachyarrhythmic events or to prevent symptomatic bradyarrhythmias (Table 24-3). Antiarrhythmic drugs may be classified into groups using the modified Vaughn Williams system, which categorizes them on the basis of electropharmacologic and electrophysiologic properties (see Table 24-5). This classification is useful and practical for the clinician but has shortcomings. These include difficulty categorizing new drugs, exclusion of some drugs with obvious antiarrhythmic properties (e.g., adenosine), and inability to correlate drug class with specific effects as antiarrhythmic agents. Another classification system, the Sicilian gambit,[15] was developed for the purpose of providing deeper insight into drug effects, therapeutic targets, mechanisms of action, and responses (Fig. 24-8). While it is too complex for use as a practical clinical tool, it provides an excellent teaching method for understanding applied pharmacology. The usual dosages and routes of administration for the antiarrhythmic agents approved by the U.S. Food and Drug Administration at the time of writing are listed in Table 24-6. A number of other drugs are currently at various stages of study for ventricular and supraventricular arrhythmia indications.

Table 24-5: Modified Vaughn Williams Classification of Drugs Approved for Antiarrhythmic Uses

Examples	Depolarization	Repolarization
Class I: Membrane-active drugs		
IA Quinidine (Quinaglute, Quinidex, Cardioquin)Procainamide (Pronestyl, Procan-SR)Disopyramide (Norpace)Moricizine (Ethmozine)	Moderate depression of Na^+ current; intermediate kinetics	Prolonged
IB Lidocaine (Xylocaine)	Limited depression of	No effect or shortened
Tocainide (Tonocard)	Na^+ current; rapid kinetics	
Mexiletine (Mexitil)		

Phenytoin (Dilantin)			
IC	Flecainide (Tambocor)	Marked depression of Na^+ current; slow kinetics	Minimal effect
Propafenone (Rhythmol)			
Class II: Beta-adrenoceptor blocking drugs			
	Propranolol (Inderal)		
	Esmolol (Brevibloc)		
	Acebutolol (Sectral)		
Class III: Drugs that prolong repolarization			
	Amiodarone (Cordarone)		
	Bretylium tosylate (Bretylol)		
	Sotalol (Betapace; Betapace AF)		
	Ibutilide (Corvert)		
	Dofetilide (Tikosyn)		
Class IV: Ca^{2+}-entry blocking drugs			
	Verapamil (Isoptin, Calan)		
	Diltiazem (Cardizem)		
Unclassified in this system			
	Digoxin (Lanoxin)		
	Adenosine (Adenocard)		

NOTE: Drugs identified by name are limited to those approved for antiarrhythmic use by the U.S. Food and Drug Administration at the time of this writing (not necessarily inclusive of all brand names).

Table 24-6: Antiarrhythmic Drugs: Dosage and Kinetics

Drug	Usual Dosing Range[a]	Half-Life, h	Therapeutic Range, μg/mL	Plasma Protein Binding, %	Major Route of Excretion
Class IA					
Quinidine	Oral sulfate: 200-600 mg q 6 h	5-7	2.3-5	80	H
	Oral long acting: 330-660 mg, q 8 h or q 6 h				
Procainamide	Oral: 250-750 mg, q 4 h or q 6 h	3-5	4-10	15	R[b]

	Oral long-acting: 500-1500 mg, q 8 h or q 6 h				
	IV: 10-15 mg/kg at 25 mg/min, then 1-6 mg/min				
Disopyramide	Oral: 100-200 mg, q 8 h or q 6 h	8-9	2-5	35-95	H/R
Moricizine[c]	Oral: 150-300 mg, q 12 h or q 8 h	6-13	-	95	H
Class IB					
Lidocaine	IV: 1-3 mg/kg at 20-50 mg/min, then 1-4 mg/min	1-2	1-5	60	H
Tocainide	Oral: 400-600 mg q 8-12 h	15	4-10	10	H
Mexiletine	Oral: 200-400 mg q 8 h	10-12	0.5-2.0	55	H
Class IC					
Flecainide	Oral: 100-200 mg q 12 h	20	0.4-1.0	40	H
Propafenone[d]	Oral: 150-300 mg q 8 h	2-10	0.5-1.5[e]	95	H
Class II					
Propanolol	Oral: 10-100 mg q 6 h	4-6	0.04-0.10	95	H
	IV: 0.1 mg/kg in divided 1-mg doses				
Esmolol	IV: 500 mg/kg per min x 1 min followed by 50 mg/kg per min x 4 min, repeat with 50-mg increments to maintenance dose to 200 mg/kg per min	9 min	-	55	H
Acebutolol	Oral: 200-600 mg q 12 h	3-4	-	26	H/R
Class III					
Amiodarone	Oral: 600-1600 mg/day × 1-3 weeks, then 200-400 mg/day	50 days	1-2.5	96	H
	IV: 15 mg/min × 10 min, then 1 mg/min × 6 h, then maintenance at 0.5 mg/min	?	?		
Bretylium	IV: 5-10 mg/kg at 1-2 mg/kg, then 0.5-2.0 mg/min	8-14	0.5-1.5	-	R

Sotalol[d]	Oral: 80-240-mg q 12 h	10-15	-	0	R
Ibutilide	IV: (for >60 kg) 1 mg over 10 min; may repeat × 1 10 min after completion of initial dose[f]	2-12	-	40	H
Dofetilide	Oral: 500 μg q 12 h; creatinine clearance must be calculated and dose adjusted accordingly	10	1.0-3.5 (in ng/mL)	60-70%	R
Class IV					
Verapamil	Oral: 80-32 mg q 6-8 h	3-8	0.1-0.15	90	H
	IV: 5-10 mg in 1-2 min				
Diltiazem	IV: 0.25 mg/kg body wt over 2 min; if response inadequate, wait 15 min, then 0.35 mg/kg over 2 min; maintenance 10-15 mg/h	3.5-5.0	0.1-3.0	70-80	H
Other					
Digoxin	Oral 1.25-1.5 mg in divided doses over 24 h followed by 0.125-0.375 mg/day	36	0.8-1.4 (in ng/mL)	30	R
	IV: Approximately 70% of oral dose				
Adenosine	IV: 6 mg rapidly; if unsuccessful within 1-2 min, 12 mg rapidly	10 s	-	-	-

[a]All dosing should follow FDA-approved guidelines as outlined in package insert or *Physicians' Desk Reference* (see also Chap. 27; does not include pediatric use in infants and young children).
[b]Parent compound metabolized to active metabolite (NAPA) in liver; both active metabolite and unmetabolized parent compound excreted by kidneys.
[c]Shares class IB and IC activities.
[d]Shares class II activity.
[e]Active metabolite limits significance of these measurements.
[f]D/C upon arrhythmia conversion or for ventricular tachycardia or non-pharmacologic prolongation of QT or QT_c.

ABBREVIATIONS: H-hepatic; R-renal.

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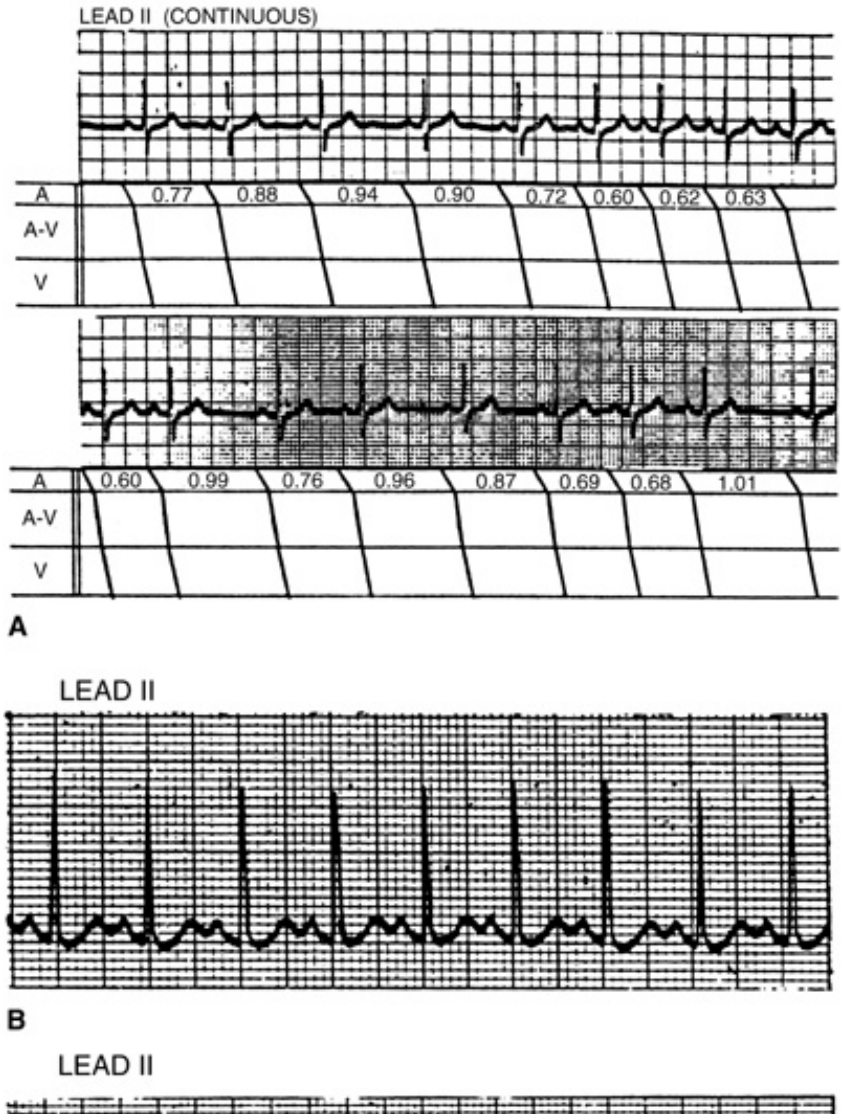
Chapter 24: RECOGNITION, CLINICAL ASSESSMENT, AND MANAGEMENT OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

SUPRAVENTRICULAR ARRHYTHMIAS

Figure 24-9 compares mechanisms, clinical features, diagnosis, and electrocardiography of the supraventricular arrhythmias described in this section.

Spectrum of Sinus Rhythms and Sinus Tachycardia

The range of rates defining normal sinus rhythm is between 60 and 100 impulses per minute. The rhythm is usually regular, but a rhythmic variation exceeding 0.12 s between the longest and shortest cycles in a sequence on a resting tracing defines sinus arrhythmia (Fig. 24-10*A*). This normal variant is most common in children and decreases with advancing age. It usually has a phasic pattern, in which the cycle lengths shorten with inspiration and lengthen with expiration. If the cycle is unrelated to the respiratory cycle, it is referred to as nonphasic.



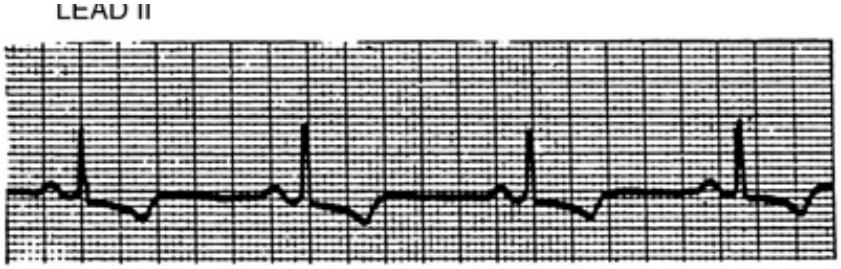


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Figure 24-10: *A.* Sinus arrhythmia. The sinus cycles are indicated in seconds in the atrial (A) tier; they range from 0.60 to 1.01 s. Note that the P-wave amplitude increases as the sinus pacemaker accelerates. *B.* Sinus tachycardia. Note normally shaped and directed P waves, normal PR interval, and a rate of almost 150 per minute. *C.* Sinus bradycardia. Note normally directed (but abnormally wide) P waves, normal PR interval, and a rate of slightly more than 50 per minute.

A sinus rhythm at a rate below 60 impulses per minute is defined as sinus bradycardia (Fig. 24-10*C*); its significance is largely dependent upon clinical circumstances (see "Sinus Bradycardia," below). It may be normal, even at rates in the mid- to low 30s, in highly trained young athletes at rest, while it is generally considered abnormal, even at rates in the high 40s, in the elderly.

A sinus rate above 100 impulses per minute is defined as sinus tachycardia. Sinus rates in excess of 100 per minute are normal in infants and children under 2 years of age. Occasionally, otherwise normal older children and adults have sinus rates persistently or intermmitently (the latter often positional) in excess of 100 per minute in the absence of normal physiologic or pathologic stimuli for heart rate increases. Such forms of inappropriate sinus tachycardia, apparently mediated by autonomic factors in most cases[16,17] and by electrophysiologic factors in some,[17] may cause disturbing or disabling symptoms.[16,17] If fast enough and persisting for months, it may precipitate a reversible form of tachycardia-induced heart failure.[17,18]

The category of physiologic sinus tachycardias includes the normal sinus rate responses to exercise, excitement, anxiety, and other emotional stresses. Pharmacologic sinus tachycardias result from medications such as epinephrine, ephedrine, amyl nitrate, isoproterenol, and atropine, and may occur upon exposure to alcohol, nicotine, or caffeine. The heart rate responses are a result of the pharmacologic properties of these drugs. Pathologic sinus tachycardia may be secondary to noncardiac systemic factors or due to specific cardiac abnormalities. Among the secondary causes are fever, hypoxemia, hemorrhage, hypotension, thyrotoxicosis, and anemia. Cardiovascular causes include congestive heart failure, myocardial infarction, and pulmonary embolism.

ELECTROCARDIOGRAPHIC FEATURES

The ECG in sinus tachycardia reveals a rate in excess of 100 per minute accompanied by a normal PR relationship and a normal P-wave vector (Fig. 24-10*B*). The upper rate range of sinus tachycardia varies according to the patient's clinical status and factors responsible for the tachycardia. For instance, in the physiologic tachycardia group, the upper limit in the normal adult during exercise testing may range from 160 to 190 per minute, whereas the highly trained athlete may attain a rate of at least 200 per minute under maximal effort. In contrast, the pharmacologic tachycardias do not commonly induce a rate exceeding 140 per minute, whereas rates secondary to pathologic states usually range from just over 100 per minute to 150 per minute (e.g., hypotension, hypovolemia, hemorrhage, or fever) to 160 per minute (hyperthyroidism or severe heart failure). In a persistent sinus tachycardia, the rate characteristically varies during the course of the day, in contrast to the fixed rate that occurs in ectopic tachycardias or AV nodal reentrant tachycardia. Carotid sinus massage usually slows sinus tachycardia transiently.

MANAGEMENT OF SINUS TACHYCARDIA

Sinus tachycardia, except when it is an appropriate response to acute physical or emotional stress, is usually categorized as persistent and is easily recognized. Its management almost always depends on control of exogenous or endogenous systemic factors or of an underlying cardiac disease. Its differentiation from other SVTs at rates of 150 or more a minute may be achieved with carotid sinus massage. Specific therapy is rarely required. When it is required, beta-adrenergic blockade will often achieve at least partial control. In uncomplicated acute myocardial infarction, the sinus rate may be controlled with small doses of propranolol (10 to 20 mg every 6 h). Persistent sinus tachycardia occurs in thyrotoxicosis, and higher doses of propranolol may be required for its control. Sinus tachycardia during heart failure or hypovolemic states will respond promptly to improving hemodynamic status. The chronic or intermittent form of nonparoxysmal inappropriate sinus tachycardia, when symptomatic or associated with tachycardia-induced heart failure, may require RF energy modification or ablation of the sinus node area[19] if it is not controllable by drug therapy.

Premature Atrial Impulses

Atrial extrasystoles or premature atrial contractions (PACs) are extremely common and may occur in normal individuals or in the presence of systemic or cardiac abnormalities. They occur at any age, including infancy. Both endogenous (febrile illnesses, thyrotoxicosis, emotional stress, etc.) and exogenous (alcohol, tobacco, or caffeine consumption) systemic factors may initiate or worsen atrial extrasystolic activity. Among cardiac causes, myopericarditis, ischemia, heart failure, and digitalis intoxication are all precipitating or contributing factors.

ELECTROCARDIOGRAPHIC FEATURES

The PAC is characterized by (1) a P wave that occurs before the next expected sinus impulse and (2) a change in the vector of the premature P wave. For example, a negative P-wave deflection in leads II, III, and aVF suggests an origin from the lower portion of the atrium. The features of the PAC in leads I and V_1 can help distinguish right and left atrial origins. If the premature P wave is positive in lead I and negative in V_1, the impulse is probably of right atrial origin. A negative P wave in leads I and V_6, and a positive P wave in V_1 is consistent with a left atrial origin. If a premature P wave is narrower than in sinus and positive in aVR and aVL, a septal origin is probable. When a premature P wave is negative in aVL and positive in the inferior leads, a right superior pulmonary vein origin should be suspected.

The PR interval of the conducted PAC may be normal or prolonged (see Fig. 24-11). Marked prolongation of the PR interval may occur when the PAC is very premature and may also indicate the presence of dual AV nodal pathways. Subtle electrocardiographic patterns include (1) superimposition of the premature P wave on the T wave of the preceding sinus impulse and (2) an unexpected pause due to failure of conduction of a PAC to the ventricles. In both instances, careful inspection of the T wave of the sinus impulse before the PAC will reveal a distortion of the T wave, sometimes minimal, indicating the presence of the PAC. When the coupling interval of the PAC to the previous sinus P wave is short, aberrant intraventricular conduction makes the diagnosis dependent upon recognition of the P wave distorting the previous T wave (Fig. 24-11*B*). The hallmark of timing of PACs is the less than fully compensatory pause. Since the premature impulse commonly resets the sinus cycle, the PAC is bracketed by a cycle terminated by the early P wave and a return cycle close to the underlying sinus cycle length (Fig. 24-11*A*). The sum of the two cycles will be less than fully compensatory. Occasionally, fully compensatory pauses or longer than compensatory pauses occur because of failure to invade and reset the sinus node cycle or delay of its return because of overdrive suppression.

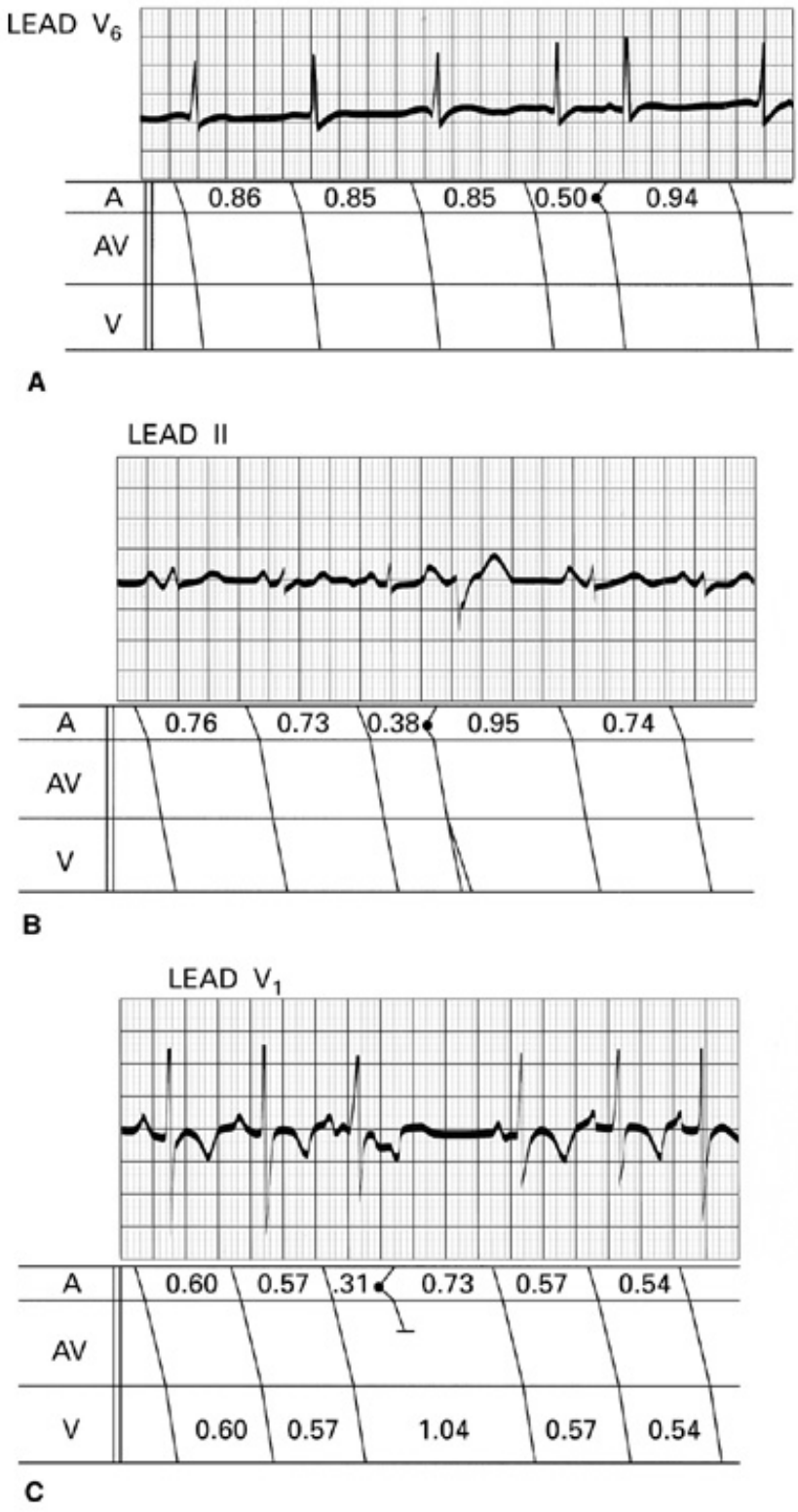

Figure 24-11: *A*. The fifth impulse is an atrial premature beat; there is a premature P wave (usually labeled P) followed by a normal QRS-T complex, and the postextrasystolic pause is longer than the sinus cycle but less than compensatory. *B*. The fourth impulse is an atrial premature beat with aberrant intraventricular conduction; there is a premature P wave followed by an anomalous QRS-T complex; the postextrasystolic pause is less than compensatory. *C*. Nonconducted atrial premature beat. Following the third ventricular complex, a P wave negatively deforms the ST segment and is not followed by a ventricular response.

MANAGEMENT OF PREMATURE ATRIAL CONTRACTIONS

PACs usually do not require treatment, especially when they occur in normal individuals or when due to systemic influences or minor cardiac abnormalities such as mitral valve prolapse and acute viral pericarditis. When PACs may be the triggering events for sustained arrhythmias, their management may become important. Generally, SVT due to AV nodal reentry or the WPW syndrome, paroxysmal atrial fibrillation, or the rare instances of induction of sustained ventricular arrhythmia by supraventricular impulses are best managed by therapy targeted to the prevention of the sustained arrhythmias, but occasionally suppression of triggering PACs is helpful. In recent years, repetitive focal PACs and atrial tachycardia on ambulatory monitor recordings from patients prone to atrial fibrillation have been identified as RF ablation targets during studies in the electrophysiology laboratory. In some patients, these forms of PACs appear to act not only as triggers, but also as drivers, of atrial fibrillation episodes.[20]

Annoying palpitations are a common symptom of PACs in patients who have either no underlying heart disease or mitral valve prolapse. Reassuring the patient of the benign nature of the arrhythmia may suffice, and no therapy is necessary other than removal of inciting factors, such as cigarettes, coffee, alcohol, and excessive fatigue. When the palpitations are sufficiently bothersome to affect on the quality of life, an intervention must be considered. A low dose of a beta-adrenergic blocking agent is preferred to more aggressive (and more dangerous) membrane-active antiarrhythmic agents. Digitalis has been tried, but no systematic studies of its efficacy have been reported.

When it is necessary to treat PACs because of intolerable palpitations, conventional antiarrhythmic agents may be effective. Depending upon tolerance and side effects, any of the membrane-active drugs or adrenoceptor-blocking agents may be considered. Few data are available on the efficacy of antiarrhythmic drug therapy for PACs, but clinical experience suggests that it may be effective, particularly in the absence of structural cardiac or pulmonary disease. Antiarrhythmic drugs have not been approved for this indication in the United States, and the threshold for their use for a troublesome but benign arrhythmia is high. Class IC (see Table 24-5) drugs should be avoided for this indication in patients with even the remote possibility of coronary artery disease because of the adverse outcome in the Cardiac Arrhythmia Suppression Trial (CAST).[21,22] Atrial distention in heart failure may induce PACs; they usually disappear as hemodynamics improve and antiarrhythmic drugs are avoided.

Supraventricular Tachyarrhythmias

Supraventricular tachyarrhythmias include all tachyarrhythmias that originate above the bifurcation of the bundle of His or incorporate tissues proximal to the bifurcation of the bundle of His in a reentrant circuit (Fig. 24-9). The diagnosis requires an atrial chamber rate of 100 impulses per minute or more; the ventricular rate may be less when AV conduction is incomplete. SVTs usually have narrow QRS complexes, but they may be wide because of aberrant conduction through the intraventricular conducting tissue, because of participation of a bypass tract in the ventricular depolarization pattern, or when bundle branch block coexists independently.

SVTs may be separated into three groups based on duration: brief paroxysms, persistent, and chronic. Arrhythmias that are paroxysmal in onset and offset [e.g., paroxysmal SVT (PSVT) due to AV nodal reentry or WPW syndrome, paroxysmal atrial fibrillation, and paroxysmal atrial flutter] tend to be recurrent and of short duration, lasting from seconds to hours. Persistent tachycardias [e.g., sinus tachycardia, ectopic atrial tachycardia (nonparoxysmal), multifocal atrial tachycardia, longer episodes of PSVT, or atrial flutter or fibrillation] may last for days or weeks and may be associated with a specific contributing pathophysiologic factor, such as decompensated chronic obstructive pulmonary disease, pulmonary emboli, electrolyte disturbances, or drug toxicity. They tend to be recurrent when an underlying structural cause, such as atrial disease or mitral valve disease, is the dominant pathophysiologic factor. When a transient

functional abnormality dominates, such as hypoxemia, heart failure, or an electrolyte abnormality, it may be an isolated clinical event, reappearing only if or when the inciting event occurs. Longstanding or chronic SVTs (e.g., chronic atrial fibrillation or chronic atrial flutter), particularly in the presence of advanced structural heart disease, generally do not revert if untreated, may fail to revert even with attempted treatment, and if reverted will frequently recur despite therapy.

THE REENTRANT PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS

PSVT may be due to AV nodal reentry, the WPW syndrome, or intraatrial or sinoatrial reentry. Most of the interventions for SVT listed in Table 24-7 are applicable to these arrhythmias.

Table 24-7: Management of Paroxysmal Supraventricular Tachycardias

Interventions	Acute	Long-Term
Physiologic interventions	Rest, sedationValsalva maneuverCarotid sinus massage	Self-administered Valsalva maneuver, carotid sinus massageAvoidance of inciting factors
Pharmacologic therapy	Drugs with direct effect on AV nodal or accessory pathway	Drugs that alter properties of AV node or accessory pathways
	Drugs that control ventricular rate	Drugs that control ventricular rate
Catheter ablation and surgical techniques	-	Ablation of reentrant pathwayModification of AV node
Electronic devices	Temporary pacingCardioversion	Permanent pacemaker

PSVT due to AV Nodal Reentry

The commonest form of PSVT is due to AV nodal reentry. The underlying disturbance in AV nodal reentry is the presence of dual AV nodal pathway physiology. Previously thought to be restricted to the compact anatomic AV node itself, the dual-pathway physiology is now known to exist in the *region* of the AV node. One pathway is capable of faster conduction and usually has a longer refractory period; the other conducts more slowly and has a shorter refractory period. Both the slow and the fast pathways have components in the low atrial approaches to the AV node as well as in the AV node itself (Fig. 24-12).

In the presence of dual AV nodal physiology, a premature atrial impulse with a coupling interval sho enough to encroach on the refractory period of the fast pathway may block in the fast pathway while allowing conduction to proceed through the slow pathway (Fig. 24-12*B*). This results in slower-than-normal conduction through the AV node, prolonging the PR interval abruptly. The slowly propagating impulse may then reenter the fast pathway in the retrograde direction and arrive at the proximal end after it has recovered excitability. When this occurs, a circuit is completed and the impulse may then reenter the slow pathway if it too has regained excitability (Fig. 24-12*C*). Once established, this reentrant pattern will continue until the relationship between conduction times and refractory periods in the two pathways is disturbed so as to interrupt the cycle. The circulating impulse progresses through the His-Purkinje system to ventricular muscle each time it passes the distal end of the reentrant loop and provides retrograde atrial activation each time it passes the proximal end. Because antegrade conduction is slow and retrograde conduction rapid, atrial activity begins soon after the onset of ventricular activation,

usually creating an inability to identify P waves on the standard ECG during AV nodal reentrant tachycardia (Fig. 24-13) because they are within the QRS complex. The characteristic alignment of electrograms recorded during AV nodal reentrant tachycardia is shown in Fig. 24-14*A*. In a much less common form of AV nodal reentry, the circulating wavefront proceeds antegradely down the fast pathway and retrogradely up the slow pathway, creating a sequence of excitation of atria that is delayed relative to ventricular activation because of slow retrograde conduction. This form of AV nodal reentrant tachycardia is characterized by a long RP interval and a short PR interval, with a clearly visible inverted P wave in II, III, and aVF (Fig. 24-9). The electrophysiologic findings in the common and uncommon forms of AV nodal reentry are compared in Figs. 24-14*A* and -14*B* (see also Chap. 23).

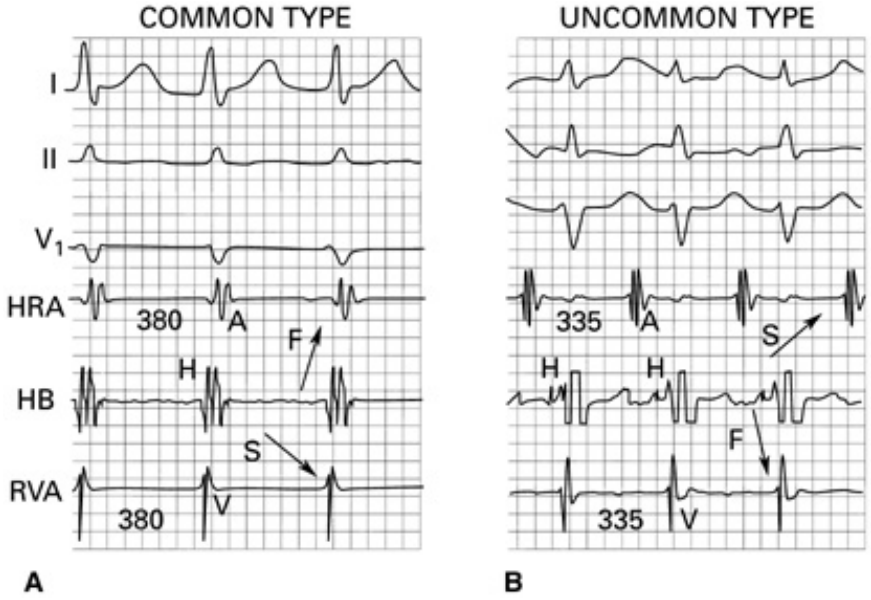

Figure 24-14: Common and uncommon forms of AV nodal reentrant tachycardia recorded during electrophysiologic studies. *A*. The common type of AV nodal reentrant tachycardia, antegrade conduction in the slow pathway and retrograde in the fast pathway, results in atrial (A) and ventricular (V) activation that are close to one another in time. Characteristically, intracardiac recordings demonstrate a 'lining up' of atrial and ventricular electrograms, indicating that the atria are activated before completion of ventricular activation. *B*. In the uncommon type of AV nodal reentrant tachycardia, antegrade fast pathway and retrograde slow pathway conduction change the relative timing pattern so that atrial activation is delayed relative to ventricular activation, and the electrograms are not in line. In this form of PSVT, the RP interval is longer than the PR interval on the ECG, which results in inscription of the retrograde P wave *after* the ST-T wave of the related ventricular impulse. The uncommon type of AV nodal reentrant tachycardia may be difficult to distinguish from other arrhythmias, such as ectopic atrial tachyarrhythmias or concealed WPW syndrome (see the text).

ELECTROCARDIOGRAPHIC FEATURES

PSVT due to AV nodal reentry is characterized by an abrupt onset and offset, and usually has a narrow QRS complex without clearly discernible P waves. Occasionally, however, P waves can be seen as "pseudo-R" waves, particularly in V_1 and the inferior leads, and more rarely as "pseudo-Q" waves, when the retrograde atrial depolarization precedes ventricular depolarization. Comparison with QRS morphology during sinus rhythm is essential to establish the presence of these waves.

The heart rate during PSVT due to AV nodal reentry is commonly in the range of 160 to 190 per minute but may be as slow as 120 to 130 per minute and occasionally faster than 200 per minute. When preexisting bundle-branch block is present, the tachycardia will reflect the preexisting wide QRS complex, and functional bundle-branch block due to tachycardia may also occur, making a distinction from ventricular tachyarrhythmias difficult (Fig. 24-15). Functional bundle-branch block may have either a left or a right bundle-branch block pattern.

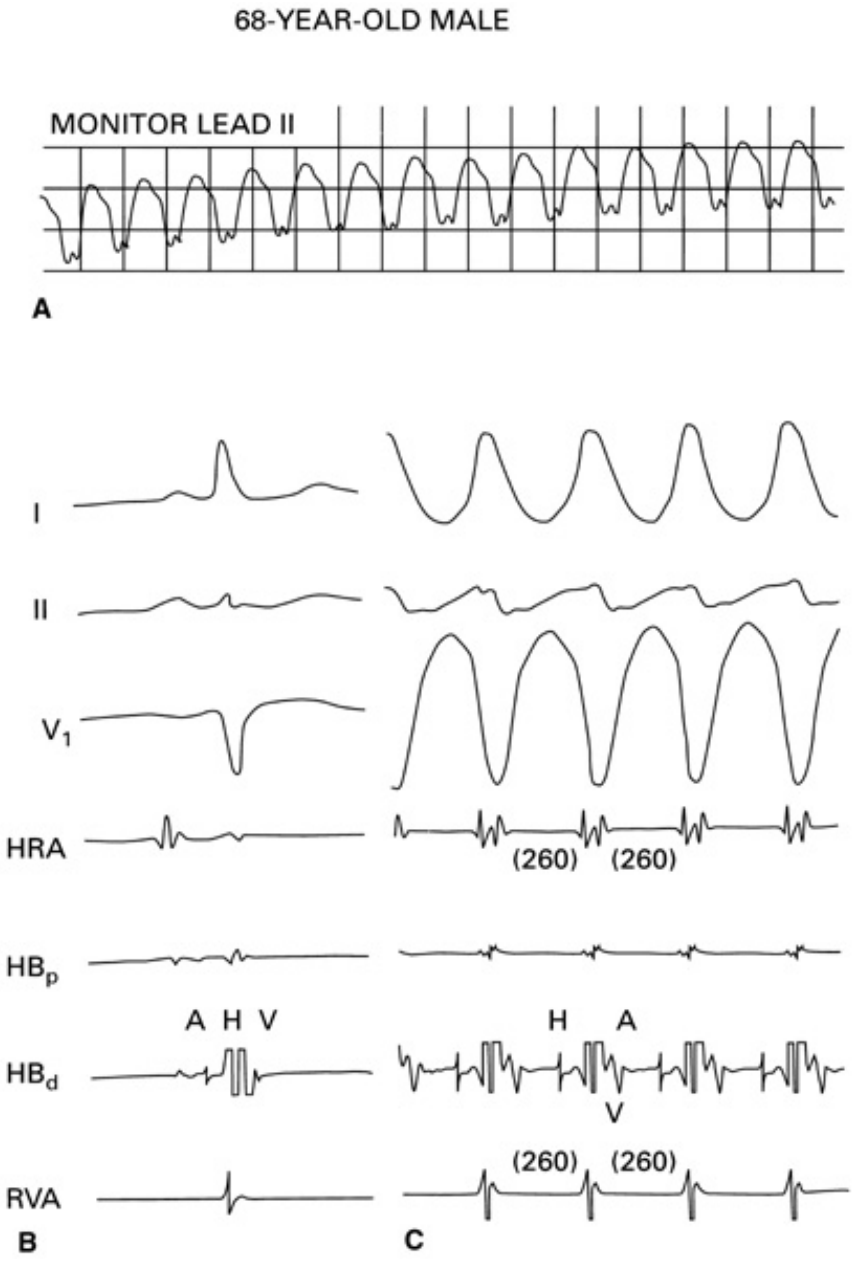

Figure 24-15: PSVT due to AV nodal reentry. *A.* The initial presenting rhythm was a wide-QRS tachycardia with a vertical axis and a left bundle-branch block pattern. *B.* A sinus impulse with intracardiac recordings demonstrating normal sequences of AV conduction. *C.* Recording during a wide-QRS tachycardia with a left bundle-branch block pattern. The nearly simultaneous A and V activation patterns in the retrograde and antegrade directions (i.e., atrial activation before the end of ventricular activation) suggest the common form of AV nodal reentry rather than ventricular tachycardia.

MANAGEMENT OF PSVT DUE TO AV NODAL REENTRY

PSVT due to AV nodal reentry is a benign disturbance requiring intervention primarily for the patient's comfort and sense of well-being. When it coexists with other disease processes in which the tachyarrhythmia is poorly tolerated, such as ischemic heart disease or mitral stenosis, it may have more serious implications. Occasionally, the rate is rapid enough to cause near-syncope or syncope in otherwise normal individuals, although such rates are more common in PSVT due to WPW (see below).

Rest, sedation, and vagotonic maneuvers are simple means of reverting acute episodes, and patients can be taught self-administered vagotonic maneuvers for recurrences. Patients should be advised to avoid inciting factors, such as smoking, alcohol, extreme fatigue, and stress. Many of the effective pharmacologic interventions for acute episodes used in the past have given way to new drug therapy. Infusions of sympathomimetic drugs (e.g., phenylephrine or methoxamine), parasympathomimetic drugs (e.g., edrophonium or neostigmine), and digoxin have been supplanted by intravenous adenosine, Ca^{2+}-entry blockers, or beta-adrenergic blockers for managing the acute episodes. Adenosine, 6 mg given intravenously (see Fig. 24-13), followed by one or two 12-mg boluses if necessary, is effective and safe[23] for acute treatment. Because of its very short duration of action and lack of the negative inotropic effects of Ca^{2+}-entry blockers, it is now preferred to other acute pharmacologic therapies, especially when managing a patient with concomitant structural heart disease. A 5-mg bolus of verapamil, followed by one or two additional 5-mg boluses 10 min apart if the initial dose does not convert the arrhythmia, has been an effective regimen in up to 90 percent of patients with PSVT due to AV node reentry.[24,25] However, it must not be used for an unknown wide QRS tachycardia because of risk of adverse effects when used in patients who have VT.[26] Intravenous diltiazem is also effective.[27,28] Initial treatment consists of a bolus of 0.25 mg/kg body weight administered over 2 min. If the response is inadequate, a repeat bolus of 0.35 mg/kg over 2 min is administered 15 min later. Intravenous digoxin, 0.5 mg infused over 10 min and repeated if necessary, may convert the arrhythmia. An additional 0.25 mg every 4 h to a maximum dose of 1.5 mg in 24 h may be used. A slow infusion of propranolol may be used;[29] 1 mg/min is given to a total dose of 5 to 10 mg or a significant fall in blood pressure. The class IA antiarrhythmic agents, which appear to depress conduction in the fast pathway, may be tried if other drugs fail,[30] a strategy that is rarely needed.

Several special points must be remembered. When the QRS complex is wide and VT is mistakenly diagnosed as SVT with aberrant conduction, intravenous verapamil frequently causes a clinically significant fall in blood pressure and potentially lethal events.[26] Unless it is known with certainty that a wide QRS tachycardia is due to aberrant intraventricular conduction or preexisting bundle-branch block, verapamil should not be used. Similarly, in patients with coexisting hemodynamically significant underlying heart disease, intravenous propranolol must be used with caution, if at all. For those few patients in whom the clinical setting demands an immediate return to a normal sinus mechanism, DC cardioversion can be employed. A low-energy shock (10 to 50 W·s) may be sufficient; larger energies are used if necessary. If DC cardioversion should be avoided, pacing the right atrium or ventricle via a temporary pacing catheter is usually successful (see Chap. 31).

Long-term prevention of recurrent PSVT due to AV nodal reentry may be achieved with pharmacologic therapy or catheter ablation. Surgical techniques and electronic devices have been used in the past but are now obsolete. Patients who have infrequent, well-tolerated episodes that are short-lived and/or respond to self-administered physiologic maneuvers (Table 24-7) may require no long-term interventions. In many others, pharmacologic therapy is sufficient. Most patients have reduced numbers and severity of attacks with simple medications such as propranolol, verapamil, or digoxin. These drugs act by altering conduction velocities and refractory periods in the AV nodal pathways, disrupting the delicate balance required for initiation or maintenance of sustained arrhythmias. Membrane-active antiarrhythmic drugs may prevent

recurrences, both by suppressing triggering premature impulses and by depressing conduction in the anterograde (fast) pathway of the AV nodal reentrant circuit.[30] However, the risk of potentially serious proarrhythmic responses, combined with other troublesome side effects, limits their use for these arrhythmias.

RF catheter ablation is safe and very effective for PSVT due to AV nodal reentrant tachycardia.[31,32] It has therefore emerged as the treatment of choice for patients with frequent arrhythmic episodes and/or poor tolerance of drugs. It is also the preferred option for pharmacologically controllable AV nodal reentrant tachycardia among patients who want to avoid pharmacologic side effects. Among women who have a history of clustering of episodes of AV nodal reentrant tachycardia when perimenstrual, RF ablation procedures should be scheduled when they are premenstrual, in order to maximize the chance of inducing the target arrhythmia during the procedure.[33]

PSVT due to Accessory Pathways: Wolff-Parkinson-White Syndrome

As in AV nodal reentry, the pathophysiology of reentrant tachyarrhythmias in WPW syndrome is a consequence of the presence of two pathways between the atria and the ventricles that have different conduction properties and refractory periods. WPW syndrome appears to be the second commonest cause of PSVT. Since it also occurs in a concealed form, in which the standard ECG is normal during sinus rhythm because of inability of the accessory pathway (AP) to conduct in the antegrade direction, the total number of PSVTs that are due to APs may be considerably higher than previous estimates. In the majority of patients, the effective refractory period of the AP exceeds that of the normal AV nodal-His-Purkinje pathway. Therefore, a premature atrial impulse may block at the AP and conduct antegradely in the normal pathway, ultimately entering the AP in the retrograde direction and reentering the atrium to establish a circus movement tachycardia referred to as orthodromic (Fig. 24-16*A*). Since the AP joins ordinary atrial and ventricular muscle and is not composed of specialized conduction tissue, AP conduction is rarely decremental (as it is in the AV node).

Because the normal pathway is responsible for ventricular activation and the AP for return to the atria, the delta wave is absent during orthodromic tachycardia, causing the QRS complex to normalize. In addition, since the AP provides retrograde conduction to the atria, P waves, if seen, are usually inverted in the inferior and lateral leads. The stability of the reentrant circuit depends upon the balance between conduction properties and refractory periods of the two pathways. In a much less common form of PSVT, a shorter refractory period in the anomalous pathway results in block of an initiating premature atrial impulse in the normal pathway, with antegrade conduction down the AP and then retrograde invasion of the normal AV nodal pathway to establish an antidromic tachycardia. The QRS complex is wide, having the characteristics of a ventricular complex originating near the insertion site of the AP (Fig. 24-16*B*). These wide QRS tachycardias may be difficult to distinguish from ventricular tachyarrhythmias if the existence of WPW syndrome is not established prior to presentation with a tachyarrhythmia. In the concealed form of WPW syndrome,[34,35] only orthodromic tachycardias can occur, because of inability of the AP to conduct in the antegrade direction. Distinction between concealed WPW syndrome and AV nodal reentrant tachycardia may be difficult, although a faster rate (greater than 200 per minute) and a visible retrograde P wave after, rather than lost within, the QRS complex favor concealed WPW syndrome. When atrial flutter or fibrillation occurs in patients with WPW syndrome, the risk of potentially lethal arrhythmias due to very rapid conduction across APs must be considered. The risk is particularly treacherous in patients with short-refractory-period APs, since atrial fibrillation may induce ventricular fibrillation in that circumstance.

PSVT in WPW syndrome may begin in childhood or may not appear until middle age. Among women, there appears to be an increased propensity for the first tachyarrhythmic event to occur during pregnancy.[36] In asymptomatic patients, the probability of losing the capacity for antegrade

conduction across the AP increases with advancing age.[37] Symptomatic arrhythmias may be due to PSVT, atrial fibrillation or flutter, or both in individual patients. In a series of 212 patients with tachyarrhythmias and WPW, PSVT alone occurred in 64 percent, atrial fibrillation alone in 20 percent, and both in 16 percent.[38] Since the reentrant tachyarrhythmias tend to be more rapid than those in patients with AV nodal reentry, they may be more symptomatic. Light-headedness, near-syncope, and syncope appear to occur more commonly in WPW with PSVT or atrial fibrillation than in AV nodal reentry. A risk of sudden death in patients with WPW has been emphasized, but the magnitude of the risk is unknown, even among those with APs that have short refractory periods. Other factors that appear to influence risk are the presence of multiple bypass tracts and a family history of premature sudden death.[39]

ELECTROCARDIOGRAPHIC FEATURES

During normal sinus rhythm, the presence of an AP capable of antegrade conduction (manifest WPW) is recognized by the presence of a short PR interval, followed by slurred initial forces of the QRS complex-the delta wave-resulting from early activation (preexcitation) of the portion of ventricular muscle because specialized conduction has been bypassed. Several algorithms have been developed to identify the location of the AP electrocardiographically.[40,41] Some useful general rules include the following:

1. If the delta wave is positive in lead I and negative in lead V_1, the AP is probably right-sided; the vectors are generally opposite for left-sided tracts.
2. If the delta wave is positive in the inferior leads, the tract is likely to be anterior, and if it is negative in these leads, posterior. If it is negative in aVL, a left lateral AP is likely (Fig. 24-17).

The most common patterns recorded during PSVT due to WPW syndrome are narrow QRS tachycardias at rates ranging from 160 to 240 per minute. Rates may occasionally be faster or somewhat slower. When the tachycardia is antidromic, the QRS complexes are wide and have characteristics similar to fully preexcited impulses during sinus rhythm or PACs (see Fig. 24-16*B*). In atrial fibrillation with WPW syndrome, if the AP has a refractory period longer than the normal pathway, the delta wave will disappear and patterns typical of atrial fibrillation with narrow QRS complexes will be recorded. In contrast, when the refractory period of the AP is shorter, wide QRS complexes dominate the tracing (Fig. 24-18). Multiple bypass tracts are suggested by multiple wide-QRS-complex morphologies during atrial fibrillation with preexcited conduction (Fig. 24-18*B*). A grossly irregular rhythm with wide QRS complexes and a mean ventricular rate in excess of 200 per minute is a clue supporting WPW with atrial fibrillation in the differential diagnosis of a wide-QRS-complex tachycardia. Another form of wide-QRS tachycardia in WPW is orthodromic tachycardia with functional bundle-branch block. When a patient with left lateral bypass tract abruptly develops a wide QRS complex with a left bundle-branch block pattern during orthodromic tachycardia, the diagnosis of SVT with aberrancy is strongly suspected when the cycle length of the tachycardia *lengthens*. Functional left bundle-branch block delays arrival of the circulating impulse at the distal end of a left-sided AP, thereby lengthening the tachycardia cycle. Under most other conditions, appearance of functional left bundle-branch block correlates with *shortening* of the tachycardia cycle length, because the accelerating tachycardia rate encroaches on the refractory period of the left bundle branch (see also Chap. 23).

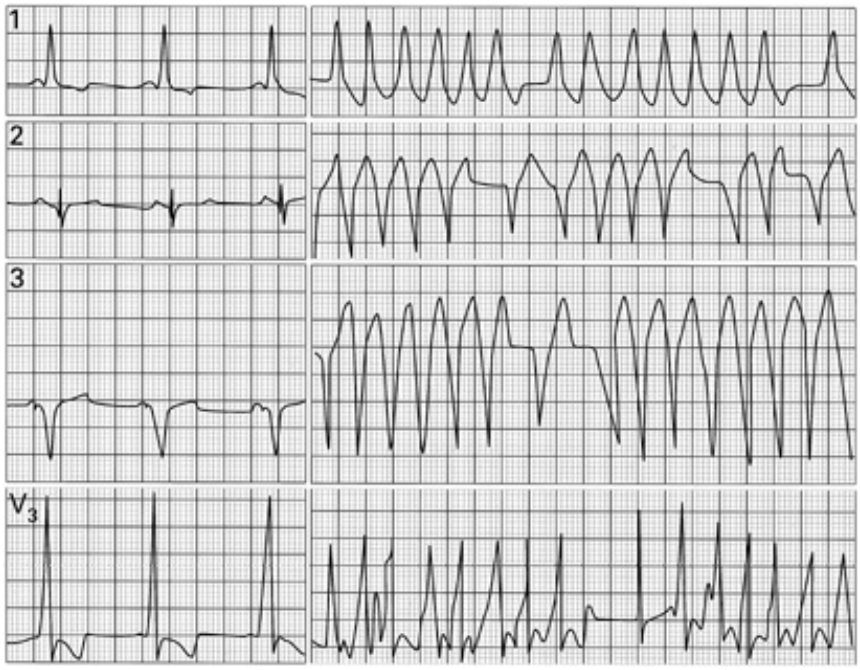

Figure 24-18: Atrial fibrillation in WPW syndrome with accessory pathway conduction. *Left.* Sinus rhythm with a typical preexcitation (delta-wave) pattern. *Right.* Accessory pathway conduction during atrial fibrillation. The QRS axis has shifted to the left, and the ventricular rhythm is now irregular, at a rate in excess of 200 per minute. (From Marriott HJL, Rogers HM. Mimics of ventricular tachycardia associated with the WPW syndrome. *J Electrocardiol* 1969; 2:77. Reproduced with permission from the publisher and authors.)

MANAGEMENT OF PSVT DUE TO WPW SYNDROME

This form of reentrant SVT is amenable to a broad range of interventions. Careful attention to the details of therapy is required because a subgroup of patients is at risk for potentially lethal arrhythmias due to very rapid conduction across the AP during atrial flutter or fibrillation. This concern influences the pharmacologic approaches to PSVT in the WPW syndrome, since drugs have different effects on APs and the AV node and because reciprocating PSVT may convert to atrial flutter or fibrillation.[42]

Physiologic interventions and vagomimetic drugs can be used safely during acute episodes of reciprocating tachycardia. In addition, adenosine, verapamil diltiazem, propranolol, and membrane-active antiarrhythmic agents, such as procainamide, quinidine, or disopyramide, may be used to convert acute reentrant tachycardias. Verapamil[43,44] and lidocaine[45] may accelerate the ventricular rate during atrial flutter or fibrillation in the WPW syndrome, however, and should be avoided if atrial fibrillation is present or if the patient has previously demonstrated alternation between atrial fibrillation and reciprocating tachycardia. Digoxin must be avoided in patients with WPW because it may shorten the refractory period of the AP[46] as well as atrial muscle. Should this occur in the presence of unrecognized atrial flutter or fibrillation or with the conversion of a reciprocating tachycardia to atrial fibrillation, the patient could develop a life-threatening tachyarrhythmia due to rapid AP conduction.[47] Whenever there is doubt, therapy should be limited to those drugs that will depress conduction in the AP or prolong its refractory period, such as the membrane-active antiarrhythmic agents (e.g., intravenous procainamide), or to agents, such as adenosine, that usually have no effect on an AP. Electrical cardioversion should be used if other means have failed or as initial therapy if the patient has extremely rapid rates causing hemodynamic intolerance of the tachycardia.

The approach to long-term management of patients with WPW syndrome is determined by the

physiologic characteristics of the bypass tract and the frequency, duration, and symptoms of arrhythmias. Two primary approaches to therapy are available: drugs and catheter ablation. The latter, using an RF energy source (Fig. 24-19), is the preferred method for treatment of patients with tachycardias symptomatic enough to limit their quality of life (e.g., near-syncope or syncope) or with symptomatic life-threatening arrhythmias in WPW (e.g, atrial fibrillation with short refractory period bypass tract)[34,48] (see Chap. 28). Surgery is a rarely used secondary approach, reserved for the occasional patients requiring treatment and not amenable to catheter ablation or pharmacologic therapy and for some who require surgery for other causes as well.[49] Although intracardiac electrophysiologic studies provide information on drug efficacy and pharmacologic effects on the bypass tract,[50] this invasive procedure is seldom performed for this purpose any longer.[51] Patients who demonstrate a good clinical response to therapy, measured in terms of reduced frequency or rate of tachyarrhythmic episodes, can be managed noninvasively; patients with an intermittent delta wave and no clinical arrhythmia need no therapy. On the other hand, patients who have frequent or poorly tolerated tachyarrhythmias, those who are prone to episodes of atrial flutter or fibrillation[52] (particularly if they develop wide QRS complexes during their tachyarrhythmias, suggesting bypass tract conduction), or those who have a family history of WPW and sudden death[39,53] should be evaluated by electrophysiologic testing. In such patients, catheter ablation using RF energy is the intervention of choice when available in an experienced laboratory and accepted by the patient.[32,48,54] In the event of failure of the technique to interrupt the tract or tracts, surgical interventions may be considered,[55,56] but the threshold for surgical intervention is higher. Among those with symptomatic or life-threatening arrhythmias for whom RF ablation is not available, accepted, or feasible, a clear-cut response to antiarrhythmic therapy is mandated. Among the antiarrhythmic agents, the class IA, IC, and III drugs (see Table 24-5) may be useful. Not all drugs in these categories are approved for this indication in the United States, but efficacy studies are impressive.[57-61] Because of its side-effect profile, the threshold for use of amiodarone has been higher, despite good efficacy[59] (see also Chap. 27). PSVT also occurs in patients with *concealed* WPW syndrome,[35,62] a condition in which the bypass tract is incapable of conducting in the antegrade direction. Thus, there is no delta wave during sinus rhythm, but intact retrograde conduction permits completion of reciprocating tachycardia circuits. The diagnosis is suggested by longer RP intervals on the ECG during tachycardia than occur in AV nodal reentry[35] and can be established by electrophysiologic testing. Management is similar to that for other WPW syndrome patients. However, even though atrial fibrillation may occur, there is no concern about risk of degenerating to ventricular fibrillation. In such patients, the ventricular rate is controlled by normal AV nodal properties, since the AP cannot provide antegrade conduction.

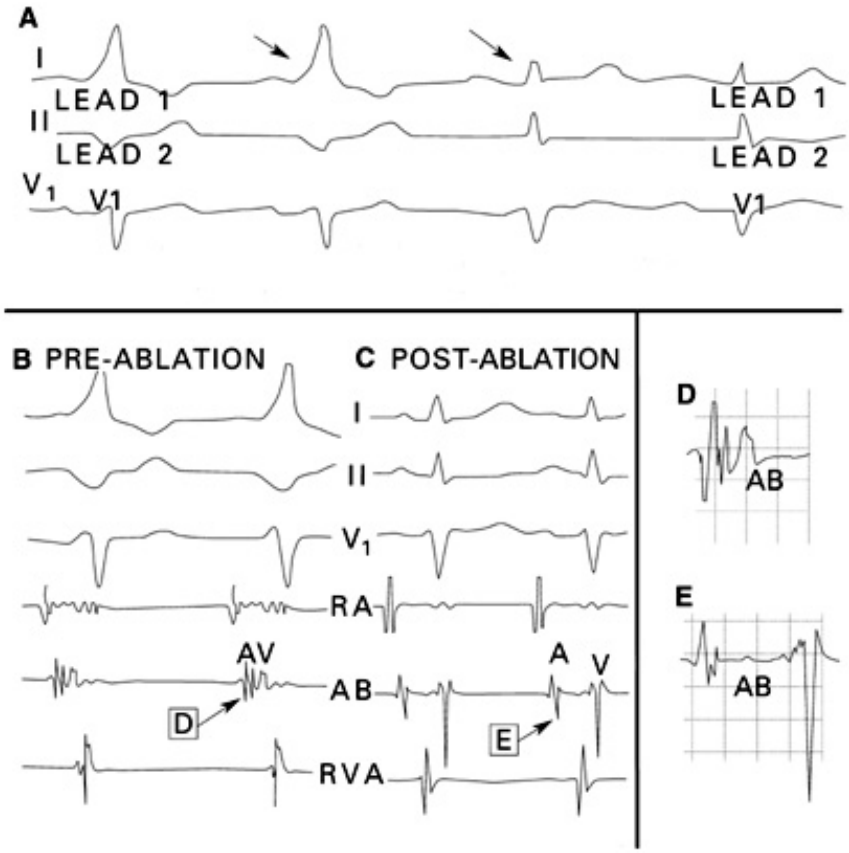

Figure 24-19: RF ablation in WPW syndrome in a 52-year-old female. The patient had frequent recurrent supraventricular tachycardias due to WPW syndrome. *A.* Standard leads I, II, and V_1 demonstrate disappearance of the delta wave from one impulse to the next 5 s after beginning the application of RF energy (compare successive QRS complexes indicated by arrows). *B.* Prior to ventricular ablation, the interval between atrial (A) and (V) activation at the site of the ablation catheter is less than 50 ms, and the sharp spike between A and V likely represents activity in the bypass tract. *C.* Immediately after ablation, the AV interval at the site of the ablation catheter is lengthened to 150 ms, and the accessory pathway spike has disappeared. *D, E.* Enlargements from panels B and C, respectively. AB, ablation catheter; RA, right atrium; RVA, right ventricular apex.

Other Paroxysmal Reentrant SVTs

The other reentrant SVTs are far less common than PSVT due to AV node reentry or WPW syndrome. The PSVT due to sinus node reentry[63,64] is difficult to distinguish clinically and by ECG from sinus tachycardia, except for its paroxysmal onset and offset. P-wave morphology is similar to that in sinus tachycardia. Intraatrial reentry[64,65] may be difficult to distinguish from certain forms of automatic ectopic atrial tachycardia. Intraatrial and sinus node reentry are distinguished from PSVT due to AV node reentry or WPW on a standard ECG because P waves precede narrow QRS complexes during these tachycardias.

Atriofascicular and nodoventricular pathways (Mahaim tracts)[66] may cause PSVT with wide QRS complexes having a left bundle-branch block pattern. Intracardiac electrophysiologic studies are usually necessary for specific diagnosis and treatment of these various PSVTs. There is no generally accepted and predictably effective approach to therapy. Intraatrial reentrant tachycardia may be treated with conventional membrane-active antiarrhythmic agents (beta-adrenergic blocking agents, or perhaps Ca^{2+}-entry blockers). Sinus node reentry may respond to digoxin, propranolol, diltiazem, or verapamil. Surgical interventions[67] are only rarely considered for these

arrhythmias because of their usually benign nature, but catheter ablation with RF energy has proved to be useful for many (see also Chap. 28).

ECTOPIC ATRIAL TACHYCARDIAS

These arrhythmias are usually persistent, are commonly referred to as "nonparoxysmal," and may be associated with specific inciting factors. There are experimental and clinical reasons to support the notion that ectopic atrial tachycardias can be due to mechanisms of reentry,[68] automaticity (enhanced spontaneous phase 4 depolarization),[69] or triggered activity.[70] An underlying toxic or metabolic cause is commonly identified as the factor responsible for ectopic atrial tachycardia, but some are persistent or recurrent, likely due to focal atrial disease. When an ectopic atrial rate is in the range of 160 to greater than 200 per minute and associated with 2:1 conduction or variable block in a patient receiving digitalis, a digitalis-toxic rhythm must be suspected strongly. Decompensated chronic lung disease, metabolic abnormalities (including acute alcohol abuse), electrolyte disturbances, and hypoxemia should be considered when digitalis toxicity has been excluded. Various forms of cardiac disease, including acute myocardial infarction, also may cause ectopic atrial tachycardia. Ectopic tachycardias also may originate from atrial suture lines in patients who have previously had complex congenital heart disease surgery.[71] The atrial arrhythmias may appear many years after the surgery.

Electrocardiographic Features

P waves are usually normal to small in amplitude and may be difficult to identify when the ventricular rate is rapid (Fig. 24-20). Atrial activity does not slow during carotid sinus massage, but AV conduction is usually impeded, making P waves more evident. When ectopic atrial tachycardia is due to digitalis intoxication or occurs in the presence of hyperkalemia, P waves may be "diminutive" (Fig. 24-21*A*).

Management of Ectopic Atrial Tachycardias

Treatment is dictated by identification and reversal of inciting factors, by ablation of a defined focal source when identifiable, and by control of the heart rate when necessary. Temporary pacing is required infrequently. More commonly, the problem is one of a rapid ventricular rate. Attempts to control the ectopic atrial arrhythmias with membrane-active antiarrhythmic drugs have not been generally successful. (Beta-adrenergic blocking agents or Ca^{2+}-entry blocking agents may be successful in controlling the arrhythmia in some patients, but a uniformly beneficial response should not be expected. Electrical cardioversion is not indicated because it is usually unsuccessful.

The mainstay of therapy remains the removal or reversal of inciting factors. If a controllable inciting factor cannot be identified or reversed, antiarrhythmic drugs may be tried. In addition, catheter ablation techniques may have a short-term success rate of as much as 80 percent among those whose arrhythmia has a structural basis.[72] It is not useful for metabolic or toxic causes and is very limited for those having multiple foci of origin.

MULTIFOCAL ATRIAL TACHYCARDIA: CHAOTIC ATRIAL RHYTHM

The diagnosis of multifocal atrial tachycardia, or chaotic atrial rhythm, requires the electrocardiographic identification of P waves having three or more different morphologies, occurring at different cycle lengths (Fig. 24-21*B*). The rhythm, as the name indicates, is usually very irregular, but the rate is not usually excessive (less than 140 per minute).[73] It is most commonly associated with underlying lung disease, metabolic abnormalities, electrolyte disturbances, and, in rare instances, toxic causes, such as digitalis intoxication. Calcium-entry blockers have been tried with some success[74] when given acutely, but there is little success with

conventional membrane-active antiarrhythmic ages. Beta-adrenergic blockers have also been suggested,[75] but feasibility of their use may be limited by the nature of the underlying disease (e.g., chronic obstructive pulmonary disease). Removal of inciting factors (e.g., improvement of P_{O_2}, P_{CO_2}, pH, and/or electrolyte status) has been the most successful approach when the rhythm is associated with pulmonary or metabolic dysfunction, but many patients are forced to tolerate a chronic low-grade tachyarrhythmia because of inefficacy of any approach. There is no role for cardioversion, implantable devices, surgery, or catheter ablation.

ATRIAL FLUTTER

Atrial flutter is a rapid, regular atrial tachyarrhythmia that is less common than the PSVTs or atrial fibrillation. It is observed infrequently in normal individuals[76] but may occur at any age in the presence of underlying atrial abnormalities, such as those secondary to mitral valve disease, congenital heart disease, cardiomyopathies, and, less frequently, coronary artery disease. Subgroups at particularly high risk for developing atrial flutter are children, adolescents, and young adults who have undergone corrective surgery for complex congenital heart diseases, most notably transposition of the great vessels, tetralogy of Fallot, or atrial septal defects.[77]

Atrial flutter has been separated into two types: classic, or type I, and type II.[78] Classic type I flutter is characterized by a single right atrial macroreentrant circuit with defined anatomic and functional boundaries and an obligate pathway through an area of slow conduction, the subeustachian isthmus. This isthmus-dependent conduction pattern in classic type I atrial flutter travels in a counterclockwise rotation up the interatrial septum, down the atrial free wall, and along the crista terminalis, which serves as an anatomic barrier.[79] The other boundaries of this reentrant circuit include the tricuspid valve ring on one side and an area of probable anatomic block in the region extending from the venae cavae to the eustachian valve and ridge on the other side. A clockwise rotation around the same circuit can generate a variant of type I atrial flutter that may occur spontaneously and may also be induced repeatedly during electrophysiologic studies.

The distinction between type I and type II atrial flutter is based upon (1) the ability to entrain and interrupt type I flutter with atrial pacing techniques and (2) a faster atrial rate in type II flutter. Untreated type I flutter usually has atrial rates between 280 and 320 per minute, commonly very close to 300 per minute. Type I, however, may occur infrequently at rates as low as 240 to 250 and as high as 340 per minute. In type II flutter, the atrial rate is commonly at least 340 to 350 per minute and occasionally may be as fast as 450 per minute. The ventricular rate in atrial flutter is usually a defined fraction of the atrial rate, for example, 2:1 conduction in type I flutter generating a characteristic ventricular rate of 150 per minute and 4:1 conduction at 75 per minute. Group beating may occur, often reflecting two levels of block in the AV junction with a Wenckebach phenomenon influencing the impulses conducting below the site of 2:1 block.[80] Clinically, atrial flutter may occur in brief, persistent, or chronic forms, and therapeutic approaches are influenced by the clinical pattern.

Electrocardiographic Features

Atrial flutter generates a defined pattern of atrial activity in the ECG. In typical type I atrial flutter with counterclockwise rotation, the classically described sawtooth pattern is identifiable in leads II, III, and aVF (Fig. 24-22). The electrical activity appears continuous in these leads, without a defined isoelectric baseline between flutter waves. In contrast, a discernible isoelectric line may appear in these leads when type I atrial flutter is slower than usual, as may occur in the presence of antiarrhythmic drugs. An isoelectric baseline may also be discernable in type I atrial flutter with clockwise rotation.

In contrast to the pattern observed in leads II, III, and aVF, other leads (most notably lead V_1)

generally have discrete flutter waves inscribed with an isoelectric line between them (Fig. 24-22). The pattern in leads II, III, and aVF likely reflects continuous electrical activity in the reentrant pathway in the low right atrium, while the pattern in lead V_1 reflects discrete wavefronts of activation approaching an area remote from the reentrant loop.

The most common AV conduction ratios in atrial flutter are 2:1 and 4:1, generating a ventricular rate of approximately 150 and 75 per minute, respectively. In young children and, rarely, in adults, 1:1 AV conduction may occur, resulting in a ventricular rate of 300 per minute. Continuous 3:1 and 5:1 ratios are very rare, but alternating 2:1 and 4:1 ratios are common, generating a bigeminal pattern. Such patterns commonly contain Wenckebach periods at the lower level of block (Fig. 24-23). Occasionally, the second impulse of the bigeminal pattern is aberrantly conducted in the ventricles, requiring a distinction between Ashman's phenomenon (aberrant intraventricular conduction due to long-short cycle sequences) and a ventricular ectopic beat. Atrial flutter associated with high-grade or complete AV block will produce a ventricular rate below 60 per minute, with dissociation between flutter waves and QRS complexes in the case of complete AV block (Fig. 24-24).

A narrow QRS complex tachycardia at a rate of 150 per minute should always lead to the consideration of atrial flutter. Carotid sinus massage will not interrupt atrial flutter but nonetheless may be very helpful in distinguishing flutter from other mechanisms because of a characteristic two-component response to this parasympathetic stimulus (Fig. 24-25). One component is impairment of AV nodal conduction, which causes an abrupt change from a rate of 150 per minute to 75 per minute or less. The unmasking of hidden flutter waves at the slower ventricular rate will make the diagnosis evident. The other component is the unique *acceleration* of the atrial rate in atrial flutter during carotid sinus massage (Fig. 24-25). The combination of abrupt *slowing* of the ventricular rate and an *increased rate* of atrial electrical activity strongly supports the diagnosis of atrial flutter. Occasionally, carotid sinus massage will cause atrial flutter to convert to atrial fibrillation.

Management of Paroxysmal Atrial Flutter

Treatment of acute paroxysmal atrial flutter differs from the treatment of PSVT due to AV nodal reentry or AV reciprocating mechanisms. Carotid sinus massage will not interrupt atrial flutter but transiently slows the ventricular rate by impairing AV nodal conduction (Fig. 24-25). The pharmacologic treatment of atrial flutter may be directed to reversion to a sinus mechanism or to control of the ventricular rate. The usual ventricular rate of 150 impulses per minute (±10 impulses per minute) may be well tolerated in the absence of myocardial dysfunction, symptomatic coronary artery disease, or mitral stenosis. The ventricular rate should be slowed with digitalis before antiarrhythmics are instituted to convert the atrial arrhythmia to avoid very rapid rates associated with drug-induced 1:1 AV conduction.[82] Control of the heart rate during the paroxysm may also be achieved with Ca^{2+}-entry blocking agents.[25] Verapamil has been studied in detail, and intravenous diltiazem is also successful.

When the ventricular rate is poorly tolerated due to effects on hemodynamics or coronary blood flow, electrical cardioversion is used as initial treatment. An attempt using 10 to 50 J may be successful; higher energies are often necessary. Membrane-active antiarrhythmic agents are used to convert flutter to sinus rhythm, but efficacy is unpredictable. Historically, quinidine has been the initial drug of choice, but the other class IA antiarrhythmic agents may be equally effective. Conventional dosing schedules are now used, in contrast to the highly toxic aggressive quinidine protocols of the past. The class IC drugs (e.g., flecainide or propafenone) may also be effective for pharmacologic reversion of atrial flutter,[57] although they slow intraatrial conduction without lengthening refractory periods. This drug effect may result in slowing atrial flutter from 300 per minute to less than 240 per minute, allowing 1:1 conduction to the ventricles at rates as high as 220 to 240 per minute. Because of the concomitant rate-dependent effect on ventricular

conduction velocity, the slowed atrial rate with 1:1 conduction may generate wide QRS complexes mimicking ventricular tachycardia.[81] Ibutelide, an intravenous drug with class III effects, is also effective for acute treatment of atrial flutter.[86] Its major concern is the short-term risk of torsades de pointes, which necessitates monitoring for several hours after administration. Failing conversion or achieving an acceptable rate with drugs, elective DC cardioversion is usually successful. If cardioversion is contraindicated or fails, an attempt to entrain the atrium with rapid atrial pacing may result in conversion to sinus rhythm[83,84] (see Chap. 31). Occasionally, rapid pacing may convert atrial flutter to atrial fibrillation, which will have a slower ventricular response. Pharmacologic management for recurrences of the paroxysmal form of atrial flutter includes long-term use of antiarrhythmic therapy to prevent the arrhythmia and the use of AV nodal blocking agents to control heart rate during recurrences. For the former, the class IA antiarrhythmic agents, especially quinidine, have been used with variable success. Class IC and class III drugs are potentially useful, but the concern with the mechanism of action of class IC drugs in atrial flutter cited above limits their use. Control of ventricular rate is best achieved with digitalis because of safety and efficacy considerations. Long-term oral use of verapamil for control of rate in recurrent atrial flutter is less predictably effective than intravenous use to slow the rate during a paroxysm.[24] Beta-adrenergic blocking agents have been used, and if the drugs are well tolerated, the dose can be titrated to clinical beta-blocking efficacy by heart rate and blood pressure criteria. Subsequent observations of ventricular rates during recurrences will establish efficacy. There is no known excess incidence of embolic events during paroxysmal atrial flutter or during its reversion. Anticoagulants are not used before, during, or after reversion. In recent years, RF catheter ablation procedures have been used with increasing frequency for patients with atrial flutter, especially for patients with frequent symptomatic episodes of atrial flutter or those resistant to drug therapy. A linear RF ablation lesion across the subeustachian isthmus, between the tricuspid valve annulus and the inferior vena cava, interrupts the reentrant pathway responsible for type I flutter. The procedure has a high probability of permanent clinical success,[85,87] avoiding the need for long-term pharmacologic therapy among these patients.

Management of Persistent Atrial Flutter

Atrial flutter may occur in a persistent form secondary to noncardiac factors, such as thyrotoxicosis or pulmonary embolism, although it is most common in the presence of chronic heart disease. Persistent or chronic atrial flutter occurs, but not commonly, in otherwise normal persons. Patients subject to recurrent episodes of persistent atrial flutter can be maintained on long-term antiarrhythmic therapy. However, RF ablation has emerged as the therapy of choice for symptomatic patients in this category.[85] Recurrence of atrial flutter after an RF ablation procedure occurs in approximately 15 percent and is usually due to gaps in the linear lesion across the isthmus, maintaining continuity of conduction in the reentrant pathway.[85,88] These gaps can often be identified and sealed during a repeat RF ablation procedure. If RF ablation fails or is not desired by the patient, therapeutic approaches during recurrences include additional antiarrhythmic agents for reverting atrial flutter and agents that will control the ventricular rate. Acute antiarrhythmic therapy may include intravenous procainamide or ibutilide[86] or orally administered drugs that prolong refractoriness (e.g., sotolol). Electrical reversion, however, may still be required.

Management of Chronic Atrial Flutter

Some patients will remain in chronic atrial flutter despite aggressive antiarrhythmic or interventional therapy, and flutter may recur predictably shortly after DC cardioversion. This usually occurs in the setting of advanced heart disease, may occur as the forerunner of chronic atrial fibrillation, and appears to be especially frequent with the variants of flutter, such as type II atrial flutter. It may occur rarely in otherwise normal persons[76] and more commonly in association with other SVTs, such as WPW and AV nodal reentry.[89] If the ventricular rate is adequately controlled and the patient is asymptomatic, chronic atrial flutter need not be treated aggressively.

In these cases, there is little justification for the use of complex antiarrhythmic drug regimens with adverse side-effect profiles. Rather, catheter ablation procedures can be used, especially for type I flutter, where the success rate is high. Surgical ablation of atrial flutter is feasible but is used only in rare circumstances, usually in conjunction with surgery being performed for another primary indication.

Control of ventricular rate is the major issue for management. AV nodal blocking agents, such as digoxin, beta-adrenergic blockers, and Ca^{2+}-entry blockers, may be tried. The major problem is the tendency for AV conduction to respond to pharmacologic control in step patterns. The patient who is well controlled with 4:1 conduction at a ventricular rate of 75 per minute may abruptly increase to 150 per minute under conditions of stress, which enhance AV nodal conduction.

In patients with enhanced AV nodal conduction and atrial flutter, it may be difficult to slow the rate below 150 per minute pharmacologically. Verapamil appears to be more effective than digoxin for the AV node with enhanced conduction but is not uniformly effective. Rarely, catheter ablation for AV node modification or interruption, with pacemaker implantation, is used for heart rate control in patients who are resistant to or intolerant of AV nodal blocking drugs and who have failed ablation attempts to interrupt the flutter pathway.

In the past, long-term anticoagulation was not generally recommended for patients with chronic atrial flutter. However, the potential risk of thromboembolism in atrial flutter has been reevaluated,[90,91] and it is now recommended to follow the guidelines of anticoagulation for atrial fibrillation in patients with atrial flutter.[92,93] Although the precise risk of stroke associated with atrial flutter has not been yet established by a large prospective clinical trial, the retrospective observations cited suggest an incidence of stroke similar to that expected in chronic atrial fibrillation. There is transesophageal echocardiographic evidence of atrial clot formation and spontaneous contrast in these patients. Finally, it is clinically difficult to ensure that a patient with atrial flutter will not have occasional periods of atrial fibrillation.

ATRIAL FIBRILLATION

Atrial fibrillation is the commonest among the cardiac rhythm disturbances that require treatment. In cross-sectional population studies, there is a large gradient of prevalence across age categories, ranging from less than 0.5 percent in young adults to 1 to 5 percent through the decades from 40 to 70 years and reaching rates in excess of 10 percent in some beyond age 70.[94] The arrhythmia should not be viewed as a single entity for practical clinical purposes. Risk, relevance, and management strategies are heavily influenced by the temporal pattern of the arrhythmia (paroxysmal, persistent, or permanent; Fig. 24-26) and by the clinical setting in which it occurs (Fig. 24-27).

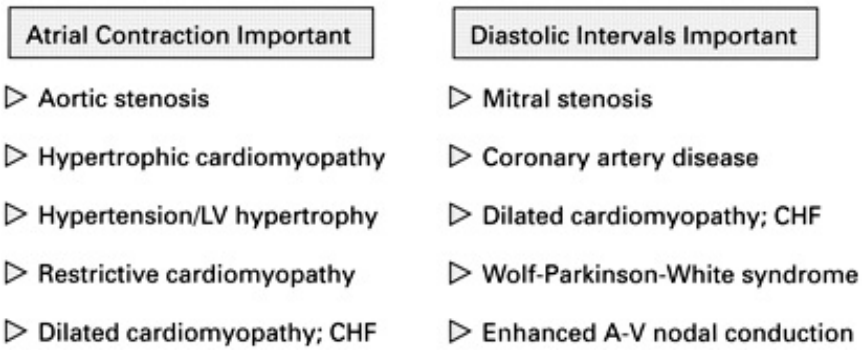

Figure 24-27: Hemodynamic factors in atrial fibrillation. Atrial fibrillation creates the potential

for two hemodynamic defects: (1) loss of atrial contraction, which provides the presystolic atrial "kick"; and (2) rate-related reduction of the diastolic filling period. Atrial contraction is important to ventricles with reduced compliance and low-output states due to myocardial factors. Diastolic filling time is important in conditions in which a longer diastolic is beneficial to impaired flow states, such as mitral stenosis, coronary atherosclerosis, and some myopathic ventricles.

The electrophysiologic mechanism of atrial fibrillation also influences treatment options. The commonest mechanism by far is multiple reentrant atrial wavelet circuits, producing loss of mechanical and electrical synchronization of the atria and variable AV nodal penetration and conduction, which in turn results in an irregular ventricular response. A less common but strategically important mechanism is focal atrial tachycardia originating in muscle fibers in the distal pulmonary veins in the left atrium or the crista terminalis or elsewhere in the right atrium.[20,95] Premature atrial impulses may be an expression of the presence of such sites of focal activity and serve as a guide to ablation therapy. They may also serve as triggers for initiation of the reentrant forms.

The clinical presentations and associations of atrial fibrillation are very broad. At one end of the spectrum is lone atrial fibrillation (absence of any form of structural cardiac abnormality) with arrhythmia symptoms that range from unrecognized to very symptomatic. The other extreme includes patients with advanced structural diseases, such as mitral or aortic stenosis, restrictive cardiomyopathies, or advanced LV dysfunction, in which the onset of atrial fibrillation may cause severe hemodynamic deterioration. Valvular heart disease has received much attention historically. The high prevalence of the arrhythmia in rheumatic mitral valve disease has been emphasized in the past, but it is likely that risk with any cause of mitral valve disease of equivalent severity is just as high. Between these extremes, atrial fibrillation may herald the presence of noncardiac disorders (e.g., thyrotoxicosis), alert to the significance of another cardiac disorder (e.g., WPW syndrome), constitute a transient complicating factor of another cardiac disorder (e.g., acute myocardial infarction or systemic arterial hypertension), or occur during the postoperative period after cardiac surgery.

The hemodynamic consequences of atrial fibrillation are due to two factors: (1) the loss of atrial systole may impair ventricular function in the noncompliant ventricle [e.g., aortic stenosis or left ventricular hypertrophy (LVH)] or the dilated ventricle with systolic dysfunction, and (2) a rapid ventricular rate will encroach upon the diastolic filling period of the left ventricle and the diastolic flow time of the coronary arteries (see Fig. 24-27). The risk of embolism and stroke is a long-term concern of special importance (see below).

Electrocardiographic Features

Atrial fibrillation is characterized electrocardiographically by grossly disorganized atrial electrical activity that is irregular in respect to both rate and rhythm. There is no visually discernible timing pattern to the atrial electrical activity on the surface ECG or to electrogram sequences recorded by catheter electrodes. Specific patterns of AV conduction sequences (ventricular responses) have been proposed as a result of sophisticated analytic techniques;[96] this analysis provides some physiologic insight but does not yet have practical clinical value. Atrial fibrillatory waves are best seen in standard lead V_1 and are usually clearly evident in II, III, and aVF as well. They may be quite large and coarse or almost imperceptible (compare Fig. 24-28*A* and *B*). In the absence of discernible atrial electrical activity, a grossly irregular ventricular rhythm still suggests the presence of atrial fibrillation. Coarse atrial fibrillation is occasionally difficult to distinguish from atrial flutter waves, but the irregular ventricular response, in the absence of a repetitive pattern, is again helpful in making the distinction. In contrast, obvious coarse fibrillatory waves with a regular ventricular response, especially when slow, suggests the coexistence of high-grade AV block with atrial fibrillation.

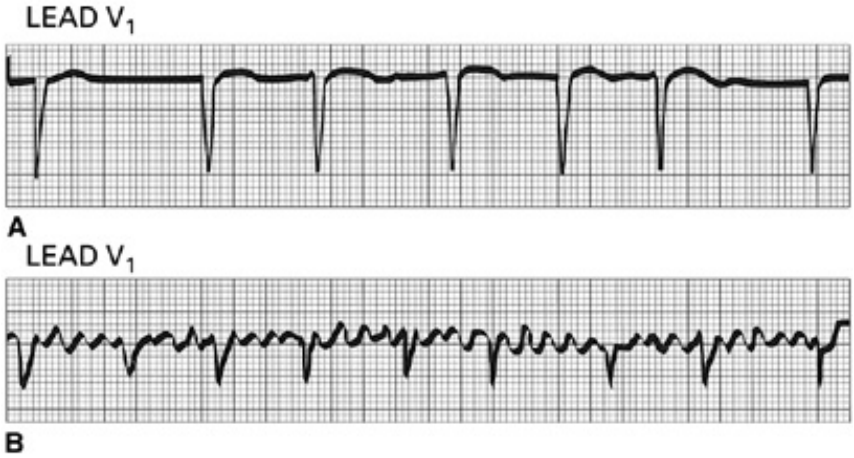

Figure 24-28: *A.* Fine atrial fibrillation, leaving virtually no imprint on the baseline ("straight-line" fibrillation). *B.* Coarse atrial fibrillation; the fibrillatory waves are the size of respectable flutter waves but are irregular.

One of the more challenging exercises in clinical electrocardiography is the distinction between aberrant intraventricular conduction and ventricular ectopy in the presence of atrial fibrillation. Aberrant conduction tends to occur when a long ventricular cycle is followed by a short cycle. This long-short cycle sequence, with the short cycle terminated by an aberrantly conducted beat, is referred to as Ashman's phenomenon.[97] It is important to recognize that *long* and *short* are relative terms in this context and carry no implications of absolute value (compare Figs. 24-29 and 24-30). A series of short cycles, if short enough, may generate runs of consecutively aberrant beats imitating VT (Fig. 24-30). Thus, additional criteria for distinction between aberrancy and ectopy are required. In general, an initial QRS vector similar or identical to that of narrow QRS complexes and a typical right bundle-branch block pattern, in association with a long-short cycle sequence, strongly favor aberrancy over ectopy.[98] Left bundle-branch block aberrancy also occurs but is far less common. It is more likely when aberrant conduction is persistent (i.e., functional bundle-branch block during a sustained SVT; see Fig. 24-15), while it is unusual in single-cycle aberrancy (Fig. 24-29). Atrial fibrillation alters intraventricular conduction only through the following mechanisms: (1) functional bundle-branch block or aberrancy (Fig. 24-31), (2) loss of delta waves in WPW syndrome with normal pathway conduction during atrial fibrillation, or (3) totally preexcited QRS complexes during atrial fibrillation in WPW syndrome (see Fig. 24-18). The QRS complex during atrial fibrillation will be similar to that recorded during sinus rhythm under all other circumstances. In patients with preexisting bundle-branch block who develop atrial fibrillation with rapid ventricular responses, the distinction from VT may be difficult.

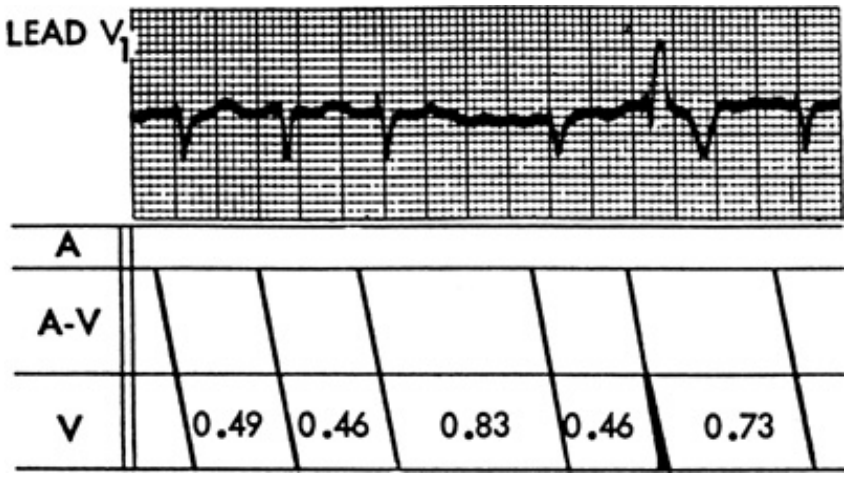

Figure 24-29: Ashman's phenomenon. During atrial fibrillation, the impulse ending a short cycle preceded by a relatively long cycle manifests aberrant intraventricular conduction. In this example, the aberrant impulse shows typical right bundle-branch block type aberration in lead V_1, with an rSR pattern and the initial deflection identical to that of the preceding and following normally conducted impulses.

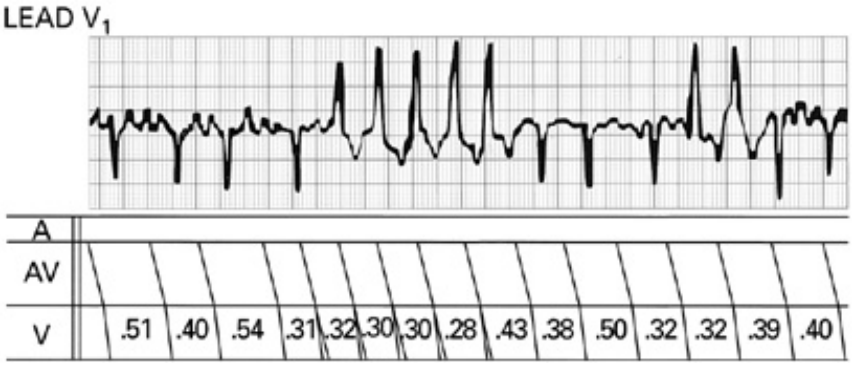

Figure 24-30: Atrial fibrillation with repetitive aberrant ventricular conduction. The impulses that end the shortest ventricular cycles (0.28 to 0.32 s) are anomalous, widened complexes. Note that the cycle preceding the onset of the salvos of anomalous beats is *relatively* long in comparison with the anomalous complexes (0.54 and 0.50 s), in accordance with Ashman's phenomenon. Thus, these almost certainly represent a right bundle-branch block type of ventricular aberration rather than ventrcular ectopy.

Evaluation and Management of the First Episode of Atrial Fibrillation

The first episode of atrial fibrillation requires special considerations. A thorough investigation of the clinical status is needed to determine whether the event is caused by a primary electrical mechanism, underlying structural heart disease, hemodynamic abnormalities, or a systemic disorder that predisposes to atrial fibrillation. Previously unrecognized mitral or aortic stenosis or regurgitation, hypertension, coronary heart disease, cardiomyopathy, atrial septal defect, pericarditis, or atrial abnormalities secondary to left or right ventricular overload are among cardiac causes that must be excluded. Heart failure may be either a cause or a consequence of atrial fibrillation. Pulmonary emboli and metabolic abnormalities such as thyrotoxicosis also must be considered. The identification of associated factors at the time of the first episode of atrial fibrillation dictate future management. In the absence of an identifiable cause, so-called lone atrial fibrillation, the prognosis is good,[99] especially if it is a single event or intermittently recurrent. Chronic lone atrial fibrillation may indicate a higher risk,[100] although conflicting data[99] question

the validity of this conclusion. In a young, healthy individual in whom there is no evidence of structural heart disease, paroxysmal episodes of lone atrial fibrillation may occur under conditions of exogenous precipitating factors, such as excessive cigarette, alcohol, and/or coffee consumption; exposure to so-called "recreational drugs," such as cocaine and amphetamines; stress or fatigue; or upon cessation of extreme exercise.

In the absence of organic heart disease or coexistent WPW syndrome, long-term management after the first episode need include no more than avoidance or removal of precipitating factors and following the patient over time to estimate the frequency of recurrences. Long-term antiarrhythmic therapy is generally not indicated following the first episode of lone atrial fibrillation. In the presence of treatable cardiac or noncardiac causes, management must include attention to precipitating and predisposing factors. For instance, in atrial fibrillation occurring during the acute phase of myocardial infarction, which has been observed in up to 18 percent of monitored patients, spontaneous reversion is very common, and rate control is the only therapy needed. In the setting of thyrotoxicosis, there is no rationale for trying to convert atrial fibrillation until the thyrotoxic state is controlled; in the interim, the ventricular rate may be slowed with propranolol and anticoagulation maintained (see below) until sinus rhythm is restored after the patient is euthyroid. When atrial fibrillation calls attention to previously undiagnosed mitral stenosis, atrial enlargement may limit success of attempts to obtain and maintain sinus rhythm.

Ventricular rate should be controlled, and conversion of atrial fibrillation can await correction of the mitral valve obstruction. In atrial septal defect, atrial fibrillation is generally a sign of advanced hemodynamic deterioration, such as pulmonary hypertension and balanced or reversing shunts; these patients must be evaluated for surgery promptly. In patients with *advanced* heart disease of any etiology and dilated atria, the first episode may herald a chronic fibrillatory state. An attempt to revert the rhythm, either pharmacologically or electrically, the latter usually with a concomitant pharmacologic agent, may be an appropriate option; but the recurrence rate is very high.[101-103] If the patient will benefit from the hemodynamic advantage provided by an atrial contraction, the attempt at reversion is warranted despite the high probability of recurrence. The recent onset of chronic atrial fibrillation has special implications for anticoagulation therapy (see below).

In hemodynamically significant mitral stenosis or aortic stenosis, acute pulmonary edema may complicate the first episode of rapid atrial fibrillation, making immediate control of heart rate or electrical cardioversion mandatory. In mitral stenosis, recurrences can be expected; but even a short time in sinus rhythm can provide hemodynamic benefit and allow institution of therapy that will control the ventricular rate for the next episode. A slower heart rate, with a resultant longer diastolic filling period, may help prevent the recurrence of pulmonary edema. In aortic stenosis, dependence upon the atrial kick for optimal hemodynamic function of the noncompliant hypertrophied left ventricle, rather than encroachment on the diastolic filling period, is the major concern.

Management of Recurrent Episodes of Paroxysmal Atrial Fibrillation

Paroxysms of atrial fibrillation lasting less than 48 h in the absence of underlying heart disease are usually managed conservatively. Rest, mild sedation with 5 to 10 mg of diazepam, and Ca^{2+}-entry blockers, beta-adrenergic blockers, or digitalis for control of the ventricular rate constitute an accepted approach. After the first episode, patients who have lone atrial fibrillation can be reassured in respect to the absence of underlying organic heart disease and guided to avoid precipitating factors. In the presence of heart disease, particularly when the hemodynamic circumstances require either the mechanical benefit of atrial systole or a properly controlled ventricular rate for adequate diastolic filling (see Fig. 24-27), immediate reversion to sinus rhythm or slowing of the ventricular rate may be mandatory. The presence of clinical signs of heart failure requires immediate cardioversion to achieve either or both of these goals.

If the patient is tachycardic but clinically stable, pharmacologic approaches to control the rate (digitalis or intravenous verapamil or diltiazem) may be attempted. The overall probability of spontaneous conversion of paroxysmal atrial fibrillation within 24 h is approximately 50 percent.[104] However, a number of antiarrhythmic drug strategies have been used to achieve earlier reversion or increase the reversion rate without electrical cardioversion. Intravenous procainamide[105,106] and ibutilide[86] have been used for pharmacologic reversion of acute paroxysms. The latter must be used with caution because it may prolong the QT interval acutely, with the short-term risk of torsades de pointes. Although not available in the United States, intravenous formulations of the class IC drugs flecainide and propafenone have also been used successfully for treatment of acute atrial fibrillation.[107] Oral bolus therapy using flecainide (300-mg dose) or propafenone (600 mg) in a single dose has been used,[108,109] although it is not clear whether it provides more or simply earlier conversions than in control subjects.[110]

Long-term pharmacologic therapy in the absence of underlying heart disease or in the presence of trivial abnormalities is intended to reduce or eliminate recurrent episodes and to control ventricular rate during recurrences, should they occur. Digitalis, beta-adrenergic blockers, or Ca^{2+}-entry blockers are used for rate control as described for atrial flutter. Digitalis controls ventricular rate at rest, although it appears less effective for limiting effort-induced increases in ventricular rate during atrial fibrillation.[111]

Prevention of episodes of atrial fibrillation may be achieved with class IA, IC, or III antiarrhythmic drugs. If episodes are clinically benign and infrequent, the threshold for such treatment is higher than if they are more frequent and symptomatic. Efficacy is uneven and proarrhythmic or toxic side effects are of concern. During short paroxysms of atrial fibrillation (up to 48 h), anticoagulation is not required prior to reversion; long-term anticoagulation is not necessary for patients subject to brief paroxysmal attacks[112] (see Fig. 24-26; Tables 24-8 and 24-9).

Table 24-9: Anticoagulation of Patients with Atrial Fibrillation

Indications
Rheumatic mitral valve disease with recurrent or chronic atrial fibrillation
Dilated cardiomyopathy with recurrent persistent or chronic atrial fibrillation
Prosthetic valves
Prior to (≥3 weeks) elective cardioversion of persistent or chronic atrial fibrillation
Coronary heart disease or hypertensive heart disease with recurrent persistent or chronic atrial fibrillation
Atrial fibrillation in thyrotoxicosis (while awaiting long-term control; elective cardioversion)
Chronic or persistent lone atrial fibrillation, age ≥60 years
Controversial, or limited data
Coronary or hypertensive heart disease with normal left atrial size, after first episode of paroxysmal atrial fibrillation
Elective cardioversion of atrial fibrillation of short duration (2-3 days) with normal left atrial size

Chronic or persistent lone atrial fibrillation, age <60 years
Not indicated
Lone atrial fibrillation, paroxysmal (<48 h, age <65)
Most clinical settings associated with short paroxysms (minutes to hours)
Relative contraindications
Difficulty controlling prothrombin times
Dementia
Malignancies, especially associated with bleeding risk
Prior major bleeding events
Uncontrolled hypertension

Management of Persistent Atrial Fibrillation

The decision to intervene in longer episodes of atrial fibrillation is based on the balance between hemodynamic tolerance and the likelihood of being able to control future episodes. Because of the demonstrated effects of "electrical remodeling" of atrial myocytes during persistent atrial fibrillation,[113] which favors persistence of the arrhythmia and resistance to reversion, there is a tendency toward a more aggressive approach to early reversion.[114]

Many patients with organic heart disease have intermittent episodes of persistent atrial fibrillation prior to establishing chronic atrial fibrillation.[115] Among these patients, antiarrhythmic efficacy for control of recurrences is unpredictable. Prediction of the ability to control ventricular rate by AV nodal blocking agents is better but still imperfect. When a patient has had multiple recurrences of persistent atrial fibrillation despite trials of several antiarrhythmic agents and the arrhythmia is well tolerated hemodynamically, many clinicians avoid repeated electrical cardioversions, especially in the presence of advanced heart disease. If elective cardioversion is to be attempted, 3 weeks of anticoagulation should precede the procedure to reduce embolic risk. A more expeditious alternative strategy is to perform a transesophageal echocardiogram to rule out the presence of atrial thrombi.[116] If results are negative, heparin can be started and chemical or electrical cardioversion performed. However, there remains some debate about the efficacy of this strategy.[117]

If cardioversion is not attempted and the patient has recurrent episodes of atrial fibrillation lasting 48 to 72 h, long-term anticoagulant with warfarin is indicated. If the patient is without structural disease, is less than 60 years of age, and has a normal echocardiogram and no prior history of embolism, long-term warfarin therapy is unnecessary.

In the presence of advanced or progressive cardiac disease, atrial fibrillation is likely to revert and recur intermittently until the condition evolves into chronic atrial fibrillation. When this occurs, the best therapeutic approach may be control of ventricular rate during recurrences. Membrane-active antiarrhythmic agents are often used in an attempt to limit the number of recurrences, but efficacy is unpredictable, and risk of side effects is high. The flecainide data suggest efficacy,[61,119] especially for patients with good LV function and those free of underlying coronary artery disease.[19] Class III antiarrhythmic drugs, including sotalol,[120] amiodarone,[121] dofetilide,[122]

and azemilide,[123] are also effective. The latter two drugs have not yet been approved for use by the U.S. Food and Drug Administration. The long-term benefit of prevention of atrial fibrillation by antiarrhythmic drug therapy versus control of heart rate remains uncertain. A large multicenter study is currently in progress to answer this question.[124]

Management of Chronic (Permanent) Atrial Fibrillation

The ventricular rate in chronic atrial fibrillation is usually more predictably controlled than in recurrent episodes of paroxysmal or persistent atrial fibrillation. Pharmacologic or electrical cardioversion in patients with advanced heart disease and atrial enlargement is attempted in the hope of achieving a hemodynamic benefit, but the probability of maintaining sinus rhythm is low.[101-103] Until more data are available, the choice between attempting to restore sinus rhythm and simply controlling heart rate (with anticoagulation) is a matter for individual clinical judgment. Among patients with advanced heart disease who have been electrically cardioverted while taking antiarrhythmic drug therapy, approximately one-third will revert to atrial fibrillation within 1 week and two-thirds within 12 months.[101-103] If the rhythm reverts to chronic atrial fibrillation shortly after cardioversion, the probability of long-term maintenance of sinus rhythm by additional pharmacologic approaches is very low. The ventricular rate is then controlled as outlined above.

Pharmacologic control of ventricular rate may be problematic in recurrent episodes of both persistent and chronic atrial fibrillation. Under both circumstances, catheter modification of the AV junction or complete interruption (catheter ablation) of the AV junction with permanent pacing may provide heart rate control.[125] Other nonpharmacologic strategies for control of atrial fibrillation include surgical procedures designed to establish sinus node control of the ventricular rate and rhythm, implantable device therapy, and catheter ablation procedures. Among the surgical approaches, the "corridor" procedure[126] establishes a pathway from sinus node to AV node, while the MAZE procedure[127] interrupts pathways necessary for maintaining fibrillation and reestablishes both rate control and mechanical function. The MAZE technique has been used both as primary surgery and as an added procedure for patients undergoing cardiac surgery for other reasons.

An implantable atrial defibrillator[128] has been developed for use in patients with chronic recurrent atrial fibrillation. It appears to have only limited applicability as a stand-alone device, but integration of the technology within the platform of conventional implantable cardioverter defibrillators (ICDs)[129] may be useful for patients with paroxysmal atrial fibrillation at risk for life-threatening ventricular arrythmias. Another device strategy being evaluated is the use of dual-site atrial pacing in an attempt to resynchronize atrial depolarization and avoid dispersion of atrial refractoriness.[130]

Catheter ablation techniques for preventing atrial fibrillation (i.e., catheter-based MAZE procedure or ablation of focal triggering sites for atrial fibrillation)[131,132] are currently being evaluated. The ultimate role for these approaches in the management of patients with recurrent or chronic atrial fibrillation remains to be determined.

Anticoagulation of Patients with Atrial Fibrillation

Patients with atrial fibrillation have a greater than fivefold increase in risk of stroke compared to control populations without atrial fibrillation.[133-136] In addition, there are specific high-risk subgroups. Among patients with rheumatic heart disease, the risk exceeds by up to 17 times that of a control group.[134,135] Other subgroups at high risk include patients with dilated cardiomyopathy, dilated left atrium of any cause, atrial fibrillation of recent onset, and a history of prior embolism. Patients with atrial fibrillation and LVH are also at increased risk, as are

thyrotoxic patients.[137] In one study, the chronic form of lone atrial fibrillation has been reported to be associated with a relative increase in risk of embolic stroke,[138] although other studies have not identified an increased risk. It is generally agreed, however, that patients older than 60 years with lone atrial fibrillation are at risk and should be anticoagulated with warfarin.[139] As a group, the nonrheumatic disease states associated with atrial fibrillation tend to have excess risks in the range of five- to sixfold, according to various studies.[94] Absolute risks differ little among the various rheumatic and nonrheumatic etiologies, however, with event rates in the range of 4 to 6 percent for each, except for lone atrial fibrillation, which has a considerably lower rate.[92,99,138] The risk of embolic events tends to cluster around changes in rhythm, the highest incidence occurring within the first year after onset of chronic atrial fibrillation[134] and a concentrated 1 to 2 percent risk occurring in the first days after restoration of sinus rhythm,[140-142] whether by pharmacologic strategies or DC cardioversion.

The issue of anticoagulation in atrial fibrillation hinges on a balance between efficacy of preventing embolic events and risk of bleeding (see Tables 24-8 and 24-9). Indicators of increased risk of embolic events, in addition to the general presence of structural heart disease, include previous stroke or transient ischemic attack, hypertension, heart failure, prosthetic heart valves, and hyperthyroidism.[137,143] Age and female gender (particularly elderly women) also identify increased risk.[139] Efficacy and risk both relate well to the level of anticoagulation with warfarin. Measured as the now-standard international normalized ratio (INR), benefit is optimal at or above an INR of 2.0, while bleeding risk increases above an INR of 3.5 to 4.0.[143] Until recently, most of the data on efficacy of anticoagulation for reducing incidence of embolic events in atrial fibrillation were from poorly controlled or uncontrolled studies, and there was no consensus based on the available data.[133] The available combination of risk data and retrospective or uncontrolled efficacy data[101,111,133] tended to result in the practice of using long-term anticoagulation for patients with a rheumatic etiology and for those with advanced structural diseases associated with atrial fibrillation (see Table 24-8). Such patients included those with coronary artery disease and a prior embolism, idiopathic dilated cardiomyopathy, and prosthetic cardiac valves. Several recent placebo-controlled studies have now provided clarification of the role and methods for anticoagulation in patients with nonrheumatic atrial fibrillation. In one multicenter randomized trial, the Stroke Prevention in Atrial Fibrillation (SPAF) Study, aspirin, 325 mg/day, and warfarin, with prolongation of prothrombin times to 1.3 to 1.8 times those of the control subjects were each compared to placebo among a population of 1330 patients.[144] During a mean follow-up of 1.3 years, ischemic stroke or systemic embolization occurred at a rate of 6.3 percent per year in the placebo group, compared to 3.6 percent per year in the aspirin-treated group, a 42 percent reduction in the treated group ($p < .02$). Among the patients eligible for warfarin, the event rate in the untreated group was 7.4 percent, compared to 2.3 percent in the treated group, a 67 percent reduction ($p < .01$). Primary embolic events and deaths combined were reduced by 58 percent in the warfarin group and 32 percent in the aspirin group.

Thus, both warfarin and aspirin were effective, but the design of the study prevented comparison of the two treatments. Although both chronic atrial fibrillation and intermittent atrial fibrillation were included in the study, the data reported do not permit a determination of any difference in risk or benefit for the two patterns. In another study, the Canadian Atrial Fibrillation Anticoagulation (CAFA) Study, the placebo group experienced a 5.2 percent embolism/stroke rate compared to 3.5 percent in a warfarin-treated group, a relative reduction of 37 percent with treatment.[145] The differences did not reach statistical significance, since the study was prematurely terminated because of outcome data from other large studies suggesting benefit. Among two other studies, the Copenhagen AFASK Study[146] and the Boston Area Anticoagulation Trial in Atrial Fibrillation,[148] warfarin again demonstrated significant reductions in risk (82 and 87 percent, respectively), while aspirin demonstrated only a 14 percent reduction in the Copenhagen study (nonsignificant),[146] even though it was associated with a 42 percent reduction in the SPAF study.[144] Collectively, these studies demonstrate a significant benefit for

reduction of embolism and stroke in nonrheumatic atrial fibrillation patients with the use of warfarin and likely with aspirin as a less effective alternative (see Chap. 89). More recent data have reaffirmed that warfarin is superior to aspirin and provided additional insight into effective warfarin dose ranges.[148] In patients at high risk for embolic events, fixed low-dose warfarin (0.5 to 3.0 mg/day; INR = 1.2 to 1.5) plus aspirin (325 mg/day) was inferior to conventional dose-adjusted warfarin (INR target = 2.0 to 3.0). Indications for anticoagulation prior to elective cardioversion have not undergone the same scrutiny for efficacy as has now been provided for intermittent and chronic atrial fibrillation. Nonetheless, there is enough information available to warrant the routine use of anticoagulation prior to elective cardioversion of recent onset (more than 48 to 72 h), persistent atrial fibrillation or chronic atrial fibrillation, particularly when associated with an enlarged left atrium or other structural diseases regardless of etiology. Anticoagulation with warfarin is started 3 to 4 weeks before elective cardioversion and is maintained for 3 to 4 weeks subsequently. If there is concern about the ability of a patient to recognize a recurrence of atrial fibrillation, it may be warranted to maintain anticoagulation indefinitely, particularly if the patient has advanced structural heart disease.

The risk-benefit data are less clear for anticoagulation prior to elective cardioversion of atrial fibrillation of short duration (less than or equal to 48 h), particularly lone atrial fibrillation or when associated with minimal structural disease and normal atrial dimensions. The potential efficacy of anticoagulation must be weighed against its risk. Patients receiving anticoagulants retain a risk of embolization ranging from 1 to greater than 3 percent per year,[94,102,142-147] depending upon disease states. Furthermore, there is a significant incidence of life-threatening bleeding or major events requiring transfusion among patients on long-term anticoagulation. In one report,[149] the incidence was 4.3 percent per treatment-year. In the SPAF study,[144] however, bleeding risk hovered around 1.5 percent and did not differ among aspirin-treated, warfarin-treated, and placebo groups. Lower warfarin dosing than used previously, titrated to an INR of 2.0 to 3.0,[150] may be one reason for the reduction of bleeding risk with warfarin use. Since the risk of bleeding is increased significantly with an INR of 5.0, the inability to control the prothrombin time, including the inability of the patient to comply with the prescribed dosages, must be considered relative contraindications. The major complication of intracranial bleeding may have an incidence of 1 to 2 percent per treatment-year.[151] Table 24-9 lists indications and relative contraindications for anticoagulation in patients with atrial fibrillation. The physician must balance accepted indications and risks in judging whether to use anticoagulation in individual patients. In most circumstances now, however, one should err on the side of use rather than avoidance if the risk-benefit relationship is not clear, assuming the INR is assiduously maintained between 2.0 and 3.0 in candidates at higher risk for bleeding complications.

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Chapter 24: RECOGNITION, CLINICAL ASSESSMENT, AND MANAGEMENT OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

ATRIOVENTRICULAR JUNCTIONAL AND ACCELERATED VENTRICULAR RHYTHMS

Rhythm disturbances that originate in the AV junction include premature AV junctional impulses, accelerated junctional rhythms, and AV junctional tachycardias that may be automatic or reentrant. Echo beats and tachycardias that incorporate the atria and AV junction as part of the reentrant pathway in PSVT due to AV nodal reentry or WPW syndrome are discussed elsewhere. Junctional escape rhythms at rates of 40 to 60 per minute during sinus bradycardia or AV block are normal physiologic backup phenomena that are usually hemodynamically stable; failure of normal junctional escape mechanisms may result in significant bradycardias.

The normal inherent rate of AV junctional automatic activity is 40 to 60 per minute, and those of subordinate pacemakers at the fascicular or ventricular level are 20 to 40 per minute. Faster rates from either of these levels are considered "accelerated" for rates up to 100 impulses per minute, at which point they take on the general definition of a tachycardia. Accelerated junctional and ventricular rhythms and most nonparoxysmal AV junctional tachycardias are thought to be due to enhanced automatic activity (phase 4 depolarization).[152,153] Other forms of abnormal automaticity, including triggered activity initiated by afterdepolarizations, may also originate in the AV junction[154,155] (see also Chap. 23).

AV Junctional Premature Beats

AV junctional premature beats occur much less frequently than do premature atrial or ventricular complexes. The timing of P waves and QRS complexes is variable, however. The P waves may precede QRS complexes by 0.12 s or less, may be concealed within the QRS complexes, or may appear in the ST segment following the QRS complex (Fig. 24-32). The P waves are usually inverted in leads II, III, and aVF; isoelectric to slightly negative in leads I and V_6; and upright in the right precordial leads. The QRS complexes are narrow except when aberrant intraventricular conduction is present. When the P waves precede the QRS complex, distinction from premature atrial complexes may be difficult, and when aberrant intraventricular conduction is present and the P wave is within or after the QRS complex, the distinction from premature ventricular complexes may be impossible without intracardiac recordings. AV junctional premature beats generally require no treatment; when treated, however, they are approached using the same principles applied to the treatment of premature ventricular complexes (see below).

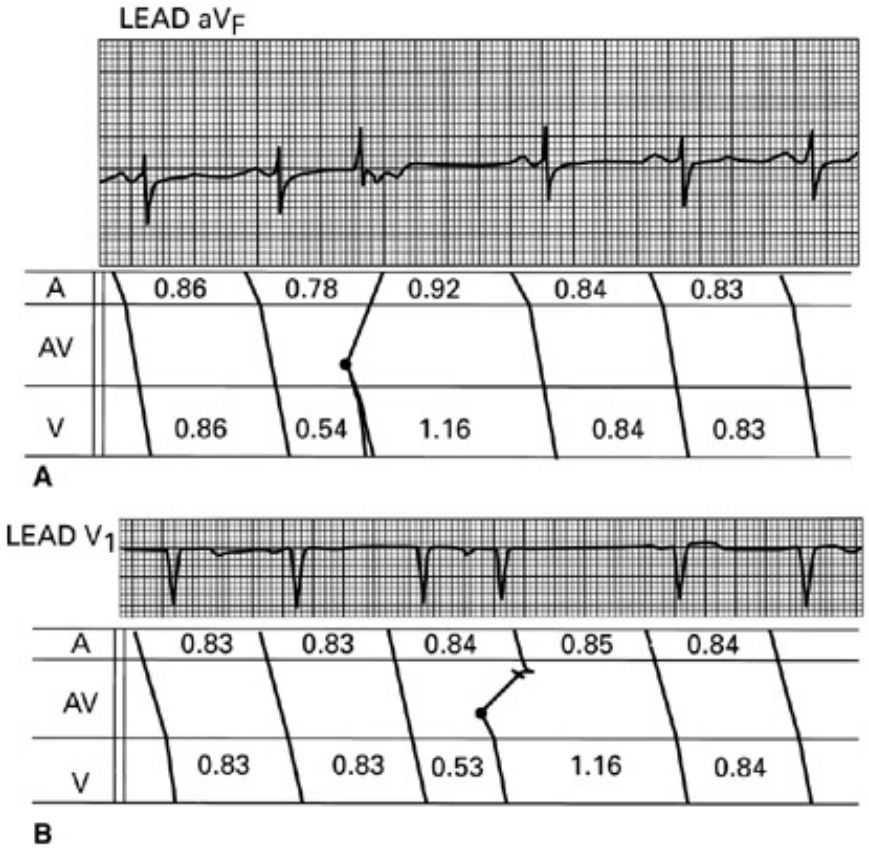

Figure 24-32: *A.* AV junctional extrasystole. The retrograde P wave follows the premature QRS complex, which shows some degree of ventricular aberration. *B.* The fourth complex is an AV premature impulse without retroconduction to the atria, leaving the sinus rhythm undisturbed.

Accelerated Junctional and AcceleratedVentricular Rhythms

Accelerated rhythms derive from subordinate pacemakers and emerge when the sinus rate is less than the normally suppressed focus. Sinus bradycardia combined with enhanced automaticity of the subordinate site is the common pathophysiology. Ischemia (especially inferior wall myocardial ischemia or infarction), digitalis intoxication, electrolyte disturbances (especially hypokalemia), and hypoxemia may enhance phase 4 depolarization in the AV junction or intraventricular specialized conducting system, accelerating the rate of impulse formation of the subordinate pacemakers located at these sites. Digitalis intoxication, various degrees of AV block, and sinus node depression may accompany AV junctional acceleration, producing complex ECG patterns. In inferior wall ischemia, subordinate pacemaker acceleration is commonly associated with sinus node depression, the latter permitting escape and usurpation of pacemaker function, even with only modest AV junctional acceleration (e.g., 60 to 70 impulses per minute). These rhythms are almost always hemodynamically stable.

The typical electrocardiographic pattern is apparent shortening of the PR interval as the PP intervals prolong, leading to emergence of the subordinate QRS complexes as they assume the pacemaker function (Fig. 24-33). After a variable duration, the PP interval begins to shorten, P waves reappear in front of the QRS complex, and ventricular capture by atrial activity is reestablished. The QRS complexes of accelerated AV junctional rhythm commonly have slightly altered vectors, durations, and morphology, often accompanied by minor changes in the T-wave vectors. Such alterations are due to slight changes in conduction patterns resulting from the altered origin of the propagating wavefront in the ventricles. These changes may be diagnostically useful.

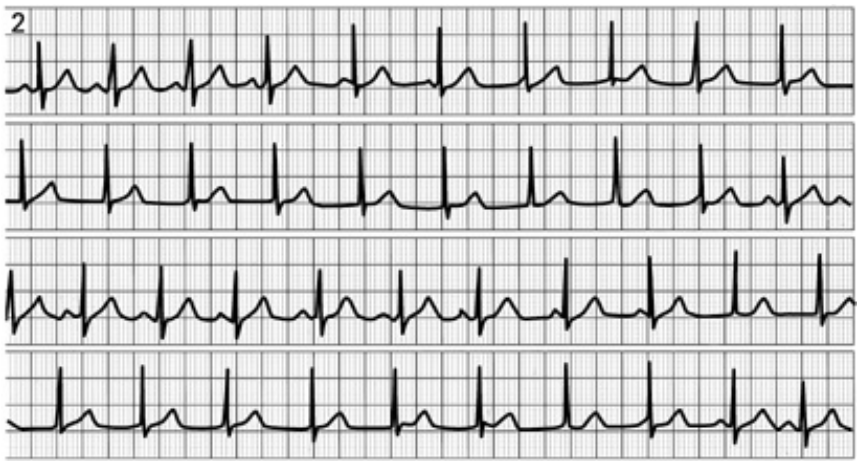

Figure 24-33: Accelerated idiojunctional rhythm with isorhythmic AV dissociation. After four sinus beats, the sinus rate slows slightly, enabling an accelerated junctional pacemaker to escape at a rate of 94 per minute. After several seconds, the sinus pacemaker accelerates and recaptures the ventricles. The same sequence is then repeated (the strips are continuous). (From Marriott HJL. *Workshop in Electrocardiography.* Tampa, FL: Tampa Tracings; 1972. Reproduced with permission from the publisher and author.)

Accelerated AV junctional and ventricular rhythms generally require no specific antiarrhythmic therapy. In ischemia, they are usually self-limiting in duration and of no major consequence hemodynamically; when associated with digitalis intoxication or electrolyte disturbances, they promptly reverse with control of these toxic or metabolic influences. In fact, specific antiarrhythmic drugs might suppress a subordinate pacemaker that is needed to maintain cardiac output in the presence of dysfunction of normal sinus node pacemakers. If a faster ventricular rate or AV sequencing is desirable for hemodynamic benefits, attempts to enhance cardiac rates may be achieved pharmacologically or by pacing. Atropine, 0.6 to 1.2 mg intravenously, may increase sinus rate and allow the sinus to resume its normal pacemaking function if AV conduction is intact. Atropine will have little or no influence on the rate of the accelerated AV junction focus. Temporary atrial or ventricular pacing may be used to support the heart rate if it is slow enough to impair hemodynamics, but pacing is rarely necessary.

AV Junctional Tachycardia

Enhanced AV junctional rhythm may occasionally double its rate abruptly to a true tachycardic range.[156] This phenomenon likely represents an automatic focus firing at the faster rate with 2:1 exit block, which abruptly changes to 1:1 exit. In acute ischemic events, it may be desirable to reduce the rate with antiarrhythmic agents. These incidents are commonly self-limited, however, and will usually cease spontaneously or revert to 2:1 exit block.

Ectopic or persistent nonparoxysmal AV junctional tachycardia may occur intermittently in patients with chronic heart disease and appears to be more frequent and more important in children, particularly after surgical correction of congenital defects.[157,158] The response to treatment is unpredictable, and the rhythm may be resistant to conventional antiarrhythmic drugs. Catheter ablation has been suggested for some patients, however.[158]

An arrhythmia referred to as permanent junctional reciprocating tachycardia (PJRT) is characterized by a long RP-short PR reentry pattern and is due to a very slowly conducting retrograde accessory pathway.[159-161] It is persistent but not truly incessant, occasionally causes tachycardia-induced cardiomyopathy, tends to occur in children, and is difficult to treat pharmacologically. Some success with class IC antiarrhythmic agents has been reported in children,[162] but catheter ablation has become the treatment of choice.

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VENTRICULAR ARRHYTHMIAS

Approaches to the evaluation and management of ventricular arrhythmias have changed dramatically in recent years. New insight into risks of ventricular arrhythmias in various clinical settings, clarification of the risk-benefit ratio of antiarrhythmic drug treatment, and the refinement of nonpharmacologic methods of therapy all have developed in parallel in recent years. The equilibrium between the risk implied by an arrhythmia and the proarrhythmic risk of a drug[163-165] was dramatically emphasized by the results of the Cardiac Arrhythmia Suppression Trial (CAST)[21,227] and Survival with Oral D-Sotalol (SWORD)[166] study, which resulted in major changes in indications and methods for treatment of some ventricular arrhythmias.

The *urge* to treat, based upon limited scientific support in the past, has yielded to indications based upon the *need* to treat, modulated by a better definition of the *risk* of treatment. Clinical approaches to the patient with ventricular arrhythmias require a clear analysis of the interrelationships between electrocardiographic forms of arrhythmias, the specific clinical setting in which it occurs, and realistic goals of therapy (see Tables 24-1 and 24-3).

Definitions, Classification of Risk, and End Points of Therapy

Forms of ventricular arrhythmias may be separated into the various patterns of ambient PVCs and of sustained arrhythmias, such as sustained VT or Ventricular fibrillation (VF). The former are present intermittently and identify risk in the presence of structural heart disease. They may also serve a triggering function for hemodynamically significant or life-threatening arrhythmias (VT or VF) under appropriate conditions.

The conventional definition of VT, three or more consecutive ventricular ectopic impulses at a rate of 120 or greater, is too broad to apply to current evaluation and management strategies. A distinction between bursts of nonsustained VT lasting for up to 30 s and sustained VT lasting 30 s or more (Table 24-10) is more useful for evaluation at the bedside, ambulatory monitoring data, the results of invasive electrophysiologic testing, and responses to therapy. In addition to defining VT by its duration, useful information is contained in the definition of VT from its ECG pattern. Slow, monomorphic patterns of nonsustained VT are less symptomatic and may denote lower risk than faster, polymorphic VT patterns.

Table 24-10: Specific Forms of Ventricular Tachycardia

Duration	ECG Pattern
Salvo (3-5 impulses)	Uniform morphology VT
Nonsustained VT (6 impulses, 29 s)	Polymorphic VT, torsades de pointes
Sustained VT (≥30 s)	Right ventricular outflow pattern
	Bidirectional tachycardia

Data on the risk predicted by PVCs after convalescence from myocardial infarction have been analyzed relative to both frequency and forms.[167-172] Based upon the frequency in Fig. 24-34, most studies demonstrate increased risk with frequencies of 10 or more ectopic impulses per hour, and one major study demonstrated a sharp increase in risk moving across the range of 1 to 9 impulses per hour.[172] Similarly, in

the hierarchy of forms, couplets indicate only a small increase in risk compared to uniform or multiform single PVCs,[172] and salvos indicate a significantly higher risk.[171,172] There are insufficient data to determine whether longer runs (i.e., nonsustained VTs of six consecutive impulses) constitute an even higher risk. Patterns such as bigeminy and trigeminy are simply an expression of frequency and contain no inherent information concerning risk beyond frequency.

HIERARCHY OF FREQUENCIES	HIERARCHY OF FORMS
CLASS 0 – NIL	CLASS A – UNIFORM MORPHOLOGY, UNIFOCAL
CLASS I – RARE < 1 ectopic impulse/hour	CLASS B – MULTIFORM, MULTIFOCAL
CLASS II – INFREQUENT 1 to 9 ectopic impulses/hour	CLASS C – REPETITIVE FORMS • COUPLETS • SALVOS, REPETITIVE RESPONSES (3–5 consecutive inpulses)
CLASS III – INTERMEDIATE 10 to 29 ectopic impulses/hour	CLASS D – NON-SUSTAINED VENTRICULAR TACHYCARDIA (from 6 consecutive ectopic impulses to runs lasting up to 30 seconds)
CLASS IV – FREQUENT ≥ 30 ectopic impulses/hour	CLASS E – SUSTAINED VENTRICULAR TACHYCARDIA (runs of ectopic activity ≥ 30 seconds)

Figure 24-34: Classification of ventricular arrhythmias based on hierarchies of frequency and forms. Hierarchical schemes for estimating risk of ventricular arrhythmias have been developed based on frequency and forms of ventricular arrhythmias. In some clinical settings, frequencies in the range of 1 to 9 ectopic impulses per hour become significant, and in most settings of clinically significant heart disease, risk based on frequency plateaus in the range of 10 to 30 ectopic impulses per hour. Among forms of ventricular arrhythmias, the repetitive forms, particularly salvos or nonsustained ventricular tachycardia, indicate higher risk in most clinical settings. (Modified from Myerburg et al.[138] Reproduced with permission from the publisher and authors.)

For evaluating risk and prescribing therapy, clinical information beyond the pattern of the arrhythmia itself must be considered. Very high frequencies and/or advanced forms usually connote little or no increased risk in the absence of structural heart disease, except for certain polymorphic nonsustained VTs. Risk begins to increase with the presence of structural heart disease and becomes prominent with falling EF.[171,172] A simplified but useful clinically based classification incorporates both form and frequency along with clinical disease information. Bigger[173] suggested classifying ventricular arrhythmias as benign, potentially malignant, and malignant based on these considerations. As an extension of this concept, frequency, forms, severity of cardiac disease, and LV function (EF) can be integrated into a clinical classification of benign (no independent increase in risk), significant (independent increase in risk), and potentially lethal (untreated, can lead to proximate fatality). While these clinically based approaches have not been quantitated, they do provide a conceptual framework for classifying arrhythmias.

Management of PVCs must be further analyzed in regard to specific etiology (e.g., low-risk mitral valve prolapse versus high-risk idiopathic dilated cardiomyopathy), and PVCs in acute or subacute clinical settings must be distinguished from those occurring in chronic settings. Finally, end points of therapy that are based upon suppression of underlying ectopy (i.e., background PVCs) are separated from end points based upon prevention of potentially lethal arrhythmias (i.e., sustained VT or VF; see Table 24-1). *There are no data supporting the notion that PVC suppression itself improves mortality rates, despite the connotation of risk in specific clinical settings. Indications for therapy are based on symptoms, evaluated in the light of the known or suspected risks of therapy.*

Premature Ventricular Contractions

ELECTROCARDIOGRAPHIC RECOGNITION OF PVCS

Ventricular arrhythmias originate in the specialized conducting tissue distal to the bifurcation of the bundle of His or in true ventricular myocardium. Accordingly, they are characterized by a prolonged ventricular depolarization (i.e., wide QRS complex), an alteration in the sequence of ventricular activation (i.e., a change in the QRS vector), and alterations in the timing sequence of consecutive QRS complexes (i.e., prematurity or escape rhythms). None of these criteria is totally sensitive and specific for ectopic impulses of ventricular origin. On occasion, PVCs demonstrate narrow QRS complexes, have a vector very similar to the normal QRS vector, or have timing little changed from the normal sinus sequence. Nonetheless, the majority of impulses originating in the ventricles have QRS complexes of at least 0.12 s and a shift in the QRS vector, and most single PVCs or initiating beats for runs of ventricular ectopic activity are premature. PVCs may fail to conduct to the atria or may demonstrate retrograde atrial activation. In either case, the sinus cycle is usually not interrupted, resulting in a *fully compensatory pause* (Fig. 24-35). The pause is characterized by an interval between the P wave of the sinus impulse immediately before the PVC and the first sinus P wave after the PVC equal to twice the sinus cycle length (Fig. 24-35*A*). If the sinus rate is relatively slow, PVCs may be interpolated between two sinus beats with no alteration of the sinus cycle length (Fig. 24-35*B*). Exceptions to the compensatory pause rule do occur (Fig. 24-36) and occasionally complicate diagnostic criteria. PVCs that presumably originate in the fascicles of the specialized conducting system may have more narrow QRS complexes with only slight alterations in the QRS vector.

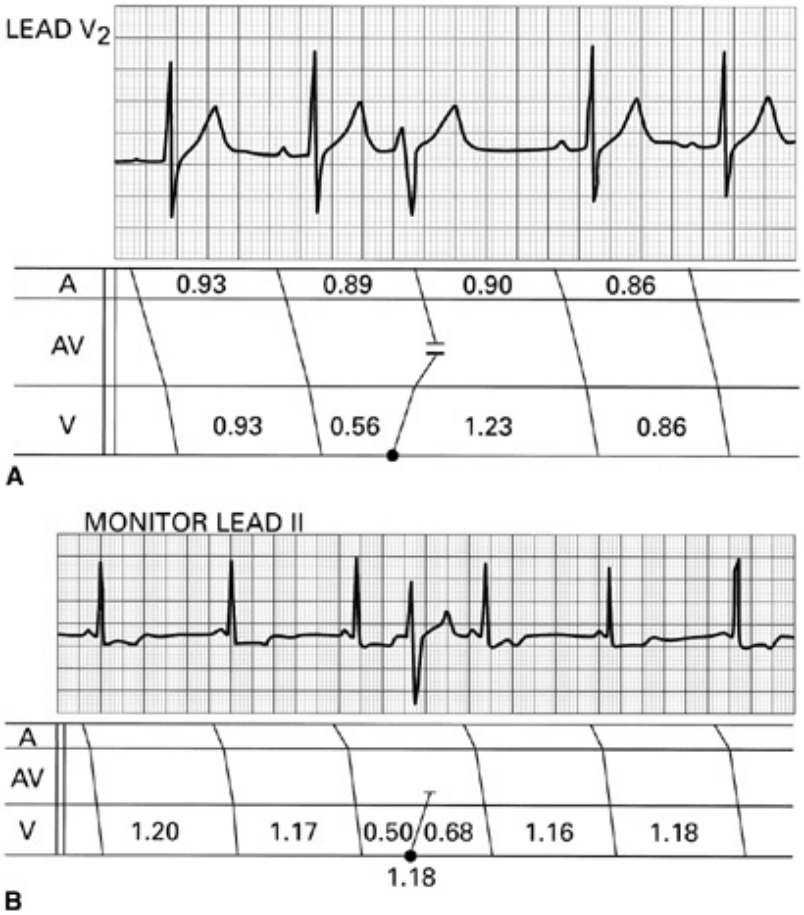

Figure 24-35: Ventricular premature contractions. *A.* The third impulse is wide and bizarre, and since the sinus rhythm is undisturbed (next sinus P wave indicated by arrow), the postextrasystolic pause is compensatory. *B.* The fourth impulse is an interpolated ventricular premature contraction; it is sandwiched between two consecutive conducted sinus beats.

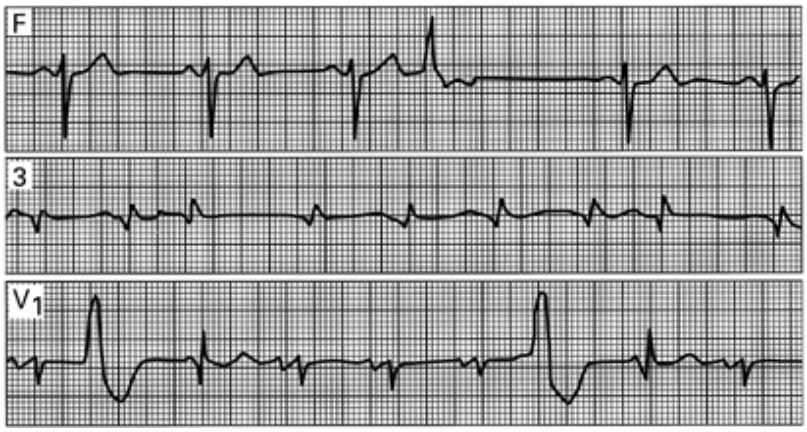

Figure 24-36: Exceptions to the rules for compensatory pauses. *Top*. Ventricular extrasystole with less than compensatory pause. Retrograde conduction to the atria (retrograde P wave deforms first part of ST segment) discharges the sinus pacemaker early and thus shortens the postextrasystolic cycle. *Middle*. Atrial premature contraction followed by fully compensatory pause. The third and eighth beats are atrial extrasystoles, but presumably because they suppress the sinus pacemaker, they are followed by compensatory pauses. *Bottom*. Ventricular extrasystoles with less than compensatory pauses. Each postextrasystolic cycle ends in an escape beat and so is slightly less than compensatory.

PVCs are usually coupled to the preceding sinus beat by a fixed coupling interval. This generalization has exceptions, in that PVCs having different QRS morphologies may have different coupling intervals,[174] and PVCs having the same morphology in a given patient may have different coupling intervals as pathophysiologic conditions change. The pattern of fixed coupling has led to a concept of a physiologic relationship between the sinus beat and the PVC, an argument in favor of reentrant or triggered-activity mechanisms for common PVCs. In contrast, parasystolic rhythms refer to an independent ectopic rhythm, with the focus of origin being protected in the sense that descending impulses cannot enter and reset the parasystolic focus but can create a field of refractoriness around it, limiting the rate and timing of impulses that exit the focus. Thus, the parasystolic focus, automatic in nature, can deliver impulses to the myocardium but cannot be reset by impulses originating elsewhere. Accordingly, the ECG reflects the presence of competing pacemakers, the sinus node, and a protected automatic ectopic ventricular focus, creating the classic triad of (1) variable coupling between sinus beats and ectopic QRS complexes, (2) fusion beats, and (3) a fixed common denominator of interectopic intervals between manifest parasystolic extrasystoles (Fig. 24-37). However, classic concepts of parasystole have been altered by the discovery that parasystole may be modulated by relationships between the parasystolic focus and impulses originating in the sinus node. Sinus impulses occurring early in the parasystolic cycle tend to shorten the cycle length of the parasystolic focus, whereas those arriving in the latter half of the cycle tend to lengthen the cycle length of the parasystolic focus.[175] Parasystolic patterns may also occur with atrial extrasystolic activity.

MANAGEMENT OF PREMATURE VENTRICULAR CONTRACTIONS

Management of PVCs in the Absence of Significant Structural Heart Disease

PVCs occur in many healthy individuals. In the absence of heart disease, there is little or no increased risk,[176] and the risk-benefit ratio of antiarrhythmic therapy does not support a need for routine treatment. For the patient who complains of disturbing or disabling palpitations due to PVCs, however, the clinician may have to treat for symptom relief (Fig. 24-38). Reassurance and avoidance of potentially aggravating factors (e.g., tobacco, coffee, caffeine-containing soft drinks, environmental stress, or stimulants) should be tried before pharmacologic therapy. For the latter, mild anxiolytic drugs or beta-adrenergic blockers (which may sedate, reduce PVC frequency, and decrease the strength of postextrasystolic impulses causing the perception of palpitations) are preferred. When used for this purpose, low doses of beta-adrenergic blockers are often sufficient. The end point, relief of symptoms, may not necessarily be accompanied by significantly reduced PVC frequency. The frequency of PVCs may be modulated by underlying heart

rate,[177] and thus manipulations of sympathetic and parasympathetic balance may be useful. Because of their side-effect profiles, class I antiarrhythmic agents are rarely indicated in this clinical setting, and the class III agent amiodarone is unnecessarily potent. PVCs are often more prominent with pregnancy and premenstrually and increase in frequency with age.[178]

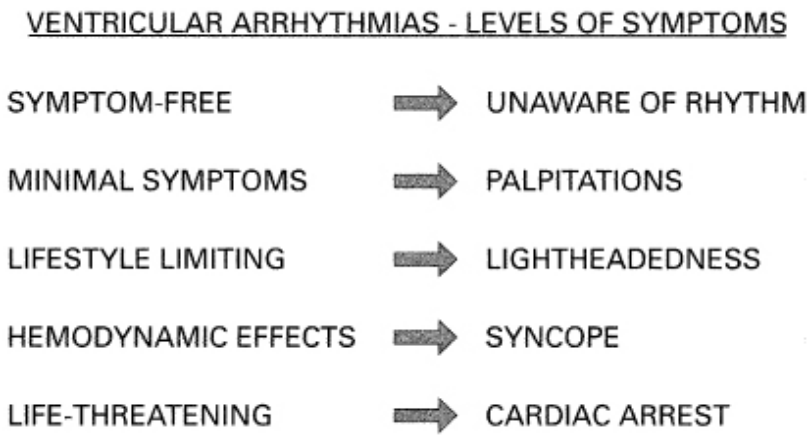

Figure 24-38: Approaches to management of ventricular arrhythmias. Treatment of ventricular arrhythmias is dictated by symptoms and clinical risk. Asymptomatic PVCs in the absence of disease usually need not be treated. Ventricular arrhythmias in the presence of advanced and/or acute disease states commonly indicate high risk, although therapy is not necessarily targeted to the PVCs themselves. A range of considerations of risk versus quality of life exists between these two extremes (see the text for details).

There may be an urge to be more aggressive in the management of patients who have advanced forms of PVCs (e.g., salvos or nonsustained VT) or a high frequency of PVCs (30 or more PVCs per hour) in the absence of structural disease. Kennedy et al.,[176] however, reported no increased risk of death in a cohort of such persons followed for a mean of over 6 years. Some specific forms of nonsustained VT, for example, polymorphic runs, may predict some increase in risk (see below).

The occurrence of PVCs in patients with mitral valve prolapse has gained special attention for three reasons: (1) the high prevalence of mitral valve prolapse, (2) the prevalence of PVCs in patients with mitral valve prolapse, and (3) the very small risk of sustained VT or VF. Annoying palpitations are a common complaint, but the arrhythmia does not require treatment in the vast majority. There are limited data suggesting that the patients at highest risk for serious ventricular arrhythmias can be subgrouped by the presence of nonspecific ST-T wave changes in leads II, III, and aVF[179,180] in conjunction with advanced grades of ventricular arrhythmias and redundancy of the mitral valve echocardiographically.[181] The approach to treatment of patients with benign forms of PVCs in mitral valve prolapse should be no different than that outlined for individuals with no structural abnormalities. Beta-adrenergic blocking agents are often sufficient to control the symptoms, and membrane-active antiarrhythmic drugs should be avoided.

Patients at risk for more serious arrhythmias, as outlined above, may require more aggressive treatment; membrane-active drugs are considered for use in this special situation for patients with salvos or nonsustained VT. The rare mitral valve prolapse patient who has had sustained VT or survived after VF is managed by the approaches generally used for these potentially lethal arrhythmias in other clinical settings (see below).

Management of PVCs in Acute Syndromes

PVCs are nearly ubiquitous in acute myocardial infarction, but the threshold for treatment remains unsettled. The original concept of "warning arrhythmias" published by Lown et al.[182] remains an indication for aggressive treatment, even though the predictive value of such warning arrhythmias remains unsubstantiated.[183,184]

The concept of routine treatment of all patients with acute infarctions with lidocaine to prevent PVCs as

well as VT or VF[185,186] is no longer applied, having yielded to a threshold for treatment at various frequencies of manifest PVCs. Suppression of PVCs in acute myocardial infarction is usually accomplished with intravenous lidocaine (a bolus of 50 to 100 mg followed by a continuous infusion of 2 to 4 mg/min), with intravenous procainamide as a second choice (100 mg every 5 min to a total dose of 500 to 750 mg, followed by an infusion of 1 to 4 mg/min). Both drugs have significant side effects, especially with improper dosing. Furthermore, these drugs have not been shown to change hospital mortality rates for patients for whom prompt medical attention and electrical defibrillation are available. Lidocaine levels and binding both increase during the course of acute myocardial infarction,[187] theoretically rendering free drug levels stable. The practice of tapering the lidocaine infusion to avoid toxicity[188] is not appropriate if free drug concentration represents active drug and does not rise (see also Chap. 42).

A number of other acute cardiac states are associated with the emergence of PVCs. For example, PVCs may emerge during and immediately after transient myocardial ischemia and are accompanied by a risk for sustained VT or VF.[189-191] The primary intervention for controlling PVCs in these settings is the reversal of ischemia.[189] On first contact, however, intravenous lidocaine or procainamide should be administered to suppress the arrhythmias. Clinical circumstances characterized by myocardial reperfusion-such as Prinzmetal's angina, thrombolysis in AMI, or balloon deflation during percutaneous transluminal coronary angioplasty (PTCA)-may cause reperfusion-induced arrhythmias. The arrhythmias generated include PVCs and accelerated ventricular rhythms (e.g., postthrombolysis or PTCA) or nonsustained VT (often polymorphic) after reversal of coronary spasm.[191] These arrhythmias are usually transient and self-limiting but may evolve into sustained VT or VF.[190,191] Although there are theoretical and experimental reasons to suspect that Ca^{2+}-mediated electrophysiologic disturbances occur during reperfusion,[192,194] intravenous lidocaine is currently used to treat reperfusion-induced arrhythmias. It is used in the same dose and with the same infusion techniques as in acute myocardial infarction. Severe heart failure and acute pulmonary edema are commonly accompanied by frequent and advanced forms of PVCs;[194,195] as in acute myocardial infarction with low-output states, the PVCs are considered secondary to the hemodynamic abnormality (see Fig. 24-1). The use of antiarrhythmic agents while the hemodynamic status is being stabilized is appropriate but may have only limited success until adequate hemodynamic control is achieved.

Acute and subacute myocarditis and pericarditis are commonly accompanied by PVCs, and sustained VT or VF may occur infrequently,[196] even in the absence of significant myocardial dysfunction. Frequent PVCs and salvos or nonsustained VT are usually treated until the carditis has resolved. In those patients who have not had sustained VT or VF conventional antiarrhythmic agents are given orally and titrated to suppression of the PVCs if possible, or at least to achieve suppression of repetitive forms. Antiarrhythmic therapy is continued for a minimum of 2 months, and then the patient is taken off antiarrhythmic drugs while still being monitored. If advanced forms do not reappear, the drug is not restarted; if they do reappear, treatment is continued for another 2 to 3 months, after which the same procedure is carried out. Myocarditis that has not evolved into a cardiomyopathic state is only rarely followed by frequent or complex forms of PVCs beyond 6 months. Virtually all other acute cardiac syndromes and many acute systemic disorders may be associated with PVCs that will abate with resolution of the initiating abnormality.

Management of Chronic PVCs in the Presence of Cardiac Disease

Chronic PVCs carry a different connotation in patients with established heart disease than in those free of disease. Sudden and total death rates are increased in patients who have frequent or repetitive PVCs in the major categories of chronic cardiac disease in the United States, including chronic ischemic heart disease,[168-172] hypertensive heart disease, and the cardiomyopathies.[1,194,195,197,198]

When frequent PVCs and/or salvos or runs of nonsustained VT are accompanied by a reduced EF, both the arrhythmia and the EF contribute to risk, and the rate of sudden death is increased.[200,201] Bigger et al.[201] observed a 2-year mortality rate of 42 percent for postinfarction patients with salvos or nonsustained VT and an EF of less than 30 percent, compared to a 2-year mortality rate of 12 percent for patients with salvos or nonsustained VT and an EF of 50 percent or more. The 2-year rate fell to 7 percent for patients with only single PVCs and an EF of 50 percent or more.

Management of frequent and repetitive forms of chronic PVCs after myocardial infarction has changed dramatically since the results of the CAST study were published.[21,199] Previous studies[200,201] as well as

CAST itself[21] had demonstrated that PVC suppression was feasible in these patients, but CAST clearly demonstrated a significant excess risk of sudden cardiovascular death among the treatment groups receiving the two class IC agents (flecainide and encainide) evaluated in the study. CAST II, the continuation of the study with moricizine, the one drug that had not crossed a boundary of significance during CAST I, demonstrated neither benefit nor adverse effect, showing only an early classic proarrhythmic mortality risk, which did not influence long-term outcome.[199] By design, the enrollment in the moricizine arm of CAST I and in CAST II was a population with more advanced disease. Meta-analyses of data derived from previous smaller randomized studies, as well as the subsequent (SWORD) study,[166] testing the effect of antiarrhythmic drugs on mortality rates after myocardial infarction, also suggested an adverse effect of most antiarrhythmic drugs when used in postmyocardial infarction patients.[202] Accordingly, the drugs used in CAST are now contraindicated following myocardial infarction in patients with asymptomatic or mildly symptomatic PVCs, and there is a trend away from the use of any membrane-active antiarrhythmic agent in such patients. Recent large randomized, placebo-controlled trials testing the possible benefit of amiodarone in postmyocardial infarction patients (EMIAT and CAMIAT) demonstrated no benefit on total mortality rates.[203,204] Beta-adrenoceptor blocking agents, however, have a substantial beneficial effect on long-term outcome in the postmyocardial infarction patient[205,206] as well as improving total mortality rates in the subgroups of the amiodarone postmyocardial infarction trials in whom beta-adrenoceptor-blocking agents were used with amiodarone.[207] In addition, beta-adrenoceptor-blocking agents are effective in suppressing repetitive forms of PVCs in many patients.[209]

Beta blockers, therefore, have evolved as the drugs of choice following myocardial infarction in patients with mildly symptomatic PVCs. While no properly randomized study directed to a sudden and total death outcome as a result of PVC suppression using beta-adrenoceptor-blocking agents has been reported, the existing randomized data on mortality rates in patients following myocardial infarction in general demonstrates beneficial effects.[205,206]

In patients with *symptomatic* PVCs (e.g., palpitations or repetitive beats) following myocardial infarction, especially when accompanied by a low EF, management becomes more difficult. Such patients have a higher mortality rate, and it is not known whether the CAST data should be extrapolated to this population. Because of CAST, class IC agents are avoided in these patients, but clinicians may use other antiarrhythmic drugs if they are well tolerated and no adverse effects are observed. However, the threshold for initiation of therapy is generally higher than it was prior to CAST. Even if the EF is depressed, beta-adrenergic blocking agents should be tried initially. If they are effective and well tolerated, they are the preferred treatment. Class III (e.g., sotalol and amiodarone) and perhaps class IA drugs also appear to be safe and may be used if treatment is necessary.

Chronic PVCs are very common in patients with advanced idiopathic dilated cardiomyopathy and in patients with hypertrophic cardiomyopathy, and both groups have a major risk of arrhythmic sudden death. In some reports, more than 90 percent of patients with dilated cardiomyopathy have frequent PVCs, and over 50 percent have salvos or nonsustained VT.[194,195] Efficacy of antiarrhythmic therapy for both suppression of chronic PVCs and prevention of VT and VF is unclear and perhaps is quite limited in these patients. Treatment is controversial. It is not known whether the CAST data can be extrapolated to this group or whether there is any mortality benefit from the use of antiarrhythmic drugs among these patients. When treatment is prescribed, the patient should be hospitalized for initiation of antiarrhythmic therapy because of proarrhythmic risk in cardiomyopathy.[214] Secondary ventricular arrhythmias in patients who have chronic heart failure (see Fig. 24-1) may respond to control of heart failure. In one carefully designed study, treatment with an angiotensin-converting enzyme inhibitor had a very favorable effect on both parameters of heart failure and ventricular ectopy.[215]

When antiarrhythmic drugs are to be used, the selection of a drug or a combination of drugs for high-risk patients with chronic PVCs is complex. The class IA drugs are moderately effective but have a high incidence of allergic reactions (e.g., procainamide) and poorly tolerated side effects (e.g., quinidine causing thrombocytopenia). They may also produce significant further myocardial depression in patients with an already reduced EF (e.g., disopyramide). Moricizine appears to be better tolerated, but all have significant risks of proarrhythmic effects, although many of these events are not life-threatening.[216] Among the class IB agents (e.g., tocainide and mexiletine), efficacy might be good in some patients and the proarrhythmic incidence is lower, but there is a high incidence of uncomfortable side effects. The currently available IC agents (flecainide and propafenone) are very effective for reducing ventricular ectopy and are well tolerated

in patients with normal or only minimally depressed LV function. Their use is not indicated for patients with ischemic heart disease because of the adverse outcome observed in CAST[21] and is limited more generally by the fact that the incidence of proarrhythmic effects and myocardial depression is highest in the subgroup at greatest need for the intervention: those with repetitive forms and impaired LV function. It is not yet known, however, whether the higher absolute risk of adverse effects in patients with abnormal LV function is balanced by a benefit in this higher-risk group.[217] Specifically, the long-term effects of the class I agents on death rates in groups of patients other than the lower-risk category enrolled in CAST are unknown at present.

There are differences in adverse proarrhythmic effects among the various drug groups. Class IA drugs are predominantly associated with classical proarrhythmia. Class III drugs have the same pattern of proarrhythmia, perhaps with a lower incidence of torsades de pointes for amiodarone. Sotalol demonstrates a dose-dependent incidence of torsades de pointes, in contrast to the idiosyncratic pattern for the class IA drugs. The common denominator between class IA and class III drugs, which likely contributes to this concordant proarrhythmic pattern, is moderate to marked prolongation of repolarization, as reflected in QT interval prolongation. In contrast, the class IC drugs, which have minimal effect on repolarization, have a low rate of classic proarrhythmia: torsades de pointes. They may, however, worsen clinical arrhythmias or generate a new rapid sinusoidal sustained VT.[219] In addition, the excess death rate in CAST, attributed to proarrhythmia, extended over the entire period of drug exposure rather than being close in time to the start of treatment. A possible explanation for this pattern is a tendency for the class IC drugs to interact with sporadic intercurrent events, such as transient ischemia or LV dysfunction.[22] Such an explanation is consistent with disturbed conduction patterns (depolarization) contributing to proarrhythmia rather than repolarization abnormalities[15] (see also Chap. 27). It is also consistent with the observation in CAST that increased risk of mortality in the flecainide and encainide arms was accompanied by a decreased incidence of nonfatal ischemic events compared to their placebo groups. Combining drug classes has been found to be effective by some, although carefully controlled studies are limited;[220] combinations such as a class IA and a class IB drug may be tried. The class II drugs, beta-adrenergic blocking agents, have been mentioned earlier, and many consider them the first choice of therapy even if the EF is reduced. They may be used in combination with class I drugs in some patients. Class III drugs have been approved only for use in life-threatening arrhythmias, although amiodarone and sotalol are both appropriate for selected patients with symptomatic runs of nonsustained VT and advanced LV dysfunction. The available data on amiodarone is promising for patients with life-threatening arrhythmias,[221,222] but the specific benefit for patients with PVCs and nonsustained VT in the presence of advanced heart disease is unclear. In the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) study, which randomized ischemic and nonischemic myopathies and PVCs to amiodarone and placebo, no mortality benefit was observed.[223] Another study, GESICA, which randomized cardiomyopathic patients to the same drug versus placebo, however, showed a survival benefit for the amiodarone-treated group.[224] PVC stratification was not carried out in the latter. In both studies, amiodarone-treated patients with nonischemic cardiomyopathies tended to respond more favorably to the drug than those with ischemic cardiomyopathies. The class IV drugs, Ca^{2+}-entry blockers, have no role in the treatment of chronic PVCs.

With any of these drugs or drug combinations, attention to underlying heart disease and systemic factors is necessary. Treatment for limiting the frequency of episodes of transient ischemia, maximizing LV function, maintaining electrolyte balance, and controlling blood pressure all may act in concert with antiarrhythmic agents to limit the risk of cardiac morbidity and mortality in patients with chronic PVCs. The end point of treatment (see Table 24-1) of patients who have structural heart disease and high-risk forms and frequency of chronic PVCs is not at all clear. The pharmacodynamics of PVC suppression differ from those of VT prevention,[225] and quantitative PVC suppression is difficult to achieve.

Suppression of advanced forms of PVCs (e.g., couplets, salvos, and nonsustained VT) is sometimes achieved,[226] even if quantitative PVC suppression fails. General guidelines have included suppression of 70 to 80 percent of total PVCs on a 24-h ambulatory monitor[227] and complete (or nearly complete) suppression of repetitive forms.[228] An ongoing trial, MADIT II, is designed to determine whether mortality rates can be improved by ICDs in postmyocardial infarction patients with PVCs and ejection fractions of 30 percent or less.[229]

Nonsustained Ventricular Tachycardia

Nonsustained runs of VT (salvos of three to five consecutive impulses or nonsustained VT of six impulses to 30 s; Fig. 24-39) are considered indicators of high risk for potentially fatal arrhythmias (sustained VT or VF) in most clinical settings. There are important exceptions, however. Patients who have no organic disease or limited cardiac abnormalities do not appear to have increased risk, although some patients who have very rapid polymorphic VT may be at increased risk. Even in the absence of an increased mortality risk, symptoms such as transient light-headedness, near-syncope, or syncope require therapy (see Fig. 24-38). At the other extreme, cardiomyopathy patients and those who have advanced coronary artery disease with a very low EF are among the highest risk groups. Conceptually, nonsustained VT may be viewed as self-terminating VTor as an intense triggering event in a susceptible myocardium.[1]

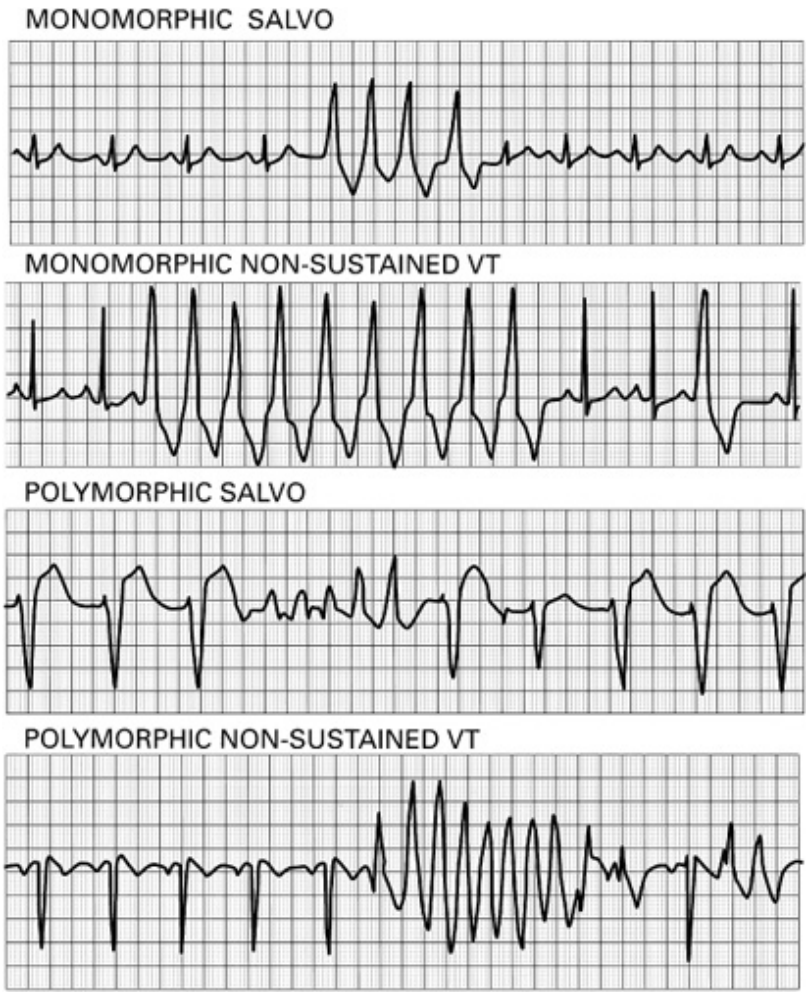

Figure 24-39: Nonsustained forms of VT. Runs of repetitive ventricular impulses (rate 100 per minute) lasting less than 30 s are subgrouped into salvos of three to five consecutive impulses and nonsustained VT of six or more impulses in duration. Both forms may be further defined according to morphology as monomorphic or polymorphic.

Treatment is generally similar to that outlined for other patterns of PVCs, although patients with prior myocardial infarction who have nonsustained VT and low EFs and are inducible into VT in the clinical electrophysiology laboratory are thought to be at higher risk than those with nonsustained VT who have better EFs and are noninducible.[210] In MADIT, ICD therapy demonstrated lower mortality rates than with the best conventional therapy in a randomized study design of such patients (nonsustained VT, EF 35 percent or less, inducible sustained VT, and failed supression of inducibility of VT during programmed stimulation-guided therapy with intravenous procainamide).[211] In the Multicenter Unsustained Tachycardia Trial (MUSTT), a similar group of patients appeared to benefit from ICDs, as opposed to electrophysiologically guided drug therapy.[230]

Repetitive Monomorphic Ventricular Tachycardia

Repetitive monomorphic VT is an uncommon form of repetitive salvos or runs of nonsustained VT, often separated from one another by only a few sinus impulses (Fig. 24-40).[233] Occasionally, this arrhythmia is continuous and fulfills the definition of sustained VT. The tachycardia rate is usually 150 or less per minute but may be greater than 200 per minute in rare cases. The syndrome is more common in women and is usually benign.[233,234] The QRS patterns of the tachycardia on 12-lead ECGs suggest a right ventricular outflow tract origin (left bundle-branch block pattern with an axis between 0° and +90°, or slightly rightward), and the mechanism is likely a form of enhanced automaticity.[235] Treatment is considered only when structural heart disease is also present, when the palpitations are poorly tolerated by the patient, or when the patient has light-headedness, near-syncope, or syncope caused by the arrhythmia. Membrane-active antiarrhythmic drugs should be avoided if possible, and beta-adrenoceptor and Ca^{2+}-entry blocking agents are effective in some. Catheter ablation is an option for the more sustained or symptomatic forms and has a high probability of success[236] (Fig. 24-41).

Sustained Ventricular Tachycardia

Sustained VT may originate in the specialized conducting system distal to the bundle of His, in ventricular myocardium, or by an interaction between the two. By definition, it occurs at a heart rate of 100 per minute or more and lasts for 30 s or more. A ventricular rhythm faster than 40 to 50 impulses per minute but slower than 100 per minute is referred to as an accelerated ventricular rhythm. Runs of VT lasting less than 30 s that impair hemodynamics enough to cause symptoms of reduced peripheral or central nervous system blood flow are considered the functional equivalent of a sustained VT. Although generally considered to be included among the life-threatening cardiac arrhythmias, benign forms of sustained VT do exist. They occur in persons without structural heart disease, and a functional basis can be identified in some instances (see below).

The etiology of VT will determine its mechanism and clinical presentation (Table 24-11). For example, in the patient with prior myocardial infarction and a defined ventricular aneurysm, sustained monomorphic VT occurs at rates ranging from 140 to 200 per minute, most commonly in the range of 150 to 180 per minute (Fig. 24-42*A*). This arrhythmia usually employs stable reentrant pathways and may be hemodynamically well tolerated. In contrast, patients with transient myocardial ischemia often have more rapid ventricular tachyarrhythmias (in excess of 200 per minute) that may be polymorphic or sinusoidal (Fig. 24-42*B*). The mechanism is not clearly defined but likely may be either reentrant or automatic, including the possibility of triggered activity. These forms of VT tend to be hemodynamically and electrically unstable, with a higher risk of degenerating to VF than chronic recurrent monomorphic VT. They tend to persist for only short periods of time, in contrast to the sustained mono-morphic VTs, which may persist for hours in some pa tients. These forms of VT either degenerate to VF, convert to a stable monomorphic VT, or spontaneously revert to sinus rhythm (see also Chap. 23).

Some patients will tolerate sustained monomorphic VT remarkably well, although the risk that sustained VT will degenerate into VF must always be kept in mind. When the hemodynamic status is stable and there is no evidence of myocardial ischemia, acute infarction, or poor central nervous system perfusion, electrical cardioversion can await a therapeutic trial of intravenous drug. With acute myocardial infarction, falling blood pressure, or evidence of ischemia, immediate cardioversion is indicated. In patients who are already receiving antiarrhythmic agents because of prior sustained VT or for treatment of other ventricular arrhythmias, recurrent sustained VT presents a challenging therapeutic problem. If it is known that the patient has not complied with antiarrhythmic regimens, standard intravenous regimens may be tried, but more commonly this is not the case. Plasma concentrations of the prescribed antiarrhythmics should be ordered at the time of presentation, even though the information may not be available for initial management. The distinction between recurrence of the previous VT and proarrhythmic effects caused by antiarrhythmic agents is a major dilemma. Proarrhythmia should be suspected if the VT morphology is different from the previously identified clinical VT morphology, if antiarrhythmic agents have been recently prescribed or changed, if there is marked prolongation of the QT interval, or if the VT has a polymorphic or torsades de pointes configuration. If there are repeated recurrences after cardioversion, the possibility of proarrhythmia should be seriously entertained, and temporary pacing may be useful. Other causes of repeated recurrence include ischemia, heart failure, autonomic surges, or electrolyte disturbances.

ELECTROCARDIOGRAPHIC RECOGNITION OF SUSTAINED VENTRICULAR TACHYCARDIA

Having met the rate and duration criteria for a sustained tachyarrhythmia, the distinction between sustained VT and supraventricular tachyarrhythmias with abnormal intraventricular conduction patterns is based upon a complex set of electrocardiographic criteria. The evaluation of the patient's general clinical status, short of cardiac arrest, is only of limited value for distinguishing very rapid SVT from VT as the cause of hypotension or syncope. Nonetheless, the distinction between SVT and VT at the bedside is important because of its clinical and therapeutic implications.

Electrocardiographic criteria derive from atrioventricular timing relationships and from QRS durations, configurations, and axes. The presence of ventriculoatrial dissociation with clearly discernible P waves independent of a regular QRS rhythm is strongly suggestive of VT (Fig. 24-43*A*), as is the presence of P waves associated with alternate QRS complexes (Fig. 24-44). The latter, best identified in lead V_1, is due to 2:1 retrograde block because of the rate of the tachycardia. The presence of a 1:1 relationship between P waves and QRS complexes, with a short RP interval (as in Fig. 24-43*B*), is also considered supportive evidence for VT. A variety of SVTs with aberrant intraventricular conduction may mimic this pattern, however, and therefore it is not conclusive. Finally, in the presence of ventriculoatrial dissociation, a fortuitously timed sinus impulse may fuse with the wide QRS complex due to VT and produce a single cycle of an altered (usually narrowed) QRS complex (Fig. 24-43*C*). Such fusion beats are helpful when present but are not common.

A QRS duration greater than 0.14 s favors VT as the cause of a wide QRS complex tachyarrhythmia. It is nonspecific, however, and is commonly observed in patients with SVT in the presence of a preexisting bundle-branch block. SVT with QRS complexes greater than 0.14 s occurs only rarely as a consequence of aberrant intraventricular conduction when QRS complexes are normal during sinus rhythm. In addition, antidromic tachycardias in WPW syndrome usually have QRS complexes longer than 0.14 s in duration and therefore may mimic VT. The mean QRS axis is also of limited help in distinguishing between SVT with aberration and VT. Abnormal left-axis deviation (-30° or beyond) favors VT but does not exclude SVT with preexisting bundle-branch block or various supraventricular arrhythmias associated with accessory pathways. Some unusual VTs are associated with a left bundle-branch block pattern and right-axis deviation.

QRS configurations have been carefully studied in both VT and SVT with aberrant intraventricular conduction and are of considerable help in distinguishing between the two. Generally, concordantly positive or negative QRS complexes across the precordium from V_1 to V_6 strongly favor VT over aberrant intraventricular conduction (Fig. 24-45). In addition, patterns in specific leads may be helpful. In V_1, a right bundle-branch block configuration that is monophasic (R) or biphasic (qR) suggests VT, while a triphasic pattern (rSR) strongly favors aberrant intraventricular conduction.[237] R-wave amplitude in V_1 during the tachycardia that exceeds that during sinus rhythm favors VT, and an initial R wave during the tachycardia of 30 ms duration or longer also favors VT. In V_1 and V_2, a notched downslope on an S wave suggests VT, as does an interval of 70 ms or more from onset of the QRS to the negative peak of the S wave. In lead V_6, a deep S wave with an R:S ratio below 1 and a qR or QS pattern both favor VT.[238,239] Each of these criteria may be altered or modified in individual cases by the presence of preexisting intraventricular conduction abnormalities.

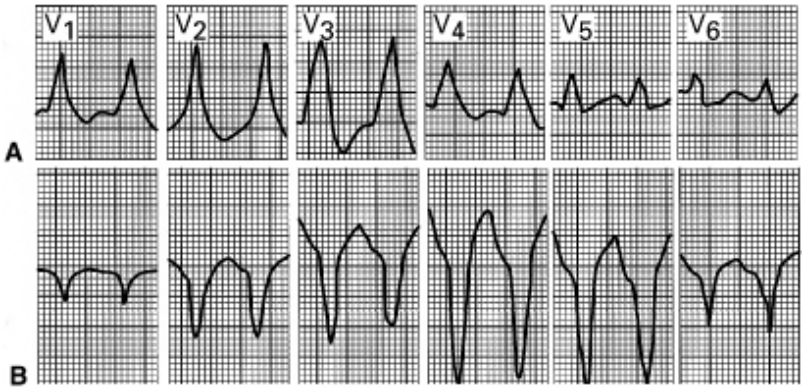

Figure 24-45: VT with concordant QRS complexes across precordium. *A.* All upright. *B.* All inverted.

Several additional features of tachyarrhythmias may be helpful. Polymorphic tachyarrhythmias are almost exclusively ventricular in origin but must be carefully distinguished from atrial fibrillation in patients with WPW syndrome who have multiple bypass tracts.[240] A tachycardia characterized by a wide QRS pattern with a left bundle-branch configuration in the precordial leads and right-axis deviation in the frontal plane leads is also usually ventricular in origin. A regular rhythm with alternating QRS axes (a bidirectional pattern) alteration is likely to be ventricular in origin, while paired group beating with bidirectional alteration is likely to be due to aberrant conduction terminating the shorter cycles. Finally, VTs, presumably originating in proximal bundle branches or fascicles, may inscribe relatively or absolutely narrow QRS complexes Fig. 24-46.

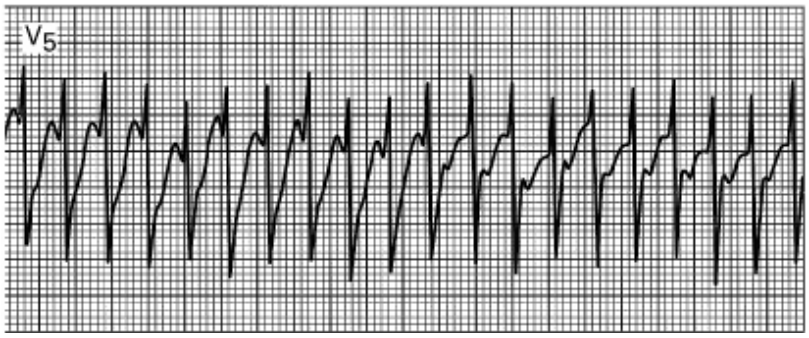

Figure 24-46: VT with narrow QRS complexes. The tracings were recorded from a 39-year-old male with ischemic cardiomyopathy and recurrent VT. Multiple VT morphologies were recorded, one of which was this narrow QRS morphology. These may be recognized by their onset if the latter is available but often may be very difficult to distinguish from supraventricular tachycardia with altered repolarization patterns. The diagnosis of the narrow QRS VT shown was confirmed by invasive electrophysiologic studies.

The cycle length of tachyarrhythmias is of little additional value in distinguishing between VTs and SVTs. Although monomorphic VTs associated with coronary heart disease and LV aneurysms tend to have rates below 220 per minute, ventricular arrhythmias due to ischemia and/or reperfusion may be considerably faster, in some instances approaching 250 to 280 per minute (Fig. 24-42*B*). SVTs, particularly those associated with WPW syndrome, may approach similar rates and may be difficult to distinguish from VTs. Antiarrhythmic drugs may also alter electrocardiographic patterns. An example is the slowing of atrial flutter by class IA or class IC antiarrhythmic agents to atrial rates of 240 per minute or less, allowing 1:1 conduction. Particularly for the class IC agents, slowed intraventricular conduction at these rates widens the QRS complexes, resulting in patterns that may be difficult to distinguish from rapid sustained *ventricular* tachyarrhythmias.

ACUTE MANAGEMENT OF SUSTAINED MONOMORPHIC VENTRICULAR TACHYCARDIA

Sustained monomorphic VT may occur in acute or chronic ischemic heart disease syndromes, in idiopathic

dilated or hypertrophic cardiomyopathy, and, less frequently, in inflammatory or infiltrative disease states. It occurs occasionally as a primary electrical disturbance. Management depends upon the clinical setting and the clinical characteristics of the tachycardia.

In acute myocardial infarction, sustained VT occurs most commonly within 24 h of the onset. Although degeneration into VF is uncommon, sustained VT carries that risk and must be treated aggressively. If the patient is clinically stable and the arrhythmia electrically stable, a 75- to 100-mg bolus of intravenous lidocaine, followed by a continuous infusion of 1 to 4 mg/min, may be tried. The infusion dose depends upon the patient's age, size, and general clinical status.[241] In heart failure and low-output states, the dose should be reduced. If the VT does not revert immediately or if the patient is hypotensive, immediate DC cardioversion is required. Following cardioversion, intravenous lidocaine is continued to prevent recurrences. If VT recurs with lidocaine, 100-mg boluses of procainamide are infused at 5-min intervals to a total loading dose of 500 to 1000 mg, followed by a constant infusion of 2 to 4 mg/min.[242] If breakthroughs occur on both drugs, the next drug of choice is intravenous amiodarone[243] or bretylium tosylate.[244] Amiodarone, currently the preferred therapy for this indication, is administered intravenously with a loading dose of 150 mg infused over 10 min, followed by a continuous infusion of 1 mg/min for 6 h and then a maintenance infusion at a rate of 0.5 mg/min. Bretylium, less commonly used than in the past, is administered as a loading dose of 5 mg/kg intravenously infused over 15 min, repeated if necessary, and followed by a 0.5- to 2.0-mg/min infusion. Total dose should not exceed 25 mg/kg per 24 h. Antiarrhythmic therapy may be stopped after 48 to 72 h, since the risk of recurrence is small at that point. Sustained VT during the acute phase of transmural myocardial infarction is due to transient factors and does not predict later recurrent arrhythmias (see also Chap. 42).

A second category of sustained VT related to acute myocardial infarction is that which occurs during the convalescent period.[245] It is unrelated pathophysiologically to the VT that occurs early and has much more serious long-term implications. It is most common in patients with large anterior wall myocardial infarction. Management of the acute event requires intravenous antiarrhythmic drugs and/or cardioversion, using an algorithm similar to that described for acute-phase VT. There is, however, a very high death rate during follow-up of these patients, in part related to the size of the infarct. One report cited an 83 percent death rate during a mean follow-up of 7 months using empiric antiarrhythmic therapy.[246] Others have reported a somewhat better outcome when such patients undergo electrophysiologic testing for evaluation of drug therapy and/or surgical interventions,[247] although mortality is still high: approximately 25 percent total mortality during a mean follow-up of 16 months. Sustained VT in patients beyond the convalescent phase of myocardial infarction (6 to 8 weeks) has a somewhat less ominous prognosis than does convalescent-phase VT but is still considered life-threatening and requires special interventions (see below).[246]

Sustained VT may complicate other acute or transient cardiac syndromes, including ischemia-reperfusion sequences associated with coronary spasm or thrombolysis early after the onset of myocardial infarction, heart failure,[248] acute myocarditis,[196] and almost any toxic or metabolic disturbance of sufficient severity. Therapeutic approaches include both conventional arrhythmia treatment, as described above for sustained VT in acute myocardial infarction, and careful attention to underlying predisposing factors.

LONG-TERM MANAGEMENT OF VENTRICULAR TACHYCARDIA IN CHRONIC ISCHEMICHEART DISEASE

The long-term management of recurrent VT in patients with chronic ischemic heart disease has evolved into a complex clinical exercise. Prevention of recurrences is related to successful management of the underlying precipitating factors, such as ischemia and hemodynamic status, as well as to specific antiarrhythmic approaches.

Four general approaches to antiarrhythmic therapy are available: (1) antiarrhythmic therapy guided by invasive electrophysiologic testing or by ambulatory monitoring or exercise testing, (2) surgical procedures designed to excise or cryoablate reentrant pathways or automatic foci, (3) catheter ablation procedures, and (4) ICDs (Fig. 24-47). The relative proportion of patients managed by each of these four techniques has changed in recent years, with fewer and more selective surgical approaches, fewer antiarrhythmic drug trials, and broader use of ICD therapy. The use of catheter ablation techniques for VT in chronic ischemic

heart disease is largely palliative,[249] often employed as adjunctive therapy with other primary approaches. As technology improves, however, it may develop broader applications (see below).

Pharmacologic Management

Invasive electrophysiologic testing to guide pharmacologic therapy in patients with recurrent monomorphic sustained VT due to ischemic heart disease has yielded, in large part, to empiric antiarrhythmic therapy (primarily amiodarone), ICD implantation, and catheter ablation. At one time the index for the initial treatment strategy for such patients, the initial study free of antiarrhythmic drugs required to demonstrate inducibility of the clinical VT and its characteristics at baseline, is now largely used for risk stratification. Several clinical trials[211,230-232] have demonstrated that inducibility predicts risk along with better outcomes with ICD therapy than with drug therapy in high-risk patients.[230] It is also useful in conjuction with ablation or surgical procedures.

Although there have been controversies about the validity of different protocols for programmed electrical stimulation in patients who have clinical sustained ventricular arrhythmias,[251] up to 95 percent of inducible sustained monomorphic VTs can be induced by right ventricular stimulation, using up to two drive cycle lengths between 600 and 400 ms from two right ventricular locations (apex and outflow tract) with up to three extrastimuli (see also Chap. 26). In at least 80 percent of patients with chronic ischemic heart disease and recurrent monomorphic sustained VT, the clinical tachyarrhythmias can be induced during a baseline study free of antiarrhythmic agents. The subsequent identification of a drug regimen that will prevent reinduction into the same sustained monomorphic VT is associated with a reduction of risk of recurrent VT at 1 year of follow-up. The risk appears to decrease from 30 to 40 percent if VT remains inducible on therapy to 10 to 15 percent if therapy results in noninducibility.[252] The results of acute intravenous testing of a drug should not be extrapolated to long-term oral therapy without retesting on the oral regimen, because intravenous regimens do not predict responses on oral drugs.[253] In addition, a drug capable of preventing induction of a VT previously induced during baseline testing can be identified in only a minority of patients (approximately 20 to 35 percent in various studies). Moreover, the success rate for membrane-active drugs is considerably lower if multiple monomorphic VTs are induced at baseline.[254] Left ventricular EF strongly influences probability of recurrence. Among cardiac arrest survivors, an EF of 30 percent or less predicts a mortality rate approximately twice as high as for patients in the same category with EFs above 30 percent.[255] A similar relationship likely exists for patients who present clinically with sustained VT. Unfortunately, all statements about the potential benefit of therapy guided by programmed electrical stimulation are based upon comparisons of groups who did (responders) or did not (nonresponders) convert from an inducible status to a noninducible status as a result of the therapy. Randomized, placebo-controlled studies of patients who convert to a noninducible status on therapy, with a similar strategy for patients with VT that remains inducible, are still lacking. Such studies would determine whether it is the therapy or simply the ability to change inducibility status that is determining outcome. In one study of patients who had had VT or VF and met criteria for both the invasive electrophysiologic approach (i.e., inducibility at baseline) and the ambulatory monitoring approach (30 or more PVCs per hour), a randomized comparison revealed a significantly lower arrhythmia recurrence rate with therapy guided by the invasive testing technique:[256] 20 percent recurrence rate of symptomatic VT at 24 months with invasive procedures versus 50 percent with noninvasive procedures. The study, however, did not identify a difference in death rate, possibly because of the small number of patients randomized. In another study, a drug or drug combination that did not prevent inducibility during invasive electrophysiologic study but did prolong the cycle length of induced VT by more than 100 ms with stable hemodynamics predicted a favorable mortality outcome, even though the incidence of recurrent VT was not different from that in those who failed to show any measure of a successful response.[257] Patients who have a partial response to a drug regimen (i.e., induced runs of 6 or more but fewer than 15 impulses) also appear to have a lower risk of recurrent VT.[258] Many electrophysiologists currently will accept induced runs of less than 10 impulses on therapy as a satisfactory end point, and almost all will accept less than 6. Any change in therapy established by invasive electrophysiologic testing because of drug intolerance or clinical failure should be evaluated by repeat testing.[252,259]

Finally, a recently reported trial in postmyocardial infarction patients, the MUSTT study, demonstrated that patients who had nonsustained VT on ambulatory monitoring with inducible VT at baseline study and failed antiarrhythmic drug therapy during repeat study had better long-term survival rates if they received ICDs than if they received drug therapy.[250] It is important to note that patients who received ICDs based on

failed electrophysiologic testing-considered a high-risk group-did even better than those who had a successful electrophysiologic study on drug therapy.

Noninvasive management strategies for VT require identification of frequent (i.e., 10 to 30 PVCs per hour in various studies) and/or repetitive PVC forms (i.e., salvos or nonsustained VT) at baseline monitoring or VT induced during exercise testing. Reduction of PVC frequency (80 percent or more suppression) and abolition of complex forms has been used as the index of a successful end point. This approach has been reported to be successful in some studies,[226,260] even among patients who have failed to achieve a successful end point by invasive electrophysiologic testing.[260] Unfortunately, the *residual risk* among many patient groups with successful noninvasive or invasive end points is still very high.[261] Thus, because of the *relative* benefit of ICDs in several patient groups compared to empiric amiodarone, many clinicians now prefer implantable devices for both primary and secondary prevention of life-threatening arrhythmias in these high-risk patients.

A large multicenter randomized trial, entitled Electrophysiological Study Versus Electrocardiographic Monitoring (ESVEM), was designed to compare programmed electrical stimulation with ambulatory monitoring techniques for guiding therapy in patients who had sustained VT, had survived cardiac arrest, or had syncope presumed due to a ventricular arrhythmia.[262,263] The data showed no difference between the two methods for prediction of efficacy or mortality benefit, although there was a small trend favoring programmed stimulation during early follow-up in the coronary disease subgroup (see Chap. 30). Failure by both invasive and noninvasive criteria connotes a poor prognosis and requires other considerations for therapy, namely, surgery or implantable devices.

Pharmacologic therapy has an increasingly important role as adjunct therapy in patients who have implanted defibrillators. It is used to reduce VT events requiring ICD therapy, slow tachycardia rates to favor antitachycardia pacing therapy over shocks, and reduce the incidence of atrial tachycardia that can initiate shock therapy unnecessarily (e.g., atrial fibrillation or flutter). A randomized trial has demonstrated that these goals can be achieved.[264]

Surgical Therapy

Patients who have recurrent sustained monomorphic VT associated with prior myocardial infarction and inducibility into a hemodynamically stable tachycardia were uniformly considered for antiarrhythmic surgery until recent years. The indication was reinforced by the presence of discrete ventricular aneurysms and bypassable coronary artery lesions. With the development of ICDs capable of flexible antitachycardia pacing programs, many patients who were formerly surgical candidates are now receiving ICDs. However, surgery is still recommended, in the absence of contraindications, for a small number of such patients,[252,265,266] particularly if they require revascularization surgery as well or their tachycardias are not easily pace-terminated during induction studies. Patients without discrete aneurysms who have large dyskinetic areas may have sites of origin of VT mapped in the cardiac electrophysiology laboratory and operating room if they are inducible into stable monomorphic tachycardias. Mapping allows the identification of areas that may be attacked by endocardial resection or surgical cryoablation.[267] Map-guided surgical procedures employing resection, cryoablation, and revascularization have markedly improved the clinical outcome of surgically treated patients.[268] Overall surgical results have also benefited from the preferred use of ICDs in patients previously referred for surgery out of desperation (see Chap. 30). Coronary bypass surgery may be used as primary therapy for patients who have recurrent VT initiated by transient ischemic episodes.[269] It is also a valuable adjunct to antiarrhythmic surgery (see Fig. 24-47).

Catheter Ablation Procedures for Ventricular Tachyarrhythmias

The combination of LV endocardial mapping by catheter techniques and RF energy delivery systems provides the capability for catheter ablation therapy of sustained, hemodynamically stable VTs.[249,270,271] While these techniques are currently limited to only a small fraction of patients as primary therapy,[271] they are useful as an adjunct to ICD therapy (Fig. 24-48). Improvements of mapping techniques capable of storage and recall of spatial activation maps[272,273] and improved energy delivery systems will enhance the use of catheter ablation as primary therapy and as more effective ancillary therapy in the future.

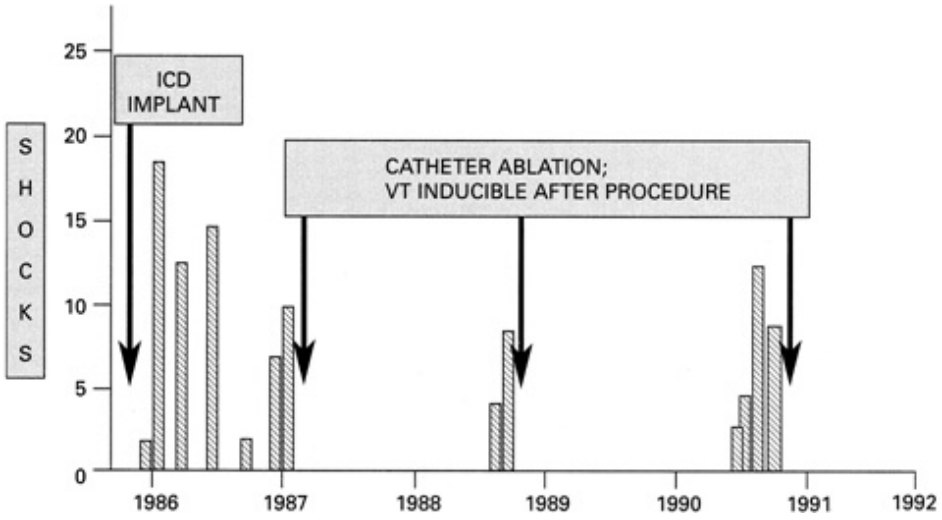

Figure 24-48: Catheter ablation for VT as an adjunct to an ICD. A 57-year-old male with recurrent life-threatening episodes of sustained VT who received an ICD had multiple shocks for arrhythmias that were resistant to all antiarrhythmic agents attempted. LV mapping and catheter ablation in a VT reentrant pathway in 1987 provided freedom from recurrent ICD discharges for approximately 19 months, after which the multiple ICD discharges recurred. Additional ablation procedures 18 or more months apart provided relief from the recurrent discharges despite the fact that VT remained inducible. While of limited value as primary therapy for life-threatening ventricular arrhythmias in patients with coronary heart disease or cardiomyopathy because of risk of recurrence (see the text), this procedure can provide benefit as an adjunct to other primary forms of therapy by avoiding frequent discharges and improving the quality of life.

Implantable Defibrillators

As a result of the outcomes of several large clinical trials[211,230-232] and advances in technology that resulted in a significant decrease in device size and range of functions, the role of ICD therapy for patients with ventricular tachyarrhythmias has expanded dramatically in recent years (see Fig. 24-47). It is no longer necessary or desirable to test a long sequence of antiarrhythmic drugs in patients with sustained monomorphic VT. For those subgroups among whom ICDs have not been demonstrated to be superior to drug therapy (e.g., those with EFs greater than 40 percent), failure of no more than one or two drugs during electrophysiologic study is generally considered an indication for ICD therapy. Their use is amplified by such enrichments as antitachycardia pacing, allowing effective programmable tiered-therapy algorithms, back-up bradyarrhythmia pacing (including dual-chamber pacing in some devices), and electrogram storage for retrieving and analyzing events.

Patients who present with clinical VT and have inducible, hemodynamically *unstable* VT associated with ischemia before surgery should receive an ICD after revascularization surgery if they remain inducible into VT. The routine use of an ICD after antiarrhythmic surgery, even if successful by postsurgical programmed stimulation study, has been advocated[275] but has gained only limited acceptance. The CABG-Patch trial tested the value of ICDs after revascularization surgery among patients with positive signal-averaged ECGs but no history of clinical VT. The results demonstrated no cumulative survival benefit of this strategy[276] even though there was a suggestion that the devices reduced arrhythmic deaths.[277]

ICDs are indicated for patients with recurrent or unstable VT whose arrhythmias cannot be controlled medically or surgically or who belong to subgroups that have been demonstrated to benefit specifically from device therapy. Antitachycardia pacing capabilities and programmable tiered therapy have expanded the scope of ICD therapy for recurrent sustained VT. The availability of antitachycardia pacing obviates the need for antiarrhythmic surgery in many patients who had been considered surgical candidates on the basis of anatomy and physiology in the past (Fig. 24-49; see also Chap. 30).

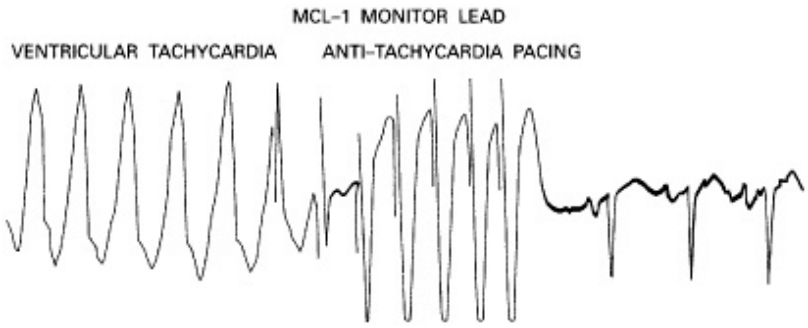

Figure 24-49: ICD with antitachycardia pacing. The figure demonstrates the end of a run of induced sustained VT (*left*) followed by antitachycardia pacing that converts the rhythm back to normal sinus (*right*). The device will revert to a defibrillator mode if programmed pacing sequences fail to convert the rhythm.

LONG-TERM MANAGEMENT OF VENTRICULAR TACHYCARDIA IN NONISCHEMIC HEART DISEASE

Sustained VT in patients with idiopathic dilated cardiomyopathy, dilated cardiomyopathies due to specific etiologies, or hypertrophic cardiomyopathies carries a poor prognosis. Management approaches differ from those used for patients with ischemic heart disease (Fig. 24-50). Invasive electrophysiologic testing, to identify risk or guide therapy is less predictably useful in the small fraction of patients with dilated cardiomyopathy who have clinical sustained monomorphic VT[278,279] than it is in coronary heart disease patients. In a subgroup of these patients, however, sustained VT is due to bundle-branch reentry,[280] which can be cured by catheter ablation of the right bundle branch. Electrophysiologically guided management does not appear useful in idiopathic dilated cardiomyopathy patients who have survived out-of-hospital VF or have clinical nonsustained VT.[281] There is almost no role for surgical therapy in these patients at present, but the ICD is an appropriate means of management. The device appears effective for reverting potentially fatal arrhythmias in patients who have cardiomyopathy,[282] but the long-term outcome may be dominated by LV function. The evaluation of ICD therapy in these patients has been confounded by the observation that, in some (perhaps a substantial fraction) of these patients, sudden death is caused by the bradyarrhythmic asystole-pulseless electrical activity complex, which would not benefit from any form of antiarrhythmic therapy.[283] The availability of ICD with electrogram storage capability should begin to clarify the magnitude of this problem. Ultimately, identification of groups at risk for specific mechanisms will help define the best therapy, but such data are currently lacking.

Sustained VT is also a late consequence and poor prognostic sign in patients with hypertrophic cardiomyopathy.[284-286] In this setting, the use of electrophysiologic testing has been limited because of unvalidated concerns about the ability to cardiovert the severely hypertrophied and obstructed ventricle,[286,287] and there is no uniform opinion regarding the best approach to management of these patients, other than the accepted need for therapy. The recent trend toward ICD therapy, rather than pharmacologic therapy, particularly among higher-risk subgroups, has now received support from multicenter observational data suggesting ICD benefit.[288] Preoperative electrophysiologic testing is generally avoided in patients with severe aortic stenosis who have survived sustained VT or VF.

Less Common Clinical Causes of Sustained Monomorphic Ventricular Tachycardia

CATECHOLAMINE- AND METABOLICALLY MEDIATED VENTRICULAR TACHYCARDIA

In a small number of patients, sustained VT appears to be mediated by catecholamines or other neurophysiologic influences.[289,290] Sustained VT in these patients is commonly induced by physical or emotional stress. Isoproterenol infusions may be used to initiate the VT, which may then be suppressed and subsequently prevented by beta-adrenergic blocking agents (Fig. 24-51). Another small group of patients have sustained VT that may respond to Ca^{2+}-entry blockers.[291-293] This is a heterogeneous group of VTs

that includes adenosine-sensitive VT,[291] and an unusual VT with a right bundle-branch block, left-axis deviation QRS pattern originating in the low interventricular septum.[293] Catecholamine-mediated VT may occur in the presence or absence of structural heart disease; when it is responsive to Ca^{2+}-entry blockers, it generally occurs in the absence of structural heart disease.

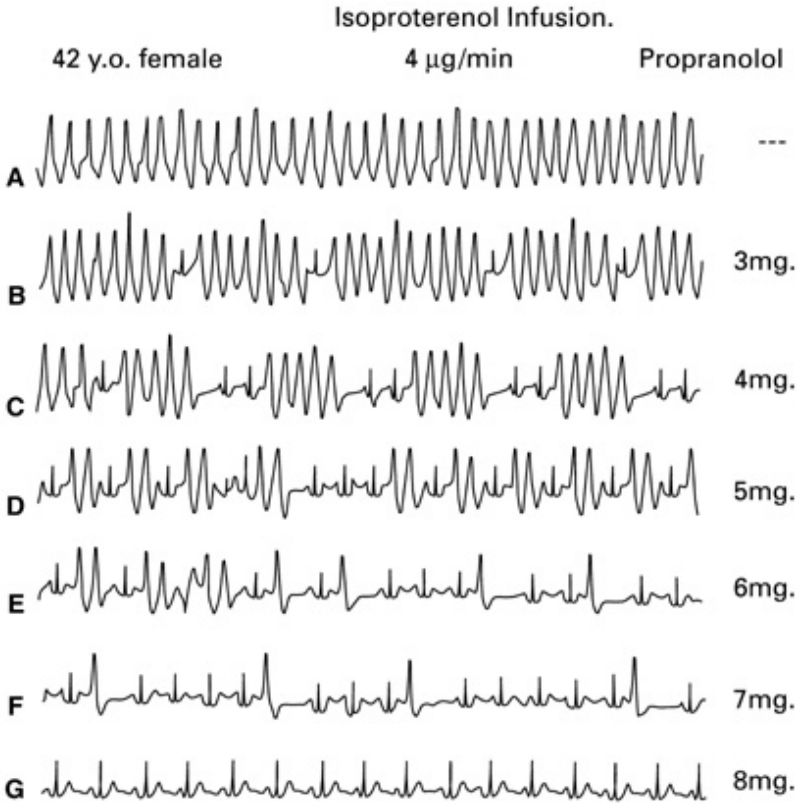

Figure 24-51: Catecholamine-mediated VT in an otherwise healthy female. Psychologic stress or isoproterenol infusion could initiate the arrhythmia in this patient. During this sequence, a 4-µg/min isoproterenol infusion initiated the VT (*A*), and the patient was treated with intravenous propranolol. After the first 3 mg of propranolol (*B*), occasional sinus beats interrupted the tachycardia. On a milligram-by-milligram basis up to a total dose of 8 mg of propranolol, there was further suppression of VT to the point of salvos (*C, D, E*), frequent PVCs (*F*), and complete suppression of ectopic activity (*G*).

RIGHT VENTRICULAR DYSPLASIA AND VENTRICULAR ARRHYTHMIAS

Arrhythmogenic right ventricular dysplasia (ARVD) or right ventricular cardiomyopathy (RVCM) may be associated with nonsustained or sustained VT and/or sudden cardiac death. Patients with a stable monomorphic VT without near-syncope may have a better prognosis,[294] but it is clear that sudden death, presumably due to VF, may be the first and only manifestation of the disease.[295]

The term isolated right ventricular cardiomyopathy[295,297] has been used as an alternative for ARVD, and, more recently, the ARVD-RVCM complex[298] is being labeled simply right ventricular dysplasia (RVD). The entity may occur sporadically or in familial clusters, with up to 40 to 50 percnt currently appearing to be familial. A number of loci are identified from linkage analyses studies in affected families,[299,300] but no specific gene abnormalities have been identified to date.

The 12-lead electrocardiographic pattern of the patient with ARVD is helpful. In sinus rhythm, anterior precordial T-wave inversions are commonly present (Fig. 24-52), sometimes with notching in the early part of the ST segment of V_1 and V_2 as well (epsilon waves). The monomorphic tachycardia has a left bundle-branch block morphology, reflecting its origin from the right ventricle.

At initial presentation, the future course cannot be predicted, and preventive measures should be aggressive. Pharmacologic and surgical approaches have been used for the management of ARVD.[294,296] Amiodarone and class IC drugs have been suggested to be effective for ARVD patients with symptomatic arrhythmias. However, because of its high risk of sudden death and unpredictable response to treatment, there is an increasing trend toward the use of ICD therapy, especially in patients with symptomatic arrhythmias, syncope, and a family history of sudden death in affected family members.

VENTRICULAR TACHYCARDIA AFTER CONGENITAL HEART DISEASE SURGERY

Sustained VT or VF may appear years after repair of complex congenital heart defects,[301] especially tetralogy of Fallot and transposition of the great vessels. The arrhythmias are potentially lethal and must be treated pharmacologically,[302] surgically,[303] or with ICDs in selected cases.

BIDIRECTIONAL VENTRICULAR TACHYCARDIA

Bidirectional ventricular tachycardia (Fig. 24-53) is usually a manifestation of digitalis intoxication and responds to standard measures.

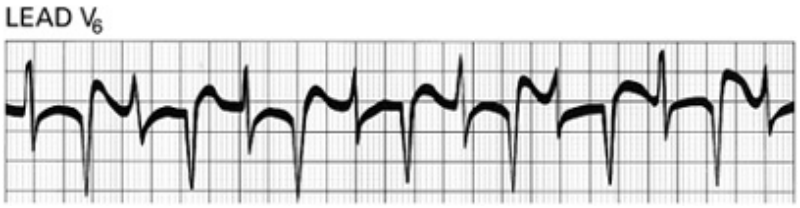

Figure 24-53: Bidirectional tachycardia. The tachycardia is regular at a rate of 160, but the vector of the QRS-T complexes alternates.

Polymorphic Ventricular Tachycardia, Including Torsades de Pointes

The polymorphic VTs, including the specific variant referred to as torsades de pointes, is a tachycardia pattern with important clinical implications. As a group, the polymorphic tachycardias tend to be more unstable electrically than the monomorphic tachycardias, occur at faster rates, have a higher likelihood of producing transient central nervous system symptoms (syncope or near-syncope) due to reduced cardiac output, and establish a higher risk for spontaneous degeneration to VF. The polymorphic tachycardias generally do not persist as long as the monomorphic tachycardias, either spontaneously reverting to a normal rhythm, degenerating to VF, or triggering a monomorphic tachycardia in susceptible patients.

The specific variant of polymorphic tachycardia characterized by QRS peaks that seem to twist around the baseline (Fig. 24-54) is referred to as torsades de pointes. The orthodox definition of torsades de pointes includes the predisposing electrocardiographic pattern, namely, a prolonged QT interval.[304] The same electrocardiographic pattern, however, may occur in the absence of QT prolongation.[305] Torsades de pointes may occur as a consequence of congenital prolongation of the QT interval or may be associated with acquired QT prolongations due to any of a group of diverse factors (see below). Less specific patterns of polymorphic VT may also occur in a number of other acquired disease settings, often not associated with prolonged QT intervals or with transient prolongations.

CONGENITAL LONG QT INTERVAL SYNDROME

The congenital long QT interval syndrome, which is present persistently from childhood, is characterized by the presence of long QT intervals and/or prominent U waves on the standard 12-lead ECG (Fig. 24-55). The affected patients are prone to episodes of torsades de pointes, which may cause transient lightheadedness, syncope, or sudden cardiac death. Arrhythmias may occur at rest, under emotional stress or with exercise (Fig 24-56). The two general patterns of the syndrome are the Romano-Ward syndrome,[306,307] which has an autosomal dominant inheritance pattern, and the much less common Jervell

and Lange-Nielsen syndrome,[308] which has an autosomal recessive inheritance pattern and is associated with congenital deafness.

For many years, congenital long QT interval syndrome has been viewed as a consequence of abnormal patterns of cardiac autonomic neural innervation, based in part upon the fact that the entity could be treated with beta-adrenergic blocking agents or surgical ablation of the left stellate ganglion.[309] Progress in the molecular genetics of the syndrome, however, has clearly demonstrated that inherited defects in membrane ion-channel molecular structure and function underlie the disease. The ion-channel abnormalities constitute the structural basis of the disorder at a molecular level; neurophysiologic, environmental, or transient risk factors (e.g., stress or hypokalemia) may then trigger the arrhythmias.

Multiple specific mutations have been identified at loci on five chromosomes and the specific gene products and their physiologic dysfunctions studied (Fig. 24-57).[311,312,325,326] The first abnormality suggested from linkage analysis was on chromosome 11. An association with the Harvey-*ras* gene was suggested, but subsequent observations demonstrated that the affected locus encodes a component of a potassium channel, I_{KS}, the slowly activating delayed rectifier channel. This channel also appears to be affected in at least one variety of the Jervell and Lange-Nielsen syndrome. Subsequently, two other gene loci have been identified among multiple families. An abnormality has been mapped to a locus on chromosome 7, which encodes HERG,[311] the rapidly activating delayed rectifier channel, I_{KR}, which carries a major repolarizing current. Another locus, SCN5A, on chromosome 3, encodes the human cardiac sodium channel gene.[312] One defective pattern on the latter gene encodes a three-amino acid deletion, which results in failure of the channel to close properly after activation. The depolarizing leak of sodium current competes with and delays repolarization by the normal potassium channels. Drugs that block the sodium channel, such as mexiletine, have been suggested as a possible pharmacologic therapy for this specific variant of the syndrome.[313] A fourth locus for an as yet unidentified genetic abnormality on chromosome 4 has been identified in a single family and may be a unique mutant in that family.[314] Finally, the fifth locus affected is chromosome 21. It encodes another subunit of I_{KS} and has a role in both the Romano-Ward and the Jervell and Lange-Nielsen forms of the syndrome. A syndrome of torsades de pointes with normal QT intervals has been described. It may also have a congenital basis, although cases are infrequent and adequate studies have not yet occurred. In addition, some subjects genotypically affected with known long QT interval variants are intermittently or persistently normal phenotypes, at least based on ECGs.

ACQUIRED LONG QT INTERVAL SYNDROME

The commonest causes for acquired long QT interval syndromes are the antiarrhythmic drugs, classically quinidine, but also other class IA agents and class III agents. Prolongation of the QT interval usually precedes the arrhythmia.[275] Bradycardia, hypokalemia, and hypomagnesemia potentiate the risk.[316-318] QT prolongation induced by class IA agents appears to be idiosyncratic, often appearing in a dose-independent manner at the onset of therapy. It occurs among a small subsegment of the population exposed to the drugs, suggesting specific individual susceptibility, but no inheritance pattern has as yet been identified. It is commoner among women because women have longer QT intervals. However, other factors that interact with repolarization may act to generate risk of arrhythmias sporadically, unrelated to initiation of therapy. These factors include hypokalemia, bradycardia, LV dysfunction, and possibly LV hypertrophy. The class III drugs, particularly sotalol, prolong the QT interval in a dose-dependent pattern, consistent with its major pharmacologic effect of blocking the delayed rectifier channel and thus prolonging the QT interval. This fact has implications for monitoring adverse drug effects at the initiation of therapy.

There is a growing list of other drugs that may also block repolarizing currents, prolong the QT interval, and establish susceptibility to torsades de pointes (Table 24-12), including the phenothiazines, certain antibiotics, pentamidine (Nebupent), cocaine, and terfenadine (Seldane) and other antihistamines, among others. The mechanisms of terfenadine-induced torsades de pointes is particularly instructive.[319] In addition to having antihistamine effects, the parent compound blocks the delayed rectifier current, which can result in prolongation of the QT interval. Under normal conditions after oral ingestion, however, the parent compound is converted by a P450 enzyme in the liver to a metabolite that is an effective antihistamine but does not block the delayed rectifier current. Concomitant use of drugs that block specific enzymes in the hepatic P450 enzyme system, [e.g., ketoconazole (Nizoral)], however, allows the parent compound to be

absorbed and to circulate, creating the propensity to torsades de pointes in a small group of patients. Sudden deaths have been reported with this combination therapy.[320] Other causes of acquired long QT interval syndrome with torsades de pointes include acute ischemia and reperfusion, acute central nervous system injury, liquid protein diets, and various other drugs.[317,321,322]

Table 24-12: Drugs Associated with Acquired Long QT Syndrome and to Be Avoided in Congenital Long QT Syndrome

Antiarrhythmics
Class IA: quinidine, procainamide, disopyramide
Class III: sotalol, dofetilide, ibutilide, bretylium, N-acetyl procainamide, amiodarone (rare)
Antibiotics
Macrolides: erythromycin, clindamycin, clarithromycin, trimethoprim-sulfamethoxazole, chloroquine, pentamidine, amantadine, ha-lofantrine
Antifungals
Itraconazole, ketoconazole
Psychotropics
Antidepressants: tricyclics (i.e., amitriptyline and desipramine), tetracyclics, fluvoxamine
Haloperidol, droperidol, thiothixene, doxepin, risperidone, phenothiazines
Antihistamines
Astemizole, terfenadine
Others
Cisapride
Glibenclamide
Organophosphate insecticides
Diuretics, with hypokalemia, hypomagnesemia, or hypocalcemia

NOTE: Some drugs cause risk only in combination (e.g., terfenadine and ketoconazole). Some observations are based on limited clinical data from case reports (e.g., clindamycin and newer nonsedating H_1 receptor antagonists); this list is current at the time of writing in an evolving field requiring continuous physician updating.

ELECTROCARDIOGRAPHIC FEATURES

Torsades de pointes is characterized by sequential beat-to-beat variations in mean QRS axis, causing the QRS complexes to appear to twist about the baseline (see Figs. 24-54 and 24-56). Characteristically, the tachycardia rate varies between 150 and 300 per minute, and the QT interval is prolonged during sinus rhythm. Episodes of tachycardia may be nonsustained or sustained, preceded by a long-short cycle sequence initiated by late PVCs, and may degenerate into VF.

Torsades de pointes is a classic proarrhythmic manifestation of class IA antiarrhythmic agents. Class IC antiarrhythmic agents may express proarrhythmia in the form of an incessant monomorphic VT that is

sinusoidal in pattern and often at rates less than 160 per minute (see also Chap. 23).

MANAGEMENT OF CONGENITAL LONG QT INTERVAL SYNDROME

The clinical expression of arrhythmias in congenital long QT interval syndrome is episodic and transient, ranging from palpitations to syncope to sudden death. Ambient arrhythmias are not usually sustained enough to make acute management a common clinical need. When required, however, intravenous beta-adrenergic blockade, intravenous Mg^{2+}, pacing, and/or lidocaine are appropriate, depending on the genetic variant and pattern of the arrhythmia. A new category of drugs, the K^+-channel openers, may ultimately prove useful as well.

Because of the continuing risk of transition of torsades de pointes to VF in patients with congenital long QT interval syndrome throughout life, careful long-term management is important from the time of diagnosis. A 12-lead ECG should be recorded in anyone with *unexplained* near-syncope, syncope, and/or symptomatic palpitations, especially with repetitive beats. In selected patients, stress testing and ambulatory monitoring may help clarify uncertain findings. Genetic testing should be carried out in selected members of affected families. An important subgroup consists of symptomatic relatives with phenotypically normal ECGs, since ECG expression appears to be intermittent, or even silent, in some.[321,322]

Long-term therapy includes beta-adrenergic blockade and/or left cardiac sympathetic denervation.[309,324] ICD implantation is indicated for patients with arrhythmias resistant to betaadrenergic blockers or survivors of cardiac arrest due to long QT syndrome. Recurrent syncope without arrhythmia documentation despite beta-adrenergic blocker therapy is also an indication, especially if there is a family history of sudden death. Finally, ICD implantation may be considered for genotypically positive relatives in a family with a strong history of fatal long QT syndrome.

The present information on a variety of genetically controlled ion-channel dysfunctions may lead to new therapeutic approaches in the future. For instance, mexiletine may be a specific therapy for the variant associated with the SCN5A gene on chromosome 3, which encodes the cardiac sodium channel.[313] It is possible that other channel-specific therapies will be identified in the future.

MANAGEMENT OF ACQUIRED LONG QT INTERVAL SYNDROME

Treatment is directed at the underlying cause, or causes, with careful attention to electrolyte and metabolic disturbances and to identifying and reversing or removing iatrogenic factors. Although electrical cardioversion may interrupt torsades de pointes, the arrhythmia frequently recurs as long as the offending influence is present. In addition, many runs are nonsustained. Intravenous magnesium sulfate is often effective, especially when torsades de pointes is due to quinidine. It may be given in a dose of 2 g over 2 min followed by an infusion of 2 to 20 mg/min. Although Mg^{2+} will effectively control the arrhythmia, it will not reduce the duration of the QT interval. That must await clearance of the offending agent.

Overdrive atrial or ventricular pacing to induce rate-related QT shortening may also be required. Acceleration of the underlying heart rate with isoproterenol infusion to shorten the acquired QT interval prolongation may be effective but should be avoided in patients with symptomatic ischemic heart disease, if possible. Lidocaine also may be beneficial, as may other class IB drugs. These drugs tend to shorten the QT interval in normal myocardium. Class IA and class III antiarrhythmic agents should be avoided, since they prolong the QT interval.

THE SYNDROME OF RIGHT BUNDLE-BRANCH BLOCK, ST-SEGMENT ELEVATION, AND LIFE-THREATENING VENTRICULAR ARRHYTHMIAS (BRUGADA'S SYNDROME)

A complex of right bundle-branch block, ST-segment elevation in the anterior precordial leads, and risk of sudden death has been described. The reported patients often have spontaneous and inducible polymorphic VT, sustained or nonsustained, with normal QT intervals. There is no associated structural heart disease described to date, and some patients are aymptomatic. It is commonest in adolescent and young adult males, among whom it appears to confer a high risk of sudden death.[325,329,330] It has been suggested as the basis for so-called "sleep death" in young Asian males.[331] The syndrome is familial, and a mutation on

chromosome 3 (SCN5A, the cardiac Na^+-channel) has been identified,[330] and others suggested.[330]

The diagnosis may be difficult because the right bundle-branch block and ST elevations may be subtle and intermittent.[325] They may be unmasked or enhanced by antiarrhythmic drug challenges with procainamide or flecainide[328,329] (Fig. 24-58), although the sensitivity and specificity of such challenges remains unknown. The entity is considered high risk, and ICD therapy has been suggested, even for asymptomatic affected individuals, particularly if there is a history of sudden death in young family members. Unfortunately, there are no prospective studies comparing ICDs to antiarrhythmic drug therapy for this disorder.

Ventricular Fibrillation and Flutter

Ventricular fibrillation is a terminal arrhythmia, uniformly requiring rapid initiation of emergency measures. Ventricular flutter with loss of consciousness and rapid unstable VT are clinical and hemodynamic equivalents of VF and treated identically when accompanied by the clinical picture of cardiac arrest. VF occurs most commonly in the setting of acute ischemic events (unstable angina pectoris or acute myocardial infarction) or unpredictably in advanced chronic ischemic heart disease. In the latter, it may be triggered by transient ischemia and perhaps transient or uncontrolled hemodynamic dysfunction. Moreover, it is the apparent mode of death in 25 to 50 percent of all cardiac fatalities. Among patients with nonischemic cardiomyopathies,[322,333] cardiac arrest is the mode of death in up to 50 percent of all fatalities. In the past, it has been assumed that VF is the mechanism of most of these events, but it is clear now that a substantial proportion of these events are due to bradyarrhythmias and asystole[333] and, it is important to note, to acute hemodynamic dysfunction.

VF may also develop during ischemia caused by coronary artery spasm, some hypoxic states, atrial fibrillation with rapid ventricular responses in WPW syndrome, pacing on the T-wave or asynchronized cardioversion, electrical accidents due to improper grounding of electrical devices, or proarrhythmic effects of antiarrhythmic drugs. A particularly high-risk setting for VF is acute myocardial infarction with right or left bundle-branch block. VF may occur de novo, but among patients with out-of-hospital cardiac arrest, VT commonly precedes the onset of VF (see also Chap. 23).

ELECTROCARDIOGRAPHIC FEATURES

The electrocardiographic pattern of VF is described by gross disorganization without identifiable repetitive waveforms or intervals (see Fig. 24-42*D* and *E*). At the onset VF may be "coarse" in pattern, but over time it loses its amplitude and becomes "fine" (less than 0.2 mV). Successful defibrillation and survival rates are decreased in patients with the fine pattern of VF. In ventricular flutter (see Fig. 24-42*C*), a sine wave configuration is present, having a cycle length in the range of 200 to 240 ms. Rapid polymorphic VTs may be difficult to distinguish from VF electrocardiographically, but maintained consciousness suggests VT rather than VF, the latter defined by loss of effective mechanical function. Hemodynamic findings may be initially stable in ventricular flutter or very rapid polymorphic VT, but hypotension, loss of consciousness, and degeneration to VF are common.

MANAGEMENT OF VENTRICULAR FLUTTER AND VENTRICULAR FIBRILLATION

There are two major goals of therapy: (1) immediate life support and resuscitation and (2) long-term prevention of recurrences. Basic life support with standard cardiopulmonary resuscitation (Chap. 34) is used until emergency defibrillation at 200 J or more can be carried out (see Chaps. 29A and 29B). After three unsuccessful shocks at energies up to 360 J, 1 mg of epinephrine should be administered by intravenous push and defibrillation attempted again.

Early defibrillation is essential to survival.[334] Resistance of defibrillation may occur due to the patient's size, improper paddle placement, improper use of conducting media, acidosis, hypoxemia, or electrolyte disturbances.[335] Some antiarrhythmic drugs may raise the defibrillation threshold. Energy thresholds for defibrillation may be decreased by administration of bretylium, lidocaine, or epinephrine, the latter especially when the fibrillatory waveform is fine. Immediate steps to improve metabolic and electrolyte disturbances are required, paramount of which is to establish an airway, followed by techniques to support

ventilation.[336] In rare instances, "spontaneous" reversion of VF[336] or "medical" defibrillation with bretylium[243] has been reported. A physiologic or pharmacologic increase in catecholamines has been postulated as the underlying mechanism.

After successful defibrillation, careful attention to the total clinical status of the patient and prophylactic antiarrhythmic drugs are required. Intravenous therapy with lidocaine is commonly used initially. For recurrent and resistant cases, intravenous procainamide or amiodarone[337] can be administered intravenously, the latter having replaced bretylium tosylate in order of priority and urgency. In addition to oxygenation and improving the metabolic milieu, aggressive steps to identify and treat or prevent recurrent ischemia or heart failure are necessary, since they may act as pathophysiologic triggers for recurrences.[4,248]

In the in-hospital setting, early recognition and aggressive treatment of VT may prevent VF. In the patient with acute myocardial infarction, early VF (48 h), as with early VT, is not associated with an independent influence on posthospital mortality risk and does not justify long-term antiarrhythmic therapy.[339-341] When VF occurs as a convalescent-phase complication of acute myocardial infarction, however, aggressive long-term antiarrhythmic management is indicated (see above).[342,343] The vast majority of patients who have VT or VF in the convalescent phase after acute myocardial infarction (3 days to 8 weeks) will have inducible ventricular arrhythmias at baseline electrophysiologic study.[247]

Among survivors of out-of-hospital VF not caused by acute myocardial infarction, control of ischemia and heart failure is essential. The clinical context[344,345] is evaluated in terms of the interaction between structural abnormalities (e.g., coronary heart disease, myopathy, hypertrophy, or anatomic electrical abnormalities) and functional states (e.g., ischemia-reperfusion, or systemic factors, including congestive heart failur, metabolic and electrolyte disturbances, neurophysiologic interactions, and toxic effects). For long-term estimate of the risk of arrhythmic death, invasive electrophysiologic testing of pharmacologic efficacy is one accepted approach.[346] Only about 33 to 40 percent of survivors, however, will be inducible into a reproducibly inducible ventricular tachyarrhythmia at baseline.[345,346] A similar fraction will be inducible into nonsustained VT or VF (Fig. 24-59), and 20 to 30 percent are noninducible. The subgroup whose unexpected VF is related to transient ischemia, in contrast to an underlying structural basis, is less likely to be inducible at baseline.[347] With high-risk forms of arrhythmias on ambulatory monitoring or exercise testing but without inducible arrhythmia at baseline by invasive testing, drug therapy can be guided by suppression of these spontaneous arrhythmias by noninvasive techniques[226,260,261] as long as the EF is greater than 40 percent. For such patients with lower EFs, the use of ICDs is emerging as the preferred treatment.

Usefulness of long-term drug therapy is limited by the fact that no more than 20 to 30 percent of the patients with inducible arrhythmias will have a drug identified that will prevent inducibility. In one randomized study without placebo control (ESVEM), a class III antiarrhythmic agent with beta-blocking effect, sotalol, appeared more effective than other drugs for survivors of VT and VF.[263] Whether amiodarone will have equivalent (or greater) benefit remains to be determined.

Patients who have recurrences despite drug therapy predicted to be effective during testing, those in whom an end point of therapy cannot be established, or those in whom the risk of recurrence remains high because underlying precipitating factors cannot be adequately controlled should receive ICDs.[345] The development of programmable devices with diagnostic electrogram storage capability and transvenous lead systems is expanding the set of circumstances in which ICDs are preferred therapy (see Chap. 30). Moreover, for secondary prevention of recurrent cardiac arrest, the relative benefit of ICDs now has been shown to be greater than that of empiric amiodarone (and likely other drugs), measured as total mortality during long-term follow-up.

PREVIOUS | NEXT

Chapter 24: RECOGNITION, CLINICAL ASSESSMENT, AND MANAGEMENT OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

BRADYARRHYTHMIAS

Bradyarrhythmias may be due to depression or failure of impulse formation or to failure of AV conduction (Table 24-13). They are often asymptomatic, requiring no treatment. However, treatment is required when symptoms of hypoperfusion occur, resulting from inadequate cerebral or coronary blood flow, or worsening of congestive heart failure at rest or during exercise. Symptoms are almost always due to inadequate heart rate, although under some circumstances, such as with aortic stenosis or hypertrophic cardiomyopathy, loss of synchronized atrial contraction may contribute to symptoms. Bradyarrhythmias may be due solely to cardiac factors but are often caused or aggravated by noncardiac factors, such as drugs, autonomic imbalance, hypothyroidism, hypothermia, or hyperkalemia.[348] Furthermore, the hypoperfusion associated with bradycardia may be multifactorial, such as may occur in acute inferior wall infarction, in which bradycardia and LV dysfunction may be additive. In all cases, careful evaluation of both cardiac and noncardiac factors is necessary. If the patient is symptomatic, the first step in management is to increase the heart rate, which is readily accomplished by parasympatholytic drugs (e.g., atropine) or sympathomimetic drugs (e.g., isoproterenol). Underdosing with atropine (e.g., 0.3 mg) may cause a centrally mediated bradycardia and should be avoided. In addition, sympathomimetics must be used cautiously in all patients and avoided in the patient with ischemic symptoms. Temporary external pacing offers a logical alternative.[349,350] Stable, reliable increases in heart rate are afforded by temporary ventricular demand pacing from a pacing catheter positioned in the right ventricular apex. Temporary dual-chamber pacing is required in cases in which synchronized atrial contraction is deemed beneficial, such as bradycardia associated with inferior wall and right ventricular infarction.[351] General circulatory support and elimination of drugs that aggravate bradycardia is the second step in management.

Table 24-13: Classification of Bradyarrhythmias

FAILURE OF IMPULSE FORMATION
Sinus bradycardia
Sinus pauses, sinus arrest, SA block
Sick-sinus syndrome
Carotid sinus hypersensitivity syndrome
Neurocardiogenic cardioinhibitory syncope
AV CONDUCTION ABNORMALITIES
First-degree heart block
Second-degree heart block
Type I (Wenckebach)
Type II
Third-degree heart block
Paroxysmal
Intermittent, transient

Chronic: congenital, acquired
AV dissociation

Failure of Impulse Formation

SINUS BRADYCARDIA

Sinus bradycardia ranges from a benign asymptomatic physiologic adjustment in heart rate to a symptomatic expression of sinus node dysfunction. The asymptomatic forms are most often benign and related to physiologic (e.g., training effect) or pathologic (e.g., inferior wall infarction) excesses in vagal tone.[352-356] Drugs that can cause sinus node depression include beta blockers, calcium channel blockers, amiodarone, lithium, cimetidine, and adenosine. Radiographic contrast materials can also cause it in sensitive patients. Although most commonly due to impaired impulse formation, it may also be caused by impaired conduction from the sinus node to atrial muscle (SA block).

Electrocardiographic Features of Sinus Bradycardia and Sinoatrial Block

Sinus bradycardia is defined as a rate less than 60 impulses per minute, with the pacemaker impulse originating in the sinus node, resulting in P waves of normal amplitude and vector. It is rarely considered outside of the physiologic range until rates are under 50 per minute. In well-trained athletes and during sleep, rates of 40 per minute or less may occur as a normal variant. Sinus bradycardia may be accompanied by some degree of sinus arrhythmia.

SA block is categorized as first-degree (delayed conduction), second-degree (intermittent), or third-degree (complete) block. Vagal stimulation, digitalis, and ischemia are the most common predisposing factors in this rare conduction disorder. SA block is recognized by the absence of expected P waves and the subsequent QRS complex. First- and third-degree SA blocks cannot be recognized on the standard clinical ECG, but second-degree SA block may be identified because of its intermittent pattern. Characteristically, in SA Wenckebach, the PP and RR intervals will progressively shorten together before a dropped P-QRS complex results in a pause; a recurrent pattern may be identified (Fig. 24-60*B*). SA Wenckebach periods are frequently overlooked or mislabeled as sinus arrhythmia. Intermittent 2:1 block may also be deduced from standard rhythm strips (Fig. 24-61), but persistent 2:1 SA block is indistinguishable from sinus bradycardia.

Management of Sinus Bradyarrhythmias

Treatment of patients who have asymptomatic bradycardia is often unnecessary. In the symptomatic patient, elimination of reversible aggravating factors is an essential step in management. When this is ineffective or negative chronotropic agents are essential to overall patient management, permanent pacing may be needed (see Chap. 31). A similar approach is taken for patients with sinus pauses, sinus arrest, or SA exit block, which may be associated with myocardial infarction, myocarditis, sinus node fibrosis, digitalis excess, or excess vagal tone.[357,358] In the patient with symptomatic hypersensitive carotid sinus syndrome,[359,360] medical treatment is usually inadequate. Permanent ventricular or dual-chamber pacing[361] is usually effective but occasionally may not relieve symptoms because of a coexisting vasodepressor reflex.[362]

The complex of neurocardiogenic syncope, or neurally mediated vasodepressor syncope, has combined manifestations of sinus bradycardia and vasodepressor responses. It is revealed by the response to head-up tilt testing and is due to an abnormal reflex, the afferent limb of which originates in the LV wall.[363] The efferent limb is parasympathetic, causing both decreases in peripheral vascular tone, leading to hypotension, and sinus node depression, leading to sinus bradycardia or a junctional escape rhythm. In the majority of patients, the vasodepressor component dominates, limiting the effectiveness of pacing therapy.[364] However, among the subgroup of patients in whom the cardioinhibitory component predominates, cardiac pacing featuring "rate-drop response" or a similar algorithm appears to be effective.[365] Among pharmacologic agents,[366,367] beta-adrenergic blockers have been most useful,

presumably by the mechanism of blocking the sympathetically mediated afferent limb of the reflex[367] (see Chap. 32).

SICK-SINUS SYNDROME

Sick-sinus syndrome[368-370] is a general term used to indicate abnormalities of cardiac impulse formation and intraatrial and AV conduction[352,371,372] that may be manifested by various combinations of brady- and tachyarrhythmias.[373] Treatment, therefore, must be individualized to each patient's manifestations of the syndrome.[374] Often the patient is asymptomatic, or the symptoms are mild and nonspecific. Negative chronotropic agents are avoided or discontinued,[370,375] and permanent pacing may be delayed until the patient is more clearly symptomatic.[376,377] Although decisions regarding therapy often can be made from the combination of clinical, ECG, and monitoring data, invasive electrophysiologic studies may assist in decision making in some patients. Quantitative measures of sinus node function, such as sinus node recovery time and perhaps SA conduction time, and of conduction system status, such as HV interval and its response to membrane suppressants, are occasionally helpful. In the clearly symptomatic patient, treatment may include a combination of antiarrhythmic agents and permanent pacing for intrinsic and drug-induced bradycardias. Ironically, the eventual development of atrial fibrillation in patients with sick-sinus syndrome may alleviate symptoms, since heart rate control in atrial fibrillation can be more consistently achieved. Dual-chamber pacing is preferred, to avoid pacemaker syndrome, since 50 to 80 percent of patients with sick-sinus syndrome have preserved ventriculoatrial conduction (see Chap. 31), and DDD pacing with rate-responsive functions is preferred for patients with intermittent or persistent sinus bradyarrhythmias. Among patients without evidence of AV nodal dysfunction or requiring AV nodal blocking drugs, pacing in the AAI mode, using a single atrial lead, is feasible. This system is less expensive and avoids the risks and complications of a second lead implant (ventricular), which may be important in patients with difficult vascular access. Later development of AV nodal disease is uncommon among these patients, and it usually presents in a slowly progressive pattern.[378-380] DDD pacing with automatic mode-switching function is useful for patients with intermittent tachyarrhythmias, and rate-responsive VVI pacing is preferred for patients with chronic atrial fibrillation.[381]

Digitalis is used with caution[375] and, when needed, is easier to titrate once the patient has a permanent pacemaker. When such patients require therapy with antiarrhythmic drugs that slow sinus rates and/or impair AV conduction (e.g., beta blockers or amiodarone), management of drug therapy may be facilitated by pacemaker backup.

It is important to recognize that the risk of development of new-onset atrial fibrillation is high in patients with sick-sinus syndrome, approximately 5.2 percent per year in a retrospective analysis of several studies. The incidence of the arrhythmia and its thromboembolic complications may be reduced by atrial or DDD pacing, compared to VVI or no pacing.[382,383] Anticoagulation should be considered part of the management of patients with sick-sinus syndrome, especially when they have documented atrial fibrillation episodes. Although there is clearly a symptomatic improvement in patients with sick-sinus syndrome by cardiac pacing and a trend toward reduction of incidence of heart failure, it is not yet known whether cardiac pacing improves survival.[382,383]

CAROTID SINUS HYPERSENSITIVITY

The pathophysiology of carotid sinus hypersensitivity is poorly understood. Among the explanations are abnormalities of the neuromuscular structures surrounding the carotid sinus mechanoreceptors, a central defect of the autonomic nervous system, and association with artherosclerotic disease.[384,385] A hypersensitive response to carotid sinus stimulation is defined as asystole due to sinus arrest of more than 3 s, a substantial symptomatic decrease in blood pressure, or both. It is important to evaluate and correlate the patient's symptoms because an abnormal response to carotid sinus pressure may be found in elderly patients or in patients sensitized by digitalis or other drugs, without clinical significance. In patients with associated syncope or near syncope, pacing is indicated.[385-388]

Atrioventricular Conduction Abnormalities

Abnormal prolongation or block of AV node conduction can be due to physiologic, reversible or permanent

acquired or congenital causes (Tables 24-14 and 24-15). Although the term *block* is applied generally to most patterns of conduction abnormalities, it is a misnomer when referring to impaired impulse conduction through the AV node or the bundle branches, in which there is an abnormal delay, rather than complete block, of conduction. Delayed conduction may result from normal physiologic variations (e.g., vagal tone) or pathologic influences.[389] Management is determined by assessing the degree of block, symptoms, and clinical setting. Recurrent episodes of the Wenckebach phenomen (type I, second-degree AV block) may be asymptomatic and require no therapy in the well-conditioned individual or athlete. These individuals may have resting heart rates of 40 impulses per minute or less and as low as 30 per minute during sleep, due to sinus bradycardia and/or second-degree AV block. Sinus pauses as long as 2.8 s may occur. All of these phenomena are due to high vagal tone in this setting.[390,391] In contrast, transient second-degree or complete AV block accompanying an acute anterior wall myocardial infarction is usually infranodal, a marker of massive muscle loss and predictive of a high mortality rate, even without symptoms of AV block and despite permanent pacing,[392,393] whether or not symptoms of AV block have occurred.

Table 24-14: Effect of Maneuvers on Sinus Node and Conducting System Function

Maneuver	Effect on SN	Functional (AV Nodal Block)	Structural (AV Nodal, Hisian, or Infrahisian Disease)
Atropine	↑ Heart rate	Improve AV conduction, decrease block	Worsen AV conduction, increase block
Exercise	↑ Heart rate	Improve AV conduction, decrease block	Worsen AV conduction, increase block
CSM	↓ Heart rate	Worsen AV conduction, increase block	Improve AV conduction, decrease block

ABBREVIATIONS: CSM = carotid sinus massage; SN = sinus node.

Table 24-15: Etiologies of AV Block

	Reversible or Transient	Permanent
Physiologic		
Heightened vagal tone (athlete, sleep apnea)	+	-
Neurogenic		
Carotid hypersensitivity syndrome	+	-
Neurocardiogenic syncope	+	-
Congenital		
Congenital heart disease	-	+
Maternal systemic lupus erythematosus	-	+
Coronary artery disease		
Acute myocardial infarction		
Anterior	+	+
Inferior	++	+

Ischemic cardiomyopathy	-	+
Cardiomyopathy	-	+
Infiltrative disease	-	+
Amyloidosis		
Sarcoidosis		
Hemochromatosis		
Infectious disease		
Endocarditis	+	++
Myocarditis		
Lyme disease	+	-
Tuberculosis, rheumatic fever, siphylis	-	+
Viral: measles, mumps,	+	+
adult varicella	++	+
Chagas disease	-	+
Collagen vascular disease	+	++
Systemic lupus erythematosus		
Rheumatoid arthritis		
Scleroderma		
Others		
Idiopathic fibrosis		
(Lev's disease)	-	+
Calcific infiltration	-	+
(Lenegre's disease)		
Drug induced	+	-
Digitalis		
Beta blockers		
Calcium channel blockers		
Amiodarone		
Lithium		
Cimetidine		
Adenosine		
Metabolic	+	-

Hyperkalemia		
Addison's disease		
Hypermagnesemia		
Traumatic	+	+
Surgery		
RF energy, catheter trauma		
Radiation		
Tumors	-	+
Mesothelioma		
Melanoma		
Rhabdomyoma		
Hodgkin's disease		
Neuromuscular disease	-	+
Myotonic muscular dystrophy		
Kearns-Sayer syndrome		
Peroneal muscular atrophy		
Erb's dystrophy		

AV block associated with inferior wall myocardial infarction is much commoner (10 to 15 percent versus 5 percent) than with anterior wall infarction and has a more benign prognosis. It is usually due to AV nodal, rather than infranodal, conduction abnormalities and is commonly vagally mediated rather than structural. Onset is within the first 24 h, and it is almost always transient and commonly reversible with atropine, if treatment is needed at all. This form of AV block is not associated with an adverse long-term prognosis, although in-hospital mortality rates are slightly increased. Temporary pacing is occasionally required, but permanent pacing is very rarely indicated.

ELECTROCARDIOGRAPHIC PATTERNS

First-degree AV block is defined as a PR interval in excess of 0.2 s at normal heart rates. When the QRS complexes are of normal duration and configuration, it is usually due to prolonged conduction at the level of the AV node. If bundle-branch or fascicular block is present, the conduction delay may be at the level of either the AV node or the His-Purkinje system.

Second-degree AV block is characterized by intermittent failure of conduction from atria to ventricles and is further subdivided into type I (Wenckebach phenomenon) and Möbitz type II second-degree block. Type I second-degree AV block is characterized electrocardiographically by progressive lengthening of the PR interval, eventually leading to a nonconducted P wave (Fig. 24-60*A*). This often recurs with regularity, and patterns of "group beating" are recognized. The degree of block can be quantified by the conduction ratio, the ratio of the number of P waves to the number of QRS complexes in each episode or period terminated by the pause. Because the magnitude of PR lengthening typically is less with subsequent RR intervals, the RR intervals themselves progressively shorten before the pause caused by the blocked P wave. Atypical patterns may demonstrate lengthening of RR intervals in later cycles of a Wenckebach

period. The greatest decrement between successive RR intervals occurs from the first to the second cycle of a Wenckebach period, and, even with atypical patterns, shortening of the second RR cycle is always present. Wenckebach block may be physiologic in athletes (especially during sleep) or induced by digitalis. It is almost always due to impaired conduction across the AV node and is usually accompanied by a QRS complex of normal duration (see also Chap. 31). A Wenckebach conduction pattern may occur rarely across an area of disease in the His-Purkinje system.

In type II second-degree AV block, appropriately timed P waves fail to conduct, but there is not a pattern of progressive PR lengthening. Isolated P waves may fail to conduct, or fixed patterns (e.g., 2:1 at rates that are expected to conduct 1:1 under normal physiologic conditions) may occur. Infranodal block is the rule, and QRS complexes tend to be widened due to disease in the His bundle or intraventricular conducting system. Type II block is most often associated with organic cardiac disease and is frequently progressive. When the QRS complex is narrow with Möbitz type II block, block in the His bundle is likely (Fig. 24-62); when it is widened, block below the His bundle is the rule. At times, the conduction ratio of P waves to QRS complexes is fixed at 2:1. Only a single PR interval is recorded, and PR lengthening cannot be discerned; therefore, the absolute distinction between type I (2:1 Wenckebach) and type II block cannot be made. A narrow QRS complex and type I block at other times on the tracing suggest that 2:1 block is a manifestation of type I block (Wenckebach-AV nodal) physiology. Wide QRS complexes favor type II block. If the PR interval of conducted beats is 300 ms or longer, conduction block is likely at the level of the AV node; if it is 160 ms or less, Hisian or infra-Hisian block is likely. Evidence of VA conduction, such as retrograde P waves following a PVC favors the His-Purkinje system as the site of block. The response to certain maneuvers can be of help establishing the site of block (see Table 24-14).[415] In the electrophysiology laboratory, recording an HV interval of greater than 80 ms (normal = 45 to 55 ms) identifies high risk for AV block, and a pacemaker is indicated if the patient is symptomatic. If the HV is 100 ms or more, a pacemaker implantation is indicated, even in asymptomatic patients.[410]

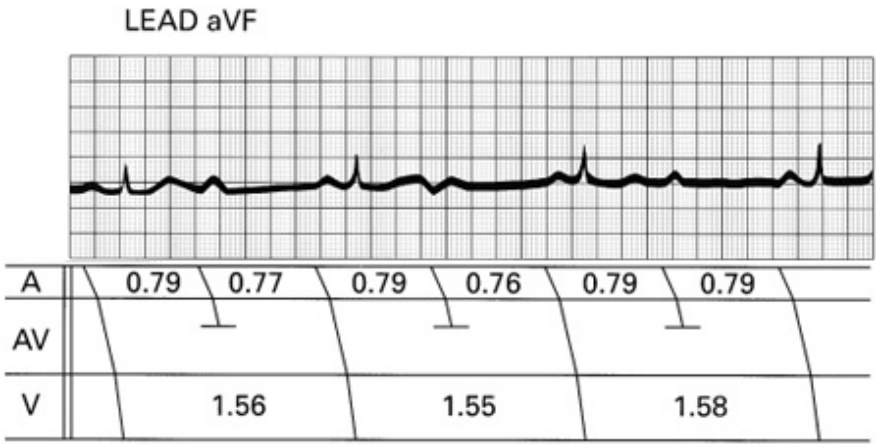

Figure 24-62: A form of second-degree AV block. There are two P waves to each QRS 2:1 AV block (alternate sinus impulses are blocked). This pattern can be caused by block in the AV node (Wenckebach), intra-Hisian block, or distal block (see the text).

Occasionally, the intervals between P waves may vary, with a pattern of shorter PP intervals when a QRS is between the two P waves, and the PP interval is longer when the two P waves are consecutive. This phenomenon is called ventriculophasic sinus arrhythmia and is related to baroreceptor reflexes. High conduction ratios, such as 3:1 and greater, may be diagnosed simply as paroxysmal or high-grade AV block.

In third-degree (complete) AV block, the atrial and ventricular rates are regular but dissociated (Fig. 24-63). At times, the P waves and QRS rates are so similar (isorhythmic dissociation) as to make this judgment difficult. Maneuvers by the patient, such as arm movement, standing up, or marching in place, may increase the sinus rate (P waves) without corresponding changes in the ventricular escape rate, confirming loss of AV conduction. In contrast, the development of 1:1 conduction suggests that the impaired conduction was at the AV nodal level. Morphology of the QRS complexes suggests the escape of junctional (narrow QRS)

or ventricular (wide QRS) subordinate pacemakers. Complete AV block may be preceded by years of varying and/or progressive lower grades of block, as well as by bundle-branch and fascicular blocks. It is common to observe long rhythm strips that demonstrate not quite complete AV block. Occasional capture beats interrupt a regular escape rhythm. The conducted P waves are critically timed within a narrow range, usually at a long interval after the preceding escape QRS complex. The clinical implication of this pattern is the same as complete heart block. Transient AV block or sinus pauses on telemetry or ambulatory monitoring are common and occasionally of concern. Occurring at night or without symptoms, sinus pauses of less than 3 s are not uncommon (2.4 percent of patients) and usually represent variations in response to autonomic fluctuations rather than disease. Pauses greater than 3 s are rarer (0.8 percent of patients) and may require further evaluation. Patients with sleep apnea may develop sinus pauses or transient AV block, usually preceded by a decrease in sinus rate, a clue of increased vagal tone. These patients require therapy for the respiratory problem rather than pacemaker implantation.[410]

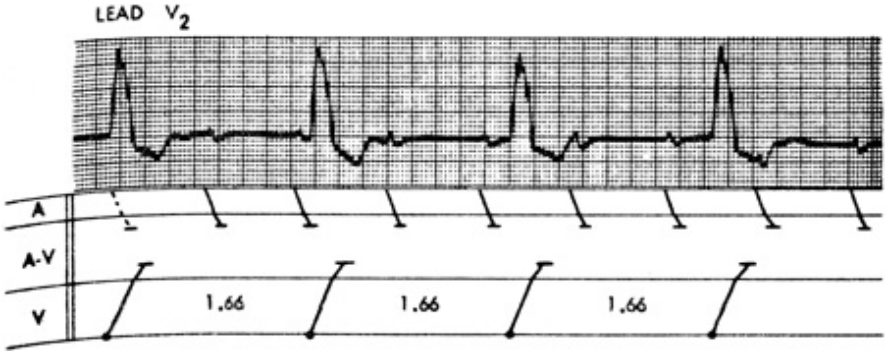

Figure 24-63: Complete (third-degree) AV block. There is a regular idioventricular rhythm at rate 36 impulses per minute, and the P waves indicate their independence by changing their relationship to the QRS complexes.

MANAGEMENT OF ATRIOVENTRICULAR BLOCK

First-Degree Heart Block

Isolated first-degree AV block is asymptomatic and is not an indication for temporary or permanent pacing.[410,416,417] However, one possible exception is a subgroup of patients with marked first-degree AV block (greater than 300 ms) associated with LV dysfunction and symptoms of congestive heart failure in whom a shorter AV interval caused by sequential AV pacing results in hemodynamic improvement.[410,414]

Second-Degree Heart Block

Möbitz type I AV block, or the Wenckebach phenomenon, is usually associated with an adequate ventricular rate and is rarely symptomatic.[415] It occurs in highly trained athletes[419] and is a normal response to rapid atrial pacing. In most patients who have the Wenckebach phenomenon secondary to AV nodal disease, routine prophylactic pacing is not advised, since it is minimally symptomatic (if at all) and tends not to progress.[369] Rarely, the effective ventricular rate is slow and patients are symptomatic, requiring pacing if vagolytic maneuvers are ineffective. The prognosis in patients who have underlying organic heart disease is determined by the extent of the underlying disease, not the Möbitz type I block.[420] Second-degree heart block is common in the acute phase of inferior wall myocardial infarction and rarely requires temporary pacing in this setting. Reversion is usually prompt-measured in hours to days.

Möbitz type II block is less common but implies more significant disease in the conduction system. The site of block is almost always below the AV node and usually below the bundle of His. Therefore, slower escape rhythms and risk of progression to complete heart block are of concern. It is almost always associated with a defined disease process. Permanent pacing is indicated,[410] except where Möbitz type II block is induced by rapid artificial pacing.[421,422] The purpose of pacing is primarily to protect against symptomatic events, such as syncope, and thus to protect the patient from injuring him- or herself or others.

Available data do not suggest that pacemakers will prolong the life of patients with Möbitz type II block. The selection among specific designs of pacing devices is discussed in Chap. 31.

A special circumstance involves 2:1 AV block in which the underlying mechanism and site of block remain obscure. The decision to treat is inferred from the clinical setting. Wide QRS complexes, sudden onset of periods of block, and inadequate escape rates favor type II block, whereas narrow complexes and coincident episodes of typical type I block favor Wenckebach block.

Another variant pattern is multilevel block in the AV junction. This commonly occurs during atrial tachycardias and may be functional, pharmacologic, or pathologic. The pattern of multilevel block during atrial tachycardia may be deceiving. This pattern is a basic 2:1 pattern with Wenckebach conduction patterns of the impulses that conduct through the area of 2:1, and it produces group beating of the ventricles. This may result in relatively slow ventricular rates, but the primary problem is the atrial arrhythmias with physiologic or insignificant pathologic responses at the level of the AV node. His-bundle electrograms may be diagnostic, but such invasive studies are indicated only when needed for a therapeutic decision.[422-425]

Paroxysmal AV Block

Runs of consecutive atrial impulses that fail to conduct to the ventricles may last for up to 10 to 20 s and may be associated with syncope. Unless a clearly defined, reversible cause is identified, permanent pacing is required. Bradycardia-dependent AV block, or phase 4 block, usually affects patients with underlying conduction system disease. It is characterized by spontaneous phase 4 depolarization of tissue in the His-Purkinje system. The partially depolarized tissue impairs ventricular conduction of propagating impulses of sinus origin, most commonly affecting the conduction in the left bundle-branch system (bradycardia-dependent left bundle-branch block). Block by this mechanism at a more proximal site in the conducting system may result in complete heart block, not responsive to atropine or isoproterenol, but only to cardiac pacing. A precordial thump may produce a PVC able to depolarize and reset the ventricle including the site of automatic activity, thereby allowing resumption AV conduction down the distal conducting system.[426-429]

Complete AV Block

Complete heart block may be acute in onset or slowly progressive and chronic; it may produce abrupt, clinically significant symptoms or may remain asymptomatic and be discovered incidentally. When acute and symptomatic, evaluation and rate support are urgently needed. Pharmacologic intervention with atropine or isoproterenol is usually most readily available.

The latter should be avoided in the presence of ischemic heart disease, and external pacing instituted if needed.[437,438] Reliable rate control is achieved by ventricular or dual-chamber temporary cardiac pacing. Permanent pacing is indicated unless those factors responsible for the heart block are reversible or when transient complete block complicates an acute inferior wall myocardial infarction.[410] Since the advent of thrombolytic therapy and primary angioplasty in acute myocardial infarction, the incidence of complete heart block in myocardial infarction has decreased. However, in acute anterior wall infarction, the prognosis remains grave, even after permanent pacemaker implantation.[395,401,404]

Isolated congenital AV block usually occurs at the level of the AV node and is accompanied by an adequate junctional escape rate. Although it is often well tolerated in the young, adult patients ultimately may develop symptoms of exercise intolerance, and thus permanent pacemaker implantation is a commonly used management strategy. When AV block coexists with other congenital structural abnormalities, the risk of symptoms with congenital AV block is higher, and pacemakers are more clearly indicated. There are specific guidelines for pacemaker implantation in the pediatric population.[410]

The choice between ventricular and dual-chamber pacing and considerations for rate-responsive pacing in various clinical conditions are discussed in Chap. 31.

Atrioventricular Dissociation

AV dissociation is not synonymous with AV block but occurs in conjunction with block as well as in its absence. It implies an abnormality of intrinsic pacemaker activity that may be slowing of normal pacemaker activity (*default*), acceleration of a normally subordinate or latent pacemaker (*usurpation*), AV block, or a combination of these phenomena.

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AV dissociation implies that the atria and ventricles each have manifest independent pacemakers. In the setting of AV block, a junctional or ventricular pacemaker emerges as an escape rhythm; if it fails or if the escape is too slow, AV block will become a symptomatic or terminal rhythm. The atria and ventricles may beat independently if a normally subordinate junctional or ventricular pacemaker discharges faster than the sinus or atrial pacemaker and 1:1 retrograde conduction is absent. Since AV block is not necessarily present, ventricular capture by impulses of sinus origin commonly occur as a result of fortuitous timing relationships between sinus node activity and ventricular refractoriness. At times, capture beats and junctional or ventricular beats coincide and generate fusion beats (Fig. 24-64).

MANAGEMENT

Treatment, when needed, is directed toward the underlying cause. It is important to evaluate whether symptoms are present and whether they are due to a rapid or slow rate. Suppression of tachyarrhythmias, such as AV dissociation in VT, is the primary goal when symptoms are related primarily to the tachyarrhythmia and an intact intrinsic or artificial pacemaker is present. Intermittent ventricular ectopy may be an escape phenomenon in an otherwise asymptomatic patient who has an underlying persistent bradycardia. In such cases, rate support with pacing is indicated to relieve bradycardia symptoms, and the escape ventricular ectopy will resolve secondarily. If initial therapy is targeted to a tachycardia in the presence of an underlying bradycardia, symptoms may worsen due to drug suppression of lower intrinsic pacemaker sites.[430]

Indications For Pacing

Pacing is indicated for symptomatic bradyarrhythmias that have no identifiable reversible cardiac or noncardiac cause.[410] Prophylactic pacing to prevent death or the onset of life-threatening symptoms is controversial, since increased risk of death is more likely related to the severity of underlying organic heart disease. The mortality benefits of pacing, though theoretically sound, often lack rigorous proof of effectiveness. Less controversial is the use of permanent pacing for morbidity benefit, namely, to reduce symptomatic bradyarrhythmic events and their consequences (see also Chap. 31).

Temporary pacing is indicated for AV block associated with acute anterior wall infarction if the heart rate is excessively slow and/or associated with rate-dependent hypotension, and if there is a newly acquired left or right bundle-branch block accompanied by hemiblock.[431] The availability of external pacing techniques[349,350] has tended to relax the sense of urgency for prophylactic pacing catheters in these settings. New left bundle-branch block or preexisting right or left bundle-branch block is managed with less immediate urgency and often does not require pacing. Permanent pacing is often recommended for those with acute anterior wall infarction who have had transient complete heart block.[432] The change in long-term survival, however, is not well documented.[433] Temporary pacing can often be avoided in AV block associated with inferior infarction, since block is often related to ischemia or parasympathetic reflexes, is usually asymptomatic, and reverses with time.[434] If hypotension occurs in inferior infarction that is not due to hypovolemia or right ventricular infarct, temporary pacing for severe sinus bradycardia or higher grades of AV block is often used. Permanent pacing after AV block in inferior infarction is required only very rarely.

Permanent prophylactic pacing in bifascicular block without symptoms of transient AV block is not routinely recommended.[435,436] In patients at high risk for complete heart block (e.g., Kearns-Sayre syndrome) or recurrent neurologic symptoms associated with advanced HV prolongation (e.g., HV longer than 70 to 80 ms), however, prophylactic pacing may be of benefit.[437] Guidelines for permanent cardiac pacemaker implantation have been published[410] and are further discussed in Chap. 31.

Pacemaker-Associated Arrhythmias

As pacemakers have become more sophisticated, there has been an increasing need to identify normal and abnormal pacemaker function and related arrhythmias electrocardiographically. The baseline pacing pattern is dependent on the pacemaker design and the interaction with the patient's intrinsic rhythm. These aspects, as well as pacemaker testing, are reviewed in detail in Chap. 31. Apparent pacemaker malfunctions are frequently due to observer inexperience and lack of knowledge of pacemaker electronics. Unusually rapid or slow rates may connote pacemaker malfunction, but programming changes, magnet activation, and over- and undersensing must be excluded. Fusion beats, pseudofusion, and ventricular-triggered pacing may cause confusion. Fusion beats occur when there is overlap in the timing of paced and normal beats and the morphology of the fused complex is midway between the normal and paced QRS complexes. Ventricular-triggered pacing becomes confusing when a PVC occurs and is thought to be triggered by the pacemaker because of the width of the complex and the presence of a pacemaker artifact. The pacing artifact occurs slightly after the initiation of the PVC, providing a clue to ventricular ectopy. Inappropriate bradycardias may be induced by oversensing by the pacemaker or by normal sensing of extracardiac stimuli, such as myopotentials (skeletal muscle activity) or extracorporeal inhibition by electromagnetic or RF waves. "Cross-talk" can result in arrhythmias, for instance, when the ventricular lead senses atrial activity.

Dual-chamber pacing may lead to a variety of arrhythmias that are actually an undesirable byproduct of normal pacemaker function. Arrhythmias may be initiated by asynchronous ventricular or atrial stimulation (DVI pacemakers), interruption of ventricular sensing during ventricular blanking (all dual-chamber pacemakers), or asynchronous atrial or ventricular stimulation in the magnet mode (all dual-chamber pacemakers). Furthermore, dual-chamber units create an artificial bypass tract that may become operative in the presence of ventriculoatrial conduction. When a ventricular event, either paced or spontaneous, results in retrograde atrial activation, the latter may be sensed by the atrial electrode returning to the ventricle after an appropriate AV delay. A paced ventricular response follows, and the process repeats itself. This artificial arrhythmia has been called an endless-loop tachycardia[438] (Fig. 24-65). Spontaneous termination of the reentry tachycardia may occur by fatigue or block in the retrograde limb. Treatment includes reprogramming of pacemaker parameters, including extension of the atrial refractory period of the pacemaker or avoidance of the DDD or VDD mode (at the extreme, the VVI mode is used). In order to guard against rapid ventricular pacing and response to sudden increases in atrial rate, physiologic pacemakers tend to have an upper rate limit control. Earlier models suddenly drop to 2:1 pacing rates. Recent models often induce a gradual Wenckebach-type response. The pacemaker electronically creates a Wenckebach phenomenon with a gradually increasing number of dropped QRS complexes (see Chap. 31).

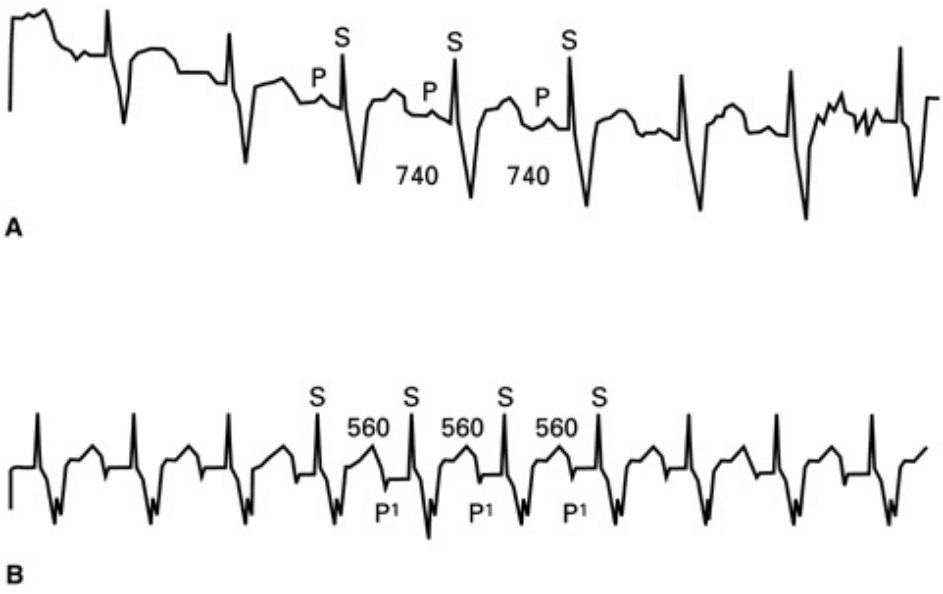

Figure 24-65: Pacemaker-mediated (endless-loop) tachycardia. The patient had a DDD pacemaker and presented with episodes of sustained rapid heart action. The tracing (lead II) demonstrates (*A*) atrial

tracking with ventricular pacing at a cycle length of 740 ms and (*B*) ventricular pacing with retrograde atrial activation. The retrograde P waves (P) following each paced QRS are sensed by the atrial sensing lead and trigger a ventricular pacing spike (S), followed by the paced QRS with repeated retrograde atrial activation.

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Chapter 24: RECOGNITION, CLINICAL ASSESSMENT, AND MANAGEMENT OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Chapter 24: RECOGNITION, CLINICAL ASSESSMENT, AND MANAGEMENT OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Figure 24-5: (Plate 74) Catheter-based mapping of the right atrium using a nonfluoroscopic electroanatomic mapping system that allows computer storage and recall of multisite activation patterns. Panels A and B demonstrate the activation sequence during normal sinus rhythm, with the earliest activation in the region of the sinus node (*arrows*) shown from (*A*) anterior and (*B*) posterior perspectives. The sequence of activation is indicated by the gradation of the color scale, based upon the reference times shown in the spectral bar. *C* and *D* were recorded from another patient who had episodic ectopic atrial tachycardia. In this oblique view, the sequence of activation during sinus rhythm is shown in *C*, with the earliest site of activation in red (*arrow*) representing the region of the sinus node. *D* was recorded during a low right atrial ectopic tachycardia. The earliest site of activation is indicated by the arrow.

Figure 24-6: Left ventricular endocardial catheter mapping and radiofrequency ablation of ventricular tachycardia (VT) *A*. Bipolar (Bi) and Unipolar (Uni) recordings from an LV mapping site. The sustained ventricular tachycardia has a cycle length ranging from 420 to 450 ms. Onset of the VT QRS is indicated by the vertical line. Fractionated electrical activity is recorded from the distal bipolar electrode pair (Bi 1-2). A small potential immediately precedes the QRS onset, and fractionated signals extend 210 ms after the onset. *B*. The tachycardia is entrained during pacing and a cycle length of 400 ms [note the identical morphology of the complexes following pacing stimuli (concealed entrainment, entrainment with concealed fusion)], and a return to the spontaneous (unpaced) VT cycle length after cessation of pacing. The interval between the pacing stimulus and the onset of the responding QRS complex is the same as the interval between the end of the fractionated electrogram in *A* and the onset of the following QRS complex. *C*. RF energy applied through a catheter positioned at the same location results in prompt termination of the tachycardia, loss of fractionated electrograms, and return to sinus rhythm. (From Stevenson WG, et al. Identification of reentry circuits sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. *Circulation* 1993; 88[part 1]:1647-1670. Reproduced with permission from the American Heart Association.)

Figure 24-7: Primary and secondary arrhythmias. When a disease process directly initiates an electrophysiologic disturbance, the resulting arrhythmia is referred to as primary. In contrast, when the disease process produces a hemodynamic abnormality that in turn initiates the electrophysiologic disturbance, a resulting arrhythmia is referred to as secondary. Antiarrhythmic drugs may be used to prevent the electrophysiologic disturbance, prevent the electrophysiologically unstable heart from developing a manifest arrhythmia, or reverse a primary arrhythmia. In secondary arrhythmias, hemodynamically active drugs are used to prevent or reverse secondary electrophysiologic disturbances, usually in conjunction with antiarrhythmic drugs. Antiarrhythmic drugs alone are less likely to be effective for secondary arrhythmias. (Modified from Myerburg et al.[1] Reproduced with permission from the publisher and authors.)

Figure 24-8: The Sicilian gambit approach to antiarrhythmic drugs. This figure summarizes the important actions of drugs on membrane channels, receptors, and ion pumps in the heart as well as on the ECG, sinus rate, and LV function. Because clinical and ECG effects are diverse, the table unavoidably includes some degree of subjectivity. Accordingly, the shading of the symbols and the direction of the arrows should not be taken as absolute. Moreover, the clinical information presented refers to the patient who does not have significantly compromised LV function prior to the drug administration. For the section on channels, receptors, and pumps, the actions of drugs on the sodium (Na+), calcium (Ca2+), potassium channels (I_K and I_f) are indicated. Sodium channel blockade is subdivided into three groups of actions characterized by fast (tau less than 300 ms), medium (tau 200 to 1500 ms), and slow (tau greater than 1500 ms) time constants for recovery from block. This parameter is a measure of use dependence and predicts the likelihood that a drug will decrease conduction velocity of normal Na+-dependent tissues in the heart and perhaps the propensity of a drug for causing bundle-branch block or proarrhythmia. The rate constant for onset of block may be even more clinically relevant.

Blockade in the inactivated (I) or activated (A) state is indicated. Drug interaction with receptors [beta-adrenergic, alpha-adrenergic, muscarinic subtype 2 (M_2), and A_1 purinergic (P)] and drug effects on the sodium-potassium pump (Na+, K+-ATPase) are indicated. The absence of a symbol indicates lack of effect. The use of a question mark indicates uncertainty concerning effect. The arrows in the clinical effect and ECG section indicate direction; no quantitative differentiation has been made between weak and strong effects. The effects listed for ECG, LV function, sinus rate, and extracardiac are those that may be seen at therapeutic plasma levels. Deleterious effects that may appear with concentrations above the therapeutic range are not listed. [From Schwartz PJ, Zaga A. The Sicilian gambit revisited. *Eur Heart J* 1992; 13(suppl F):23-29. Reproduced with permission from the publisher and authors.]


Figure 24-9: Comparison of mechanisms, electrocardiographic and clinical features, responses to adenosine, activation patterns, and electrocardiographic appearance of the various supraventricular rhythms. See the text for description of the individual arrhythmias.


Figure 24-10: *A.* Sinus arrhythmia. The sinus cycles are indicated in seconds in the atrial (A) tier; they range from 0.60 to 1.01 s. Note that the P-wave amplitude increases as the sinus pacemaker accelerates. *B.* Sinus tachycardia. Note normally shaped and directed P waves, normal PR interval, and a rate of almost 150 per minute. *C.* Sinus bradycardia. Note normally directed (but abnormally wide) P waves, normal PR interval, and a rate of slightly more than 50 per minute.


Figure 24-11: *A.* The fifth impulse is an atrial premature beat; there is a premature P wave (usually labeled P) followed by a normal QRS-T complex, and the postextrasystolic pause is longer than the sinus cycle but less than compensatory. *B.* The fourth impulse is an atrial premature beat with aberrant intraventricular conduction; there is a premature P wave followed by an anomalous QRS-T complex; the postextrasystolic pause is less than compensatory. *C.* Nonconducted atrial premature beat. Following the third ventricular complex, a P wave negatively deforms the ST segment and is not followed by a ventricular response.


Figure 24-12: Mechanism of PSVT due to AV nodal reentry. This arrhythmia is due to the presence of dual AV nodal pathways with different conduction properties and refractory periods. Although the fast and slow pathways were previously thought to be within the anatomic AV node, the pathways are now viewed as having critical components in the atrial approaches to the AV node. Nonetheless, the dual-pathway physiology concept is valid. *A.* During sinus rhythm in the presence of a dual AV nodal pathway, the fast pathway (which generally has a longer refractory period) is primarily responsible for AV transmission because of slower propagation in the other pathway. *B.* A premature atrial impulse blocks in the fast pathway because of its longer refractory period and propagates down the slow pathway, prolonging the PR interval and allowing retrograde invasion of the fast pathway because its tissue remains polarized due to block of the descending impulse. *C.* Echo beats or AV nodal reentrant tachycardia will occur when the time relationships between slow pathway conduction and recovery of excitability at the site of block in the fast pathway allow the impulse to reenter the slow pathway after retrograde fast pathway transmission. The atria are also activated retrogradely. In a much less common form of AV nodal reentry, a shorter refractory period in the fast pathway reverses the loop, with antegrade conduction down the fast pathway and retrograde conduction up the slow pathway (see Fig. 24-13 for examples). RF energy for slow pathway ablation therapy is applied at the site indicated by the asterisk.


Figure 24-13: PSVT due to AV nodal reentry. Narrow QRS complexes with ST-segment depression are seen (*upper panel*). Adenosine, 6 mg intravenously, abruptly alters AV nodal properties and terminates the tachycardia (*lower panel*). The ST-T wave pattern immediately returns to normal.

Figure 24-14: Common and uncommon forms of AV nodal reentrant tachycardia recorded during electrophysiologic studies. *A.* The common type of AV nodal reentrant tachycardia, antegrade conduction in the slow pathway and retrograde in the fast pathway, results in atrial (A) and ventricular (V) activation that are close to one another in time. Characteristically, intracardiac recordings demonstrate a "lining up" of atrial and ventricular electrograms, indicating that the atria are activated before completion of ventricular activation. *B.* In the uncommon type of AV nodal reentrant tachycardia, antegrade fast pathway and retrograde slow pathway conduction change the relative timing pattern so that atrial activation is delayed relative to ventricular activation, and the electrograms are not in line. In this form of PSVT, the RP interval is longer than the PR interval on the ECG, which results in inscription of the retrograde P wave *after* the ST-T wave of the related ventricular impulse. The uncommon type of AV nodal reentrant tachycardia may be difficult to distinguish from other arrhythmias, such as ectopic atrial tachyarrhythmias or concealed WPW syndrome (see the text).

Figure 24-15: PSVT due to AV nodal reentry. *A.* The initial presenting rhythm was a wide-QRS tachycardia with a vertical axis and a left bundle-branch block pattern. *B.* A sinus impulse with intracardiac recordings demonstrating normal sequences of AV conduction. *C.* Recording during a wide-QRS tachycardia with a left bundle-branch block pattern. The nearly simultaneous A and V activation patterns in the retrograde and antegrade directions (i.e., atrial activation before the end of ventricular activation) suggest the common form of AV nodal reentry rather than ventricular tachycardia.

Figure 24-16: WPW syndrome with reciprocating tachycardia. *A.* Before and during an "orthodromic" tachycardia. *B.* From another patient before and during an "antidromic" tachycardia.

Figure 24-17: Localization of accessory pathways in patients with WPW syndrome. The line drawings illustrate the anatomic relationships between the tricuspid (TV) and mitral valves (MV), the coronary sinus (CS), AV conducting system, and accessory pathways. For each accessory pathway location indicated, the combination of QRS vectors most likely to result are shown, based on upright (+) or inverted (-) QRS waveforms. These vectorial guidelines are generally useful but not necessarily precise, since activation patterns from specific sites may vary in individual patients. Nomenclature for accessory pathway location: RA, anterior; RAL, right anterolateral; RL, right lateral; RPL, right posterolateral; RP, right posterior; PSTA, posteroseptal tricuspid annulus; CSOs, coronary sinus ostium; MSTA, mid-septal tricuspid annulus; AS, anteroseptal; RAPS, right anterior paraseptal; MCV, middle cardiac vein (coronary vein); CS, coronary sinus; venous anomaly (coronary sinus diverticulum); PSMA, posteroseptal mitral annulus; LP, left posterior; LPL, left posterolateral; LL, left lateral; LAL, left anterolateral. (From Arruda MS et al.[40] Reprinted with permission from the publisher and authors.)

Figure 24-18: Atrial fibrillation in WPW syndrome with accessory pathway conduction. *Left.* Sinus rhythm with a typical preexcitation (delta-wave) pattern. *Right.* Accessory pathway conduction during atrial fibrillation. The QRS axis has shifted to the left, and the ventricular rhythm is now irregular, at a rate in excess of 200 per minute. (From Marriott HJL, Rogers HM. Mimics of ventricular tachycardia associated with the WPW syndrome. *J Electrocardiol* 1969; 2:77. Reproduced with permission from the publisher and authors.)

Figure 24-19: RF ablation in WPW syndrome in a 52-year-old female. The patient had frequent recurrent supraventricular tachycardias due to WPW syndrome. *A.* Standard leads I, II, and V_1 demonstrate disappearance of the delta wave from one impulse to the next 5 s after beginning the application of RF energy (compare successive QRS complexes indicated by arrows). *B.* Prior to ventricular ablation, the interval between atrial (A) and (V) activation at the site of the ablation catheter is less than 50 ms, and the sharp spike between A and V likely represents activity in the bypass tract. *C.* Immediately after ablation, the AV interval at the site of the ablation catheter is lengthened to 150 ms, and the accessory pathway spike has disappeared. *D, E.* Enlargements from panels B and C, respectively. AB, ablation catheter; RA, right atrium; RVA, right ventricular apex.

Figure 24-20: Ectopic atrial tachycardia. *A.* A 20-s continuous recording demonstrates a regular tachycardia at a ventricular rate of approximately 140 per minute. *B.* During carotid sinus massage, ventricular conduction becomes irregular, and diminutive P waves at twice the basic ventricular rate are evident. Impaired AV conduction with little or no effect on atrial activity is characteristic of the response of an ectopic atrial tachycardia to carotid sinus massage.

Figure 24-21: *A.* Atrial tachycardia with 2:1 AV block due to digitalis intoxication. Note the diminitive P waves, barely visible even in V_1. *B.* Multifocal (chaotic) atrial tachycardia. Note the constantly changing form of the ectopic P waves and the irregular rhythm at a mean rate of 122 per minute. Three or more distinct P-wave morphologies are required to make the diagnosis.

Figure 24-22: Atrial flutter. Note the "sawtooth" pattern in leads II and III, discrete atrial waves in V_1, and poorly registered atrial activity in leads I and V_6.

Figure 24-23: Atrial flutter with alternating 4:1 and 2:1 conduction. This common cause of bigeminal rhythm is almost always due to 2:1 AV conduction high in the AV junction and 3:2 Wenckebach periods at a lower level, as diagrammed.

Figure 24-24: Atrial flutter (type II) with complete AV block. The atrial rate is 366 per minute, and the ventricular rate is 40 per minute. The ventricular rhythm remains regular, while the relationship between atrial and ventricular complexes varies.

Figure 24-25: Atrial flutter and carotid sinus massage. At the beginning of the strip, AV conduction is occurring at the common 2:1 ratio, and flutter waves can be suspected but not proved. However, during carotid sinus massage, the conduction ratio increases to 4:1, and the flutter waves are easily recognized. Note the tendency of the atrial (flutter) rate to increase slightly during the parasympathetic stimulus.

Figure 24-26: Clinical expression of atrial fibrillation. Atrial fibrillation may occur in brief paroxysms, a more persistent form lasting from days to weeks, or chronically. Approaches to therapy are dictated by these patterns in conjunction with the hemodynamic considerations shown in Fig. 24-27. Methods of management include sedation while awaiting spontaneous conversion, DC cardioversion, bolus antiarrhythmic therapy (oral or intravenous), and standard oral antiarrhythmic therapy. There is a relationship between the efficacy of each therapy and the clinical expression of the arrhythmia. Short-lasting paroxysmal atrial fibrillation (less than 1 h) undergo spontaneous return to sinus rhythm by definition, but DC cardioversion may be necessary based on the hemodynamic response in patients with cardiac diseases such as aortic stenosis or mitral stenosis. Longer-lasting paroxysms of atrial fibrillation or persistent patterns of atrial fibrillation (see the text) may be treated with bolus therapy, standard therapy, or cardioversion, the latter having better efficacy in patients with more advanced disease if they are pretreated with antiarrhythmic agents. Chronic atrial fibrillation will not convert spontaneously but may respond to the various therapies listed. However, long-term maintenance of sinus rhythm is limited among patients in this category, particularly if the heart disease is advanced.

Figure 24-27: Hemodynamic factors in atrial fibrillation. Atrial fibrillation creates the potential for two hemodynamic defects: (1) loss of atrial contraction, which provides the presystolic atrial "kick"; and (2) rate-related reduction of the diastolic filling period. Atrial contraction is important to ventricles with reduced compliance and low-output states due to myocardial factors. Diastolic filling time is important in conditions in which a longer diastolic is beneficial to impaired flow states, such as mitral stenosis, coronary atherosclerosis, and some myopathic ventricles.

Figure 24-28: *A.* Fine atrial fibrillation, leaving virtually no imprint on the baseline ("straight-line" fibrillation). *B.* Coarse atrial fibrillation; the fibrillatory waves are the size of respectable flutter waves but are irregular.

Figure 24-29: Ashman's phenomenon. During atrial fibrillation, the impulse ending a short cycle preceded by a relatively long cycle manifests aberrant intraventricular conduction. In this example, the aberrant impulse shows typical right bundle-branch block type aberration in lead V_1, with an rSR pattern and the initial deflection identical to that of the preceding and following normally conducted impulses.

Figure 24-30: Atrial fibrillation with repetitive aberrant ventricular conduction. The impulses that end the shortest ventricular cycles (0.28 to 0.32 s) are anomalous, widened complexes. Note that the cycle preceding the onset of the salvos of anomalous beats is *relatively* long in comparison with the anomalous complexes (0.54 and 0.50 s), in accordance with Ashman's phenomenon. Thus, these almost certainly represent a right bundle-branch block type of ventricular aberration rather than ventrcular ectopy.

Figure 24-31: Irregular wide QRS tachycardia. A rapid irregular rhythm with wide QRS complexes having a left bundle-branch block pattern is recorded. The rhythm is atrial fibrillation with abnormal intraventricular conduction. Irregular, wide QRS tachycardias also occur in WPW syndrome, with atrial fibrillation and conduction down the accessory pathway or in rare cases of irregular ventricular tachycardia.

Figure 24-32: *A*. AV junctional extrasystole. The retrograde P wave follows the premature QRS complex, which shows some degree of ventricular aberration. *B*. The fourth complex is an AV premature impulse without retroconduction to the atria, leaving the sinus rhythm undisturbed.

Figure 24-33: Accelerated idiojunctional rhythm with isorhythmic AV dissociation. After four sinus beats, the sinus rate slows slightly, enabling an accelerated junctional pacemaker to escape at a rate of 94 per minute. After several seconds, the sinus pacemaker accelerates and recaptures the ventricles. The same sequence is then repeated (the strips are continuous). (From Marriott HJL. *Workshop in Electrocardiography*. Tampa, FL: Tampa Tracings; 1972. Reproduced with permission from the publisher and author.)

Figure 24-34: Classification of ventricular arrhythmias based on hierarchies of frequency and forms. Hierarchical schemes for estimating risk of ventricular arrhythmias have been developed based on frequency and forms of ventricular arrhythmias. In some clinical settings, frequencies in the range of 1 to 9 ectopic impulses per hour become significant, and in most settings of clinically significant heart disease, risk based on frequency plateaus in the range of 10 to 30 ectopic impulses per hour. Among forms of ventricular arrhythmias, the repetitive forms, particularly salvos or nonsustained ventricular tachycardia, indicate higher risk in most clinical settings. (Modified from Myerburg et al.[138] Reproduced with permission from the publisher and authors.)

Figure 24-35: Ventricular premature contractions. *A*. The third impulse is wide and bizarre, and since the sinus rhythm is undisturbed (next sinus P wave indicated by arrow), the postextrasystolic pause is compensatory. *B*. The fourth impulse is an interpolated ventricular premature contraction; it is sandwiched between two consecutive conducted sinus beats.

Figure 24-36: Exceptions to the rules for compensatory pauses. *Top*. Ventricular extrasystole with less than compensatory pause. Retrograde conduction to the atria (retrograde P wave deforms first part of ST segment) discharges the sinus pacemaker early and thus shortens the postextrasystolic cycle. *Middle*. Atrial premature contraction followed by fully compensatory pause. The third and eighth beats are atrial extrasystoles, but presumably because they suppress the sinus pacemaker, they are followed by compensatory pauses. *Bottom*. Ventricular extrasystoles with less than compensatory pauses. Each postextrasystolic cycle ends in an escape beat and so is slightly less than compensatory.

Figure 24-47: figuremeasure Therapeutic options for patients with ventricular tachyarrhythmias or cardiac arrest in association with coronary artery disease. Six categories of arrhythmias or clinical events are presented, and for each the associated observations during programmed electrical stimulation are provided. Four categories of therapeutic option are shown. Under "Drug Therapy," membrane-active antiarrhythmic drugs include amiodarone unless amiodarone is cited specifically, in which case the other membrane-active antiarrhythmic drugs are not considered therapeutic options. Also included in drug therapy are the beta-adrenergic-blocking agents. The second category is surgical and interventional approaches, which include antiarrhythmic surgery and catheterbased and surgical revascularization procedures. The third category is implantable devices, under which indications and preferred programming modes are presented. Catheter ablation is the final category. For each of the categories of therapy, indications shown on the bottom of the illustration discriminate patients with EFs greater than 35 percent (*blue*) and those with EFs of 35 percent or less (*red*). Therapeutic categories are not mutually exclusive and may be competing primary therapy options, primary versus secondary choices, or in some cases primary and adjunctive therapies. Specific details are provided in the text.

Figure 24-48: Catheter ablation for VT as an adjunct to an ICD. A 57-year-old male with recurrent life-threatening episodes of sustained VT who received an ICD had multiple shocks for arrhythmias that were resistant to all antiarrhythmic agents attempted. LV mapping and catheter ablation in a VT reentrant pathway in 1987 provided freedom from recurrent ICD discharges for approximately 19 months, after which the multiple ICD discharges recurred. Additional ablation procedures 18 or more months apart provided relief from the recurrent discharges despite the fact that VT remained inducible. While of limited value as primary therapy for life-threatening ventricular arrhythmias in patients with coronary heart disease or cardiomyopathy because of risk of recurrence (see the text), this procedure can provide benefit as an adjunct to other primary forms of therapy by avoiding frequent discharges and improving the quality of life.

Figure 24-49: ICD with antitachycardia pacing. The figure demonstrates the end of a run of induced sustained VT (*left*) followed by antitachycardia pacing that converts the rhythm back to normal sinus (*right*). The device will revert to a defibrillator mode if programmed pacing sequences fail to convert the rhythm.

Figure 24-50: Therapeutic options for patients with VTs or cardiac arrest due to nonischemic cardiomyopathies. See the legend for Fig. 24-47 for a description of the figure design. The surgical/angioplasty category is excluded for the nonischemic cardiomyopathies. The indications, based upon priorities of therapy, are the same as described for coronary heart disease-related arrhythmias. See the text for further details.

Figure 24-51: Catecholamine-mediated VT in an otherwise healthy female. Psychologic stress or isoproterenol infusion could initiate the arrhythmia in this patient. During this sequence, a 4-μg/min isoproterenol infusion initiated the VT (*A*), and the patient was treated with intravenous propranolol. After the first 3 mg of propranolol (*B*), occasional sinus beats interrupted the tachycardia. On a milligram-by-milligram basis up to a total dose of 8 mg of propranolol, there was further suppression of VT to the point of salvos (*C, D, E*), frequent PVCs (*F*), and complete suppression of ectopic activity (*G*).

Figure 24-52: Right ventricular dysplasia with VT. Episodic wide QRS tachycardia with near-syncope in a 33-year-old man. The left bundle-branch block pattern of the tachycardia suggests a right ventricular origin, and the inverted T waves in V_1 to V_3 are characteristic of right ventricular dysplasia.

Figure 24-53: Bidirectional tachycardia. The tachycardia is regular at a rate of 160, but the vector of the QRS-T complexes alternates.

Figure 24-54: Torsades de pointes. The patient, a 49-year-old female, has complete heart block and was receiving quinidine sulfate for a ventricular arrhythmia. The rhythm shown in the bottom two strips occurred shortly after institution of therapy. Note the prolonged QT(U) interval (0.67 s) and the onset of classical torsades de pointes.

Figure 24-55: Congenital long QT interval syndrome. A 12-lead ECG was recorded in a 25-year-old female with congenital deafness and a history of recurrent syncope throughout her life (Jervell and Lange-Nielsen syndrome). Many episodes of syncope occurred during or immediately after exercise and were commonly preceded by palpitations. She had never been treated. The tracing reveals a corrected QT interval of 610 ms with marked notching of the TU waves in the anterior precordial leads.

Figure 24-56: Congenital long QT interval syndrome. Treadmill stress testing was carried out in the patient shown in Fig. 24-55. *A*. At 4 min and 2 s into a Bruce protocol, ST-T alternans was observed, followed shortly by torsades de pointes (*B*).

Figure 24-57: Genetic basis for congenital long QT interval syndromes. Abnormalities have been linked to five chromosomes among families with the Romano-Ward form of congenital long QT interval syndromes. At present, specific genetic abnormalities and gene products are identified, in part, for four of the five. Multiple mutations or deletions are possible at each locus. The genetic basis for the Jervell and Lange-Nielsen syndrome (autosomal recessive inheritance and associated deafness) includes LQT-1 abnormalities in some families, but other loci are likely as well. The last two columns provide the gene products and defective currents for each of the known loci. See the text for further details.

Figure 24-58: Syndrome of right bundle-branch block and ST-segment elevation in the anterior precordial leads and risk of sudden cardiac death (Brugada). In this syndrome, the electrocardiographic hallmarks of right bundle-branch block and ST elevation in the anterior leads are not consistently present, but they may be evoked by drug provocation using procainamide or flecainide. The left panel shows strips from leads V_1, V_3, and I, recorded from a 17-yearold male with Brugada's syndrome and a strong Family history of sudden cardiac death in males. The baseline ECG was normal. After a 300-mg oral bolus of flecainide, an ECG recorded 2 h later revealed a ST-segment elevation and a right bundle-branch block pattern in leads V_1 and V_2. After 4 h, this had reverted to baseline. See the text for details.

Figure 24-59: Programmed electrical stimulation study in a survivor of out-of-hospital cardiac arrest. The patient had ischemic heart disease, and polymorphic VT degenerating to VF was reproducibly induced prior to bypass surgery. After surgery, the tachycardia was no longer inducible.

Figure 24-60: Wenckebach phenomenon. *A*. A 5:4 and 6:5 AV Wenckebach period. Note that the PR interval progressively lengthens, but by a decreasing increment; therefore, the ventricular cycle tends to shorten (at least for the first two cycles following the dropped beat). *B*. A 3:2 and 4:3 SA Wenckebach period with 2:1 SA block at beginning and end of strip. (From Hurst JW, Myerburg R. *Introduction to Electrocardiography*. New York: McGraw-Hill; 1973. Reproduced with permission from the publisher and authors).

Figure 24-61: SA block. In each pause the entire P-QRS-T sequence is missing, and the long cycle is approximately equal to two of the sinus cycles. The pattern is the equivalent of a Möbitz-type II block at the level of the AV junction.

Figure 24-62: A form of second-degree AV block. There are two P waves to each QRS 2:1 AV block (alternate sinus impulses are blocked). This pattern can be caused by block in the AV node (Wenckebach), intra-Hisian block, or distal block (see the text).

Figure 24-63: Complete (third-degree) AV block. There is a regular idioventricular rhythm at rate 36 impulses per minute, and the P waves indicate their independence by changing their relationship to the QRS complexes.

Figure 24-64: AV dissociation *A*. Sinus arrhythmia. The bradycardic phase enables the AV node to escape, with resulting dissociation. *B*. AV tachycardia. The tachycardia enables the AV pacemaker to usurp control of the ventricles, with resulting dissociation; the seventh and eighth beats are ventricular captures, the seventh, ending the shorter cycle, showing ventricular aberration. *C*. High-grade AV block permits the AV node to escape (second, fourth, and fifth beats), with resulting dissociation.

Figure 24-65: Pacemaker-mediated (endless-loop) tachycardia. The patient had a DDD pacemaker and presented with episodes of sustained rapid heart action. The tracing (lead II) demonstrates (*A*) atrial tracking with ventricular pacing at a cycle length of 740 ms and (*B*) ventricular pacing with retrograde atrial activation. The retrograde P waves (P) following each paced QRS are sensed by the atrial sensing lead and trigger a ventricular pacing spike (S), followed by the paced QRS with repeated retrograde atrial activation.

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Chapter 24: RECOGNITION, CLINICAL ASSESSMENT, AND MANAGEMENT OF ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 25:

LONG-TERM CONTINUOUS ELECTROCARDIOGRAPHIC RECORDING

Authors: R. Joe Noble, Eric N. Prystowsky

Long-term electrocardiographic recording is a method of recording the electrocardiogram (ECG) over extended time periods; the recording is subsequently analyzed for rhythm and ST-segment and T-wave alterations.[1-3] Technological advances in the past few years have provided a diversity of recording, transmitting, and analysis systems.

INDICATIONS

Ambulatory ECG (AECG) recording may be helpful in recognizing, characterizing, and less frequently, quantitating arrhythmias in patients with symptoms potentially related to an arrhythmia; the recording of a rhythm disturbance simultaneous with a patient's symptoms may be the only means of diagnosis, particularly when the symptoms and arrhythmia are relatively infrequent (Fig. 25-1). Importantly, the recording of a normal rhythm when the patient is symptomatic may prove equally valuable in excluding a rhythm disturbance as the cause for the patient's symptoms. Not only is it important to correlate an abnormal rate and rhythm with the symptom complex but, from the ambulatory record, also to determine the precise mechanism of arrhythmia. Some concept of the frequency of the arrhythmia, as demonstrated by the ambulatory record, is clinically helpful, but precise quantitation of the frequency of premature ventricular complexes, for instance, is rarely required.

AECG recordings may be indicated in certain patients to assess risk for future cardiac events-specifically in those patients with idiopathic hypertrophic cardiomyopathy, patients who have survived myocardial infarction with substantial left ventricular (LV) dysfunction, patients with long QT intervals, patients with dilated cardiomyopathy and symptoms consistent with arrhythmia, and in some patients with the Wolff-Parkinson-White syndrome.[4] The value of AECG in predicting risk is compromised by low sensitivity and specificity. Furthermore, since the effect of treatment of any arrhythmia recorded in these conditions is unclear, there is little support for routine AECG recording in risk stratification.[4]

Patients who undergo treatment for complex arrhythmias, such as sustained supraventricular tachyarrhythmias or ventricular tachycardia, may benefit from AECG recordings in order to assess the efficacy of therapy-both suppression of arrhythmia and rate control (Fig. 25-2). Similarly, patients in whom pacemakers have been implanted who have symptoms consistent with pacemaker malfunction or who require evaluation of their rate-responsive physiologic pacing function may require long-term AECG recording.

Heart rate variability and QT dispersion may be measured accurately by long-term AECG recording, which also may be helpful in patients with sleep apnea or those having suffered a previous myocardial infarction in whom further prognostic information is sought. However, the predictive value of the measurement limits it application.[4]

The recording of the pattern on AECG (as opposed to the rhythm) may be helpful in the detection

of myocardial ischemia. Long-term AECG recording is indicated for patients suspected of Prinzmetal's variant angina, in whom the simultaneous recording of ST-segment elevation with symptoms should confirm the diagnosis (Fig. 25-3). Long-term recording may be of diagnostic help in patients with symptomatic angina who are unable to undergo exercise testing; preoperative risk stratification would be one indication.

Another potential use of prolonged ECG pattern recording is to correlate symptoms that occur during normal daily activity with ECG evidence of ischemia. In this setting, the demonstration of significant ST segment-T-wave alterations that cannot be reproduced by hyperventilation or by change in position, particularly when reinforced by documentation in the patient's diary of simultaneous symptoms of angina, proves highly suggestive of ischemic heart disease. Particularly in patients in whom exercise testing produces negative results yet symptoms highly suggestive of myocardial ischemia continue with other specific activities, AECG recording provides useful information.

The reader is referred to *Guidelines for Ambulatory Electrocardiography*, published jointly by the American College of Cardiology and the American Heart Association, for a more complete consideration of clinical indications for ambulatory AECG recordings.[4]

NEXT

Chapter 25: LONG-TERM CONTINUOUS ELECTROCARDIOGRAPHIC RECORDING

RECORDING TECHNIQUES

Three general types of instruments for acquiring data are currently available: continuous recorders, intermittent or event recorders, and instruments for real-time recording and transmission of ECGs (Table 25-1).

Table 25-1: Types of Electrocardiographic Recording Instruments

Type	Recording	Scanning	Transmitting
HOLTER			
Analog	All ECG complexes 'Full Disclosure'	Technician with computer assistance, templating, area determination and superimposition	None
Digital-continuous recording	All ECG complexes 'Full Disclosure'	Technician with computer assistance, templating, area determination and superimposition	Transtelephonic
Digital-real-time analysis	Computer analysis of ECG and selected ECG printouts	Real time by microprocessor with retrospective technician editing	None
EVENT RECORDER			
'Postevent,' nonlooping, without memory			
Hand-held (including credit card size) wristwatch-type	ECG, selected by patient activation	Direct visualization	Transtelephonic
Automatic electronic sensor, in DDD pacemaker	ECG, when activated automatically by sensor	Direct visualization of analysis or ECG	Direct telemetry
'Preevent,' looping, with memory monitor worn with attached electrodes	ECG, selected by patient activation, with memory of pre-event	Direct visualization	Transtelephonic
Subcutaneous, implanted digital recorder	ECG, selected by patient activation with memory of pre-event	Direct visualization	Direct telemetry

Automatic electronic sensor, in ICD or pacemaker	ECG, when activated by firing of ICD or recognized by sensor in pacemaker, with memory	Direct visualization of analysis or ECG	Direct telemetry
REAL TIME			
Real-time transtelephonic monitoring	ECG at central monitoring station-no recording at device	Direct visualization	Transtelephonic

Continuous Recorders

The ECG can be recorded continuously on cassette tape or digitally in solid-state memory. The tape recorder is a battery-powered, miniature device with a very slow tape speed that is small enough to be suspended by a strap over the shoulder or around the waist.

All digital recording systems amplify, digitize, and store the ECG in solid-state memory. Two types of digital recorders are available. In the first, each QRS complex is recorded, similar in this sense to the continuous tape recording. "Full disclosure" of the ECG is provided by enhanced storage capacity on a memory card the size of a credit card. With the second, microcomputers and microelectronic circuits sample the cardiac rhythm in real time as it is being recorded, convert the analog signal into a digital signal, and analyze the data in terms of maximal and minimal rates, RR intervals, and changes in RR intervals. Within minutes of the instrument's disconnection from the patient, the information can be retrieved in the form of a histogram covering the entire recording period, and a printout of selected segments in real time can be obtained. This instrument is different from those used to make continuous tape or digital recordings in that the actual ECG has not been recorded on tape; only the histogram has been stored. Selected brief segments of the patient's ECG, e.g., 6- to 10-s intervals, also can be stored, however. Microcomputers that can analyze electronic data over prolonged periods, even several days, have been developed.

The lead systems on recorders vary from one manufacturer to another. Meticulous attention must be paid to placing the electrodes on the patient's chest, since poor electrode contact will produce technically inadequate recordings.

Event Recorders

An alternative method records not continuously but only when the patient senses symptoms or an event. Of the numerous event recorders available, there are two basic types, which are differentiated on the basis of memory.

In the *postevent recorder*, without memory, the unit may continuously monitor the ECG via attached leads. The patient wears the recorder continuously, activating it when symptoms appear; this device does not record the ECG until it is activated. Alternatively, the patient may carry a miniature solid-state recorder (sufficiently small to fit into a pocket or purse) with which the rhythm can be recorded whenever the symptoms appear simply by placing the unit on the precordium. Some newer devices are the size of a credit card, to be carried in a wallet or worn as a necklace or wristwatch. The recorded data are stored in memory until the patient submits the information either directly or transtelephonically to an ECG receiver, where it is recorded. When a tape is employed, the tape is then erased, and subsequent data can be recorded and transmitted to facilitate the recording of rhythm or pattern during several symptomatic episodes. When digital

acquisition devices are used, a prolonged, continuous event can be recorded and stored or the device can be programmed to acquire multiple events.

With a *preevent recorder*, employing a memory loop, the rhythm is monitored continuously via leads either at the extremities or over the precordium, connected to a recorder typically worn on a belt. Patients activate the unit when they experience symptoms so that an abnormal rhythm or an ECG synchronous with the symptoms can be recorded. The loop recorder is capable of recording information several seconds or minutes before or after a recognized event; the number of events that can be recorded and the allotment of recording time prior to and after activation of the unit are programmable.

A miniaturized *event recorder* has been developed that can be implanted subcutaneously to be mechanically activated by the patient to record an ECG when the patient suffers serious symptoms (such as syncope) at widely spaced intervals.[5,6] Incorporating a memory loop, the preevent ECG is recorded, and the resulting recording is transmitted by telemetry to a receiver for analysis.

Event recording is also provided by some newer-generation DDD pacemakers and implantable cardioverter defibrillators (Fig. 25-4). These instruments automatically recognize abnormal rhythms, such as tachycardia, and provide, via telemetric transmission, either actual ECG records or an analysis of the number, rate, and duration of recognized arrhythmias.

Real-Time Monitoring

As another variation, the device that acquires data can transmit the ECG information directly and transtelephonically, in real time, without recording the data in the unit. With such a device, for instance, the patient can transmit his or her ECG daily or even multiple times each day, with or without symptoms, at some distance from the medical institution to the recording station.

Recordings of ST Segments and T Waves

For several reasons, both technical and physiologic, long-term ECG recording devices do not provide the same degree of reliability in interpretation of the pattern of the ST segment and T wave as in the detection of rhythm disturbances.[7,8] Technical limitations include certain characteristics of the patient's ECG; normal sinus rhythm, an isoelectric ST segment, and absence of broad Q waves, intraventricular conduction delays, and LV hypertrophy are prerequisites. The patient cannot be treated with digitalis and some other drugs that alter ST-segment-T-wave morphology. Electrode preparation and placement must be meticulous. AECG recordings of ST-segment-T-wave morphology should be performed only by physicians and institutions trained and experienced in these techniques. With these considerations, however, newer-generation digital recording systems and those with improved low-frequency characteristics more accurately reproduce ST-T segments; some new systems either directly record or derive full 12-lead ECGs.

Even more important than these technical considerations, however, are certain physiologic limitations. For instance, standing, hyperventilation, eating, anxiety, use of drugs, and change in heart rate or autonomic tone are all daily events that may result in depression of the ST segment or inversion of the T wave to simulate ischemic changes. Striking ST-segment elevation has been recorded during prolonged recording in patients without organic heart disease.[9]

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SCANNING AND ANALYSIS TECHNIQUES

The recording can be analyzed by scanning the tape or digital record at high speed, by printing it out directly, or-as in the case of microcomputers-by processing during the recording and printing out the analysis at the end of sampling.

Scanning techniques include technician-dependent analysis, in which a technician interprets the cardiac rhythm as it is played back at high speed on an oscilloscope at 30 to 240 times the speed of the actual event. One commonly used method of scanning superimposes each QRS complex on the immediately preceding complex so that identical QRS contours present as a stationary image. Variations in QRS contour then become readily apparent. Simultaneously displayed on the oscilloscope for each cardiac cycle is a vertical bar graph, the height of which is directly proportional to each RR interval and QRS morphology. Thus the occurrence of a premature ventricular extrasystole would alter the stationary image by producing a variation in the QRS contour, alter the pitch and sound of the audio signal, and shorten the vertical bar reflecting cycle lengths. When such an abnormal event is noted, the tape can be played at a normal rate of speed for analysis on a standard ECG machine.

To minimize the human factor and provide accurate quantitative data, the tape can be analyzed by a semiautomated electronic analyzer, which quantitates the number of abnormalities it recognizes. The accuracy of the system depends on the system's ability to distinguish abnormal from normal.

A computer can be interfaced with the scanner to quantitate the data even more accurately. The playback analysis can occur at up to 240 times the normal rate. Electronic analyzers and computers, as well as the scanner, can be programmed to recognize the patient's own QRS complex template and then to recognize any deviation from normal. The computer program can provide summaries of heart rates, heart rate variability, frequency of premature atrial or ventricular extrasystoles, coupling intervals, runs of tachycardia or other arrhythmias, and variations in QRS, ST, QT, or T-wave pattern during any time period. Hard copies can be printed out for verification. When arrhythmias or pattern changes are detected, an automatic ECG printout can be triggered by the event marker or by the computer.

Scanning services are available and generally can provide reasonably accurate analysis at less cost than can small institutions or offices with smaller volumes of long-term ECG recordings. Recorders can be purchased, leased, or rented.

An alternative to scanning is the direct printout of the entire record. Prolonged ECG records are compressed to reduce the amount of paper that the physician must examine; when brief events are recorded, compression is not necessary. By writing out the entire ECG directly, the need for a trained technician and scanners may be obviated.

Since microcomputers assess the ECG in real time, as it is recorded, there is no need for a scanner or expert technician when the results are printed out. The physician evaluates the trend chart or any recorded rhythm strip.

As noted in Table 25-1, all the event recordings, the real-time recording, as well as some of the continuous recordings can be transmitted transtelephonically to receivers for analysis and

interpretation. These recordings of implanted pacemakers or defibrillators are available by telemetry.

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COMPARISON OF TECHNIQUES FOR PROLONGED ELECTROCARDIOGRAPHIC RECORDING

Operator-dependent high-speed audiovisual analysis of the tape, without direct printout or electronic analysis, recognizes serious rhythm disturbances. On the other hand, the operator can fail to recognize as many as one-third to two-thirds of ventricular and supraventricular arrhythmias. Operator-dependent systems are affected by the capabilities of the operator. If quantitation is unimportant, this system of analysis is quite adequate.

Electronic analysis systems improve on the sensitivity and specificity of interpretation of long-term ECG recordings. Computer analysis systems are said to be 90 to 95 percent accurate in quantitating ectopic complexes.[10-12] Current computer-based systems that permit operator editing are even more sensitive and accurate, but both electronic and computer analysis systems increase cost. One reason for the stated accuracy of computer interpretations is that ventricular ectopy is responsible for most broad, complex beats. Supraventricular ectopy with aberrancy or intermittent preexcitation is not accurately diagnosed by computer, but the relatively low frequency of these complexes does not statistically alter sensitivity calculations. In fact, the accuracy of arrhythmia diagnosis is also questionable when the data are not fully disclosed.

"Full disclosure"-i.e., hard-copy printout of the entire record-provides a visual analysis of the record to identify complex disturbances such as ventricular tachycardia or prolonged asystolic intervals. In addition, it is often useful to have hard-copy ECG data available (as opposed to those derived from analysis of the ECG data) with which to compare subsequent records. The direct printout does not quantitate the actual number of events. Assuming care in interpretation, the direct printout may be more sensitive than high-speed operator-dependent and semiautomated systems with operator editing in identifying pairs or triplets of consecutive ectopic complexes.

An event recorder does not require a scanner or an experienced technician; however, the continuously recording event recorder itself is more expensive than a continuously recording tape recorder. The postevent recorder, without memory, which the patient applies only when symptoms appear, is less expensive. Both types of event recorders provide an ECG record more quickly than a system that requires scanning,[13] but neither creates a long-term record of the ECG during asymptomatic intervals. The automatic event recorders incorporated in pacemakers and implantable defibrillators are limited by the accuracy and sensitivity of the algorithm used to detect abnormalities yet enhanced by analysis of intracardiac signals. Any event recorder clearly allows correlation between the patient's symptoms and the rhythm. The only technique currently available to record rhythm events leading up to and following infrequently occurring symptoms is the memory-loop event recorder.

When more rapid identification of a rhythm abnormality in an outpatient is essential, as in the patient with a potentially dangerous rhythm disturbance, real-time transmitters permit frequent and even automatic transtelephonic transmission of the ambulatory record to a hospital or clinic telemetry receiver. The monitor technician can then quickly identify a serious rhythm abnormality and arrange for the patient's proper management.

Those microcomputers which analyze the rhythm in real time, simultaneous with the recording, should prove at least as accurate as other high-speed playback analysis systems. More important,

longer periods can be monitored than are practical for other systems. The cost of the analysis is independent of the duration of recording, so patient cost should be less for prolonged periods of monitoring. Finally, the analysis of the entire recording and the actual printout of the specific ECG segment are available within minutes of the recording. On the other hand, only limited segments of actual ECG records are generally available, and the accuracy of abnormal rhythm or pattern recognition remains dependent on the computer algorithm; this recognition is far from perfect, since many problems in the computer analysis of complex rhythm disturbances remain unsolved.

When the ECG pattern is monitored for ischemia, newer-generation methodologies-either digital or with enhanced low-frequency recording-are required. Whichever system is employed, the ultimate accuracy of ECG interpretation depends on the technician and overreading physician; scanners and computers cannot differentiate complex patterns (supraventricular arrhythmias with aberrancy as opposed to ventricular arrhythmias or preexcitation) or even artifacts. The clinical application of the data is solely the function of the responsible physician. No data-acquisition system or scanner, no computer, and no technician can substitute for the well-trained physician in determining the significance of any recorded data and their clinical utility.

Selection of Device

The ultimate selection of a long-term ECG recording system depends on individual patient needs. If a precise count of ectopy is required, a continuous recorder with computer-based analysis is essential. These devices are also very useful to evaluate ventricular rate control in atrial fibrillation (see Fig. 25-2). On the other hand, if the purpose of the recording is to detect ventricular tachycardia or asystole, an event recorder, a microcomputer, or direct printout of the entire record would be an excellent choice. Either a microcomputer or an event recorder provides an opportunity to monitor over prolonged periods of time, and either is of benefit to the patient whose rhythm disturbance occurs infrequently. When the goal is to correlate the patient's rhythm or ECG pattern with symptoms that are very infrequent (at weekly intervals or less), the patient-applied and patient-activated event recorder is the optimal choice. However, if the patient's symptoms are of such brief duration (seconds) or severe (frank syncope) to preclude capture by such a unit, then a loop event recorder is required. This and the direct printout are less expensive for an individual physician's or small clinic's use, and both are more cost-effective than prolonged ambulatory (Holter) recordings, whether indicated for assessment of palpitations[14,15] or such serious symptoms as syncope[15] (see Fig. 25-1). The implantable event recorder with memory may prove optimal for those patients with syncopal events so widely spaced (months) as to render other devices impractical.[6]

Except with large scanning services, it is impractical for an individual physician to have available all the monitoring techniques for each individual patient's needs. Hence the physician's selection of a system is based on his or her own patient population, the frequency of using this test, the availability of dependable scanning services, and the associated cost analysis. The physician would do well to realize that any or all of the systems described herein are available alone or in combination. The more detailed and precisely quantitated the final report, generally the more expensive are the equipment and personnel required. All systems recognize marked tachycardia or bradycardia and, qualitatively at least, detect ectopy. For clinical purposes, this amount of information is usually sufficient. The practicing physician does not really require precise quantitation, since the therapeutic and prognostic significance of such quantitation is not yet known. In short, technology exceeds clinical assimilation of the results at the present time.

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DURATION OF RECORDING

Arrhythmias are often evanescent, occurring only rarely. In such patients, 24-h ECG recordings are unlikely to detect the abnormal rhythm. Even when arrhythmias are frequent, marked variation in the frequency and complexity of the rhythm disturbance is expected, with variations occurring during and between days. Spontaneous reduction in the frequency of ventricular ectopy of 50 to 90 percent is common.[16,17] For screening purposes, 24-h ECG tape recording seems an optimal compromise between the practical limits of recording and the point of diminishing return.[18-20]

If a reduction in total number of premature ventricular complexes is the goal of antiarrhythmic therapy, then more than one control 24-h ECG recording and several recordings while the patient is receiving therapy are required to prove efficacy.[18,19] The total number of premature ventricular complexes must be reduced by about 80 percent.[16,17,21,22] On the other hand, since it has not yet been demonstrated that reducing the total number of premature ventricular complexes necessarily implies the elimination of more dire ventricular rhythm disturbances or sudden death, this is often not the physician's goal. Instead, simply preventing sustained, symptomatic ventricular tachycardia may be the therapeutic goal,[23] in which case multiple 24-h recordings are less essential.

The frequency and degree of ST-segment depression also vary chronologically.[24-26] Forty-eight hours is probably the optimal duration for monitoring ST-segment changes.[27] When comparing a 48-h recording prior to and following therapy, the frequency of ST-segment deviation must be reduced by 75 percent to infer a therapeutic efficacy.[28]

The ideal duration of recording varies from patient to patient, depending on the physician's goals. If the objective is to correlate the cardiac rhythm or pattern with a symptom such as syncope, palpitations, or chest pain, then the monitoring period must be extended sufficiently to incorporate a symptomatic period, whether these intervals occur with a frequency of hours or months. The actual recording period, however, may be only seconds.

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ARTIFACTS AND ERRORS

Artifacts registered during prolonged ECG recording have mimicked virtually every variety of supraventricular and ventricular bradycardia and tachycardia and have led to misdiagnosis[29,30] and inappropriate and unnecessary treatment.[31]

Most of these artifacts are identical to those plaguing the standard 12-lead ECG but are simply detected more frequently due to the length of the recording; however, many are unique to extended recording by virtue of the magnetic tape recorder.

Probably the most common artifact is that resulting from a loose electrode (Fig. 25-5) or mechanical "stimulation" of the electrode. Failure of either the battery or the motor of the recorder generally results in a slowing of the tape speed as the ECG is recorded. When played back, the heart rate will appear fast; i.e., it will mimic a tachycardia (Fig. 25-6). The interpreter may be alerted to the artifact by the concomitant shortening of all ECG intervals (PR, QRS, QT, and RR) and decrease in QRS voltage. Conversely, transient slowing or sticking of the tape during playback will suggest bradycardia or atrioventricular (AV) or intraventricular conduction disturbances (Fig. 25-7). Recording an ECG on a previously used tape that is incompletely erased results in the simultaneous registration of two ECGs and potentially the misinterpretation of a "parasystolic" ectopic rhythm (Fig. 25-8). Digital recording in solid-state memory eliminates these various mechanical failures of tape recordings.

The technician and/or physician who interprets prolonged ECG recordings must have a working knowledge of these and other potential artifacts in order to interpret the records properly.

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 26:

TECHNIQUES OF ELECTROPHYSIOLOGIC EVALUATION

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The recording of intracavitary electrocardiographic signals and various forms of pacing programs have experienced enormous growth during the past 3 decades. Recordings of intracardiac signals from the region of the His bundle, initially made by Scherlag et al.,[1] were rapidly applied to clinical problems including atrioventricular (AV) blocks and supraventricular and ventricular tachyarrhythmias.[1-10] Such recordings were then complemented by pacing to unmask sinus node dysfunction and AV conduction abnormalities as well as to initiate supraventricular tachycardias (SVTs).[3-8] Intracardiac electrophysiologic studies (EPSs) have since found utility in a variety of cardiac arrhythmias, including sinus node dysfunction, intraventricular and AV conduction disturbances, SVTs, ventricular tachycardias (VTs), preexcitation syndromes, and ventricular fibrillation (VF). Such studies are now also employed as a prelude to correction of various arrhythmias and conduction defects. This chapter addresses recording and pacing techniques and their clinical utility.[9,10]

TECHNIQUES OF INTRACARDIAC ELECTROPHYSIOLOGIC STUDIES

The exact type of electric signal recordings, specific equipment used, and pacing protocol depend upon the nature of the clinical problem, the type of electrophysiologic assessment, and the anticipated course of action. Routine cardiac EPSs are performed while patients are in a nonsedated postabsorptive state.[11] Although some degree of sedation is advisable in apprehensive patients, the use of drugs that may alter the properties of the cardiac conduction system should be avoided. Antiarrhythmic drugs are usually stopped prior to these studies. In selected cases, antiarrhythmic drugs may be continued if a clinical event occurred while the patient was on a specific agent. Customarily, other cardioactive drugs that are necessary for nonarrhythmic cardiovascular problems such as hypertension, angina, and heart failure are continued.

The typical electrode catheters used for both recording and cardiac stimulation are multipolar (sizes varying from 4 to 8 F). Catheters can be inserted via peripheral veins such as the antecubital or femoral veins and, at times, the subclavian or internal jugular veins. When a catheter is intended to be left in place for several days, subclavian and internal jugular veins are preferable. After using local anesthesia, a guide wire is inserted percutaneously through a needle, and a sheath is advanced over the guide wire. A catheter is then guided fluoroscopically through the sheath to position in the appropriate cardiac chamber. For most electrophysiologic testing, the catheter is placed in the high right atrium, at the His bundle, or at the right bundle branch region across the tricuspid valve and right ventricular apex or outflow. For accessory pathways or AV junctional tachycardias, a catheter is placed in the region of the coronary sinus. Heparinization is recommended at approximately 1000 units per hour. For EPSs, good contact between the electrodes and the walls of the various chambers is critical. For His bundle and right bundle branch recording, the catheter is introduced via the femoral vein, advanced across the tricuspid valve, and gradually withdrawn until an appropriate recording from the right bundle and/or the His bundle is obtained (Fig. 26-1). A coronary sinus catheter can be placed via an arm, internal jugular, or subclavian vein. If necessary, coronary sinus catheterization can also be accomplished via a femoral approach. Right atrial catheter placement can be done via any of the

larger peripheral veins. For a routine study, left-sided heart catheterization is seldom necessary. In patients with VT and/or left-sided accessory pathways, however, this is performed for diagnostic or therapeutic purposes. Continuous heparinization is desirable for left heart catheterization to avoid thromboembolic complications.

Electrophysiologic Recordings

Once the electrode catheters are placed appropriately, the connections are made via a junction box and isolation units to prevent excess current in the event of random electrical surges. All of the electrograms are displayed simultaneously on a multichannel oscilloscopic recorder. In addition to the intracardiac signals, several unfiltered surface electrocardiographic leads (i.e., X, Y, and Z or leads I, II, or aV_F and V_1) are recorded. To reduce the noise generated with the low-frequency signals, the usual filtering frequency for intracardiac signals is between 30 and 40 Hz for the high-pass and 500 Hz for the low-pass filters. Although appropriately placed electrode catheters will record desired signals at any filtering frequency, filter settings between 30 to 40 and 500 Hz are best suited for sharp intracardiac signals such as those from the His bundle and accessory pathways (Fig. 26-2). Undesirable low-frequency signals can be reduced by a high-pass filter setting of more than 50 to 100 Hz. On the other hand, 60-cycle interference can be eliminated with a low-pass filter setting at 50 Hz. Alteration in the high-bandpass filter for surface electrocardiography can markedly alter the scalar electrocardiographic morphology. Amplification is frequently necessary to identify desirable signals from the specialized conduction system. This can lead to superimposition of the larger myocardial signals on various electrocardiographic tracings. In most recording equipment, however, limiting filters allow the adjustment of amplitude limits.

The main value of intracardiac/electrocardiographic tracings is timing of electric events and to determine the direction of impulse propagation. To acquire true local electrical activity, a bipolar electrogram with an interelectrode distance of less than 1 cm is desirable. When unipolar electrograms are obtained, a rapid intrinsic deflection will identify a point of local activation. For routine intracardiac electrocardiographic studies, unipolar electrograms provide relatively limited advantage over bipolar signals, and therefore the latter are more often utilized. The foregoing description relates to the routine diagnostic invasive EPSs. In other clinical situations, different types of diagnostic methods are employed. For example, during intraoperative mapping, direct placement of electrodes over the epicardium or endocardium is necessary to get appropriate signals for identifying the precise origin and route of impulse propagation.[12] These electrodes can be in the form of either hand-held probes or plaques that can be placed or sutured over the myocardium. Socks and balloons incorporating several electrodes can also be used for epicardial and endocardial mapping techniques, respectively.[13,14] All electrical signals can be recorded on either a disk or frequency-modulated tape for permanent storage.

More recently, several other types of mapping and recording equipment have emerged to locate the origin of cardiac arrhythmias more accurately. Two of the systems likely to find clinical utility in the mapping of arrhythmic origins are (1) nonfluoroscopic electromagnetic endocardial mapping ([CARTO, Biosense (Cordis Webster) Marlton, NJ] and (2) noncontact mapping (EnSite, Endocardial Solutions, Saint Paul, MN).

1. The CARTO system consists of a magnetic field generator locator pad placed under the patient table, a sensor-mounted catheter and a reference catheter placed intracardially, a mapping system and a graphic computer.[15] The catheter tip allows orientation in relation to the reference signal. The accuracy of catheter tip position is within a millimeter of arrhythmia location in this low magnetic field. By moving the sensor sequentially, one can generate a three-dimensional (3D) activation map. By color coding, both the earliest and the latest directions of electrical activation can be recorded. Once the initial fluoroscopy-guided placement of reference catheter and other catheters is satisfactory, several points are acquired. A 3D map is generated, and sensor-mounted

catheters are manipulated further without the help of fluoroscopy.

Aside from creation of an accurate map guiding the origin and activation sequence, the CARTO system is also helpful in separating micro from macro reentry circuits. For example, in atrial flutter, by virtue of its large circuit, the impulse propagation along the entire route can be outlined. The atrial tachycardia, on the other hand, can be distinguished by its radial spread from an atrial focus. A typical map generated during this technique is shown in Fig. 26-3, Plate 75.

2. Noncontact mapping using the Endocardial Solutions EnSite 3000 system.[16] The Endocardial Solutions EnSite 3000 is a new endocardial mapping system that takes a different approach to such mapping (Fig. 26-4, Plate 76). Like the CARTO system, the EnSite 3000 system also makes use of an amplifier and computer system with custom software. The EnSite catheter uses a balloon design with a 64-electrode array arranged over the outside of the balloon. This balloon is positioned in the center of the chamber and does not come in contact with the walls of the chamber being mapped. Using data from the 64-electrode array catheter, the computer uses sophisticated algorithms to compute an *inverse solution* to determine the activation sequence on the endocardial surface. Data from all points in the chamber are acquired simultaneously.

To create a map, the balloon catheter is positioned in the chamber and deployed. A conventional (roving) deflectable catheter is also positioned in the chamber and used to collect geometry information. A 5-kHz signal is emitted from the tip electrode of the conventional catheter, and the computer analyzes this signal to determine the position of the roving catheter relative to the position of the balloon. The roving catheter is moved throughout the chamber, and the location information is collected by the system. Using this information, the computer creates a model, called a *convex hull*, of the chamber during diastole. After the chamber geometry is determined, mapping can begin. The arrhythmia is induced, and data are acquired. The data acquisition process is performed automatically by the system, and all data for the entire chamber are acquired simultaneously. The inverse-solution computations are performed by the system in real time and projected on to the surface of the convex-hull model, creating a 3D model showing the activation sequence within the chamber. Following this, the segment must be analyzed by the operator to find the early activation or vulnerable region of the reentry circuit. The locator technology that was used to collect the geometry information for the convex hull can then be used to guide an ablation catheter to the proper location in the heart.

Because data from the entire chamber are collected simultaneously with the EnSite 3000 system, it can be used to map nonsustained rhythms such as premature atrial complexes, irregular rhythms such as atrial fibrillation or polymorphic VT, and rhythms that are not hemodynamically stable. The system is highly useful for identifying focal arrhythmias (Fig 26-4) and atrial flutter. Currently approved indications, however, are for the right atrium only. The other significant limitation of the system results from its reliance on the large-diameter balloon catheter with its current 9.5-F lumen.

These mapping systems, both of which are relatively new, provide electrophysiologists with new tools for diagnosing and treating what are often complex arrhythmias. They make use of state-of-the-art technology to accomplish their objectives and improve the state of the art in arrhythmia management. Because these technologies are so new, further enhancements can be expected that will further the usefulness of advanced mapping techniques in the practice of electrophysiology.

Programmed Electrical Stimulation

After satisfactory placement of the electrode catheters, patches, or other forms of recording equipment, baseline recordings are made and programmed stimulation is initiated. The usual site of pacing is the right atrium or left atrium via the coronary sinus. For ventricular stimulation, the pacing sites are the right ventricular apex, outflow tract, and rarely some other right ventricular

site. A variety of pacing programs can be utilized, depending upon the nature of the underlying arrhythmic problem under investigation. At least two formats of pacing protocol are common. The first is incremental pacing, which is pacing at a constant cycle length with gradual shortening until the occurrence of a desirable event, such as induction of a tachycardia or production of AV block. Otherwise the incremental atrial pacing is continued until the onset of AV nodal Wenckebach's phenomenon: a physiologic response at faster pacing rates. Fixed-cycle-length ventricular pacing is also used for the induction of supraventricular tachyarrhythmias and study of ventriculoatrial conduction. Bursts of pacing at a constant cycle length are occasionally used to induce SVT, VT, or VF or for study of sinus node function and integrity of subsidiary pacemakers.

The second pacing format is premature (or extra) stimulation from atrial or ventricular sites. For the study of a physiologic phenomenon, refractory periods, and conduction characteristics, a single extra stimulus is usually applied after a series of beats with a constant cycle length (Fig. 26-5). The scanning is initiated late during electrical diastole, and the coupling interval is progressively decreased until the atrial and/or ventricular muscle is refractory. For induction of SVTs, single, two, or more extra stimuli are delivered (Fig. 26-6). For the induction of VT, up to three ventricular extra stimuli are employed. The sensitivity of pacing protocols seems to be directly related to the number of extra stimuli utilized.[17] This occurs, however, at the expense of specificity when polymorphic VT/VF can be induced at very short coupling intervals by using multiple extra stimuli. Regardless of the pacing protocol, the induction of sustained monomorphic VT constitutes a specific response and is seldom induced in patients not prone to such arrhythmias clinically. In contrast, the induction of polymorphic VT/VF with three extra stimuli at short coupling intervals can be nonspecific and does not provide a reliable guide for serial testing. Both polymorphic VT and VF can be avoided to a great extent at short coupling intervals (<200 ms) and the induction of latency between the stimulus artifact and the local ventricular electrograms is avoided.[18]

During routine EPSs, a variety of electrophysiologic parameters are measured, including sinus node function and intraatrial, AV nodal, and His-Purkinje system conduction. Initiation of SVT and VT is attempted to determine the mechanisms, the site of origin (by pacing and mapping techniques), and the potential of overdrive termination as a therapy option. After baseline studies, intravenous drugs are frequently administered to facilitate either induction of tachycardias, aggravation of sinus node function, or production of AV block (Fig. 26-7), or to determine drug efficacy.[17] At the completion of testing, the catheters are withdrawn, and gentle pressure is applied at the area of catheter insertion. Unless arterial catheterization is performed, patients are usually allowed to ambulate after 4 to 6 h. The role of EPSs in patient management has evolved over the past decades from a purely diagnostic method to a frequently applied therapeutic tool. A brief outline of the value of clinical EPSs in various arrhythmia settings is outlined separately under diagnostic and therapeutic categories.

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INVASIVE ELECTROPHYSIOLOGIC STUDIES FOR DIAGNOSIS

Sinus Node Dysfunction

EPSs are generally performed to detect suspected sinus node dysfunction in patients with dizziness, presyncope, syncope, etc., in whom the diagnosis cannot be made noninvasively. The most frequently performed test is that of sinus node suppression by using overdrive atrial pacing. After pacing at several basic cycle lengths for a period of approximately 30 s or longer, the pacing is interrupted. The resultant escape interval, which is called *sinus node recovery time*, is measured. By deducting the predominant sinus cycle length from this interval, one can obtain the so-called corrected sinus node recovery time. In one study, sinus node recovery time in patients with sinus node disease averaged 3087 ms,[3] and averaged 1073 ms in normal individuals. In another series,[6] the value for corrected sinus node recovery time was less than 525 ms in normal individuals and exceeded those values in patients with overt sinus node dysfunction. Direct sinus node recordings have been obtained by amplification of recording from catheters placed in close proximity to the sinus node,[20,21] where both the sinus node automaticity and sinoatrial conduction can be determined more accurately.

In the vast majority of patients with true sinus node disease, sinoatrial conduction abnormalities are the predominant reason for sinus node dysfunction. The sinoatrial conduction time in the absence of obvious sinus node disease is less than 100 ms. The sensitivity of sinus node recovery time for the detection of sinus node dysfunction is 54 percent, whereas that of sinoatrial conduction time is 51 percent, with a combined sensitivity of the two tests of around 64 percent. Poor sensitivity of such testing relates in part to the fact that, in previous studies, documented episodes of sinus bradycardia or sinus arrest due to neurocardiogenic mechanisms may have been included as examples of sinus node dysfunction.[22] The specificity of the two tests combined is approximately 88 percent. It is important to test the AV conduction in patients with sinus node dysfunction, since the former is also frequently abnormal. In patients with bradycardia/tachycardia syndrome, tachycardias are frequent, particularly those arising in the atrium, and testing may also be necessary for the proper diagnosis and therapy of the concomitant tachyarrhythmia.

Atrioventricular Block

In asymptomatic patients with first-degree AV block (prolonged PR interval), electrophysiologic assessment is unnecessary, regardless of the QRS morphology of the conducted beats. In asymptomatic individuals with second-degree AV block, electrophysiologic assessment is used to find the site of the block (Fig. 26-8). Patients with intra-Hisian or infra-Hisian block tend to have a more unpredictable course, and permanent pacing is desirable.[23] On the other hand, asymptomatic patients with AV nodal block generally do not require permanent pacing. Even though the intranodal block usually presents as Wenckebach's phenomenon or Mobitz type I, it is not uncommon to see Wenckebach phenomena within the His-Purkinje system or within the His bundle. There is no difference in prognosis regardless of how the infra- or intra-Hisian second-degree block manifests itself, i.e., type I versus type II (Fig. 26-8). On occasion, intranodal blocks are preceded by no discernible change in PR interval and from a surface electrocardiogram may appear as forms of Mobitz type II. The absolute length of the PR interval is usually quite diagnostic in that it is markedly prolonged (i.e., >300 ms), and there is a PR shortening exceeding 100 ms following the block beat (Fig. 26-8). In symptomatic patients with second-degree

AV block, the role of EPS is limited because permanent pacing is the appropriate intervention. On the other hand, if the patient's symptoms cannot be explained on the basis of AV block and may be related to another arrhythmia, such as VT, EPSs should be considered. In patients with third-degree or complete AV block, EPSs are seldom required, and permanent pacing is the obvious option in symptomatic patients.

For EPSs to determine the site of AV block, it is critical to have the catheter across the AV junction that records the His bundle. A discernible His bundle recording enables one to determine the exact site of AV conduction abnormality, i.e., proximal to, within, or distal to the His bundle region. This, in combination with surface electrocardiographic morphology of conducted beats, enables one to identify precisely the location of conduction abnormality. The normal atrial to His bundle activation time (A-H) is approximately 50 to 140 ms, whereas the His to ventricular myocardial depolarization interval (H-V) measures 35 to 55 ms.

If 1:1 AV conduction is noted during EPSs in patients suspected of intermittent AV block, incremental atrial pacing should be done to see whether AV block can be reproduced. AV block in the His-Purkinje system is abnormal during incremental atrial pacing but is a physiologic response during atrial extrastimulation (see Fig. 26-5*A*) or with abrupt acceleration of atrial pacing rate. First- and second-degree blocks in the AV node are considered physiologic responses during incremental atrial pacing or atrial extrastimulation (see Fig. 26-5*B*).

Wide QRS Tachycardia

Wide QRS tachycardia occurs due to a variety of electrophysiologic mechanisms, both from supraventricular and ventricular mechanisms in the presence and absence of accessory pathways (Fig. 26-9).[24] The underlying nature of the wide QRS tachycardia is critical for both prognosis and therapy. EPSs have proven invaluable in distinguishing the various etiologies (Fig. 26-10). With few exceptions, when the nature of the arrhythmic problem is not known and the direction of therapy is not clear, patients with wide QRS tachycardia should undergo EPS. This is particularly true in situations where nonpharmacologic therapy is the desired goal.

Unexplained Syncope

Unexplained syncope is predominantly due to cardiovascular mechanisms. The two most common reasons for cardiovascular syncope are cardiac arrhythmias and neurocardiogenic dysfunction, often referred to as *vasodepressor syncope*.[23-28] Electrophysiologic evaluation constitutes an integral part of the evaluation of patients with unexplained syncope. During such studies, all arrhythmic possibilities such as sinus node dysfunction, AV conduction abnormalities, SVT, and VT should be excluded. Neurocardiogenic mechanisms constitute the most common causes of syncope in patients without structural heart disease, and incomplete assessment of these patients may lead to inappropriate therapy (Fig. 26-11).[22,25] The possibility of neurocardiogenic dysfunction should always be considered in younger patients (<50 years of age) with syncope and documented bradycardia (sinus arrest or AV block) and can be unmasked on a tilt table. The triage of patients toward one or the other, i.e., electrophysiologic testing versus head-up tilt, is fairly simple and predicted by clinical history and the presence or absence of structural heart disease.[25-30] Patients with underlying structural heart disease, such as old myocardial infarction, primary myocardial disease, or poor left ventricular function, generally have underlying VT to explain the symptoms of syncope (Fig. 26-12). When arrhythmias occur in patients without overt structural heart disease, sinus node dysfunction, AV block (particularly intra-Hisian block), or SVTs are likely. Less frequently, VT can occur in the absence of an overt structural heart disease.

Survivors of Sudden Cardiac Death

In most patients with documented episodes of cardiac arrest from the onset, VF can be documented. Patients dying suddenly generally have underlying structural heart disease (usually coronary artery disease or primary myocardial disease) and are prone to VT/VF due to electrical instability. It seems prudent to investigate both the nature and extent of organic heart disease and also to assess vulnerability to recurrent VT/VF. At present, EPS is considered a routine part of the overall patient assessment in this group of individuals.[31,32]

EPSs in survivors of VT/VF are desirable for a variety of reasons. Some are listed here:

1. Not infrequently, the underlying VT leading to cardiac arrest is bundle branch reentry or BBR (Fig. 26-13). Almost 40 percent of patients with monomorphic VT in association with idiopathic dilated cardiomyopathy and valvular heart disease have BBR as the underlying mechanism. This arrhythmia is preferably managed with bundle branch ablation, which is curative, rather than with an implantable cardioverter defibrillator (ICD) alone.

2. Several VT morphologies or other types of tachycardia may be induced in addition to VT. Lack of awareness of such arrhythmias may complicate patient management. For example, the presence of rapid SVT may require separate attention to prevent unnecessary ICD shocks.

3. In some cases, supraventricular arrhythmia may trigger VT/VF. This may happen in patients with severe coronary artery disease, congestive heart failure, Wolff-Parkinson-White syndrome, etc. Elimination of the underlying causes is a more rational therapeutic approach in such cases.

4. Patients with VT/VF often have underlying sick sinus syndrome or AV block, which can be further aggravated with antiarrhythmic drugs and may require permanent pacing. Assessment for this eventuality can be done during the conduct of an EPS and may help selection of a particular device. Because of the increasing flexibility of these devices this need for EPS may be less relevant in the future.

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INVASIVE CARDIAC ELECTROPHYSIOLOGIC STUDIES FOR THERAPEUTIC INTERVENTION

Because of the episodic nature of most cardiac arrhythmias, the efficacy of any therapeutic intervention is difficult to assess unless the arrhythmia in question can be replicated. Diagnostic EPS provides that opportunity, and it seems logical to use the same tool to assess therapeutic interventions.[34-36] This method to assess efficacy can be applied for both pharmacologic and nonpharmacologic therapy.

Pharmacologic Therapy

It is arguable whether the assessment of pharmacologic intervention is essential in patients with relatively benign cardiac arrhythmias. The clinical course can be observed to determine whether control has been achieved. With life-threatening tachycardias, such as VT/VF, or with severe manifestations of cardiac arrhythmias, such as syncope or presyncope, it is desirable to assess efficacy of pharmacologic intervention (Fig. 26-14).[35,36] The technique of drug testing has been developed whereby the elimination of inducibility of a given tachycardia is assessed following a drug administration. Both the drug efficacy or inefficacy can be evaluated by this method. When drug therapy does eliminate induction of a previously inducible tachycardia, the addition of isoproterenol will frequently demonstrate reversal of therapeutic drug effect.[37,38] This is helpful in considering additional beta-blocker therapy. The latter can be accomplished with ease in patients with good left ventricular function, whereas the addition of beta blockers may pose a problem in patients with VT and poor left ventricular function. Failure of serial drug testing is associated with a significant recurrence rate and a strong indication for nonpharmacologic intervention.

Some controversy has arisen regarding the value of EPS for prediction of drug efficacy in comparison to ambulatory monitoring.[39] However, because of the infrequency of spontaneous VT/VF in most patients with life-threatening ventricular arrhythmias, ambulatory monitoring is an impractical approach. At present, serial drug studies with multiple oral antiarrhythmic agents are seldom carried out for SVT or VT.

Nonpharmacologic Therapy

Nonpharmacologic intervention has become an integral part of patient management in cardiac arrhythmias. With documented cardiac arrest from VF, implantation of an automatic ICD is fairly common, and electrophysiologic assessment before such therapy is routine.[40] Both preoperative and postimplant electrophysiologic evaluation can be done through permanent leads of an ICD through a wand and programmer. Pacing, antitachycardia function, low-energy cardioversion, and cardiac defibrillation can all be programmed with newer devices. When problems are encountered following discharge of a patient with an ICD, electrophysiologic reassessment via ICD is frequently necessary, both for reprogramming and for the detection of any unexplained events. For assessment of certain other electrophysiologic parameters (e.g., AV conduction and mechanism of SVTs), however, transvenous catheterization may be necessary.

Patients with coronary artery disease and mappable VT are also candidates for VT surgery when it

cannot be managed with ICD, antiarrhythmic drugs and for catheter ablation.[41-43] Preoperative EPS assessment for this possibility is important. Surgery for VT in the form of endocardial resection or cryoablation can be performed very effectively and relatively safely in patients with a left ventricular ejection fraction greater than 20 percent. This curative procedure provides effective control in approximately 75 percent of the patients who have monomorphic VT that can be appropriately mapped, and it may be considered when other forms of therapies are ineffective.

Surgery for SVT has gone through a significant evolution. The introduction of catheter ablative techniques has made it rare for patients to undergo surgery for Wolff-Parkinson-White syndrome and/or AV nodal reentrant tachycardia. Some individuals with resistant atrial fibrillation and flutter and those who fail catheter ablative therapy may still be considered candidates for such a procedure, but this is now becoming exceedingly less frequent.

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Chapter 26: TECHNIQUES OF ELECTROPHYSIOLOGIC EVALUATION

CATHETER ABLATION TECHNIQUES

The realization that the origin of VT and SVT can be effectively mapped has made the catheter ablative technique a rational approach. The radiofrequency form of energy delivered through a catheter has permitted controlled trauma to cardiac tissue to abolish or modify reentrant circuits. This is true for both SVT and VT. Unifocal atrial tachycardia, AV nodal reentry of all varieties, and accessory pathways including atriofascicular fibers can be cured in over 90 percent of patients with radiofrequency catheter ablation. Among the VTs, BBR tachycardia seen in association with dilated cardiomyopathy (both ischemic and nonischemic) and valvular disease is an ideal substrate for catheter ablation. Patients with monomorphic VT associated with myocardial scarring or other substrates can also be considered candidates, particularly when they are not suitable for VT surgery and have failed drug therapy. Additionally, in patients with incessant VT or frequency VT with inadequate control despite ICD therapy, VT ablation should be considered. By using the electromagnetic mapping, the scarred area can be mapped during sinus rhythm and ablation of this substrate can effectively eliminate VT. Noncontact mapping techniques outlined earlier are likely to further help improve ablation success rate with unifocal or possibly multifocal tachycardias.

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IATROGENIC PROBLEMS ENCOUNTERED DURING ELECTROPHYSIOLOGIC STUDIES

Mechanical irritation from catheters during placement and even when not being manipulated can cause a variety of arrhythmias and conduction disturbances.[49] These include induction of atrial, junctional, and ventricular ectopic beats and right bundle branch block and thus AV block in the His-Purkinje system in patients with preexisting left bundle branch block during right ventricular catheterization.[47] Obviously, AV block in the His-Purkinje system can occur in patients with preexisting right bundle branch block during left ventricular catheterization. Ventricular stimulation can also occur from physical movement of the ventricular catheter coincident with atrial contraction, producing electrocardiographic patterns of ventricular preexcitation. Recognition of all these iatrogenic patterns is important for avoiding misinterpretation of electrophysiologic phenomena and the significance of findings in the laboratory.

Certain types of arrhythmias must be avoided at all costs, such as atrial and VF. Atrial fibrillation will obviously not permit study of any other form of SVT, and VF will require prompt cardioversion, making it difficult to continue the EPS. If atrial fibrillation must be initiated for diagnostic purposes (i.e., to assess ventricular response over the accessory pathway in Wolff-Parkinson-White syndrome), it should be done at the end of the study. Patients with a prior history of atrial fibrillation are more prone to the occurrence of sustained atrial fibrillation in the laboratory. Frequently, this will occur during initial placement of catheters, and excessive manipulation of catheters in the atria should therefore be avoided. Catheter trauma resulting in abolition of accessory pathway conduction or reentrant pathway may make the curative ablation difficult or impossible.

Risks and Complications

The complication rate is relatively low when only right heart catheterization is done, with almost negligible mortality.[50,51] Other complications include deep venous thrombosis, pulmonary embolism, infection at catheter sites, systemic infection, pneumothorax, and perforation of a cardiac chamber or coronary sinus. Potentially lethal arrhythmias such as rapid VT or VF are common in the laboratory. These are not necessarily counted as complications, however, but are often expected and anticipated. Nonetheless, their common occurrence makes the electrophysiology laboratory a place for only highly trained personnel equipped to handle such problems.

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List of Figures

Figure 26-6: Induction of supraventricular tachycardia (SVT) in Wolff-Parkinson-White syndrome. The tracings are labeled. Atrial pacing from coronary sinus (CS) is done at a 700-ms basic cycle. During the basic drive pacing, left free wall accessory pathway conduction to the ventricle produces ventricular preexcitation. A single premature beat (S_2) blocks in the accessory pathway (AP) and conducts over the normal pathway with a left bundle branch block morphology, and the SVT is initiated. Note the intermittent normalization of the QRS complex during this SVT. (From Jazayeri et al.[53] Reproduced with permission from the publisher and authors.)

Figure 26-7: Atrioventricular (AV) block in the His-Purkinje system (HPS). *A*. Control. A 1:1 AV conduction is depicted in a patient with unexplained syncope. Following 150 mg of intravenous procainamide (*B*), a second-degree AV block in the HPS is noted (i.e., His bundle potential is not followed by a QRS complex), an abnormal response to a small dose of procainamide suggesting AV block in the HPS as a potential cause of syncope.

Figure 26-8: His bundle (HB) electrograms in atrioventricular (AV) block. The tracings are from three different patients with second-degree AV block. In *A* and *B*, the conducted QRS complexes are wide and associated with bundle branch block. In *A*, the block is within the AV node (i.e., the A wave on the HB is not followed by an HB deflection). In *B*, it can be appreciated that the block is distal to the HB even though the surface electrocardiogram (ECG) demonstrates a Wenckebach phenomenon. The latter can obviously occur in the His-Purkinje system as well, as depicted in this figure. *C*. The site of the block is within the HB. This is suggested by split HB potentials (labeled H and H′), and the block is distal to the H but proximal to the H′. Intra-His block is difficult to diagnose from the surface ECG but can be suspected when a Mobitz type II occurs in association with a normal PR interval and a narrow QRS complex. (From Akhtar.[11] Reproduced with permission from the publisher and author.)

Figure 26-9: Wide QRS tachycardia. Routes of impulse propagation during a wide QRS tachycardia in various settings are depicted. It should be noted that only in *A* and *B* is His bundle activation expected to precede ventricular activation. This helps the delineation from other causes of wide QRS tachycardia shown in *C* and *D*.

Figure 26-10: Wide QRS tachycardia. *A*. Wide QRS complexes of at least two varieties are seen. Those showing a left bundle branch block pattern are due to conduction over an accessory pathway, while those with a right bundle branch pattern are aberrant in nature. Note the His bundle activation prior to both narrow and aberrant complexes but not before preexcited complexes. A right posteroseptal preexcitation can be appreciated in *B*, with a short PR, a delta wave (*d*), an His to ventricle (HV) of zero, and negative delta wave in lead V_1.

Figure 26-11: Asystole in neurocardiogenic syncope. Note the normal heart rate (HR) and blood pressure (BP) in supine position. At the beginning of head-up tilt at 70° (*B*), some degree of tachycardia is noted. Seven minutes after the onset of tilt (*C*), an episode of atrioventricular block occurs and is followed by sinus arrest and a total asystole of 20 s. Syncopal episodes follow. Presyncope is still present when asystole is prevented by atropine (*F*). Findings in *C* might tempt one to prescribe permanent pacing, an inappropriate choice of therapy. In this patient with neurocardiogenic syncope, disopyramide (*G*) prevented hypotension and syncope without the need for a permanent pacemaker. This patient has remained asymptomatic on this therapy for more than 6 years now. (From Sra et al.[22] Reproduced with permission from the publisher and authors.)

Figure 26-12: Arrhythmic causes of syncope. *A*. Sinus rhythm in a patient with unexplained syncope. Sinus bradycardia, bifascicular block, and a long PR interval from surface electrocardiogram suggest possible bradycardia etiology. In this patient, however, ventricular tachycardia (*B*) was inducible with ventricular extrastimulation and was the actual cause of syncope. Control of ventricular tachycardia (VT) without a pacemaker was sufficient to prevent syncope in this patient. Termination of tachycardia and restoration of sinus rhythm are shown in *B*.

Figure 26-13: Induction of sustained ventricular tachycardia due to bundle branch reentry (BBR). The surface electrocardiogram and intracardiac tracings are labeled. Basic cycle length (S_1S_1) is 400 ms during ventricular pacing. Sustained BBR is induced with two extra stimuli (S_2S_3). Note that the His bundle and right bundle (RB) deflections precede the QRS, suggesting supraventricular tachycardia with aberrant conduction. However, there is 2:1 ventricular atrial (VA) block, indicating the ventricular nature of this tachycardia. Without His bundle/right bundle (HB/RB) recordings, the diagnosis can be difficult and, consequently, the likelihood of inappropriate therapy will be high. RB-RB and V-V (ventricular) intervals are labeled. (From Jazayeri et al.[54] Reproduced with permission from the publisher and authors.)

Figure 26-14: *A.* Control. *B.* Post procainamide (PA) + mexiletine. Initiation of sustained monomorphic ventricular tachycardia (VT) of myocardial origin is shown in *A.* After oral procainamide and mexiletine, the sustained VT could not be induced despite using a more aggressive pacing protocol.

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Chapter 26: TECHNIQUES OF ELECTROPHYSIOLOGIC EVALUATION

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 27:

ANTIARRHYTHMIC DRUGS

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Antiarrhythmic drugs have been developed with the expectation that they would extend and improve life for many patients with cardiovascular disease and those with a history of life-threatening arrhythmias. Their usefulness, however, has been, limited by ineffectiveness and/or toxicity. In mortality trials, benefit has not been clearly demonstrated, and worsened mortality rates have been observed with several drugs. Care must be taken, therefore, in deciding on the mode of treatment or in fact whether to treat at all. Many antiarrhythmic agents are available today, and more are under development. So many are needed because no agent is completely effective for all patients, and every agent has the potential for inducing serious adverse effects. Drug selection is often empiric. In fact, the side-effect profiles of the available drugs are very different and are often the determining factor in drug selection. Known side effects may completely eliminate the use of certain classes of drugs for a specific patient. Because of the narrow margin between effective and potentially toxic dosages, it is essential that physicians be thoroughly familiar with the clinical pharmacology, dosage, and adverse effects of any of these agents.

The use of antiarrhythmic drugs has been dramatically altered by the findings of the Cardiac Arrhythmia Suppression Trial (CAST).[1] This landmark study was designed to test the hypothesis that suppression of asymptomatic ventricular arrhythmias in patients with recent myocardial infarction would reduce mortality rates due to cardiac arrest and/or arrhythmic sudden death. Prior to the CAST, antiarrhythmic drugs were prescribed for these patients to suppress asymptomatic arrhythmias and thus improve mortality rates. Based on the results of a feasibility and planning trial, the Cardiac Arrhythmia Pilot Study (CAPS), the CAST evaluated encainide, flecainide, and moricizine. These drugs were chosen because they were all tolerated and had reasonable ability to suppress symptomatic ventricular arrhythmias. In April 1989, the CAST was interrupted by the Data Safety and Monitoring Committee, and encainide and flecainide were removed because they had been found to increase mortality rates two- to threefold. The CAST II continued to evaluate the remaining drug, moricizine. However, the CAST II was also terminated prematurely in August 1991 when it became apparent that moricizine was producing a similar trend toward harm, and there was no reasonable chance that a beneficial effect on the mortality rate could be detected.[2] These results shocked the medical community but have influenced thinking in this and many other areas of medicine. Hine et al.[3] reported a meta-analysis of the CAST and similar studies with sodium channel-blocking antiarrhythmic drugs and found overall support for the conclusion of the CAST. The CAST has also led to recommendations by the U.S. Food and Drug Administration (FDA) for more restrictive labeling for all sodium channel-blocking antiarrhythmic drugs. In 1991, these drugs were given class labeling with indications for the treatment of documented ventricular arrhythmias that, in the judgment of the physician, are life threatening. Exceptions among the sodium channel-blocking drugs are quinidine, propafenone, and flecainide, which have an additional indication for supraventricular arrhythmias.

Because of discouraging results with sodium channel-blocking drugs, drugs that prolong the action potential (often termed class III) have been studied. Developers had been encouraged, since one drug with this action, amiodarone, may improve, or at least not worsen, mortality rates in

patients with cardiac disease.[4,5] Dofetilide, ibutilide, and the *d*-isomer of sotalol all prolong the action potential duration and were developed in the hope that they would have the efficacy of amiodarone but lack its propensity to cause serious side effects. However, the first of these drugs to be evaluated in a mortality trial, *d*-sotalol, was found to increase mortality rates after myocardial infarction.[6] Development of *d*-sotalol was halted, but the other two have been marketed with restrictions placed on their indications and/or clinical use. Clearly, antiarrhythmic drugs are the most complex drugs in clinical use today and require care in their use.

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs are often classified according to their electrophysiologic effects.[7] The scheme most often employed was originally proposed by Vaughan Williams as a classification of drug actions that should be antiarrhythmic, not a classification of drugs.[7] This is a subtle but important distinction that is made for the following reasons:

- Most antiarrhythmic drugs have multiple actions; hence, their pharmacology is more complex than indicated by a simple drug classification scheme.
- The actions of a given drug differ in different cardiac tissues.
- Many antiarrhythmic agents have pharmacologically active metabolites whose activity may be quite different from and in a class other than that of the parent compound.
- The relative amounts of these metabolites produced are genetically determined for several of these drugs and often vary extensively within the population.

Drugs having class I action possess "local anesthetic," or "membrane-stabilizing," activity. Their predominant action is to block the fast inward sodium channel. This produces a decrease in the maximum depolarization rate, $_{max}$, of the action potential (phase 0) and slows intracardiac conduction. These agents have been further subclassified as belonging to class IA, IB, or IC on the basis of their effects on specific aspects of intracardiac conduction and refractoriness.[8] Drugs having class IA action include quinidine, procainamide, and disopyramide. These agents also produce measurable increases in ventricular refractoriness and prolongation of the QT interval. Lidocaine, mexiletine, and tocainide have actions belonging to class IB. Their potency for blocking sodium channels is only moderate, and in isolated tissues they shorten the action potential duration (APD) and refractoriness. They generally exert little effect on PR, QRS, or QT intervals. Drugs with class IC actions are the more potent agents: flecainide and propafenone. Because these are potent sodium channel inhibitors, slowing conduction velocity while having little effect on repolarization, they increase the PR and QRS intervals but cause little change in QT.

Class II action refers to beta-adrenergic antagonism, possessed by agents such as propranolol, timolol, and metoprolol. While these drugs are effective for treatment of supraventricular arrhythmias and tachyarrhythmias secondary to excessive sympathetic activity, they are not very effective in the treatment of severe arrhythmias, such as recurrent ventricular tachycardia. Although the mechanism is unknown, they are the only antiarrhythmic drugs found clearly effective in preventing sudden cardiac death in patients with prior myocardial infarction.

Drugs whose predominant effect is to prolong the duration of the cardiac action potential and refractoriness have class III action. These drugs include amiodarone, sotalol, bretylium, ibutilide, dofetilide, and *N*-acetylprocainamide (NAPA), the major metabolite of procainamide.

Class IV action is calcium channel antagonism. Antiarrhythmic drugs with this action include verapamil, bepridil, diltiazem, and nifedipine.

Because of the many limitations of the Vaughan Williams classification of antiarrhythmic drugs, a new approach has been proposed,[9] termed the Sicilian gambit. This classification system is based

on the differential effects of antiarrhythmic drugs on (1) channels, (2) receptors, and (3) transmembrane pumps. The grouping is based primarily on the predominant action of drugs but also considers the other ancillary actions that may be clinically relevant. As shown in Fig. 27-1, because of the sequence of drugs listed, the symbols for these primary actions are generally aligned diagonally. For example, in this system quinidine is a sodium channel antagonist with potassium channel- and alpha-blocking activity. This provides a more complete and accurate description of the pharmacologic actions of the drugs than simply designating it class IA. When combined with an understanding of the electrophysiologic role of these actions, one can predict the effects likely to occur in vivo. In this case one would expect conduction slowing, increased APD (and refractoriness), and vasodilation to result from these three actions of quinidine.

The Sicilian gambit also creates a framework in which newly discovered actions of drugs can be readily added. It emphasizes the multiple actions of drugs and the subtle differences and similarities that exist, and is more complete. At present, our understanding of the pharmacology of these drugs has progressed to the point that oversimplification can be misleading. The increased detail of the new system reflects the current state of our knowledge at a level necessary for optimal use of these drugs.

Due to the low efficacy of any one agent, the treatment of acute or chronic ventricular arrhythmias frequently necessitates the use of multiple drugs, sequentially or in combination. One may produce increased sodium channel blockade and, it is hoped, increase drug efficacy by using combinations of drugs with different kinetics of interaction with the sodium channel. Basic to these considerations is an understanding of the regulation of sodium channel function. Hodgkin and Huxley[10] proposed that sodium channels exist in three distinct states: open, closed, and inactivated. According to the modulated receptor theory of cardiac sodium channel regulation proposed by Hille and by Hondeghem and Katzung,[11] sodium channels in each of these states have differing affinities for a given local anesthetic drug (Fig. 27-2).

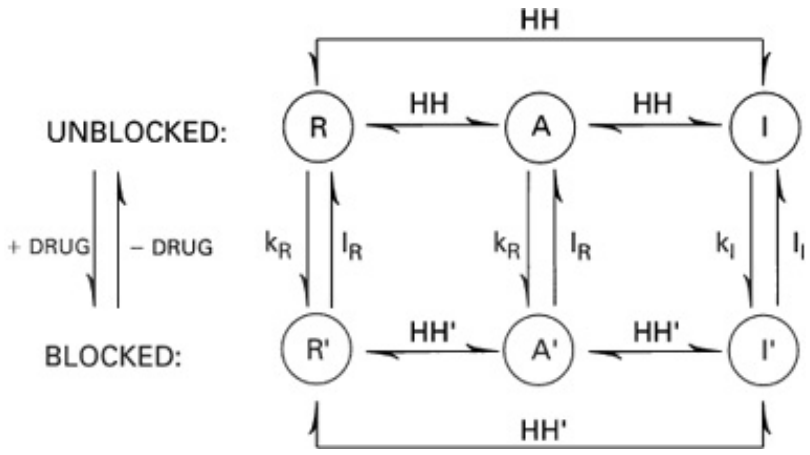

Figure 27-2: Diagram of the modulated receptor mechanism for antiarrhythmic drug action. The three fractions of the sodium channel population proposed by Hodgkin and Huxley are represented in the upper part of the figure in the drug-free condition and in the lower part of the figure blocked by an antiarrhythmic agent (R′, A′, and I′, respectively). HH, standard Hodgkin-Huxley rate constants; HH′, HH with voltage dependence altered by drug binding; k_R, k_A, and k_I, association rate constants; I_R, I_A, and I_I, dissociation rate constants for the respective channel fractions. (From Hondeghem and Katzung,[11] reproduced with permission from the authors and the American Heart Association.)

The theory also provides a potential explanation for the phenomenon of "frequency," or "use,"

dependence. Use dependence is the increase in conduction block observed at an increasing rate of stimulation in response to sodium channel-blocking antiarrhythmic agents. Since an increase in the rate of stimulation increases the number of sodium channels in the open and inactivated states, antiarrhythmic agents having greater affinity for activated (open) or inactivated channels (as opposed to rested channels) would have a greater opportunity to bind to the receptor and slow conduction. Therefore, greater block will occur during tachycardia, leaving less drug action at normal heart rates. Also, antiarrhythmic drugs have different affinities for the different states of the sodium channel, and this is manifested as different rates for onset or recovery from block. Drugs that slowly associate with the receptor will cause block to accumulate over the first few cardiac cycles, such as shown for procainamide in Fig. 27-3. Drugs that associate more rapidly, such as lidocaine, produce little additional block after the first beat in a train of stimuli. This effect is compared to that of procainamide in Fig. 27-3. Likewise, drugs dissociate from the sodium channel at different rates, leading to differences in rates of recovery from block. The rate of onset of block of sodium channels has been proposed as a means of subclassifying antiarrhythmic drugs.[12] This is the electrophysiologic correlate of the subclassification of sodium channel blockers proposed by Harrison that was based on differences in clinical effects of the drugs.[8]

This chapter reviews the clinical pharmacology and applications of the currently available antiarrhythmic drugs, excluding digoxin, beta-receptor antagonists, and calcium channel blockers, which are addressed in other chapters. The drugs reappear in the same order as listed in Fig. 27-1, an updated revision of the Sicilian gambit classification. The pharmacokinetics, usual dosages, and ranges of plasma concentration for the major drugs are listed in Tables 27-1 and 27-2.

NEXT

Chapter 27: ANTIARRHYTHMIC DRUGS

DRUGS

Lidocaine (Xylocaine)

CLINICAL APPLICATIONS

Lidocaine, introduced as a local anesthetic, was first used as an antiarrhythmic agent in the 1950s for the treatment of arrhythmias arising during cardiac catheterization.[13] It is still the most widely used intravenous antiarrhythmic drug. Since extensive first-pass metabolism makes it unsatisfactory for oral use, congeners such as mexiletine were developed that would possess similar sodium channel-blocking actions and be active when taken orally.

Lidocaine is very often the drug of first choice for the acute suppression of ventricular arrhythmias. Although such therapy does not reduce total mortality rates, it is effective in decreasing the incidence of primary ventricular fibrillation in patients with documented acute myocardial infarction.[14,15] Because of the complex pharmacokinetics of lidocaine, a monitored environment is desirable to permit evaluation of the patient's response and detection of toxicity.

Lidocaine has little effect on atrial tissue in vitro,[16] consistent with the clinical observation that it has no value in treating supraventricular tachyarrhythmias. Although lidocaine has been used to decrease the ventricular response during atrial fibrillation in patients whose atrioventricular (AV) conduction follows an accessory pathway,[17] some workers have reported accelerated conduction,[18] and other drugs, such as procainamide, are preferred in this situation.

MECHANISM OF ACTION

In concentrations similar to those attained during clinical use, lidocaine reduces $_{max}$ and produces shortening or no change in APD and the effective refractory period of normal Purkinje fibers. This contrasts with quinidine and procainamide, which additionally block potassium channels and produce lengthening of APD.[19,20] Lidocaine has little effect on the electrophysiology of the normal conduction system, but in patients with conduction system abnormalities, it has produced variable effects. Some studies have failed to detect significant changes in conduction,[21,22] while others have found slowing of ventricular rate or potentiation of infranodal block in patients with conduction system defects.[23,24] Variability in dosage and pharmacokinetics may explain some of these discrepancies.

CLINICAL PHARMACOLOGY

Orally administered lidocaine is well absorbed, but it has poor oral bioavailability because it undergoes extensive first-pass hepatic metabolism. Lidocaine clearance is well approximated by measurement of liver blood flow.[25,26] The two desethyl metabolites, which are excreted by the kidneys, have less antiarrhythmic potency than the parent drug and may contribute to the production of central nervous system side effects occurring with lidocaine.[27,28] Following intravenous administration, lidocaine's biphasic disposition is well represented by a two-compartment pharmacokinetic model.[29] Since antiarrhythmic activity is correlated with lidocaine's concentration in the central compartment and the half-life of distribution out of this

compartment is rapid (8 min), regimens employing a series of multiple loading doses and a maintenance infusion should be used to achieve and then maintain a therapeutic concentration in plasma and myocardial tissue.

Regardless of the initial regimen employed, during prolonged constant infusion the lidocaine concentration eventually reaches steady state, dependent only on the drug infusion rate and clearance of lidocaine. The time required to reach steady-state conditions is approximately 8 to 10 h in normal individuals and up to 20 to 24 h in some patients with heart failure and/or liver disease. This is longer than often anticipated because of the failure to recognize the relatively long elimination half-life (1.5 to 2 h in normal subjects and longer in patients with heart failure or hepatic disease).

DOSAGE AND ADMINISTRATION

The primary use of lidocaine is for acute rapid suppression of highly symptomatic ventricular arrhythmias. Single intravenous boluses will achieve only transient therapeutic effects because the drug is rapidly distributed out of the plasma and myocardium; therefore, multiple loading doses should be used in order to achieve more sustained therapeutic plasma levels of lidocaine rapidly. Based on pharmacokinetic models validated in clinical studies, several regimens have been designed to maintain a relatively constant therapeutic level. For a stable patient, a total loading dose of lidocaine should be approximately 3 to 4 mg/kg body weight administered over 20 to 30 min. After injection of an initial dose of 1 mg/kg over 2 min, a series of three loading boluses can be administered slowly (approximately 50 mg each over 2 min) 8 to 10 min apart, while the patient is continuously observed for the development of side effects. Loading should be stopped should the transient, usually mild, central nervous system side effects persist or serious unwanted effects occur.

Another effective and well-tolerated loading regimen was suggested by Wyman et al.[30] For a 75-kg person, an initial bolus of 75 mg is recommended, followed by 50 mg every 5 min repeated three times to a total dose of 225 mg. This regimen usually achieves and maintains plasma concentrations within usual therapeutic guidelines (1.5 to 5 μg/mL). A priming dose of 75 mg followed by a loading infusion of 150 mg over 18 min has also been used successfully.[31] At the time of initiation of the loading regimen, a maintenance infusion, designed to replace ongoing losses due to drug elimination, should be started. This may be calculated as the product of the desired plasma concentration (about 3 μg/mL) and the expected clearance. This calculation usually yields a dosage in the range of 20 to 60 μg/kg of body weight per minute.

Even in normal individuals, there is great variability in the peak plasma concentration and, consequently, in the calculated size of the central compartment for lidocaine. Therefore, during loading, the patient's electrocardiogram (ECG), blood pressure, and mental status should be monitored; the process should be stopped at the first sign of lidocaine excess. When symptomatic arrhythmias persist in the presence of documented adequate dosage, defined by side effects or plasma concentration in excess of 5 to 7 μg/mL, another agent should be used.

If the maintenance infusion has reached steady state but the concentration is below the level needed to prevent recurrence and the arrhythmia reappears while side effects are absent, the appropriate actions are as follows: (1) obtain a plasma sample for measurement of lidocaine concentration for future reference, (2) administer a small bolus of lidocaine (25 to 50 mg over 2 min), and (3) increase the maintenance infusion rate proportionally. The plasma concentration can be used to estimate clearance for calculation of the final maintenance infusion (i.e., maintenance dosage = clearance × desired plasma concentration, and clearance = infusion rate ÷ plasma concentration measured at steady state). Little therapeutic effect is evident at lidocaine plasma concentrations below 1.5 μg/mL, while the risk of toxicity increases above 5 μg/mL. In some patients, however, concentrations in the range of 5 to 9 μg/mL may be required for arrhythmia

suppression and can safely be achieved with cautious drug administration.[32]

Once steady-state conditions have been achieved, simply terminating a lidocaine infusion will result in a gradual decline in plasma levels over the next 8 to 10 h as elimination occurs. Not only is there no reason to taper lidocaine infusions, but it may be dangerous if oral antiarrhythmic therapy is initiated too early, since unpredictable additive effects may occur between lidocaine and newly started oral therapy. If a patient has reached steady-state equilibrium, it is possible to estimate when the plasma lidocaine concentration will fall below usually therapeutic levels. The plasma lidocaine concentration should be determined at the time the infusion is terminated, and the number of half-lives needed for that level to reach approximately 1.5 μg/mL can be estimated. The half-life of lidocaine for an individual patient can be estimated from the following equation: $t_{1/2}$ = plasma concentration × V_D × 0.693/infusion rate, where V_D is the final volume of distribution.

The measured plasma concentration and the infusion rate are known components of the equation. V_D is usually 1.1 L/kg but may be reduced by 50 percent or more in patients with heart failure.

MODIFICATION OF DOSAGE IN DISEASE STATES

Initial loading regimens require no adjustment in patients with renal or liver disease[29]; however, maintenance infusions must be decreased in liver disease and heart failure to compensate for decreased clearance. Since clearance alone is altered in liver disease, with little change in the volume of distribution, the half-life of elimination is prolonged greatly (as much as 5 h), and steady-state conditions may not be achieved until 20 to 25 h following the institution of an intravenous infusion. Despite the fact that lidocaine metabolites are excreted by the kidneys, renal disease has not been reported to exert any significant effect on lidocaine dosing regimens. With mechanical ventilation, there is often a decrease in cardiac output and hepatic blood flow, and a decrease in lidocaine dosage may be required.[33] Patients with congestive heart failure achieve lidocaine levels that are almost double those in normal individuals given the same dose.[29] Since the central volume of distribution is generally halved in heart failure, loading doses should be reduced by 50 percent; since clearance is also approximately halved, maintenance doses should be reduced proportionately from an infusion rate of 30 μg/kg body weight per minute used for usual patients to about half that figure. The time required to achieve steady-state conditions following the institution of a maintenance infusion is still 8 to 10 h in many patients with heart failure because of concomitant changes in V_D and clearance, resulting in a half-life similar to that seen in patients without heart failure.

In summary, general recommendations for initial lidocaine dosage selection should be adjusted for each patient based on clinical presentation, clinical response, and the results of plasma level monitoring. Some patients with congestive heart failure may experience toxicity when given an infusion as low as 0.5 mg/mL; thus, blood level monitoring is essential for proper dosage adjustment. In postmyocardial infarction patients receiving lidocaine infusions for more than 24 h, plasma lidocaine levels can increase, and the elimination phase half-life can increase up to 50 percent.[34] This increase is due, in part, to changes occurring in protein binding of lidocaine during the first few days of therapy. Assays for plasma lidocaine measure the sum of both protein-bound and free lidocaine as total lidocaine and thus do not give a true picture of the amount of free drug available. An increase in plasma lidocaine occurring at this time often reflects an elevation in plasma levels of alpha-1-acid glycoprotein (AAG), to which it binds,[35] and does not always indicate an increase in free, active drug. In this case, the lidocaine dosage should not be reduced to compensate for the higher total plasma concentration as long as the patient displays no adverse effects. Subsequent decreases in AAG concentrations will result in an apparent decrease in plasma lidocaine, which may reflect a drop in only that fraction bound to AAG.

ADVERSE REACTIONS

Central nervous system symptoms are the most frequent side effects of lidocaine administration. A rapid bolus can induce tinnitus or seizures. With more gradual attainment of excessive levels, drowsiness, dysarthria, confusion, hallucinations, and dysesthesia may occur. Excessive lidocaine can also cause coma, which should be a consideration in patients after cardiac arrest. Lidocaine can depress cardiac function, which decreases its clearance, and produces an even greater increase in lidocaine concentrations. Advanced degrees of sinus node dysfunction have been reported in isolated instances.[36,37] In patients with known conduction abnormalities below the AV node, lidocaine should be administered cautiously, if at all, unless a temporary pacemaker is readily available.

DRUG INTERACTIONS

An additive or synergistic depression of myocardial function or conduction may occur when using lidocaine combined with other antiarrhythmic agents,[38] especially during conversion from lidocaine to another antiarrhythmic agent. A pharmacokinetic drug interaction between propranolol and lidocaine has been described experimentally and in humans in which beta-adrenergic blockade caused decreases in cardiac output and liver blood flow, with a resultant decreased lidocaine clearance.[39] Cimetidine has been reported to decrease lidocaine's volume of distribution, decrease splanchnic (and hence liver) blood flow, and inhibit the enzymes responsible for lidocaine metabolism. This may raise lidocaine plasma concentrations, and both loading and maintenance dosages may require downward adjustment in patients receiving cimetidine.[40]

Mexiletine (Mexitil)

CLINICAL APPLICATIONS

Mexiletine is used in the treatment of ventricular arrhythmias and has, on occasion, been effective in treating arrhythmias that were refractory to other agents. Success rates vary between 6 and 60 percent, and more than half of the studies suggest limited efficacy (less than 20 percent).[41] Mexiletine does not prolong the QT interval and therefore can be useful for patients with a history of drug-induced torsades de pointes or long-QT syndrome when quinidine, sotalol, procainamide, or disopyramide are contraindicated. While the rate of response to mexiletine when used alone is low, it has been combined successfully with quinidine,[42] propranolol,[43] or procainamide.[44] This mode of therapy takes advantage of the additive, and perhaps synergistic, antiarrhythmic response produced by the combination of these agents. Since lower than usual dosages of both agents can be used, dosage-related adverse effects are reduced concomitantly. Mexiletine exerts minimal effects on both hemodynamics and myocardial contractility, even in patients with severe congestive heart failure.[45]

MECHANISM OF ACTION

Mexiletine is an orally active lidocaine congener with class IB sodium channel-blocking activity and structural similarity to tocainide. It was originally developed as an anorexiant and anticonvulsant agent, and its antiarrhythmic properties were only later recognized. Mexiletine blocks fast sodium channels, decreasing $_{max}$ and shortening the repolarization phase of ventricular myocardium.[46]

CLINICAL PHARMACOLOGY

The systemic bioavailability of mexiletine approximates 90 percent,[47] with a large volume of

distribution (5.5 to 9.5 L/kg), reflecting extensive tissue uptake. About 1 percent of total body content of mexiletine is in the plasma compartment, with approximately 70 percent of this bound to serum proteins. Mexiletine has little first-pass metabolism but is eliminated primarily by hepatic metabolism, with only 10 to 15 percent being excreted unchanged in the urine. Its half-life of elimination is between 8 and 20 h (9 and 12 h for healthy subjects), with the time needed to reach steady state ranging between 1 and 3 days.[48] Mexiletine undergoes extensive hepatic metabolism by cytochrome P450 2D6 (CYP2D6),[49,50] and, consequently, clearance is extremely variable (see below).[51]

DOSAGE AND ADMINISTRATION

Mexiletine therapy should be initiated with a low dosage, which is increased at 2- to 3-day intervals until efficacy or intolerable side effects, such as tremor or other central nervous system symptoms, develop. With normal renal function, the recommended initial oral mexiletine dosage is 200 mg every 8 h. As with most drugs having extensive liver metabolism, clearance will be widely variable within the population. This is especially true for mexiletine because CYP2D6, responsible for its metabolism, is absent in 7 percent of the Caucasian population. Also, consideration of dosage adjustment to compensate for the action of agents (discussed below) that induce or inhibit hepatic mexiletine metabolism is required.

MODIFICATION OF DOSAGE IN DISEASE STATES

Patients with renal failure who also inherit a deficiency of hepatic CYP2D6 are likely to have extremely slow elimination for mexiletine,[52] and for this reason, all renal failure patients should be given low initial doses. Elimination half-life and clearance may be prolonged by overt congestive heart failure[53] and hepatic failure,[54] and dosage reduction is required.

ADVERSE REACTIONS

Adverse reactions to mexiletine are dose-related and neurologic and include tremor, visual blurring, dizziness, dysphoria, and nausea. Thrombocytopenia has been reported to occur infrequently with mexiletine therapy,[55,56] and a positive antinuclear antibody test result occurs rarely. Severe bradycardia and abnormal prolongation of sinus node recovery time have been reported in patients with the sick-sinus syndrome,[57] and, at high concentrations, worsening of heart block has been reported.[58] Oral mexiletine does not depress ventricular function or induce increased heart failure,[59] although intravenous mexiletine, which is not available in the United States, has been noted to increase congestive heart failure.[60]

DRUG INTERACTIONS

The hepatic metabolism of mexiletine can be increased by phenobarbital, phenytoin (Dilantin), or rifampicin, which reduce the half-life of mexiletine, possibly changing an effective dose to an ineffective one.[41,48,61] Conversely, if treatment with an inducing agent is stopped, an effective dose may become toxic.

In one study, mexiletine decreased the clearance and increased the plasma concentrations of theophylline.[62] Quinidine inhibits the CYP2D6 enzyme primarily responsible for the metabolic clearance of mexiletine, and plasma concentration of mexiletine may increase in those individuals who express the enzyme (93 percent of Caucasians).

Procainamide (Pronestyl-SR, Procan-SR)

CLINICAL APPLICATIONS

Procainamide, like quinidine, is effective against both supraventricular and ventricular arrhythmias.[63] Although the two drugs have similar electrophysiologic effects, they are clinically different, and one agent may be effective for a patient when the other is not. Procainamide is useful in acute management of patients with reentrant supraventricular tachycardia and atrial fibrillation and flutter associated with Wolff-Parkinson-White syndrome.[64]

Although lidocaine is more often used, procainamide is also used intravenously to suppress ventricular arrhythmias occurring immediatiely following myocardial infarction or to convert sustained ventricular tachycardia. Since it takes approximately 20 min to administer a loading dose of procainamide safely, its use is limited to those situations where adequate time is available. Its advantage over lidocaine is the potential for conversion to oral therapy using the same agent. Lidocaine is usually used, however, because the initial loading dose can be given within a 2- to 5-min period.

The active metabolite of procainamide, *N*-acetylprocainamide (acecainide or NAPA), produces class III antiarrhythmic activity in some patients, although not always those who respond to procainamide.[65] This is most likely due to the very different electrophysiologic actions of procainamide and NAPA.[66] NAPA was investigated as an antiarrhythmic drug and was shown to be effective in the treatment of ventricular arrhythmias, but since its use was limited by a narrow therapeutic index, development was halted.[65]

The development of procainamide as an antiarrhythmic agent resulted from a systematic search for a useful congener of procaine, whose use was precluded by adverse reactions.[67] Since procainamide is an effective agent but is not without adverse effects, it has served as a prototype for development of several of the newer antiarrhythmic agents.

MECHANISM OF ACTION

Like other agents demonstrating class I activity, procainamide slows conduction and decreases automaticity and excitability of atrial and ventricular myocardium and Purkinje fibers.[68] Because of its effect on potassium channels, it also prolongs APD and refractoriness. Compared to quinidine, procainamide has very little vagolytic activity and does not prolong the QT interval to as great an extent.[63] NAPA has predominantly class III antiarrhythmic activity; it prolongs APD and refractoriness in both atrial and ventricular myocardium and prolongs the QT interval.[69,70] It has little or no effect on $_{max}$ in either Purkinje fibers or ventricular cells and does not alter His-Purkinje conduction velocity because of its very low potency as a sodium channel antagonist.

CLINICAL PHARMACOLOGY

Procainamide is rapidly absorbed and 100 percent orally bioavailable. About 15 percent of procainamide is bound to serum proteins. Its short half-life of elimination, 2 to 4 h in patients with normal renal function, necessitates dosing every 3 to 6 h. Dosing every 6, 8, or 12 h is possible with sustained-release preparations, and the frequency depends upon the formulation. The varied formulations and their very different dosing requirements often create confusion and can lead to dangerous mistakes in dosing.

Slightly more than half of the general population are phenotypically rapid acetylators of procainamide and quickly convert it to NAPA, a metabolite with very pure class III antiarrhythmic action.[65] As would be expected, however, the response to one agent does not predict response to the other. When each is given as the sole agent, the usually effective plasma concentration is 4 to 8 μg/mL for procainamide and 7 to 15 μg/mL for NAPA.[65] During oral

procainamide therapy, both agents are present in variable amounts, and there is no way to determine readily the contribution of NAPA to arrhythmia suppression under these conditions. Consequently, the utility of measuring plasma levels of procainamide during chronic therapy is limited because of this variable hepatic conversion to NAPA. Monitoring plasma concentrations for determination of compliance or prevention of toxicity is feasible and recommended (see below).

DOSAGE AND ADMINISTRATION

Procainamide is available for either intravenous or oral use. With normal renal and cardiac function, the initial recommended oral maintenance dose is 50 mg/kg per day. Frequent administration is required for oral procainamide, which is inconvenient and makes compliance difficult. Sustained-release forms of procainamide are available, which permits dosing every 6, 8, or 12 h, depending upon the formulation. During chronic therapy, levels of NAPA may accumulate to effective or toxic levels in some individuals, resulting in achievement of maximum pharmacologic effect long after the time procainamide has reached steady state.[65,71] Therefore, the elimination half-life of 2 to 4 h for procainamide may be misleading as a predictor of time to the occurrence of stable pharmacologic action. Thus, dosage should be initiated at conservative levels, and the patient should be monitored carefully until both procainamide and its metabolite have reached steady state. Patients with ventricular tachycardia may need higher dosages[65] for prevention of arrhythmia induction by programmed stimulation,[72] although such dosages often lead to adverse effects. Since the electrophysiologic effects of procainamide and NAPA are quite different, monitoring of patients receiving procainamide should at some point include measurement of plasma concentrations of both agents to determine their relative concentrations. Patients who are rapid acetylators or who have impaired renal function usually have plasma concentrations of NAPA higher than those of procainamide at steady state. These individuals should be monitored for excessive accumulation of NAPA during dose titration to maintain plasma levels of NAPA below 20 μg/mL. The practice of using the sum of the plasma concentration of procainamide and NAPA is not recommended.

When administered intravenously, procainamide can be given as a constant 25-min loading infusion of 275 μg/min per kilogram of body weight or by a series of doses (100 mg delivered over 3 min) given every 5 min, up to a total dose of 1 g.[73,74] If the loading infusion is well tolerated with no hypotension and less than 25 percent QRS or QT widening, a maintenance intravenous infusion of 20 to 60 μg/kg per minute can then be given. Larger and more rapid loading infusions of 1 g over 15 to 20 min have been given in the electrophysiology laboratory to prevent induction of ventricular tachycardia by programmed ventricular stimulation. A second loading infusion of 0.5 to 1 g has been given in some instances where an initial loading infusion was well tolerated but ineffective. These large dosages are accompanied by a higher incidence of hypotension and conduction disturbance and often result in attainment of unacceptably high plasma concentration.

MODIFICATION OF DOSAGE IN DISEASE STATES

With renal dysfunction or a low cardiac output, both procainamide and NAPA in usual doses may accumulate to potentially toxic levels, and the dose should be reduced.[75] Increased plasma levels of procainamide and/or NAPA may occur with congestive heart failure because of decreased urinary excretion and hydrolysis of procainamide.[76] On the other hand, one study of procainamide pharmacokinetics following a single intravenous bolus revealed no difference in volume of distribution, clearance, elimination half-life, unbound drug fraction, and peak procainamide concentrations between patients with congestive heart failure and normal individuals.[77] Although intravenous procainamide does depress myocardial contractility and lower blood pressure, worsening of heart failure is uncommon during oral therapy when the usual dosages and plasma

concentrations are maintained.

ADVERSE REACTIONS

Side effects associated with long-term procainamide therapy limit its usefulness. Up to 40 percent of patients discontinue therapy in the first 6 months due to adverse reactions. The potential exists for arrhythmia aggravation, including the development of torsades de pointes due to procainamide or, more often, NAPA.[78] Therefore, just as with all agents possessing class IA activity, procainamide should not be used in patients with a long-QT syndrome, a history of torsades de pointes, or hypokalemia.[79] In order to reduce the occurrence of proarrhythmia, potassium levels should be maintained above 4 meq/L when taking procainamide. Heart block and sinus node dysfunction can occur in patients with preexisting conduction system abnormalities.[80]

Between 15 and 20 percent of patients receiving chronic oral procainamide therapy develop a lupus-like syndrome, which is often difficult to recognize but regresses with discontinuation of treatment. The syndrome usually begins insidiously as mild arthralgia but progresses to frank arthritis, fever, malar erythematous rash, and pleural and/or pericardial effusions, with serum antibodies against nucleoprotein (histone) appearing as antinuclear antibodies with a "smooth" or "diffuse" pattern. These symptoms abate if procainamide is discontinued and generally resolve at a rate proportional to their duration.

Almost all patients treated chronically develop detectable antinuclear antibodies, but only 15 to 20 percent develop symptoms of the lupus syndrome. Therefore, it is unnecessary to discontinue therapy solely because of the positive antinuclear antibody titer. The patient should be fully informed of the symptoms, which should be reported, so that therapy can be discontinued at the earliest symptoms or signs of the lupus syndrome. Continuing procainamide after the development of the early symptoms of the lupus syndrome is dangerous because of the above-noted possibility of pleural effusion and potentially lethal pericardial tamponade.[81]

More recently, procainamide therapy has been associated with the development of agranulocytosis. It has been suggested, but not proven, that the sustained-release form of the drug may be especially capable of inducing this toxicity.[82] The manufacturer recommends that a white blood count be obtained every 2 weeks for the first 3 months.

DRUG INTERACTIONS

Unlike quinidine, procainamide does not cause an increase in digoxin levels. There are few reports of interactions between procainamide and other drugs. Its clearance is reduced between 30 and 50 percent by cimetidine, which blocks the renal tubular secretion of procainamide.[83,84] A similar competition has been found between procainamide and its predominant metabolite, NAPA.[85] Ranitidine affects procainamide pharmacokinetics by reducing both its renal clearance and its absorption, the former by 14 to 23 percent and the latter by 10 to 24 percent, depending on the dose.[86]

Disopyramide (Norpace)

CLINICAL APPLICATIONS

Disopyramide is effective against a broad range of supraventricular and ventricular arrhythmias, its antiarrhythmic profile being similar to that of quinidine and procainamide. Disopyramide, in contrast to quinidine and procainamide, is better suited for long-term therapy, having relatively little associated chronic toxicity. While newer than quinidine or procainamide, disopyramide is still one of the older antiarrhythmic agents, having been in use in the United States since 1977. Its

negative inotropic and anticholinergic actions occur frequently and limit its usefulness.

MECHANISMS OF ACTION

The class IA antiarrhythmic effects of disopyramide are predominantly those associated with sodium and potassium channel blockade. Its effects are similar to those of quinidine and procainamide on automaticity, conduction, and refractoriness in atrial and ventricular tissue.[87]

CLINICAL PHARMACOLOGY

The oral bioavailability of disopyramide is 80 to 90 percent.[88] Its half-life of elimination, usually 6 to 8 h, is lengthened to as much as 15 h in cardiac patients.[89] About half of the compound is eliminated by the kidneys unchanged, and the remainder as an active metabolite resulting from hepatic *N*-dealkylation.[90] Protein binding of disopyramide is complex, with between 20 and 50 percent of disopyramide being bound to plasma proteins. For most drugs, the percentage bound to plasma protein is a constant over the usual range of therapeutic concentrations. The saturation of disopyramide-binding sites on plasma proteins at usual doses means that there are disproportionate increases in levels of free drug in plasma compared to the magnitude of dosage increment.[91]

DOSAGE AND ADMINISTRATION

Loading doses are not recommended with disopyramide. The usually effective dosage for disopyramide is 100 to 400 mg three to four times daily, to a maximal dose of 800 mg/day. Therapy should be very carefully titrated, beginning with low doses and allowing ample time for achievement of steady-state equilibrium.

While rapid fluctuations in plasma concentration are undesirable, they are difficult to avoid because of disopyramide's saturable protein binding. The controlled-release form of disopyramide may be useful in reducing adverse effects by decreasing fluctuations in the concentration of free disopyramide in plasma.[92] Because of saturable protein binding,[16] the generally accepted therapeutic range for total disopyramide in plasma, 2 to 5 μg/mL, should not be strictly relied on. While monitoring the plasma concentrations of free disopyramide has been recommended,[93] the range of concentrations associated with arrhythmia suppression has not been clearly delineated and overlaps with that causing adverse effects.

MODIFICATION OF DOSAGE IN DISEASE STATES

The patient's response to disopyramide should be monitored especially closely following acute myocardial infarction because both the absorption and elimination of disopyramide are decreased at this time.[94] In fact, in view of the negative inotropic actions of disopyramide and changes in levels of binding proteins in plasma following a myocardial infarction, other antiarrhythmic agents should be considered first.

Disopyramide is contraindicated in patients with uncompensated heart failure because it can worsen failure.[95] The initial dosage of disopyramide should be reduced to 50 to 100 mg every 12 h in patients with renal insufficiency[96] or decreased hepatic function.[97]

ADVERSE REACTIONS

The predominant side effects of disopyramide include new or worsened congestive heart failure and symptoms resulting from dose-related anticholinergic actions, including urinary retention, constipation, dry mouth, and esophageal reflux. Because of this anticholinergic action, patients

with obstructive uropathy or glaucoma should not receive this agent.[98] For some patients, the anticholinergic side effects can be prevented or alleviated by concomitant use of cholinesterase inhibitors, such as physostigmine and neostigmine, without reduction in antiarrhythmic efficacy.[99] As with all agents that prolong repolarization, disopyramide should not be used in patients with long-QT syndrome, hypokalemia, or a history of torsades de pointes[100] because of the potential for arrhythmia aggravation. Direct actions of disopyramide on the sinus node can lead to excessive bradycardia in patients with sinus nodal dysfunction,[101] and this may contribute to development of torsades de pointes in patients with hypokalemia.[102]

DRUG INTERACTIONS

Disopyramide does not increase digoxin levels,[103] and the effects of warfarin are not potentiated by disopyramide.[104] Phenytoin, rifampicin, and phenobarbital induce hepatic metabolism of disopyramide, thus increasing its elimination and potentially leading to loss of antiarrhythmic effect.[105] Significant depression of myocardial contractility may result from the combined administration of disopyramide with beta-adrenergic or calcium channel antagonists and should be avoided in patients with impairment of ventricular function.[106]

Quinidine (Quinaglute, Quinadex, Others)

CLINICAL APPLICATIONS

Quinidine has been used successfully for a variety of supraventricular and ventricular arrhythmias, including conversion of atrial fibrillation or flutter,[107,108] supraventricular tachycardia,[107,108] ventricular extrasystoles,[109] and ventricular tachycardia and fibrillation.[110,111] Digitalis is used in the treatment of atrial fibrillation, atrial flutter, and other arrhythmias. This important drug is discussed in Chap. 23.

A grouped analysis of six small placebo-controlled trials in patients with atrial fibrillation showed a statistically significant increase in mortality rate for the patients treated with quinidine.[112] Because of the similar negative effects on mortality rate seen in the CAST and CAST II, one must assume that the results of this meta-analysis are valid until a definitive prospective study is available.

MECHANISM OF ACTION

Quinidine has multiple actions, but the action thought by many to be primarily responsible for its efficacy is block of the rapid inward sodium channel. This results in a decrease in $_{max}$ of the action potential upstroke and slowed conduction, more marked in the His-Purkinje system than in the atria. The effects of quinidine on sodium channels are greatest at increased heart rate and less negative membrane potential; that is, they are pH-, rate-, and voltage-dependent. Dose-related changes in the ECG are increases in PR, QRS, and QT_c intervals, which reflect the multiple actions of quinidine.[113]

CLINICAL PHARMACOLOGY

The effective dosage of quinidine varies among individuals because of several factors. Although quinidine sulfate is usually administered every 6 h, there are wide interindividual differences in its elimination half-life, which varies from 3 to 19 h.[114] Plasma protein binding also varies widely, ranging from 50 to 95 percent.[114] Oral bioavailability is approximately 70 percent, and clearance after oral administration ranges from 200 to 400 mL/min. Quinidine is inactivated or eliminated by both hepatic metabolism (50 to 90 percent) and renal elimination (10 to 30 percent). Several

potentially active metabolites are formed in amounts that vary among individuals,[115] but for most, their clinical role has not been determined. One of the metabolites of quinidine, 3-hydroxyquinidine, has been shown to possess antiarrhythmic activity when given to humans.[115] Experimental data indicate some contribution by metabolites of quinidine to its antiarrhythmic action.[116,117,118]

DOSAGE AND ADMINISTRATION

Quinidine therapy (as the sulfate) is usually initiated with an oral dosage of 200 mg every 6 h, and the dosage is carefully titrated every 3 or more days. Elderly patients often require lower dosages of quinidine because of both reduced clearance and volume of distribution. Quinidine is available commercially in at least three different forms: quinidine sulfate, gluconate, and polygalacturonate. Since the quinidine content varies among these at 83, 62, and 60 percent, respectively, the need for dosage adjustment should be considered if one form is substituted for another. The usually effective dosage of quinidine sulfate ranges from 800 to 2400 mg/day, with the maximum recommended single dose being 600 mg. Because the half-life varies from 3 to 19 h, one should wait 4 days between dosage increases to prevent unexpected drug accumulation. The range of therapeutic plasma concentrations measured using assays that differentiate quinidine from its metabolites is 0.7 to 5.5 μg/mL.[119,120] Rapid escalation in quinidine dosage has been used to convert atrial fibrillation, but this therapy is no longer recommended because of unnecessary toxicity.

Intravenous therapy with quinidine is usually avoided if alternatives are feasible. Vasodilation and hypotension result from quinidine-induced alpha-adrenergic blockade. If quinidine is given intravenously (as quinidine gluconate), the patient should be carefully monitored and the infusion rate should be no greater than 16 mg/min. This should be discontinued if hypotension is observed or the QRS is prolonged by more than 30 percent.

MODIFICATION OF DOSAGE IN DISEASE STATES

No adjustment in initial dosage is usually needed for patients with renal or hepatic disease,[121,122] although, due to decreased protein binding in patients with hepatic failure, lower than usual total plasma concentration can produce toxicity.[123] Slower dose titration is advisable to permit attainment of steady state and complete accumulation of active metabolites; however, because the usual range of effective dosages is wide, dosage for these patients is not markedly different. Patients with rapid quinidine elimination may require higher dosages (up to 600 mg every 6 h). This is often due to induction of hepatic metabolism caused by other drugs.

Patients with congenital long-QT syndrome, hypokalemia, or a history of torsades de pointes[124] should not be given quinidine because of their increased risk for this form of proarrhythmic event. For patients with congestive heart failure, problems associated with use of quinidine are proarrhythmia and digitalis (either digitoxin or digoxin) toxicity. Prudent use of quinidine in individuals taking digitalis requires the following: (1) that titration begin at a reduced dosage, (2) that dosage of any cardiac glycoside being administered concomitantly be reduced, and (3) that plasma electrolyte levels, especially potassium levels, be maintained above 4 meq/L.

Although quinidine does possess some direct negative inotropic effects, they are usually counteracted by its vasodilatory effect; therefore, oral quinidine is well tolerated hemodynamically when given at dosages producing usual plasma concentrations, even in patients with reduced ventricular function.[125] In a study of over 650 patients, 35 percent of whom had congestive heart failure, quinidine therapy resulted in no induction or worsening of congestive heart failure.[126] On the other hand, a significant problem for patients with congestive heart failure receiving quinidine therapy is proarrhythmia, with quinidine-induced torsades de pointes being potentiated in the setting of bradycardia and low serum levels of magnesium or potassium.[102,127]

ADVERSE REACTIONS

Marked prolongation of the QT interval has been seen in some patients receiving low or usual dosages of quinidine, and the risk of torsades de pointes is markedly increased. This arrhythmia may be responsible for quinidine syncope, which occurs in as many as 5 to 10 percent of patients within the first days of quinidine treatment, and for quinidine-induced sudden death.[128] Torsades de pointes usually occurs in patients (more often females than males) with low serum concentrations of quinidine, hypokalemia, poor ventricular function, and bradycardia.[128,129] In a study by Drici et al., dihydrotestosterone reduced the sensitivity to the effects of quinidine on the QT interval in animals.[130] This study[130] and a subsequent study by Benton et al.[131] in which women were shown to be more sensitive to the effects of quinidine on the QT interval, provide evidence that sex hormones have direct effects on cardiac tissue that may be responsible for the difference in the incidence of torsades de pointes in men and women.[129]

For patients who develop torsades de pointes, treatment with pacing or isoproterenol is very effective. Magnesium sulfate injection is often recommended as initial therapy for torsades de pointes, although controlled trials are not available. These measures should also include correction of hypokalemia. Clinically, it is essential to distinguish torsades de pointes from polymorphic ventricular tachycardia occurring in the setting of a normal QT interval, because the latter should be treated with local anesthetic antiarrhythmic drugs and may be worsened by the above-mentioned treatment for torsades de pointes.

Since quinidine acts via alpha-adrenergic blockade to produce vasodilatation,[132] hypotension may occur, especially in patients concomitantly receiving nitrates or other vasodilators. Other adverse effects include a high incidence of diarrhea and vomiting, tinnitus at high plasma levels, rare thrombocytopenia,[133] and, in unusual cases, conduction block in patients with existing conduction system disease.[126] In patients treated with quinidine for atrial flutter without prior AV nodal blockade by digitalis, there have been reports of sudden increases in AV conduction and rapid ventricular rates.[132] This results from a slight reduction of the flutter rate and enhanced AV nodal conduction due to the anticholinergic effects of quinidine. This permits 1:1 conduction through the AV node, often at 200 to 250 beats per minute. This may be of particular concern for patients receiving other drugs that increase conduction time through the AV node, such as beta-adrenergic agonists.

DRUG INTERACTIONS

Quinidine metabolism is inhibited by cimetidine[134] and induced by phenytoin, phenobarbital,[135] and rifampicin,[133] with the latter agents leading to reduced, often subtherapeutic, quinidine concentrations. Clinical digoxin toxicity has been described in 20 to 40 percent of patients receiving quinidine and digoxin concurrently.[134] The magnitude of this interaction is dependent on quinidine dosage, and in some patients it may not appear until the dosage is increased to higher levels.[136,137] The rise in digoxin levels appears with the first dose of quinidine; therefore, it is suggested that digoxin dosage be halved when quinidine therapy is initiated. A similar interaction has been reported for quinidine and digitoxin.

Quinidine is a potent inhibitor of the hepatic cytochrome P450 (CYP) specific for debrisoquine metabolism (CYP2D6),[138,139] although it is not metabolized by this specific P450 isozyme.[140,141] Thus, it may interfere with the biotransformation and actions of pharmacologic agents dependent on this cytochrome for their metabolism, which include propafenone, mexiletine, flecainide, metoprolol, timolol, sparteine, and bufuralol.[142] Quinidine worsens neuromuscular blockade in patients with myasthenia gravis[143] and may prolong the effects of succinylcholine.[144]

Propafenone (Rythmol)

CLINICAL APPLICATIONS

Propafenone was developed in Germany, where it has been marketed since 1977. It is similar to other antiarrhythmic agents in overall efficacy and tolerance by patients. It has a role in the treatment of many types of arrhythmias, including supraventricular arrhythmias.[145]

CLINICAL PHARMACOLOGY

Propafenone has been described as having class IC antiarrhythmic activity because of its potent ability to slow conduction velocity with little change in APD.[146,147] It has a marked structural similarity to propranolol, and studies have shown that propafenone can accumulate during continued administration to levels capable of producing clinically significant beta-adrenergic inhibition.[148]

Propafenone, like mexiletine and flecainide, is eliminated by a metabolic pathway that has a polymorphic pattern of inheritance. Patients deficient in CYP2D6 activity have very slow elimination of propafenone and fail to form measurable quantities of the potentially active metabolite, 5-hydroxypropafenone.[149] The accumulation of high concentrations of propafenone leads to significant beta-receptor antagonism at both low and high dosages in poor metabolizers but only at high dosages in extensive metabolizers of propafenone.[150] Although metabolic phenotype does not seem to dramatically influence the antiarrhythmic response to propafenone in many patients,[149] it clearly influences the degree of beta blockade occurring during therapy.

DOSAGE AND ADMINISTRATION

Effective dosages range from 300 to 900 mg/day in two to four divided dosages. In order to prevent unexpected accumulation of pharmacologic action, propafenone dosage should not be changed more frequently than every 3 days; there is slow elimination of the parent drug in poor metabolizers, and there is slow accumulation of the metabolite or metabolites in extensive metabolizers.

Patients with reduced ventricular function, especially those receiving propafenone, should be carefully monitored for deterioration in ventricular function, which may result from beta-adrenergic receptor antagonism and/or the direct negative inotropic effect.[151]

MODIFICATION OF DOSAGE IN DISEASE STATES

Dosage recommendations for patients with cardiac, renal, or hepatic dysfunction are not yet available.

DRUG INTERACTIONS

It is very likely that there will be drug interactions between propafenone and other agents that utilize or inhibit cytochrome CYP2D6 for their metabolism. Such an interaction has been documented already between propafenone and metoprolol[152] and should be expected with timolol, many antidepressants, many neuroleptics, and perhaps other agents. Quinidine, which inhibits this cytochrome, inhibits the formation of 5-hydroxypropafenone in extensive metabolizers[153]; however, the clinical consequence of such inhibition is unknown and difficult to predict. One would expect greater beta blockade to occur after combining quinidine with propafenone therapy because of the resulting higher propafenone concentrations.

Flecainide (Tambocor)

CLINICAL APPLICATIONS

Flecainide is very effective in suppressing a variety of ventricular and supraventricular tachycardias.[154,155] The finding of increased mortality rates when flecainide is given to patients with ischemic heart disease has led to restricted usage (see above); however, there has been no evidence to indicate that this increase in mortality rate is seen when flecainide is given to treat supraventricular arrhythmias in patients without known coronary artery disease.[156] Overall, the antiarrhythmic response to flecainide in patients with symptomatic life-threatening ventricular arrhythmias is not markedly better than with older agents, such as quinidine or procainamide.[154,157] Although it is far better tolerated than older agents, the negative inotropic actions of flecainide restrict its use to patients having moderately well-preserved ventricular function. Likewise, its potential to increase mortality rates in patients with ischemic heart disease limits its usefulness.

MECHANISM OF ACTION

Flecainide has sodium channel-blocking activity and is considered to have class IC actions. It has also been found to block the delayed rectifier potassium channel in feline ventricular myocytes, and this action may be clinically relevant.[158]

Flecainide slows intraventricular conduction velocity more than it prolongs effective refractory periods.[159] It prolongs AH and HV intervals and measurably increases PR and QRS intervals on the surface ECG at therapeutic doses. The QT_c interval is slightly increased, primarily due to prolongation of the QRS, but its ability to block the delayed rectifier potassium channel may contribute to QT changes.

CLINICAL PHARMACOLOGY

The systemic bioavailability of oral flecainide is 90 to 95 percent,[160] and flecainide is predominantly metabolized in the liver to compounds that are not pharmacologically active at the concentrations usually found in plasma.[154] Flecainide, like many other antiarrhythmic agents, is metabolized by CYP2D6.[161] Because flecainide is also eliminated by the kidneys to a considerable extent, the enzyme deficiency has little effect on the pharmacokinetics of flecainide. If, however, those patients without the enzyme develop renal insufficiency or if renal patients are given a drug that blocks the metabolism of flecainide, extremely high plasma concentrations are likely to occur.[162] A potential advantage of flecainide is its very slow elimination, with half-life ranging from 7 to 23 h in normal individuals and tending to be even longer (14 to 26 h) in patients with cardiac disease, even in the absence of heart failure.[160,163]

DOSAGE AND ADMINISTRATION

The usual dosage of flecainide for ventricular arrhythmias is 100 to 150 mg every 12 h in patients without cardiac or renal failure. A total daily dosage of more than 400 mg may sometimes be used under close medical monitoring (see below). Patients with supraventricular tachycardia are recommended to receive 50 mg every 12 h as a starting dose. The range of therapeutic plasma concentrations of flecainide is reported to be between 200 and 1000 ng/mL, although adverse effects may occur in some patients at concentrations within this range,[164,165] and many patients tolerate concentrations well above this range. To reduce the incidence of adverse effects, flecainide therapy should start with a low dosage that is maintained until steady state has been reached (at least 4 days) and altered relative to clinical response.

MODIFICATION OF DOSAGE IN DISEASE STATES

With cardiac failure, the usual initial dose is 50 to 100 mg every 12 h. Since 7 percent of Caucasian patients with renal failure will not have the CYP2D6 enzyme and because flecainide is usually eliminated by both metabolism and renal excretion, all patients with renal failure should be given very low dosages and titrated very carefully. Plasma concentration monitoring will be essential in patients with renal disease or cardiac or hepatic dysfunction. Any significant reduction in ejection fraction should be expected to lengthen elimination half-life and hence the time needed to attain steady-state equilibrium, while reductions in clearance may occur in renal or hepatic dysfunction and lead to higher plasma concentrations at steady state.

ADVERSE REACTIONS

Although aggravation of arrhythmias seen in the early days of the evaluation of flecainide was often due to excessive initial doses and frequent dose increments, flecainide has a potential to induce proarrhythmic events, even when prescribed as recommended. This is especially true in patients with severe heart disease and if flecainide is given in higher dosages.[166] Because of its negative inotropic effects at dosages necessary to suppress arrhythmias, flecainide produces a measurable decrease in left ventricular function in most patients.[167,168] The increased mortality rate seen in the CAST seemed to be confined to patients with structural heart disease.[156] A retrospective study of five multiple-dose efficacy trials showed that, of patients with a history of congestive heart failure, oral flecainide precipitated heart failure in 15 percent. A dose-related depression of myocardial performance was found after rapid (1 to 2 mg/kg) intravenous injections.[169]

Other side effects of flecainide include depression of sinus node activity in patients with preexisting sinus node dysfunction[170] and prolongation of QRS and PR intervals on the surface ECG. If below 25 percent, these effects do not necessarily indicate excessive dosage.

Flecainide increases pacing thresholds by as much as 200 percent and should therefore be used with caution in patients dependent upon pacemakers.[171,172] Since it also increases the threshold for electrical defibrillation, patients with implanted devices should be evaluated carefully.[173]

DRUG INTERACTIONS

Cimetidine reduces flecainide clearance and prolongs flecainide elimination half-life.[174] Studies in normal volunteers have demonstrated an increase in the plasma concentrations of digoxin and propranolol when flecainide is coadministered.[175,176] Not unexpectedly, propranolol and flecainide have been found to have additive negative inotropic effects. An interaction with amiodarone, resulting in elevation of plasma flecainide concentration and necessitating reduction of flecainide dosage, has been described.[177]

Calcium Channel Blockers

Some calcium channel blockers are also used as antiarrhythmic agents.[178,179] Verapamil and diltiazem are useful in the management of supraventricular tachycardia, where they are administered to slow the ventricular rate in patients with atrial fibrillation or flutter and to treat and prevent AV nodal reentrant tachycardia. Intravenous diltiazem is useful for the temporary control of rapid ventricular rate during atrial fibrillation and flutter. In controlled clinical trials, conversion to sinus rhythm occurred with diltiazem and placebo with equal frequency.

Bretylium (Bretylol)

CLINICAL APPLICATIONS

Bretylium is effective for acute therapy of ventricular tachycardia and/or ventricular fibrillation. Because of its sympatholytic activity, bretylium tosylate was first evaluated in the 1950s for the treatment of hypertension; however, a very high incidence of orthostatic hypotension and unreliable oral absorption led to its disfavor for chronic therapy. After its antiarrhythmic activity was discovered in animals,[180] it was eventually marketed in the United States as intravenous therapy for life-threatening ventricular arrhythmias. Bretylium is usually employed only after patients have not responded to lidocaine.

MECHANISM OF ACTION

In addition to the indirect electrophysiologic changes caused by a biphasic action on postganglionic autonomic neurons, bretylium has a direct class III action that causes an increase in APD and refractoriness in ventricular muscle and Purkinje fibers.[181] When clinically relevant concentrations of bretylium are studied in normal tissues, no changes are seen in $_{max}$, maximum diastolic potential, or conduction velocity. Studies have found that bretylium reduces the degree of dispersion of repolarization across the boundary between normal and ischemic tissue by acting predominantly on normal tissue.[182] Transient increases in membrane potential and conduction velocity are seen early after bretylium administration and are presumed to be due to the local release of catecholamines.

When initially administered, bretylium causes the release of norepinephrine from postganglionic adrenergic neurons.[183] Bretylium is transported into the neuron by the norepinephrine pump, and extensive accumulation in the neuron is then associated with a blockade of further release or uptake of norepinephrine by the neuron. The blockade of uptake of circulating or infused catecholamines leads to supersenitivity that is functionally similar to a denervated state.

CLINICAL PHARMACOLOGY

Bretylium is poorly absorbed after oral administration, with average bioavailability of approximately 25 percent, and is available only for parenteral administration. It is eliminated almost entirely unchanged in the urine, and clearance correlates well with creatinine clearance.[184]

DOSAGE AND ADMINISTRATION

The usual intravenous dosage for bretylium is 5 mg/kg given at a rate dependent upon the clinical setting.[185] During cardiac emergencies, it should be given by rapid injection into a central intravenous line. In less acute situations, giving a loading infusion of the same dose, but over 10 to 20 min, will reduce the incidence of nausea and vomiting. The loading dose should be repeated after 20 min if the arrhythmia is still present. A total loading dose of 20 mg/kg may be required, and dosages up to 9 g in 24 h have been given without serious adverse effects. Maintenance infusions of 1 to 4 mg/min should be given, depending upon body size and renal function. Heart rhythm and blood pressure should be monitored carefully, especially during the first few hours of bretylium therapy.

MODIFICATION OF DOSAGE IN DISEASE STATES

In patients with renal insufficiency, bretylium clearance is reduced and half-life prolonged; therefore, the maintenance infusion for bretylium should be reduced to the lowest effective dosage. There are few data to guide dosage adjustment in cardiac or hepatic impairment, but it is unlikely that the dosage should be altered in these patients.

ADVERSE REACTIONS

When bretylium is given by rapid intravenous injection, many patients experience nausea and vomiting. The release of norepinephrine by bretylium has the potential to cause increased blood pressure, but severe hypertension has not been described. Increased frequency of ventricular arrhythmias is often seen at this time and can lead to the need for more frequent cardioversion. The reduction in peripheral vascular resistance can cause symptomatic hypotension in volume-depleted patients, but this can be readily corrected if recognized, although hypotension could prove dangerous in patients with fixed valvular obstruction. Bradycardia has been reported in some patients with abnormalities of the conduction system when given large intravenous dosages of bretylium.

In stable patients, either initial or subsequent doses of bretylium can cause a transient increase in heart rate, blood pressure, contractility, peripheral vascular resistance, and arrhythmia frequency, followed by a fall in standing blood pressure and peripheral vascular resistance.[186] Orthostatic hypotension is almost uniformly seen in patients receiving bretylium and sometimes lasts for days after discontinuation of therapy. Dosages that are well below those required for antiarrhythmic efficacy are capable of causing orthostatic hypotension. When hypotension develops during bretylium therapy, it should be corrected with intravenous volume expansion to enable adequate doses of bretylium for suppression of arrhythmias.

DRUG INTERACTIONS

Other than those with tricyclic antidepressants, no drug interactions have been reported. One would expect, however, that there might be competition for renal tubular secretion with procainamide, NAPA, cimetidine, and other organic bases.

Sotalol (Betapace)

CLINICAL APPLICATIONS

Sotalol has been used for up to 20 years in many countries for angina and hypertension, and it was in this setting that its value as an antiarrhythmic agent was first observed. Sotalol is unlike other beta-adrenergic antagonists in that it prolongs the action potential, producing a dose-related increase in refractoriness of cardiac tissues.[187] This unique combination of properties makes sotalol effective in a variety of supraventricular and ventricular arrhythmias. It has been found to be effective in patients with sustained ventricular tachycardia evaluated by programmed ventricular stimulation. In a controlled comparison to procainamide, sotalol was effective in 30 percent of patients with inducible sustained ventricular tachycardia, whereas only 20 percent responded to procainamide ($p < .2$).[188] This is consistent with the response rate for sotalol (31 percent) in the Electrophysiology Study Versus ECG Monitoring (ESVEM) trial sponsored by the National Institutes of Health, which compared therapy guided by programmed electrical stimulation to therapy guided by ambulatory monitoring.[189] In this study, a mean of only 12 percent of patients responded to the other antiarrhythmic drugs evaluated.

MECHANISM OF ACTION

Sotalol has two main actions, each of which can contribute to its antiarrhythmic efficacy.[190] The drug was originally synthesized for its actions as a beta-adrenergic receptor antagonist. Unlike other beta-receptor antagonists, it markedly prolongs refractoriness in atrial and ventricular tissues, a class III antiarrhythmic action. These actions slow heart rate, decrease AV nodal conduction, and increase refractoriness of atrial, ventricular, AV nodal, and AV accessory pathways in both the anterograde and retrograde directions.[191] When given in dosages between

160 and 640 mg/day, there are increases of 40 to 100 ms in the QT interval and 10 to 40 ms in QT_c.[192]

CLINICAL PHARMACOLOGY

Oral bioavailability of sotalol is greater than 90 percent, and peak concentrations are seen 2.5 to 4 h after a dose. It is not bound to plasma proteins and is eliminated by the kidneys unchanged, with an elimination half-life of approximately 12 h. Because of the relatively long half-life and twice daily dosing regimen, it is recommended that testing for efficacy be conducted near the end of the dosing interval at steady state. The age of the patient per se does not influence the pharmacokinetics of sotalol other than that due to the natural decline in renal function that occurs with age.

DOSAGE AND ADMINISTRATION

Sotalol is available only in the oral form in the United States. The recommended initial dose of sotalol is 80 mg every 12 h. In patients with relatively normal renal function, steady state is reached in 2 to 3 days. If evaluation at this dosage indicates a lack of response without evidence of excessive effects on repolarization (QT below 500 ms), the dosage may be increased to 160 mg twice daily and, if necessary, to 240 mg twice daily. Some patients with life-threatening arrhythmias have required dosages of 640 mg/day. Accelerated titration regimens have been used with close monitoring without apparent increase in the frequency of adverse events.[193]

MODIFICATION OF DOSAGE IN DISEASE STATES

Because sotalol is mainly eliminated unchanged in the urine, the dosage must be adjusted for altered renal function. For patients with a creatinine clearance greater than 60 mL/min, the usual dosing interval is every 12 h. If the creatinine clearance (CL_{CR}) is between 30 and 60 mL/min, the recommended interval between doses is 24 h. For patients with CL_{CR} between 10 and 30 mL/min, the interval should be every 36 to 48 h or the usual dose halved and given every 24 h. The dosage for patients with CL_{CR} below 10 mL/min should be individualized. Because of the increased risk of proarrhythmia and congestive heart failure, patients with reduced cardiac output should be given lower doses and monitored carefully.

ADVERSE REACTIONS

A major concern with sotalol treatment has been the occurrence of torsades de pointes. Reports of this syndrome have predominantly been cases of suicidal overdoses or in patients who were receiving concomitant diuretics and inadequate potassium replacement. Clearly, hypokalemia and bradycardia are predisposing factors for the development of this arrhythmia during sotalol therapy, as they are with quinidine, disopyramide, and procainamide. The manufacturer observed an overall incidence of torsades de pointes of 2 percent, broken down to 4 percent of patients with sustained ventricular tachycardia and 1.5 percent of patients with supraventricular arrhythmias. It is more common in females and patients with congestive heart failure and those with a history of sustained ventricular tachycardia (7 percent). The incidence of torsades de pointes should be minimized by careful screening and consideration of predisposing factors, such as gender, bradycardia, baseline prolongation of the QT interval, and electrolyte disturbances, (especially hypokalemia); careful dose escalation beginning at 160 mg/day; and limiting the maximum QT-interval prolongation to less than 550 ms.

The incidence of new or worsened congestive heart failure is only about 3 percent. This may be attenuated because of the increased inotropy produced by its action to prolong repolarization. Other side effects typical of beta blockers are to be expected, including bronchospasm in

asthmatic patients, masking the signs and symptoms of hypoglycemia in diabetic patients, and catecholamine hypersensitivity withdrawal syndrome.

DRUG INTERACTIONS

Concomitant use of sotalol with agents that prolong repolarization has the potential to increase the likelihood of torsades de pointes. No pharmacokinetic interactions have been seen with sotalol and/or warfarin, digoxin, cholestyramine, or hydrochlorothiazide. Because of the beta-blocking actions of sotalol, it is likely that there would be increased pharmacologic effect if the drug is combined with amiodarone, calcium channel blockers, antihypertensive agents, or antiarrhythmic agents.

Amiodarone (Cordarone)

CLINICAL APPLICATIONS

Although amiodarone has been reported to have efficacy in a wide range of arrhythmias, the FDA has recommended it only for life-threatening ventricular arrhythmias refractory to other available forms of therapy. Nevertheless, there are now numerous trials in the literature describing the efficacy of amiodarone in the conversion and slowing of atrial fibrillation, AV nodal reentrant tachycardia, and tachycardias associated with the Wolff-Parkinson-White syndrome.[194,195] The reasons for the limited labeling of amiodarone are (1) the documented potentially lethal complications of chronic amiodarone therapy, (2) the complications associated with its variable onset of action, and (3) multiple dangerous drug interactions.

After the results of CAST, antiarrhythmic drugs have been examined for their effects on mortality rate. After several small or uncontrolled trials seemed to indicate that amiodarone could have a beneficial effect on mortality rate,[4,196] adequate trials were undertaken. The Veteran's Administration trial, Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF STAT),[5] examined the effects of amiodarone on total mortality rate in patients with a history of congestive heart failure, more than 10 premature ventricular contractions per hour on ambulatory monitoring, and an ejection fraction below 40 percent. The study found no difference in the placebo- and amiodarone-treated arms. Two other major trials have evaluated amiodarone in patients with recent myocardial infarction. The Canadian Myocardial Infarction Amiodarone Trial (CAMIAT)[197] and the European Myocardial Infarction Amiodarone Trial (EMIAT)[198] were recently completed. The results of these trials are mixed, in that neither found amiodarone to reduce overall mortality rate, but the Canadian trial reported a reduced incidence of ventricular fibrillation or arrhythmic death among survivors of myocardial infarction with ventricular ectopy. It is important to note that there was no increase in mortality rate, as has been seen with other antiarrhythmic drugs. In recent years, there have been attempts to perform meta-analyses of the many trials with amiodarone.[199,200] They have generally confirmed a modest reduction in mortality rate in cardiac patients. One study concluded that the benefit could be extended to patients with congestive heart failure,[200] but another did not.[199] The NIH-sponsored Antiarrhythmics versus Implanted Devices (AVID) trial found that the devices were superior to amiodarone in reducing mortality rates in patients who had been resuscitated from sudden death or who had sustained ventricular tachycardia.

In 1993, an intravenous formulation of amiodarone became available in the United States. Although it had been used extensively in most countries for many years, controlled trials only became available in recent years. Three completed controlled trials demonstrated the value of amiodarone in patients with recurrent life-threatening ventricular tachycardia or fibrillation. A comparison of three dosages found that the recurrence of arrhythmia decreased with increasing dosages of 125, 500, and 1000 mg per 24 h.[201] Hypotension was the major side effect seen, but it occurred equally in all groups, about 26 percent. The second study in a similar group of patients

was a comparison of bretylium to two doses of amiodarone.[202] The arrhythmia event rate for the first 48 h of therapy was equivalent for the high dose of amiodarone and bretylium, and both were more effective than the low dose of amiodarone. Hypotension was common in all groups but significantly higher in the bretylium group. Amiodarone was approved for intravenous therapy of ventricular arrhythmia by the FDA in 1998. Although not yet approved in labeling, a recent study found intravenous amiodarone effective for prevention of postoperative atrial fibrillation.[203]

MECHANISM OF ACTION

Amiodarone is an iodinated benzofuran that has structural similarity to thyroxine and procainamide and was originally developed as an antianginal agent. It was incidentally noted to suppress a wide variety of ventricular and supraventricular arrhythmias. This efficacy has been assumed to be due to its prolongation of refractoriness and APD in myocardial tissue (Vaughan Williams class III antiarrhythmic activity), although amiodarone has been found to have many diverse pharmacologic actions (see Table 27-1); the action or actions responsible for its high degree of antiarrhythmic efficacy remain unidentified.

In intracellular recordings of rabbit cardiac myocytes, amiodarone prolongs APD and increases refractoriness of both atrial and ventricular myocardium, Purkinje fibers, and sinus and AV nodal tissues. Amiodarone decreases phase 3 depolarization of myocardial cells, blocks sodium channels that are in the inactivated state, and slows phase 4 depolarization of the sinus node as well as conduction through the AV node.[204,205] The electrophysiologic actions of the major metabolite of amiodarone, desethylamiodarone (DEA), differ from those of amiodarone, with the metabolite having greater effects on sodium channels and, hence, upon conduction.[206] Intracoronary injection of amiodarone has shown little cardiac effect compared to the ability of DEA to prolong cardiac refractoriness.[207]

Electrophysiologic changes in humans depend on the route of administration and the duration of therapy. Following acute intravenous amiodarone administration, prolongation of the AH interval and an increase in the refractory periods of the AV node and bypass tracts are seen, but this may be due to the presence of the solubilizing agent polysorbate 80 (Tween 80) in the intravenous formulation. No acute changes occur in either sinus rate or atrial or ventricular refractoriness, which are prolonged during chronic oral therapy. Chronic amiodarone therapy also prolongs the AH and HV intervals and the PR and QT intervals of the surface ECG. Data conflict on the time course of these changes and how they may relate to antiarrhythmic efficacy.

Changes in APD and refractoriness are seen in hypothyroidism that are similar to changes resulting from oral amiodarone therapy.[208] Since these changes can be prevented in animals by coadministration of thyroid hormone with amiodarone,[209] some have concluded that the antiarrhythmic efficacy of amiodarone is due to production of "cardiac hypothyroidism." This is supported by the observation that the major metabolite of amiodarone causes noncompetitive inhibition of thyroid hormone binding to nuclear receptors.[210] On the other hand, amiodarone also causes noncompetitive blockade of alpha and beta receptors[211] and muscarinic receptors,[212] and both calcium and sodium channel blockade, any combination of which may contribute to its antiarrhythmic efficacy.

CLINICAL PHARMACOLOGY

Amiodarone is a highly lipid-soluble compound with extremely variable and complex pharmacokinetics. It is slowly absorbed from the gastrointestinal tract, and bioavailability varies over a fourfold range.[213] Amiodarone is extensively metabolized to DEA, and little, if any, is excreted unchanged in the urine. Concentrations of DEA in plasma vary from 0.4 to 2.0 times that

of amiodarone during chronic therapy.[214] This metabolite has antiarrhythmic potency equal to or greater than amiodarone in in vitro and animal models.[215] Amiodarone is rapidly concentrated in some tissues, including myocardium, but accumulates more slowly in others, such as adipose tissue. It redistributes out of myocardial tissue while still accumulating in adipose and other tissues.[214,216] Until all tissues are saturated, rapid redistribution out of the myocardium may be responsible for early recurrence of arrhythmias after discontinuation of therapy or rapid reduction of dosage. Because of drug accumulation in tissues, the volume of distribution for amiodarone is very large, 20 to 200 L/kg.[216] After intravenous administration, the measured half-life in plasma is from 4.8 to 68.2 h,[217] with tissue uptake being the primary factor responsible for the decline in plasma concentration. As tissues become saturated, however, the decline in plasma levels is slow, reflecting mainly elimination and slow redistribution of the drug out of adipose and muscle tissues. This leads to slow and extremely variable elimination from plasma, with half-lives ranging from 13 to 103 days at steady state.[216] It is also possible that amiodarone inhibits its own elimination after chronic therapy, contributing to the differences between half-life early in therapy to that after prolonged therapy.

DOSAGE AND ADMINISTRATION

Without a loading-dose regimen, amiodarone requires several weeks to months before producing its antiarrhythmic action. Large intravenous dosages or oral loading dosages can hasten the onset of therapeutic effects. From small prospective studies, loading dosages have varied from 600 to 1400 mg/day for 2 to 21 days.[218] Recent large clinical trials have utilized a lower loading dose, of 600 to 800 mg daily for 14 days.[5,219] Because of relatively rapid redistribution out of myocardial tissue, the dosage should be tapered over a period of several weeks. The usual maintenance dose varies from 200 to 600 mg/day, and because of the severe nature of adverse reactions, the lowest effective dosage should be prescribed. Patients with supraventricular arrhythmias may respond to lower dosages than those with ventricular arrhythmias, but there are many exceptions. Because of the variable pharmacokinetics and oral bioavailability, such generalizations may be unreliable. Some patients with extensive absorption (approximately 80 to 90 percent bioavailability) of even low doses may have the same drug exposure as a person with limited bioavailability given a high dose.

For intravenous administration, the manufacturer recommends a three-phase infusion over the first 24 h: 150 mg over 10 min, followed by 360 mg over the next 6 h, followed by 0.5 mg/min. The drug can be continued at this rate, but monitoring of plasma concentrations is recommended. An additional 150 mg can be infused over 10 min for those patients who continue to have recurrent ventricular tachycardia or fibrillation or whose arrhythmia recurs during downward titration of the infusion. Concentrations of drug greater than 3 mg/mL should be infused through a central catheter to prevent phlebitis. Also, the surfactant properties of the drug alter the size of a drop of infusate, and pumps that count drops will give approximately 30 percent less drug than intended.

Amiodarone concentrations are usually between 1 and 2 μg/mL during effective oral therapy.[220,221] Similar concentrations of DEA accumulate during therapy and, although this is unproven, are likely to contribute to antiarrhythmic efficacy. Because of extensive overlap between the range of concentrations required for arrhythmia suppression and those associated with toxicity, monitoring of plasma concentrations is of limited value. Clearly, levels of amiodarone above 3 to 4 μg/mL for prolonged periods of time are associated with a higher incidence of adverse effects.[222]

MODIFICATION OF DOSAGE IN DISEASE STATES

Long-term oral therapy with amiodarone appears to be well tolerated hemodynamically in patients with congestive heart failure. In the CHF STAT study, discussed above, amiodarone failed to

prolong life for congestive heart failure patients with arrhythmias but was associated with improved ventricular function as measured by radionuclide ejection fraction.[5]

ADVERSE REACTIONS

Intravenous amiodarone at dosages greater than 5 mg/kg decreases cardiac contractility and peripheral vascular resistance, producing severe hypotension in some instances. Some of this effect, like the electrophysiologic effects described earlier, may be due to the effects of polysorbate 80 or benzyl alcohol, since oral administration at usual dosages improves myocardial contractility.

The safety of amiodarone is controversial. The early reports found it to be very well tolerated and described it as the "ideal antiarrhythmic drug." Some studies continue to find that it is relatively safe and effective, even in the treatment of arrhythmias in children.[223] The early experience with amiodarone in the United States, with a very high incidence of intolerable and sometimes lethal reactions, may have been the result of high dosages required for control of life-threatening arrhythmias. In less urgent conditions, lower dosages are given and are much better tolerated. Determination of the incidence of adverse reactions is difficult because of highly variable dosages and durations of treatment.[204,224]

The most serious adverse reaction is lethal interstitial pneumonitis,[204,225] which may be more common in patients with preexisting lung disease. Monitoring is essential, since the pneumonitis is reversible if detected early. A chest x-ray every 3 months may be useful, but serial pulmonary function tests are of little value for follow-up. Hyper- or hypothyroidism is seen in about 4 percent of patients treated chronically.[208] Accumulation of corneal microdeposits is almost uniform during long-term therapy and in many cases can progress to the point of interfering with vision.[226] Some Caucasian patients develop a slate-gray or bluish discoloration of sun-exposed areas of the skin.[227] Many also complain of photosensitivity, which can sometimes be prevented or alleviated with sunscreens and garments. Thirty percent or more of patients have abnormally elevated serum hepatic enzyme levels, and progression to jaundice and cirrhosis has been reported.[228,229] Serial laboratory tests to screen for amiodarone toxicity can be costly and generally are of limited value; however, it is wise to obtain a reliable assessment of baseline test results, including complete blood count, blood chemistry, tests of thyroid and pulmonary function, a slit-lamp examination, and measurement of blood levels of other drugs whenever possible.

DRUG INTERACTIONS

Amiodarone interferes with the clearance of many drugs. This may involve the formation of a metabolically inactive cytochrome P450 Fe(II)-metabolite complex, which has been described in animals treated with amiodarone,[230] and may explain the reduced metabolism and unexpected accumulation of warfarin,[231] quinidine, procainamide, disopyramide, mexiletine, and propafenone[232] and the resulting bleeding, heart block, or torsades de pointes. It does not, however, explain interaction with drugs eliminated predominantly by the kidneys, such as digoxin.[233] The elimination of other drugs may be impaired by amiodarone, and the lowest effective dosage should be sought.

Ibutilide (Corvert)

CLINICAL APPLICATIONS

Ibutilide was given FDA approval for the rapid conversion of recent-onset atrial fibrillation or flutter in 1995.[234,235] It has completed testing in other arrhythmias or in patients with atrial fibrillation or flutter of long duration (greater than 90 days). It should not be given to patients who

have hypokalemia, hypomagnesemia, or QT_c prolongation at baseline greater than 440 ms. In placebo-controlled studies summarized in the manufacturer's labeling, the placebo conversion rate for atrial fibrillation or flutter was approximately 2 percent. Ibutilide terminated the arrhythmia in approximately 44 percent of patients treated with 1 mg followed by either 0.5 or 1 mg. Approximately 20 percent of patients responded to the first infusion, and approximately 25 percent of those not responding to the first infusion responded to the second infusion. Response usually occurred at 20 to 30 min, ranging from 5 to 88 min after infusion. The response in patients with atrial fibrillation and atrial flutter was not significantly different in the early trials performed. However, in patients with postoperative arrhythmias, there was a greater response in patients with atrial flutter, with an overall conversion rate of 57 percent compared to 15 percent with placebo.[236] Ibutilide may have value in conversion of atrial fibrillation in patients with Wolff-Parkinson-White syndrome.[236]

MECHANISM OF ACTION

Ibutilide is a remarkably potent methanesulfonamide analog of sotalol that has class III action to prolong cardiac refractoriness and action potential duration.

The mechanism of action of ibutilide is unclear. The manufacturer's data indicate that the class III action of the drug is due to an increase in inward sodium current, as observed in guinea pig ventricular myocytes at 10^{-7}-*M* concentrations. They observed that higher concentrations (10^{-5} *M*) increase an outward potassium current to shorten action potential duration.[237] Other investigators reported that, as has been seen with dofetilide, sotalol, and other methanesulfonamides, 10^{-8} *M* concentrations of ibutilide block the rapid component of the delayed rectifier potassium current, I_{KR}, in mouse and human cardiac cells.[238]

CLINICAL PHARMACOLOGY

Ibutilide is available only for intravenous administration. When given over 10 min, it distributes rapidly in a multiexponential fashion, with the relevant component having a half-life from 2 to 12 h (mean 6 h). The plasma concentration and pharmacokinetics are highly variable, and dosing is recommended on the basis of weight. The drug is mainly eliminated by oxidative hepatic metabolism, and systemic clearance is rapid (about 29 mL/min per kilogram). Since formal drug interaction studies have not been performed, it is not possible to anticipate which enzymes are likely responsible for its elimination.

DOSAGE AND ADMINISTRATION

Ibutilide is given undiluted or diluted in saline as an infusion over 10 min. The recommended dose for a patient over 60 kg is 1 mg and for a patient under 60 kg, 0.01 mg/kg. For patients whose arrhythmias have not converted by 10 min after completion of the first dose, a second dose of equal size may be administered. Since conversion of the arrhythmias is usually associated with peak levels, slower infusion rates are not likely to be as effective.

It is essential that patients receiving ibutilide be treated in a carefully monitored environment during and at least 4 h subsequent to treatment. The FDA-approved labeling recommends that skilled personnel, facilities, and medication for defibrillation or resuscitation be readily available.

MODIFICATION OF DOSAGE IN DISEASE STATES

Although specific studies with heart failure and renal or hepatic disease have not been conducted, current information does not indicate that any dosage adjustments should be necessary in these conditions. Patients with severe left ventricular dysfunction, however, have a higher risk of

developing ventricular arrhythmias, including torsades de pointes. Since the duration of drug effect is determined by distribution, it is very possible that patients with severe congestive heart failure will have decreased volumes of distribution and hence an exaggerated and prolonged duration of effect.

ADVERSE REACTIONS

The most serious adverse reaction to ibutilide is torsades de pointes. There were, however, only 586 patients participating in trials before marketing, and patients with a QT_c greater than 440 ms or potassium concentrations less than 4 meq/L were excluded. In spite of these precautions, the incidence of sustained polymorphic ventricular tachycardia requiring cardioversion was 1.7 percent. Another 2.7 percent developed nonsustained polymorphic ventricular tachycardia, 4.9 percent had nonsustained monomorphic ventricular tachycardia, 1.5 percent had AV block, and 1.9 percent had bundle-branch block. The risk of polymorphic ventricular tachycardia was highest in patients who were female and/or who had evidence of reduced ventricular performance. The incidence of these adverse effects may well be higher in general clinical use, where electrolyte disorders and concomitant therapies may be more common. Bradycardia and multiple episodes of sinus arrest have been reported.[236,239] A single case of acute renal failure has been reported with ibutilide.[240]

DRUG INTERACTIONS

No specific drug interaction studies have been performed. Concomitant beta-receptor or calcium channel antagonists do not apparently interact, although data are limited. The manufacturer's labeling warns against combining ibutilide with other drugs that prolong the QT interval. During the development of ibutilide, such drugs were discontinued for at least five half-lives prior to administration of ibutilide and were not allowed until at least 4 h after administration.

Dofetilide (Tikosyn)

CLINICAL APPLICATIONS

Dofetilide was approved and marketed in 2000 for oral therapy of atrial fibrillation and flutter. In controlled trials of approximately 1000 patients, about 30 percent of patients with atrial fibrillation given a dosage of 500 μg bid converted to normal sinus rhythm, compared to 6 percent in the control group treated with sotalol and 1 percent of patients given placebo. Prevention of recurrence was demonstrated, with 62 to 71 percent remaining in sinus rhythm after 6 months, compared to 59 percent for sotalol and 26 to 37 percent for placebo (personal communication, S. Singh, Washington, DC). A large mortality trial (the Danish Investigators of Arrhythmia and Mortality on Dofetilide trial, or DIAMOND) in 1518 patients with reduced ejection fraction and symptoms of heart failure examined the effects of dofetilide on mortality rate and atrial fibrillation. A decrease in the incidence of hospitalization for heart failure was observed. Although the antiarrhythmic efficacy of dofetilide was confirmed in the lower incidence of atrial fibrillation, a positive effect on mortality rate was not observed. However, because of the previously observed increases in mortality rate with sodium channel blockers (CAST[1,241] and CAST II[2]) and with *d*-sotalol (SWORD[6]), the lack of harm in the DIAMOND trial with dofetilide[242] was interpreted as a positive indication of the safety of the drug. A caveat to this safety was the potentially important role of extensive screening and monitoring for potential harm. Even with these efforts, 3.3 percent of patients in this trial developed torsades de pointes. Because of the risk of torsades de pointes, the manufacturer will require physicians to receive special training prior to prescribing dofetilide, and the FDA has required that labeling include a warning that therapy should be initiated in the hospital, with continuous ECG monitoring for at least 3 days.

MECHANISM OF ACTION

Dofetilide is one of the most potent I_{KR} blockers of the rapid component of the delayed rectifier potassium current (I_{KR}) ever synthesized. Perhaps an additional advantage is the twofold greater ability to prolong action potential duration in atrial compared to ventricular tissue.[243] It does not depress cardiac function at usual dosages, even in patients with reduced ejection fraction.

CLINICAL PHARMACOLOGY

Dofetilide is well absorbed after oral administration and is partially metabolized by cytochrome P450 3A4[244] to inactive metabolites and excreted predominantly in urine. In most patients, the elimination half-life ranges from 8 to 10 h but is prolonged, and clearance is reduced in patients with renal failure. Dofetilide is susceptible to several drug interactions because it is metabolized by CYP3A4 (see below). It is very likely that these interactions increase the risk of torsades de pointes.

DOSAGE AND ADMINISTRATION

The recommended dosage of dofetilide is 500 μg bid. Lower dosages are recommended for patients who develop excessive QT_c prolongation on 500 μg bid. In the largest clinical trial, excessive was defined as greater than 550 ms or greater than 20 percent longer than baseline.

MODIFICATION OF DOSAGE IN DISEASE STATES

Dosage should be reduced in patients with renal disease (250 mg bid for creatinine clearance 60 to 40 mL/min and 250 mg daily for creatinine clearance 40 to 20 mL/min). Data are not available for adjustment of dosage in patients with liver disease. It is not clear whether the greater risk of torsades de pointes in women is influenced by a pharmacokinetic difference between sexes.

ADVERSE DRUG REACTIONS

The major adverse effect of dofetilide is torsades de pointes. The overall incidence during clinical development was 0.9 percent. In the DIAMOND trial, 3.3 percent of patients with a history of heart failure developed torsades de pointes.

DRUG INTERACTIONS

Concomitant administration of dofetilide with verapamil, ketoconazole, or cimetidine (but not ranitidine) results in increased plasma concentrations of dofetilide, especially in patients with reduced renal function.[245] Because it is known to be a substrate for CYP3A4, there may be other important interactions with erythromycin, other macrolides, or antifungals. No interactions have been seen between dofetilide and digoxin or warfarin.

Beta-Receptor Antagonists

See Chap. 40 for a discussion of beta-receptor antagonists.

Adenosine (Adenocard)

CLINICAL APPLICATIONS

Adenosine is very effective for the acute conversion of paroxysmal supraventricular tachycardia

(PSVT) due to reentry involving the AV node. Sixty percent of patients respond at a dose of 6 mg, and an additional 32 percent respond when given a higher dose, of 12 mg. Because of the fleeting and relatively selective action of adenosine on the AV node, some have suggested that it be used as a diagnostic tool in patients with narrow- and wide-complex tachycardia.[246] However, it is preferable, when possible, to make the correct diagnosis before giving any drugs, because of their risk of adverse effects.

MECHANISM OF ACTION

Adenosine is a nucleoside formed in the body by serial dephosphorylation of adenosine triphosphate (ATP), from cyclic adenosine monophosphate, or from hydrolysis of *S*-adenosylhomocysteine. It is formed both intra- and extracellularly, and its actions are rapidly terminated by active transport into cells followed by metabolism. The actions of adenosine are highly dependent on the rate and route of administration. A rapid intravenous injection into a central venous line is thought to activate carotid body chemoreceptors and usually produces an initial increase in blood pressure of 10 to 15 mmHg, followed by a small and transient decrease. These reflexes are attenuated during surgery, and in this setting adenosine decreases peripheral vascular resistance, increases cardiac output, and increases heart rate moderately. Bolus injections also produce biphasic effects on heart rate. Approximately 20 s after injection, sinus bradycardia occurs for 10 to 15 s, followed by sinus tachycardia thought to be due to chemoreceptor activation. Activation of the carotid chemoreceptors stimulates respiration and causes secondary activation of pulmonary stretch receptors. Adenosine has a direct effect of slowing AV nodal conduction, which can result in transient AV block. Although adenosine has no direct effect on the His-Purkinje system, it does attenuate the effects of catecholamine stimulation and, in patients with heart block, can block acceleration of the ventricular escape rate by isoproterenol. Adenosine usually has no effect on anterograde or retrograde accessory pathway conduction. Pathways that demonstrate decremental conduction often respond to adenosine, probably because they are partially depolarized and can be hyperpolarized by adenosine. Slow injections into a peripheral line often produce no clinical benefit or changes in blood pressure or heart rate.

The development of synthetic agonists and antagonists of adenosine receptors has made possible the subclassification of A_1 and A_2 receptor subtypes. The A_1 receptors are present in myocardial cells and mediate the negative inotropic, dromotropic, and chronotropic actions of adenosine. The A_2 receptors are present in the endothelium and vascular smooth muscle cells and cause coronary vasodilatation when activated.

The efficacy of adenosine in PVST is most likely due to the following actions in atrial myocardium and the AV node: (1) hyperpolarization of sinoatrial nodal cells and slowing of rate of firing, (2) shortening of the action potential of atrial cells, and (3) depression of conduction velocity in the AV node. These actions are due to activation of A_1 adenosine-receptor subtypes, which leads to activation of cyclic AMP-independent, acetylcholine/adenosine-regulated potassium current, $I_{K_{ACh,Ado}}$.

CLINICAL PHARMACOLOGY

After intravenous injection, adenosine is rapidly transported into red blood cells and endothelial cells. A half-life of elimination has ranged from 1.5 to 10 s. The drug is rapidly metabolized in the plasma and in cells to form inosine and adenosine monophosphate. Maximal pharmacologic effects are seen within 30 s after injection into a peripheral intravenous line but occur within 10 to 20 s when given into a central line.

DOSAGE AND ADMINISTRATION

Adenosine should be injected intravenously into a proximal tubing site and flushed quickly with saline solution. For adults, the initial dose is 6 mg injected over 1 to 2 s. If the arrhythmia persists, a 12-mg dose can be injected 1 to 2 min later. This can be repeated, but doses larger than 12 mg are not recommended by the manufacturer. A dosage regimen based on body weight has been proposed, with an initial dose of 50 μg/kg incremented by 50 μg/kg until the PSVT is terminated or side effects become intolerable.[246] Higher doses may be required for patients who have received caffeine or theophylline because of their antagonistic effects at A_1 receptors. Lower doses are recommended if the patients are receiving dipyridamole or carbamazepine.

MODIFICATION OF DOSAGE IN DISEASE STATES

Although the pharmacokinetics of adenosine are unlikely to be altered in patients with renal or hepatic disease, these patients often have electrolyte imbalances that could alter the clinical response. Although patients with congestive heart failure have not been reported to respond abnormally, cardiac transplant patients appear to require one-third to one-fifth of the usual dose because of denervation hypersensitivity.[247]

ADVERSE REACTIONS

Adenosine is contraindicated in patients with sick-sinus syndrome or second- or third-degree heart block unless the patient has a functioning artificial pacemaker. Because of the rapid clearance of adenosine, side effects such as facial flushing, dyspnea, or chest pressure last less than 60 s. Although intrapulmonary administration of adenosine has precipitated bronchospasm in asthmatic patients, this has not been reported with intravenous administration. Other less frequent side effects include nausea, lightheadedness, headache, sweating, palpitations, hypotension, and blurred vision. Intravenous theophylline, which has been recommended to reverse the effects of adenosine, should be prepared and ready for injection in high-risk patients.

DRUG INTERACTIONS

Several proven interactions can increase or decrease the activity of adenosine. Dipyridamole pretreatment increases the potency of adenosine, probably because it blocks cellular uptake of adenosine.[248] On the other hand, caffeine and theophylline antagonize the actions of adenosine.[249] The manufacturer cautions that carbamazepine may potentiate the actions of adenosine.

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INVESTIGATIONAL DRUGS

Only a few new antiarrhythmic agents are currently under development in the United States. Several of these are analogs of amiodarone, such as ATI-2001,[250] dronedarone,[251] and SR-33589.[252] Some impetus for the development of these agents lies in the hope that they will have the efficacy of amiodarone without complex pharmacokinetics and/or its toxicity.[250,251,252]

Azimilide is another drug with class III action that was initially believed to be a highly selective blocker of the slow component of the delayed rectifier (I_{KS}), but recent studies suggest that azimilide also blocks I_{KR}. It is unclear whether the effects on I_{KS} contribute any novel aspects to its actions or safety. I_{KS} blockade is thought to be desirable because the effect is resistant to antagonism by isoproterenol. Other drugs, such as ambasilide, are also in clinical development, and chromanol 293B is in preclinical testing.

A new class of serotonergic antagonist drugs is being developed. Stimulation of 5-HT_4 receptors increases atrial chronotropic and inotropic responses. Whether other electrophysiologic effects are produced is unknown. In humans and swine, 5-HT_4 receptors are present only in atrium. In porcine atrial tissue, RS-100302 prolonged the effective refractory period and minimally slowed conduction velocity. The drug produced no electrophysiologic effects on ventricular tissue. It terminated pacing-induced atrial flutter in six of eight animals and atrial fibrillation in eight of nine animals, and prevented reinduction of sustained tachycardia in all animals. The electrophysiologic profile of RS-100302 suggests that it may have atrial antiarrhythmic potential without producing ventricular proarrhythmic effects.

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Figure 27-1: Summary of the potentially most important actions of drugs on membrane channels, receptors, and ionic pumps in the heart. Listed are drugs used to modify cardiac rhythm. Most are marketed as antiarrhythmic agents. The drugs (rows) are ordered in a fashion similar to the columns so that generally the darker symbols for their predominant action or actions form a diagonal. Drugs with multiple actions (e.g., amiodarone) depart strikingly from the diagonal trend. The actions of drugs on the sodium, calcium, and potassium channels are indicated. Sodium channel blockade is subdivided into three groups of actions characterized by fast (300 ms), medium (med; 300-1500 ms), and slow (greater than or equal to 1500 ms) time constants for recovery from block. This parameter is a measure of "use dependence" and predicts the likelihood that a drug will decrease conduction velocity of normal sodium-dependent tissues in the heart and perhaps the propensity of a drug for causing bundle-branch block or proarrhythmia. Drug interactions with receptors alpha, beta, M_2, and P (alpha- and beta-adrenergic, muscarinic subtype, and A_1 purinergic) and drug effects on the sodium-potassium pump (Na/K ATPase) are indicated. Symbols indicate the type of actions at receptors or channels (Antagonist relative potency: ○ low; ▪, moderate; ▪, high; ▲, agonist; ▲, agonist/antagonist). Filled triangles for bretylium indicate its biphasic action to initially stimulate alpha and beta receptors by release of norepinephrine, followed by blocking of norepinephrine release and indirect antagonism of these receptors. (Adapted from the Task Force of the Working Group on Arrhythmias of the European Society of Cardiology,[9] with permission.)

Figure 27-2: Diagram of the modulated receptor mechanism for antiarrhythmic drug action. The three fractions of the sodium channel population proposed by Hodgkin and Huxley are represented in the upper part of the figure in the drug-free condition and in the lower part of the figure blocked by an antiarrhythmic agent (R′, A′, and I′, respectively). HH, standard Hodgkin-Huxley rate constants; HH′, HH with voltage dependence altered by drug binding; k_R, k_A, and k_I, association rate constants; I_R, I_A, and I_I, dissociation rate constants for the respective channel fractions. (From Hondeghem and Katzung,[11] reproduced with permission from the authors and the American Heart Association.)

Figure 27-3: Rate- (interval-)dependent depression of .$_{max}$ by lidocaine and procainamide. Following a 20-s rest period, a train of 16 action potentials was elicited using interstimulus intervals (ISIs) of 1 s or 200 ms in the presence (triangles) or absence (circles) of lidocaine or procainamide. For the duration of the train, $_{max}$ was relatively constant when measured at either ISI in the absence of drug. *A*. In the presence of lidocaine (22 μ*M*), stimulation at an ISI of 1 s produced no use-dependent block. *B*. However, stimulation at 200 ms produced a 50 percent reduction in $_{max}$ from baseline, which was first observed for the second action potential and was constant thereafter. *C*. A different pattern is seen in the presence of 276 μ*M* procainamide, which produced a significant depression of $_{max}$ at an ISI of 1 s. *D*. This depression was more pronounced when the ISI was shortened to 200 ms. Unlike the case for lidocaine, the use-dependent depression of $_{max}$ due to procainamide required multiple action potentials to approach steady-state values. (From Ehring BR, Moyer JW, Hondeghem LM. Quantitative structure activity studies of antiarrhythmic properties in a series of lidocaine and procainamide derivatives. *J Pharmacol Exp Ther* 1989; 244:479-492. Reproduced with permission from the publisher and authors.)

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 28:

TREATMENT OF CARDIAC ARRHYTHMIAS WITH CATHETER-ABLATIVE TECHNIQUES

Authors: Eugen C. Palma, Melvin M. Scheinman

Over the past several years, various techniques have been introduced using catheter ablative procedures for patients with cardiac arrhythmias. Particularly impressive are some of the newer techniques using radiofrequency energy sources for patients with supraventricular arrhythmias. This chapter reviews the techniques, results, and clinical indications for these procedures.

TECHNIQUES

Ablation of the Atrioventricular Junction

The technique of catheter ablation of the atrioventricular (AV) junction was first developed in canines[1] and subsequently applied for control of drug-refractory atrial arrhythmias in patients.[2,3] Multipolar electrode catheters are inserted by vein and positioned just across the tricuspid valve and against the apex of the right ventricle (Fig. 28-1). The catheter across the tricuspid valve is manipulated to allow recording of the largest unipolar His bundle potential[2] (Fig. 28-2). Radiofrequency energy of 350 to 500 kHz is applied between the distal electrode and a large back patch. After persistent AV block is observed, a permanent cardiac pacemaker is inserted (Fig. 28-3).

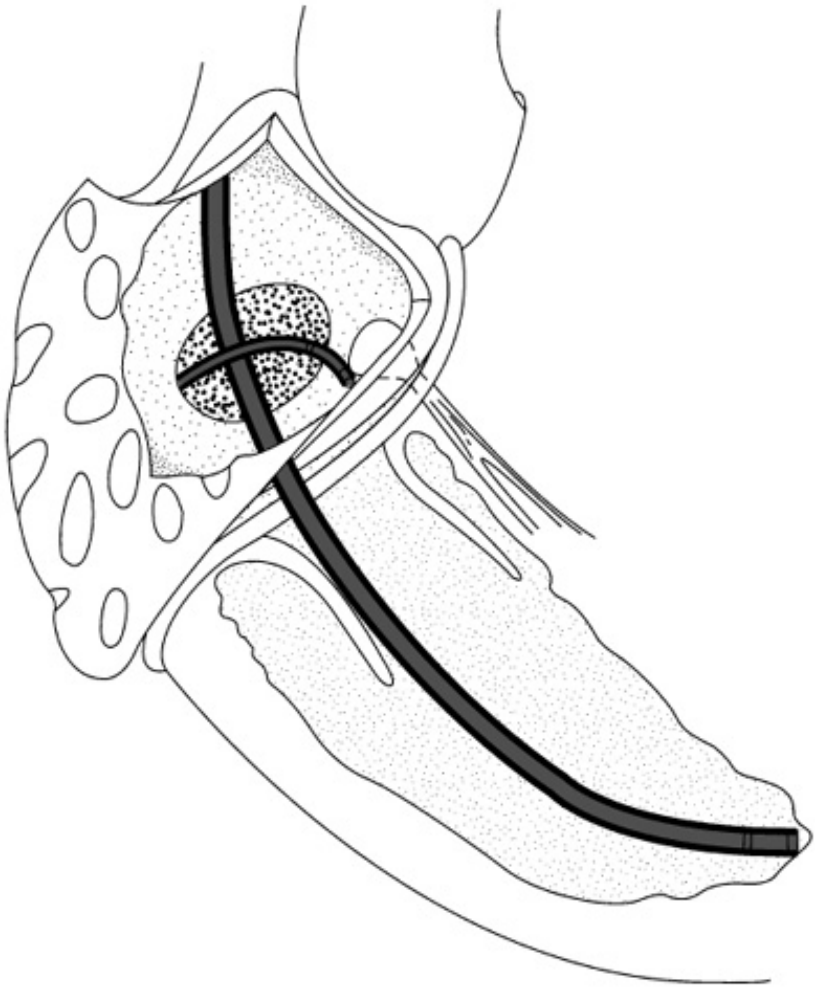

Figure 28-1: Catheter positions for patients undergoing AV junctional ablation. One catheter is placed over the region of the AV node, while a second catheter is placed against the apex of the right ventricle.

AV Nodal Modification for Patients with Atrial Fibrillation

A more recent innovation has been the use of AV nodal modification for achieving rate control in patients with atrial fibrillation.[4-6] This technique involves placement of radiofrequency lesions over the posterior or midseptum in order to achieve the desired reduction in rate during atrial fibrillation. The procedure entails a 16 percent risk of inducing complete AV block, which usually occurs within the first 72 h after the ablation.[6] In addition, a late recurrence of rapid rate has been reported in approximately 10 percent of patients.[6] The available data over a 19-month follow-up period suggest that the bulk of suitably selected patients with atrial fibrillation and rapid rate resistant to drug therapy will respond to AV nodal modification. However, this technique is of no value for the relief of symptoms related to the irregular rhythm per se.

Ablation of Accessory Pathways

Patients with accessory extranodal pathways often experience reentrant arrhythmias, with the circuit of the tachycardia involving antegrade conduction over the normal AV nodal conduction system and retrograde conduction over the accessory pathway.[7] Surgical techniques have in the past proved very effective and safe in the interruption of these pathways.[8] More recently, a number of catheter techniques have been introduced for catheter ablation of these pathways. Fisher et al.[9] were the first to use this technique for ablation of left free wall accessory pathways

via the coronary sinus. Accessory AV pathways occur anywhere along the cardiac annulus or in the septum. The majority of pathways are found traversing the left AV groove. These pathways are currently approached by inserting a steerable multipolar electrode catheter into the femoral artery with retrograde catheterization of the left ventricle.[10] The catheter is then placed under the mitral annulus in the putative site of the accessory pathway (Fig. 28-4). An alternative technique involves use of transseptal catheterization with placement of the catheter along the atrial margin of the mitral annulus.[11] One or more applications of radiofrequency energy are used to ablate the pathways. In contrast, most septal and all right free wall pathways are approached by right-sided catheterization.

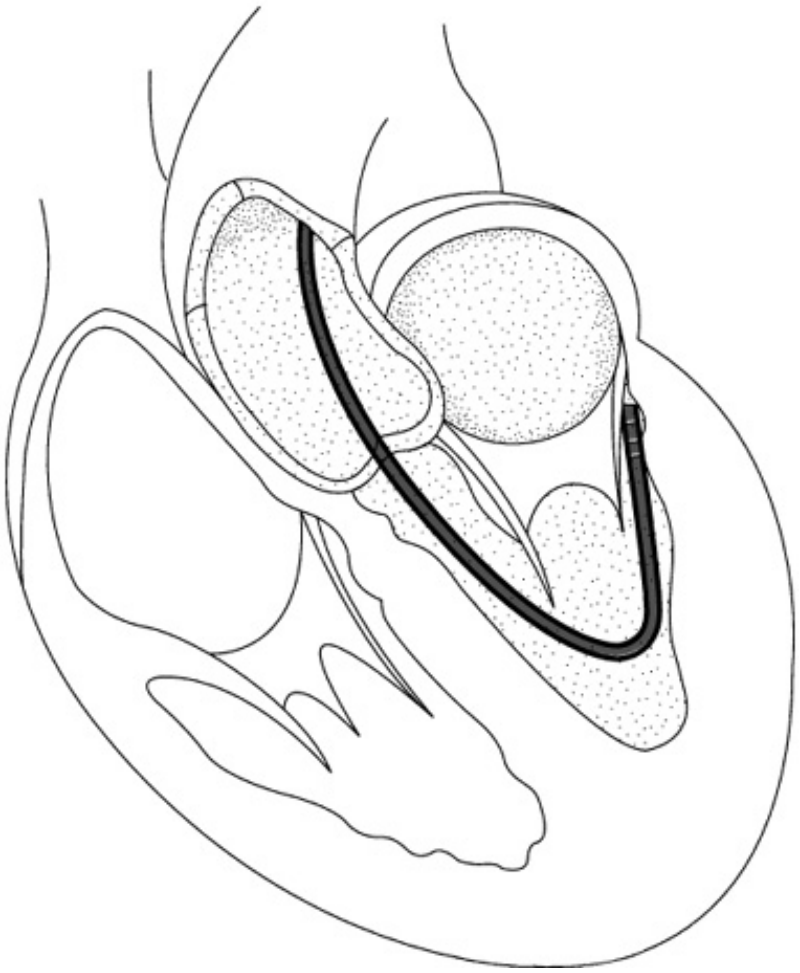

Figure 28-4: Schema depicting retrograde aortic technique for ablation of a left free wall accessory pathway. The catheter is passed across the aortic valve and placed under the mitral annulus.

Modification of the AV Node in AV Nodal Reentrant Tachycardia

Patients with AV nodal reentrant tachycardia are thought to have two pathways within or in close proximity to the AV node. These pathways show fast and slow conducting properties and have different refractory periods. Techniques have been introduced that allow for selective ablation of either pathway. The fast pathway is approached by withdrawing the catheter to a more proximal location while recording the His bundle potential, which is associated with a large-amplitude atrial electrogram and a very small or absent His deflection.[12] Application of radiofrequency energy to this area results in abrupt prolongation of the PR interval, since ablation of the fast pathway forces

conduction to occur over the slow pathway. An alternative technique for ablation of the slow pathway was introduced by Roman et al.,[13] where the radiofrequency energy is applied posteriorly between the os of the coronary sinus and the septal leaflet of the tricuspid valve. Successful application of the latter technique does not result in a change in the PR interval. The approach described for slow-pathway ablation may be accomplished successfully either by using anatomic landmarks or searching for specific so-called slow-pathway potentials. This technique has proved to be more effective and safer than attempts at fast-pathway ablation.

Ablation of Atrial Flutter/Atrial Tachycardia

Very effective techniques have been introduced recently for ablation of atrial flutter. Patients with a "typical" flutter pattern have a reentrant circuit localized to the right atrium. The critical slow zone appears to reside in the isthmus between the inferior vena cava and the tricuspid annulus.[14] A catheter is used to apply serial lesions, creating a line of block across the isthmus, with initial results suggesting success in 85 to 90 percent of patients.[15]

Patients with atrial tachycardia may be treated with catheter-ablative techniques.[16] The catheter is manipulated to find the earliest endocardial atrial potential relative to the surface P wave (Fig. 28-5). Foci of atrial tachycardia are localized along the crista terminalis or atrial appendage in the right atrium. Left atrial foci occur around the superior pulmonary veins or left atrial appendage.[17] Once the earliest site is located, radiofrequency energy is applied to ablate the atrial focus (Fig. 28-6).

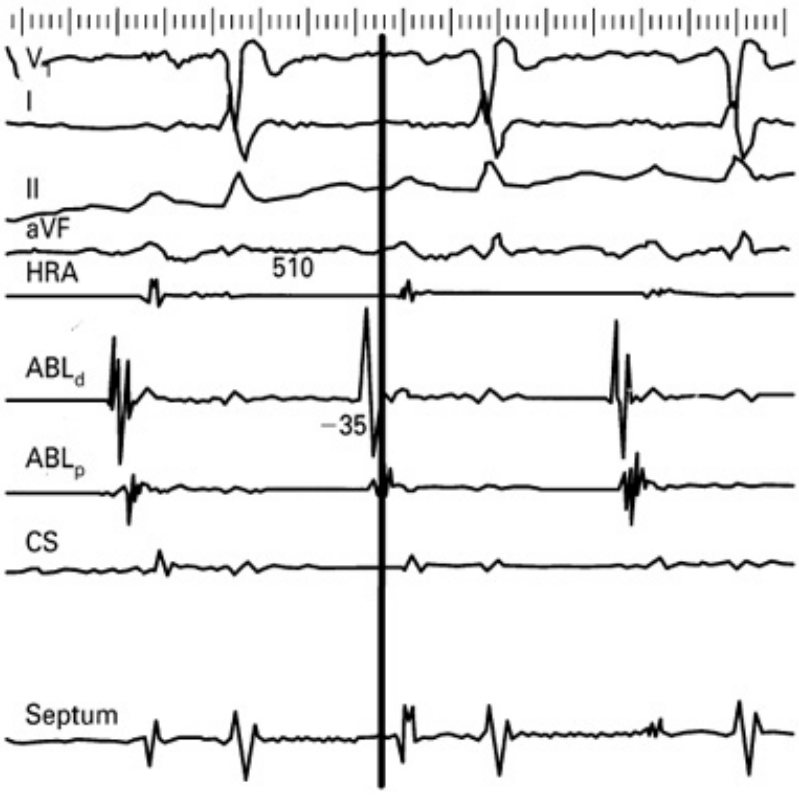

Figure 28-5: Simultaneous surface V_1, I, II, and intracardiac recordings from the high right atrium (HRA), distal (ABL_d), and proximal (ABL_p) electrodes from the ablating catheter, coronary sinus (CS), and low right atrial septum (Septum) in a patient with atrial tachycardia. The earliest atrial electrogram was 35 ms prior to inscription of the surface P waves.

Ablation of Focal Atrial Fibrillation

Recently, a subset of patients with atrial fibrillation has been discovered to have the initiation of atrial fibrillation arise from foci located in the pulmonary veins.[18,19] The successful ablation of these initiating foci has been encouraging as a possible cure for this subset of atrial fibrillation. However, while the initial results have been encouraging, further study on the efficacy and short- and long-term complications of this procedure is still needed. In order to map the site of these initiating foci, one or more multipolar catheters are positioned in the different pulmonary veins via a transseptal puncture. These catheters are then used to map the earliest signal arising from the pulmonary veins that initiate either atrial fibrillation or atrial premature beats as a surrogate of atrial fibrillation. Criteria to predict successful sites of ablation while limiting complications including that of pulmonary vein stenosis are still being developed.

Modification of Sinus Node Function in Patients with Inappropriate Sinus Tachycardia

Patients with inappropriate sinus tachycardia have a resting tachycardia with abrupt increases in rate with mild exertion.[20] Typically, the arrhythmia shows diurnal variation, with slowing to normal rates at night. These patients have an increased intrinsic heart rate and excessive response to exercise or catecholamines.[20] Catheter-ablative techniques have been introduced that allow for identification of the most rapid pacemaker region of the sinus node complex.[21] This is usually found over the superior crest of the crista terminalis. One or more radiofrequency lesions are placed in this area, producing dramatic decreases in the sinus rate.[22] In addition, when this procedure is successful, there is marked attenuation of the heart rate response to exercise or catecholamines. However, narrowing of the superior vena cava-right atrium junction has been reported,[23] and the long-term follow-up of these patients may not be as encouraging as previously thought.

Ablation of Ventricular Tachycardia Foci

One of the most demanding of the catheter-ablative techniques is attempted ablation of foci initiating ventricular tachycardia. For this procedure, multipolar electrode catheters are inserted into the right ventricle, coronary sinus, and left ventricle. Ventricular tachycardia is induced by using standard stimulation protocols, and the catheters are manipulated within the ventricles to determine the earliest ventricular endocardial electrogram (during ventricular tachycardia) in relation to at least three reference orthogonal surface leads.[24] Ventricular overdrive pacing is used in an attempt to entrain the tachycardia and to prove that the earliest endocardial potentials precede (rather than follow) the tachycardia complex. In addition, the putative focus of ventricular tachycardia is paced in an effort to determine whether the paced complexes are identical or similar to the induced tachycardia.[25] The latter procedure is known as *pace mapping*. For patients with ventricular tachycardia due to coronary artery disease, concealed entrainment is manifest by a prolonged paced spike to QRS, a paced QRS identical to spontaneous tachycardia, and a postpacing interval identical to the spontaneous ventricular tachycardia cycle length, which appears to best identify the critical slow zone for the ventricular tachycardia reentrant circuit.[26] Once the putative isthmus is found, one or more radiofrequency applications are delivered from the distal electrode near this endocardial site to a chest-wall patch.

A subset of patients with ventricular tachycardia and structural heart disease particularly amenable to catheter ablation are those with bundle-branch reentrant arrhythmias. These patients are recognized by having a left intraventricular conduction delay or a frank pattern of left bundle-branch block. The majority have an associated cardiomyopathy, and all have prolonged infranodal conduction. In these patients, the tachycardic mechanism involves bundle-to-bundle conduction.[27] Catheter cure may be achieved by ablation of the right bundle branch. The right bundle usually is draped superficially over the right septal surface, and the right bundle potential usually is located easily. The right bundle may be ablated either by direct current or preferably by radiofrequency

discharges.[27] Even after successful ablation of the right bundle branch, further electrophysiologic testing is in order to exclude ventricular tachycardia emanating from myocardial sources.

Other forms of ventricular tachycardia that may be particularly amenable to catheter ablation are those occurring in patients without structural cardiac disease. These patients present with tachycardia emanating from either the right ventricular outflow tract[28] or from the inferior left septum.[29] Patients with tachycardia emanating from the right ventricular outflow show a pattern of left bundle-branch block with an inferior axis. The arrhythmia is often exercise-induced and may respond to carotid massage or treatment with adenosine or beta blockers. This arrhythmia is thought to be a cyclic AMP-dependent triggered arrhythmia. The hallmark of proper ablation includes detection of early areas in the outflow tract and a precise correspondence between the paced map and spontaneous ventricular tachycardia. Another important site of ventricular tachycardia in normal hearts may emanate from the left apical septum. This arrhythmia is characterized by a pattern of right bundle-branch block associated with a left superior axis. This arrhythmia most often responds to intravenous verapamil. Ablative approaches include recording a Purkinje potential just in front of the QRS complex and/or a paced map that corresponds to the spontaneous tachycardia.

NEXT

Chapter 28: TREATMENT OF CARDIAC ARRHYTHMIAS WITH CATHETER-ABLATIVE TECHNIQUES

RESULTS OF CATHETER-ABLATIVE PROCEDURES

AV Junctional Ablation

In 1998, the largest prospective study in the United States relating to the various ablative procedures was gathered from the voluntary ablation registry of NASPE[30] (Tables 28-1 and 28-2). At present, AV junctional ablation is performed using radiofrequency energy application, with a success rate of 98.2 percent and very infrequent complications. The most serious complication is postprocedure death, which occurred in 1 of 629 patients undergoing ablation. The death was due to loss of pacemaker capture after the procedure.

Table 28-2: Results of Catheter Ablation for Ventricular Tachycardia from NASPE Voluntary Registry, 1998

	VT with CAD	VT with Cardiomyopathy	VT with Structurally Normal Heart
Total performed	53	42	119
Success (%)	58.5	61.9	84.9

ABBREVIATIONS: VT, ventricular tachycardia.
SOURCE: Unpublished data from NASPE Voluntary Registry, 1998.

Ablation of Accessory Pathways

In the NASPE voluntary registry,[30] ablation of accessory pathways was attempted in 654 patients. The overall rate of successful ablation for left-sided pathways was 94 percent, as compared with a success rate of 96 percent for right free wall and 84 percent for septal accessory pathways. Significant complications, including 4 procedure-related deaths, occurred in 1.8 percent of patients. The major complications reported were hematoma/bleeding (12 patients), cardiac tamponade (7 patients), inadvertent heart block (5 patients), and damage to the coronary arteries, including a patient who required angioplasty.

Ablation for Patients with AV Node Reentry

The largest reported series of patients undergoing catheter treatment of AV node reentry again comes from the NASPE voluntary registry,[30] which included 1197 patients who underwent ablation of a slow pathway. The success rate was 96 percent in these patients, with the development of inadvertent AV block in only 4 patients (0.33 percent).

Ablation of Atrial Flutter/Atrial Tachycardia

A total of 477 patients underwent attempted flutter ablation in the NASPE registry. The reported success rate for flutter was 85 percent and for atrial tachycardia (227 patients) 72 percent. Reported complications included development of complete AV block (3 patients) and cardiac tamponade (3 patients).

Ablation of Focal Atrial Fibrillation

To date, in the published series of patients who have undergone ablation of focal atrial fibrillation, no recurrence of atrial fibrillation has been reported in 62 and 86 percent of patients in 8- and 6-month follow-up periods.[18,19] Reported complications[19,32] have included cerebral transient ischemic attacks (2 patients), hemothorax (1 patient), hemopericardium (1 patient), and pulmonary vein stenosis (5 patients).

Ablation of Ventricular Tachycardia

Successful ablation was more frequent in those with ventricular tachycardia associated with no structural heart disease (85 percent), including those with right ventricular outflow tract tachycardia or left septal tachycardia, compared with ablation for ventricular tachycardia associated with coronary artery disease (58 percent) or idiopathic cardiomyopathy (62 percent).[30] Major complications included a post-procedural death from presumed respiratory failure and cardiac tamponade, pulmonary edema, systemic emboli, AV block, and femoral artery thrombosis.

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Chapter 28: TREATMENT OF CARDIAC ARRHYTHMIAS WITH CATHETER-ABLATIVE TECHNIQUES

ADVANTAGES AND DISADVANTAGES OF CATHETER-ABLATIVE TECHNIQUES

Advantages

The use of catheter-ablative techniques has greatly affected our approach to the management of patients with supraventricular tachycardia. Catheter ablation of the AV junction has replaced the need for surgical ablation of the His bundle for patients with atrial arrhythmias refractory to drug therapy. Furthermore, use of catheter procedures allows cure of patients with reentrant supraventricular arrhythmias. The initial reports suggest a cure rate of 90 to 100 percent with minimal serious adverse effects.[31] For selected patients with ventricular tachycardia, catheter-ablative procedures may obviate the need for surgical intervention. This is particularly true for patients with bundle-branch reentry or for those with right ventricular outflow tract or left septal tachycardias.

Disadvantages

The chief disadvantage of AV junctional ablation is the need for chronic cardiac pacing after successful ablation. Another serious adverse effect is the reported 2 to 4 percent incidence of polymorphous ventricular tachycardia occurring in the postablative period.[33] This arrhythmia is more common in patients with severe myocardial disease, bradycardia, and electrolyte abnormalities, and may be prevented by temporarily pacing the heart at relatively fast rates immediately after ablation. The chief complication reported for patients undergoing AV modification procedures for AV nodal reentry is the risk of complete AV block. Attempted ablation of the slow AV nodal pathway promises to diminish or obviate this risk.

The risks of catheter ablation of accessory pathways appears to be related to the pathway site. Reported complications for left free wall pathways include the risk of systemic embolization, tamponade, or damage to the left circumflex coronary artery. Ablation of septal pathways carries the risk of causing inadvertent complete AV block. Fortunately, the risk of significant complications appears to be on the order of approximately 2 percent.

Major complications have been reported in the use of catheter-ablation treatment of ventricular tachycardia. Such complications include the risk of cerebrovascular accidents, damage to the aortic valve, or tamponade.

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CONCLUSION

The introduction of catheter-ablative techniques has completely revolutionized our approach to the management of patients with supraventricular tachycardia. These techniques have evolved to the point where curative ablative procedures are recommended as the treatment of choice for all symptomatic patients with tachycardias mediated by accessory pathways or with atrial flutter and for most patients with symptomatic AV nodal reentrant tachycardia. Complete AV junctional ablation is the procedure of choice for those with drug-refractory atrial arrhythmias, whereas selected patients with ventricular arrhythmias may benefit from catheter-ablative techniques; however, the vast majority of these patients are best managed by drugs, devices, or surgical therapy.

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 29A:

PRINCIPLES OF EXTERNAL AND INTERNAL CARDIOVERSION AND DEFIBRILLATION

Authors: Bernard Lown, Regis A. DeSilva

The application of electrical current is standard treatment for termination of atrial and ventricular tachyarrhythmias in emergency situations and when these conditions are refractory to pharmacologic treatment.[1] *Cardioversion* is the discharge of electrical energy synchronized on the R wave, while *defibrillation* refers to unsynchronized discharge. Cardioversion is, by definition, a synchronized direct-current discharge; thus this term does not apply to ventricular defibrillation or to the pharmacologic reversal of arrhythmias. The standard unit of measurement is the joule (J), and 1 J equals 1 watt-second. As there may be a wide discrepancy between the stored energy level indicated on the defibrillator and the actual delivered energy, the device should be periodically checked across a standardized resistance for reliability. The electrophysiologic basis for cardioversion is probably the closure of the "excitable gap" in a reentrant electrical circuit. Abolition of the circuit for the arrhythmia may be accomplished with energy levels as low as 1 to 5 J, and this might account for the success in terminating reentrant arrhythmias such as atrial flutter and ventricular tachycardia. Defibrillation requires much higher energy levels, which may be due to the necessity for depolarizing a large number of multiple asynchronous reentrant circuits. Energy requirements for cardioversion and defibrillation may be affected by such factors as the duration of the arrhythmia, electrolyte imbalance, underlying metabolic states, and the use of antiarrhythmic drugs such as amiodarone.

PROCEDURE

Elective cardioversion should preferably be done early in the morning in the fasting state. In urgent cases, meals should be withheld for as long as possible. Serum levels for electrolytes, digoxin, blood urea nitrogen, and creatinine should be obtained and hypokalemia corrected before cardioversion is attempted. Digitalis glycosides should be withheld only on the day of cardioversion, but if digitalis toxicity is suspected, the procedure is postponed until the problem is resolved. An intravenous line is inserted, vital signs and the electrocardiogram (ECG) are monitored, and equipment for cardiopulmonary resuscitation (CPR) is made available. General anesthesia is administered via a face mask or intravenous diazepam or midazolam is used for sedation.

Synchronization with the tallest R wave on the ECG prevents accidental triggering of ventricular fibrillation (VF); (see Fig. 29B-1) resynchronization should be checked after each discharge, as the device may revert to the default setting for defibrillation. Improper synchronization may occur when there is bundle-branch block with a tall R wave, when the T wave is highly peaked, and with artifactual spikes from a malfunctioning pacemaker. Electrodes are placed in either an anterolateral or an anteroposterior position. The anterior electrode is placed parasternally over the right second and third intercostal spaces. The lateral electrode is positioned over the cardiac apex. If a flat posterior electrode is available, it is placed at the tip of the angle of the left scapula. Current flow in either configuration is along the long axis of the heart, encompasses the bulk of cardiac tissue and minimizes travel through high-impedance bony tissue. Electrode paste, with firm pressure on the paddles, should be used to provide adequate electrical contact and reduce transthoracic impedance. Bridging of the electrodes by conductive paste

should be avoided, as this will reduce the amount of energy delivered to the heart. Pregelled adhesive electrodes may also be used in the positions described above. Prior to discharge, cardiopulmonary resuscitation (CPR) should be stopped and an "All clear" signal should be given to avoid the accidental shocking of attendants. Defibrillator waveforms are discussed in Chap. 29B.

Energy titration reduces both energy use and complications. The initial setting may be as low as 10 J, as this may be successful for atrial flutter and stable ventricular tachycardia. Energy output is increased progressively to 25, 50, 100, 200, and 360 J. Lead II of the ECG is monitored to determine whether normal sinus rhythm (NSR) has been reestablished. If serious ventricular arrhythmias emerge after a discharge, especially if digitalis toxicity is suspected, the procedure is discontinued. Alternatively, xylocaine may be administered prophylactically before the next discharge and cardioversion cautiously continued. Following cardioversion, a proper airway is maintained and adequate ventilation delivered until recovery from anesthesia occurs. Vital signs and cardiac rhythm are monitored for at least 24 h to detect the late emergence of malignant ventricular arrhythmias or recurrence of the underlying arrhythmia.

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Chapter 29A: PRINCIPLES OF EXTERNAL AND INTERNAL CARDIOVERSION AND DEFIBRILLATION

TREATMENT OF SPECIFIC ARRHYTHMIAS

Atrial Fibrillation

Approximately 50 percent of patients admitted to hospital for atrial fibrillation (AF) will revert spontaneously to normal sinus rhythm (NSR) within 48 h.[2] Cardioversion is the treatment of choice if spontaneous or pharmacologic reversion to NSR does not occur, if the patient is symptomatic with chest pain during myocardial infarction, or during rapid ventricular rates in preexcitation syndrome when VF may supervene. Normal rhythm following cardioversion obviates the need for long-term anticoagulation. There is also a decrease in fatigue, increase in exercise capacity, and improvement in cerebral blood flow. Both physical and electrical remodeling occurring with AF may be reversed following cardioversion, with changes in right and left atrial volumes.[3,4] Treatment with sotalol, quinidine, disopyramide, or verapamil for at least 48 h before cardioversion may prevent early recurrence. Success of cardioversion in maintaining NSR is dependent on factors such as the duration of arrhythmia, the size of the left atrium, underlying conduction system disease, presence of valvular heart disease, and the patient's age. Overall, the success rate is over 90 percent using 200 J or less and the mean energy level required is 87 J (see also Chap. 29B). The use of atropine to abolish high vagal tone facilitates reversion to NSR.[5] Infusion of ibutelide promotes reversion to NSR experimentally. The use of high-energy cardioversion with 720 J has also been described for refractory AF.[6] Recurrence of arrhythmia is predicted by a left atrial size of 45 mm or greater and a less than 10 percent increase in the *a* wave on Doppler echocardiography following cardioversion.[7]

Higher energy levels may be required to terminate AF in congestive heart failure. Treatment of heart failure before cardioversion will increase the success rate. Acute myocardial infarction is not a contraindication to cardioversion and, in fact, prompt reversion will help prevent infarct extension by decreasing heart rate and reducing oxygen consumption. In patients with conduction system disease, emergence of atrial ectopic activity, severe sinus bradycardia, sinus arrest, junctional rhythm, or multifocal atrial tachycardia may follow cardioversion, with gradual restoration of NSR. In such cases, atropine or isoproterenol treatment may be required. If conduction system disease is suspected (e.g., a slow ventricular response in the absence of drug treatment), a temporary pacemaker is inserted prior to cardioversion, as asystole may result following the shock. Energy titration, as described earlier, anticipates this complication, and if pacing is not available, cardioversion should be abandoned if the first few discharges evoke severe bradyarrhythmia.

Cardioversion may not benefit patients with severe mitral valve disease who have "giant" scarred atria, those with mitral valve replacement, and patients with chronic recurrent paroxysmal atrial tachyarrhythmias. Although successful low-energy internal cardioversion can be performed and implantable devices are available for long-term treatment of AF, these methods are rarely indicated and seldom justified.

Thromboembolism is a major risk of atrial fibrillation resulting from stasis and inadequate emptying of the left atrial appendage and low transmitral flow velocity. Anticoagulation reduces the incidence of emboli and is recommended in the absence of contraindications.[8,9] Warfarin is

started a minimum of 3 weeks before cardioversion to maintain a prothrombin time of 1.3 to 1.5 times the control value, or an International Normalized Ratio (INR) of 2.0-3.0. Treatment is maintained for 4 weeks after cardioversion because delayed embolism may occur. Such embolism may result if there is delayed resumption of atrial activity due to "stunning" after successful cardioversion of AF. Doppler echocardiography is useful in documenting the presence of atrial contraction, as the absence of an atrial *a* wave suggests electromechanical dissociation.[7] Anticoagulation beyond 4 weeks may be indicated in the presence of recurrent bouts of AF, prosthetic valves, or cardiomyopathy or if there is a history of previous embolization or stroke.

In cases where AF is known to be of acute onset (i.e., <24 h) or in emergency situations, cardioversion may be performed without long-term anticoagulation. Heparin is started and simultaneous treatment with warfarin may be necessary, as AF may recur or embolization may occur later due to delayed resumption of atrial contraction. In elective cases, the absence of thrombus documented by transesophageal echocardiography (TEE) is not an adequate reason to withhold anticoagulation as it does not protect the patient from the risk of thromboembolism.[10-13] Because of differences in sophistication of the equipment used for TEE, patient selection, and conflicting data, absence of intraatrial clot by TEE cannot be recommended as the standard for decision making prior to cardioversion.[12] Late embolic complications result from one of three possible mechanisms: delayed resumption of atrial mechanical activity due to stunning of the atria, formation of clots after cardioversion during sinus rhythm, or relapse of AF. In 98 percent of cases, embolization occurs within 10 days of cardioversion.[14] If warfarin is contraindicated, aspirin may be utilized, but there is no persuasive evidence that such treatment protects against embolism during or following cardioversion.

Atrial Flutter

If drug treatment with an agent such propafenone or sotalol is unsuccessful, cardioversion is the treatment of choice for this arrhythmia. In many cases, the arrhythmia does not recur and maintenance of drug treatment may be unnecessary. The arrhythmia is often benign unless there is 1:1 atrioventricular conduction, when syncope may occur. Low-energy shocks easily revert atrial flutter to sinus rhythm. The mean energy level generally required is 25 J, and in 95 percent of cases 50 J or less suffices. Anticoagulation should be administered before and after cardioversion, as for AF, because of the risk of embolism.

Supraventricular Tachycardia

Because this arrhythmia is often responsive to vagal maneuvers and/or to several antiarrhythmic drugs, cardioversion is only rarely necessary for reversion. If such treatment fails, cardioversion with energy levels between 100 and 360 J is required. In paroxysmal atrial tachycardia with block due to digitalis intoxication, cardioversion is extremely hazardous, as VF and death may result. When digitalis toxicity is suspected, energy titration is cautiously attempted, with xylocaine pretreatment for ventricular arrhythmia if necessary. If low-energy discharges provoke high grades of arrhythmia or atrioventricular block, cardioversion is discontinued.

Ventricular Tachycardia

When a chest thump and intravenous xylocaine or procainamide fail to terminate ventricular tachycardia (VT), cardioversion should be performed promptly. Unless the arrhythmia is clinically unstable, sedation is administered. Energy titration is performed in stable VT and as little of 1 to 5 J may succeed; in 90 percent of cases, 10 J or less is successful in terminating the arrhythmia. Only rarely is more than 100 J necessary. When VT is rapid and the QRS complex and T wave indistinguishable, or if the patient becomes syncopal due to hemodynamic deterioration, an unsynchronized discharge of 100 J is delivered immediately. If this attempt fails, discharges of

200, 300, and 360 J should be administered consecutively until sinus rhythm is restored. Polymorphic VT and torsades de pointes, which are not self-terminating or responsive to drugs, may be similarly treated.

Ventricular Fibrillation

Unsynchronized discharge is the treatment of choice for VF and is performed using a standard defibrillator or an automatic external defibrillator (AED). This setting is also used for "blind defibrillation" in an unmonitored patient in cardiac arrest; the electrode positions are similar to those used for cardioversion. The procedure for defibrillation is delivery of an initial shock of 200 J following institution of CPR, followed by a second 200- or 300-J shock and a third 360-J shock if VF persists. If these attempts fail, 0.5 to 1.0 mg of intravenous epinephrine is given and defibrillation at 360 J is attempted again. There is no clear evidence that there is a relationship between body weight and energy requirements for defibrillation. For children, 1 to 2 J/kg is recommended; in small children and infants, a little as 10 J might suffice.

A variety of lightweight AEDs using either damped sinusoidal or monophasic truncated exponential waveforms, with varying types of hardware and software, are now available.[15-17] These devices include features such as strip-chart recorders, screen displays, and voice-synthesizer messages for the operator and devices to record the ECG and the voices of the operators. These defibrillators are equipped with computerized algorithms that recognize VF or rapid VT, permitting automatic or semiautomatic firing of the device within 8 to 10 s. These devices are intended for use in the field, where highly trained personnel are not available and therapeutic options are limited. Adhesive defibrillator pads are attached to the patient's chest in the position suggested for standard defibrillation. Resuscitative maneuvers are stopped and radio transmitters and receivers not operated during initial signal recording so as to prevent interference. Signal recognition may take up to 15 s before the defibrillator discharges; prior to this the device will automatically announce the imminent delivery of a shock by providing a printed message, a visual alarm, or a voice statement so that the attendants are not accidentally shocked. Following delivery of the first shock, CPR is not reinstituted so that the device can accomplish signal analysis and deliver additional shocks if necessary. Following successful termination of ventricular fibrillation, the airway is kept clear of secretions and vomitus, adequate ventilation with supplemental oxygen is continued, and the patient is monitored in an appropriate setting for further management. If defibrillation occurs outside of a medical facility, the patient is intubated if necessary, hemodynamically stabilized, and transported to a hospital as soon as possible.

The major determinant of success or failure of defibrillation relates to the time elapsed between the onset of cardiac arrest and defibrillation. Failure to terminate VF may be due to operator error or due to irreversibility of the underlying condition. In refractory VF, correction of hypoxia, acid-base imbalance, and electrolyte derangements as well as administration of isoproterenol (to convert fine-grain fibrillation to coarse-grain fibrillation) all render successful defibrillation more likely. If this approach is unsuccessful, rapid serial delivery of two or three 360-J shocks may succeed owing to reduction in transthoracic impedance following consecutive shocks. Rarely, fine-grain fibrillation may appear as asystole on a monitor and defibrillation should be attempted. In this setting, automatic defibrillators may fail to trigger a discharge. Current-based defibrillation (rather than an energy-based system) delivering approximately 30 to 40 A per shock has been advocated to increase success rates.[17-19] Automatic measurement of transthoracic impedance (ranging from 70 to 80 ohms in adults) before delivery of the shock avoids delivery of high currents in patients with low chest impedance and low currents in those with high impedance. Thus, success rates for defibrillation may be increased and cardiac damage minimized. If all defibrillation attempts fail to revive the patient, a rapid and thorough assessment of the resuscitative and defibrillation procedures is necessary to check for errors, such as improper electrode placement and the use of inappropriate energy levels. With AEDs, it is essential to check

for proper contact of the defibrillator pads and for proper signal analysis. If, however, no errors are detected and if the patient is unresponsive, a decision about terminating resuscitation is warranted, as severe brain damage occurs with prolonged resuscitation.

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Chapter 29A: PRINCIPLES OF EXTERNAL AND INTERNAL CARDIOVERSION AND DEFIBRILLATION

COMPLICATIONS

Morphologic and functional cardiac damage may follow the use of high-energy shocks. Creatine kinase elevation following electrical discharge is transient, derives from skeletal muscle, and usually does not mask the diagnosis of acute myocardial infarction. Intracellular potassium is released from electrical trauma and may contribute to the intractability of ventricular fibrillation. Hyperkalemia may result from repeated high-energy shocks. The occurrence of postcardioversion ventricular arrhythmias is related to the presence of hypokalemia, digitalis toxicity, severe heart disease, improper synchronization, and the repeated use of high-energy discharges. Asystole and cardiac arrest are rare and occur when there is severe conduction system disease. When VF occurs several hours after cardioversion, it may be due to toxicity from digoxin, quinidine, or other antiarrhythmic agents.

Pulmonary edema following cardioversion occurs most often in the presence of mitral or aortic valvular disease or left ventricular dysfunction. It may also relate to electrically induced alterations in myocardial function, fluid overload, delayed return of atrial function, and pulmonary embolism. The risk of systemic embolization has already been discussed. Unexplained hypotension, possibly due to vasodilation, sometimes occurs after cardioversion; fluid replacement will usually correct this problem.

In the presence of implanted cardioverter-defibrillators (ICD) and pacemakers, defibrillator electrodes should be placed at least 12 cm from the generator before discharge to prevent temporary or permanent malfunction. Additionally, the metal generator may absorb electrical energy and reduce the effectiveness of the discharge. Following cardioversion or defibrillation, pacing thresholds may increase due to myocardial burns caused by transmission of electrical energy to the paced site. Because the pacing threshold may increase gradually over weeks with subsequent loss of capture by the pacemaker, serial threshold measurements should be checked not only immediately following discharge but also for 2 months afterward.

Cardioversion has been safely performed during pregnancy and fetal death has not been reported as a direct consequence of treatment. Nonetheless, fetal monitoring with an obstetrician in consultation is appropriate in this situation. Despite the possible complications described with the use of electrical energy, cardioversion and defibrillation have been performed for several decades now with a high degree of safety.

The implantable atrial defibrillator is discussed in Chap. 29B.

Chapter 29A: PRINCIPLES OF EXTERNAL AND INTERNAL CARDIOVERSION AND DEFIBRILLATION

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 29B:

CLINICAL APPLICATION OF EXTERNAL AND INTERNAL CARDIOVERSION AND DEFIBRILLATION

Authors: Hein J. J. Wellens, Carl Timmermans, Luz-Maria Rodriguez

Electricity was first applied to the heart in 1775 when Abildgaard used electric current both to stun and to revive animals.[1] The first successful human ventricular defibrillation was reported by Beck in 1947.[2] Cardioversion of atrial fibrillation to sinus rhythm by a synchronized direct current shock was introduced by Lown in 1962[3] (see Chap. 29A). Nowadays, the application of electric current is a standard treatment for termination of atrial and ventricular tachyarrhythmias. *Cardioversion* refers to the discharge of electrical energy synchronized on the R wave, whereas *defibrillation* refers to an unsynchronized discharge. Further progress in the electrical treatment of tachyarrhythmias was made when external defibrillation paddles or skin patches were replaced by internal defibrillation electrodes (or patches) and when biphasic, instead of monophasic sinusoidal, defibrillator waveforms were used (see also Chap. 29A).

EXTERNAL CARDIOVERSION AND DEFIBRILLATION

Technique

After the procedure has been explained to the patient, a physical examination should be performed prior to elective external cardioversion. Patients should be cardioverted in a fasting state. The serum potassium level should be normal. Knowledge of renal function is helpful in guiding the dosage of adjunctive medication. If there is clinical or electrocardiographic suspicion of digitalis toxicity, the procedure needs to be postponed. The use of anticoagulation is discussed in the section "Treatment of Specific Arrhythmias," below. The patient should have a reliable intravenous access, and dentures should be removed. A short-acting anesthetic or sedative agent (preferably with amnesic effects, e.g., midazolam) is administrated by a qualified physician. The cardioversion should be carried out in an area with facilities for an eventual cardiopulmonary resuscitation. A 12-lead electrocardiogram is recorded before and after the procedure, and during the cardioversion, a rhythm strip is obtained, or at least the patient's rhythm should be shown on a monitor screen. Synchronization of shock delivery with the R wave of the QRS complex is essential during cardioversion. Although properly synchronized shocks rarely, if ever, induce ventricular fibrillation, unsynchronized shocks may be delivered in the ventricular vulnerable period of the preceding beat (near the apex of the T wave) and result in ventricular fibrillation (Fig. 29B-1). The appropriateness of synchronization of each shock delivery always should be verified because a large or tall T wave or P wave, artifacts, or noise can be misidentified as the R wave. Improper synchronization also may occur when the QRS complex has a right bundle-branch block configuration with a tall secondary R wave.

The two standard electrode positions are the anterolateral and anteroposterior positions. In the anterolateral position, the anterior electrode is placed parasternally over the right second and third intercostal spaces, and the lateral electrode is placed just below the fourth intercostal space in the midaxillary line. In the anteroposterior position, the anterior electrode is placed as previously mentioned, and the posterior electrode is positioned just below the left scapula. In case of failure to terminate the arrhythmia, shock delivery can be repeated using the other electrode location.

Some authors do not recommend the anterolateral position for cardioversion of atrial fibrillation because this position probably does not provide optimal current flow through the atria.[4]

Successful defibrillation and cardioversion requires sufficient flow of electric current through the appropriate chambers of the heart. Current flow is determined by the shock strength and the transthoracic impedance. Most available defibrillators have a maximum energy setting of 360 J, representing the maximal amount of energy delivered through a 50-Ω resistance. It was determined that the transthoracic impedance in adults of a first shock of 100 J or more varies between 25 and 150 Ω, with an average of 75 Ω.[5] If the impedance is high, low-energy shocks will fail to terminate the arrhythmia. Several authors reported on the different factors that influence transthoracic impedance, including the electrode size, the distance between the electrodes, the couplant medium and pressure between the electrode and the chest wall, the phase of respiration, a recent sternotomy, and previous shocks.[4,6] Optimal electrode size seems to be 8 to 12 cm in diameter for adults. This electrode size also should be used for children weighing more than 10 kg. Wide separation of the electrodes must be maintained especially if the coupling medium is a paste or gel. In women, the lateral electrode should be placed lateral to or under the breast. Although self-adhesive disposable electrode pads have advantages in certain circumstances with high-risk cardiac patients, their slightly higher impedance makes their use not optimal in patients predisposed to a high transthoracic impedance. Firm electrode pressure with the patient in full expiration reduces transthoracic impedance and enhances the likelihood of shock success. A sternotomy reduces transthoracic impedance for at least 1 month after the procedure. Finally, impedance also lowers after repeated shock delivery.

Prior to each shock delivery, attendants should be warned in order to avoid their accidental shocking. Following cardioversion, a proper airway is maintained, and adequate ventilation is delivered until recovery from anesthesia occurs.

Defibrillator Waveforms

Alternating current was first used for ventricular defibrillation. It is a sine wave that oscillates between positive and negative polarity with a well-defined frequency (Fig. 29B-2*A*). Because of significant side effects and technical constraints, alternating current was replaced by a single-capacitor discharge or direct-current defibrillation.[7] A single-capacitor discharge generates a high-voltage peaked wave with an exponential decay (undamped exponential waveform,[3,7] see Fig. 29B-2*B*). Rounding of this initial peak using an inductor (damped capacitor discharge) gave rise to the until now most frequently used monophasic damped sinusoidal waveform for external defibrillation and cardioversion (Fig. 29B-3). Depending on the defibrillator characteristics and the impedance of the patient, the monophasic sinusoidal waveform does not oscillate between the baseline (critically damped capacitor discharge; Edmark waveform, see Fig. 29-3*A*) or has one or more terminal negative components (underdamped capacitor discharge; Lown or Gurvich waveform).[7] Less frequently, a defibrillator uses an undamped capacitor discharge with a long time constant that is then truncated so that it resembles a square or trapezoidal wave (monophasic truncated exponential waveform,[7] see Fig. 29-3*B*). Only limited clinical information is available on the effectiveness of this waveform.[8]

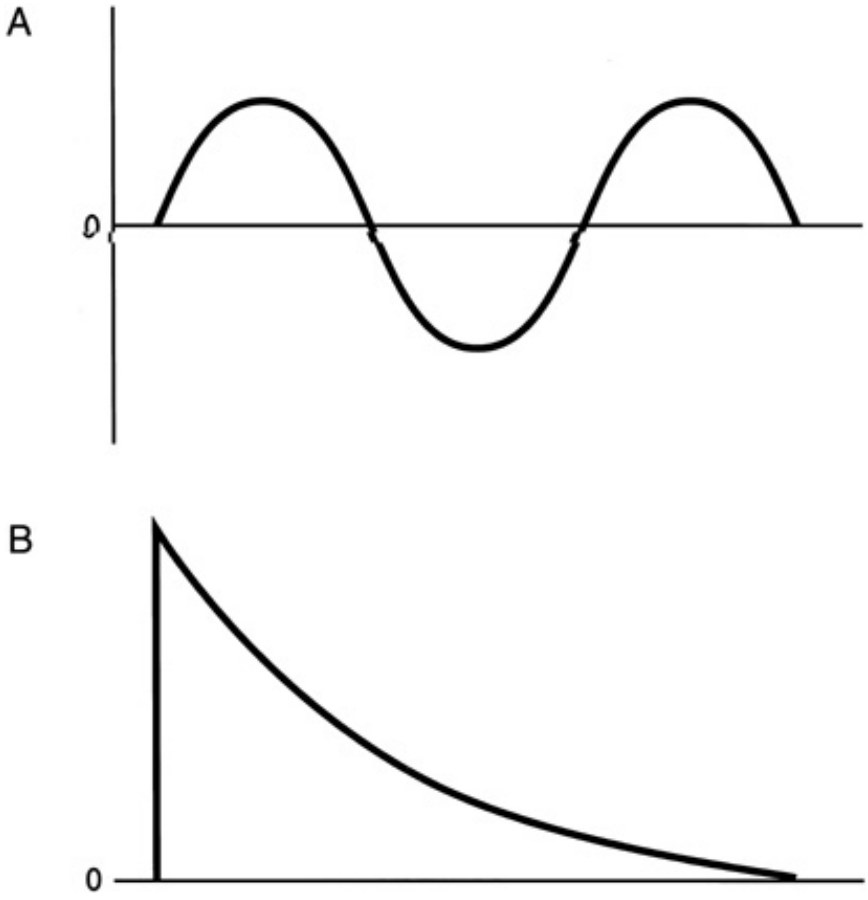

Figure 29b-2: *A.* Alternating current. *B.* Direct current.

Due to the development of an implantable cardioverter defibrillator, biphasic waveforms have been examined in several experimental and clinical studies over the last two decades. A biphasic truncated waveform, which consists of both a positive and a negative phase (see Fig. 29-3*C*), may offer several technical advantages over a monophasic sinusoidal waveform and seems to allow external defibrillation at lower energy levels. These lower amounts of energy, together with removal of the inductor, makes an external defibrillator using a biphasic waveform small, light, cheap, and easy to maintain. In a multicenter study it was demonstrated that 115- to 130-J biphasic truncated transthoracic shocks defibrillate ventricular fibrillation as well as 200-J monophasic damped sine-wave transthoracic shocks.[9] However, in this study, the 115- or 130-J biphasic shocks appeared to be not as successful as the 360-J monophasic shocks.

Recently, low-energy impedance-compensating biphasic waveforms have been evaluated for the treatment of ventricular as well as atrial arrhythmias. These defibrillators automatically adjust the duration of the waveform for the transthoracic impedance of the patient during shock delivery.[10]

NEXT

Chapter 29B: CLINICAL APPLICATION OF EXTERNAL AND INTERNAL CARDIOVERSION AND DEFIBRILLATION

TREATMENT OF SPECIFIC ARRHYTHMIAS

Atrial Fibrillation

Because cardioversion of atrial fibrillation is a safe and effective method to restore sinus rhythm, the procedure should be attempted at least once in every patient with chronic atrial fibrillation. Furthermore, due to the proarrhythmogenic effect of antiarrhythmic drugs, cardioversion also may be preferred to the intravenous administration of these drugs in patients with symptomatic, long-standing paroxysmal atrial fibrillation. Overt congestive heart failure and hyperthyroidism should be controlled as much as possible before cardioversion. Acute myocardial infarction is not a contraindication to cardioversion; prompt restoration of sinus rhythm would help prevent infarct extension by decreasing the heart rate and reducing oxygen consumption. If atrioventricular conduction disturbances are suspected (e.g., a slow ventricular response in the absence of antiarrhythmic drug treatment), cardioversion should be avoided because asystole may result or should be performed after the insertion of a temporary transvenous pacing catheter.

The immediate success rate of external cardioversion varies between 70 and 94 percent.[3,11] This variation in outcome may be due to the use of different definitions for a successful cardioversion, other patient characteristics, and pretreatment with antiarrhythmic drugs. The probability of a successful cardioversion depends mainly on the duration of the atrial fibrillation episode.[3,11] Other factors such as the transthoracic impedance,[5] left atrial size, and the patient's age[12] are also important for acute success. The maintenance of sinus rhythm after cardioversion is less favorable. In a metaanalysis performed by Coplen et al.,[13] only 45, 33, and 25 percent of the patients who were not taking antiarrhythmic drugs remained in sinus rhythm at 3, 6, and 12 months after cardioversion, respectively. Although the administration of antiarrhythmic drugs prolongs to a certain extent the arrhythmia-free period after external cardioversion, use of these drugs is not without risk. Several clinical variables including etiology and duration of atrial fibrillation, age, and echocardiographic variables such as size and function of the left atrium and left atrial appendix are considered to have a certain predictive value for the recurrence of the arrhythmia.

The initial shock strength should be 100 J, followed by a second 200-J shock and a third 360-J shock if atrial fibrillation persists. In patients in whom 360 J fails to restore sinus rhythm, a second 360-J shock may be delivered again. Shocks lower than 200 J are particularly likely to be effective when the duration of atrial fibrillation is shorter than 24 h or when the patient does not have structural heart disease or is not receiving antiarrhythmic drugs.[14]

Patients undergoing electrical cardioversion are at risk for thromboembolic complications. Two mechanisms may be responsible: (1) dislodgment of a preexisting atrial thrombus after resumption of mechanical atrial activity and (2) left atrial appendage stunning or impaired function immediate after cardioversion. It is recommended for patients with atrial fibrillation of unknown or long duration that anticoagulation should be given for 3 weeks before elective cardioversion to maintain an international normalized ratio (INR) of 2.0 to 3.0. Anticoagulation should be continued for 4 weeks after successful cardioversion. It is usual clinical practice not to give anticoagulation to patients certain to have had the onset of atrial fibrillation within the preceding 24 to 48 h.[15] The absence of a thrombus documented by transesophageal echocardiography is not

an adequate reason to withhold anticoagulation because it does not protect the patient from the risk for thromboembolism.[16] Even if short-term anticoagulation is combined with transesophageal echocardiography, this approach has not yet proved to be safer than the prophylactic anticoagulation 3 weeks before cardioversion.[17] In any case, the short-term anticoagulation needs to be extended to 4 weeks after cardioversion.

Other Supraventricular Tachycardias

Presently, recurrent episodes of atrial flutter are usually permanently cured with radiofrequency catheter ablation.[18] In patients with atrial flutter and 1:1 atrioventricular conduction, external cardioversion can restore sinus rhythm effectively and safely. In contrast to atrial fibrillation, most episodes of atrial flutter are terminated with lower amounts of energy ranging from 50 to 100 J. An initial shock strength of 100 J is more efficient for restoration of sinus rhythm and induces less frequent atrial fibrillation compared with 50 J.[19] Patients with atrial flutter are considered at low risk for thromboembolism due to the synchronous atrial contraction. Nevertheless, several studies suggest that the thromboembolic risk at the time of cardioversion is higher than expected.[20,21] Intermittent transition to atrial fibrillation may explain the development of thrombi, and patients with atrial flutter are also at risk of developing atrial stunning after cardioversion. Therefore, consideration should be given to anticoagulate patients with atrial flutter the same as patients with atrial fibrillation.[15]

Other supraventricular tachycardias rarely require external cardioversion unless they produce hypotension, heart failure, or myocardial ischemia (see also Chap. 29A). These arrhythmias also may be terminated by external cardioversion if they are refractory to antiarrhythmic drugs.

Ventricular Tachycardia

When a hemodynamically well-tolerated sustained monomorphic ventricular tachycardia outside an acute ischemic episode cannot be terminated by intravenous procainamide,[22] a low-energy synchronized shock ranging from 25 to 50 J should be delivered. However, these low amounts of energy incidentally may induce ventricular fibrillation. In hemodynamically not tolerated sustained monomorphic ventricular or polymorphic ventricular tachycardia, a 200-J shock should be given, followed by 300 and 360 J if earlier shocks are not successful. In hemodynamically unstable patients with fast ventricular tachycardia, the QRS complex is often indistinguishable from the T wave, and unsynchronized shocks are recommended.

In pediatric patients with hemodynamically not tolerated (supra-) ventricular tachycardia, it is recommended to deliver an initial synchronized shock of 0.5 J/kg. The dose is increased with subsequent attempts if necessary.[23]

Ventricular Fibrillation

Ventricular fibrillation is best explained as a re-entrant mechanism where the waves initially follow certain routes and thereafter degenerate into smaller reentry circuits. This pattern of ventricular activation causes loss of coordinated myocyte contraction and results in loss of mechanical function of the ventricles, leading to death. The arrhythmia is eminently treatable with an unsynchronized discharge of electrical energy. The recommended first shock strength for defibrillation is 200 J. If the first shock fails to defibrillate, a second 200- or 300-J shock should be delivered. The following arguments favor the administration of a second shock of 200 J. First, every defibrillation attempt with a selected amount of energy has a certain probability to terminate ventricular fibrillation. For repeated shocks, the probability should be additive. Second, since transthoracic impedance lowers after repeated shocks, higher current will be delivered to the myocardium using a second shock of the same energy as the first one. The argument favoring the use of a second shock of 300 J is that a greater and more predictable increase in current will occur.

If ventricular fibrillation persists after two shocks, a third 360-J shock should be given.[23] In case of recurrent ventricular fibrillation after a successful defibrillation, shocks with the same energy level as those which were effective previously should be delivered. Higher shock energies should be used only if a shock fails to terminate ventricular fibrillation.

With the advent of biphasic defibrillators, the American Heart Association stated that low-energy (150-J), nonprogressive (150 J-150 J-150 J) biphasic waveform defibrillators may be used for both out-of-hospital and in-hospital ventricular fibrillation arrest, including persistent or recurrent ventricular fibrillation that does not respond to the initial low-energy shock.[24] Ventricular fibrillation is uncommon in children; if it occurs, usually an initial shock strength of 2 J/kg is used. If successful defibrillation has not been obtained, the shock strength should be doubled and repeated. If defibrillation fails, a second shock of 4 J/kg needs to be delivered.[23]

Ventricular fibrillation is the most common cardiac mechanism for sudden death. In the chain-of-survival concept, early defibrillation is a key link to improve survival.[25] Technological improvements in automated external defibrillators, developed almost 20 years ago, made possible the use of defibrillation by non(para)medics. Self-adhesive pads attached to the patient on the standard electrode positions recommended for conventional external defibrillation are used for recording the electrogram and for eventual defibrillation. The automated external defibrillators are fitted with accurate arrhythmia analysis algorithms that recognize ventricular fibrillation or rapid ventricular tachycardia when presented with approximately 8 s of cardiac rhythm, permitting defibrillation within 8 to 10 s either automatically or by advising a rescuer to press a button that delivers a shock. A potential clinical advantage of automated external defibrillators using the conventional monophasic waveform over newer devices equipped with biphasic waveforms for treatment of patients in out-of-hospital arrest awaits proper clinical trials.[24]

Complications

The overall incidence of complications with external cardioversion and defibrillation is low. No myocardial injury occurs following the delivery of even high-energy shocks, as detected by the release of the cardiac isotype of troponin I, a highly specific marker of myocardial lesions.[26] After cardioversion, ST-segment elevation and negative T-waves occasionally may occur. The ST-segment changes usually persist several minutes after shock delivery, whereas the T-wave changes usually last longer. These electrocardiographic changes are related to the amount of energy delivered, but their exact mechanism is unknown. It has been postulated that postshock transient enhanced permeability of the cellular membrane occurs, allowing ionic exchange that leads to membrane depolarization (electroporation).[27] The electroporation is macroscopically manifested as ST-segment changes.

The occurrence of serious ventricular arrhythmias is related to the presence of hypokalemia, digitalis toxicity, severity of heart disease, improper synchronization, and the repeated use of high levels of energy. Asystole and cardiac arrest are rare and occur when there are severe conduction disturbances. Postshock bradycardia may be due to an underlying sick sinus syndrome, the use of antiarrhythmic drugs, or the presence of myocardial ischemia. The risk of embolization after cardioversion of atrial arrhythmias is prevented by adequate anticoagulation.

Damage to the electric circuitry of pacemakers or to the electrode-myocardial interface may occur following cardioversion or defibrillation.[28] Defibrillation electrodes should be placed as far from the pacemaker as possible, preferably in the anteroposterior position. Because pacing thresholds may increase gradually over weeks with subsequent loss of capture by the device, serial pacing threshold measurements for 2 months are recommended. Pulmonary edema, occurring minutes to hours after cardioversion, is a rare complication. It may be due to delayed return of left atrial function, left ventricular dysfunction, and possibly neurohumoral mechanisms.[29] Unexplained hypotension sometimes occurs after cardioversion, and fluid treatment will correct this problem.

External cardioversion and defibrillation cause first-degree skin burns, which are related to the amount of energy used.[30] Rarely, fractures of vertebrae or long bones following cardioversion or defibrillation may occur.

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Chapter 29B: CLINICAL APPLICATION OF EXTERNAL AND INTERNAL CARDIOVERSION AND DEFIBRILLATION

INTERNAL CARDIOVERSION AND DEFIBRILLATION

Initially, the intracardiac delivery of energy was used for the development of implantable cardioverter defibrillators. Chapter 30 is dedicated to the use of these devices for the treatment of ventricular tachyarrhythmia. Only recently, internal cardioversion was introduced as a new treatment modality for patients with atrial fibrillation. The gradual replacement of external defibrillation paddles or skin patches by defibrillation electrodes resulted in effective intracardiac cardioversion of atrial fibrillation using only a small fraction of the energy required for external cardioversion. An esophageal electrode-cutaneous patch configuration allowed the cardioversion of patients with atrial fibrillation with an amount of energy three to four times lower than the energy required for conventional external cardioversion.[31] An early attempt to obtain lower atrial defibrillation thresholds using a single right atrial electrode in combination with a cutaneous patch was disappointing.[32] However, a randomized comparison of this technique with conventional external cardioversion demonstrated a higher immediate success rate of internal cardioversion compared with external cardioversion.[33] In the first study where both defibrillation electrodes were located in the right side of the heart, none of the patients with atrial fibrillation were cardioverted successfully.[34] Only after experimental studies in sheep was it recognized that the optimal lead configuration for internal defibrillation of atrial fibrillation required electrodes encircling as much of the fibrillating atrium as possible.[35] In that study, four right atrial electrode positions (superior vena cava, right atrial appendage, and middle and low right atrium) and three left atrial positions (coronary sinus, left pulmonary artery, and left axillary subcutaneous patch) were evaluated. Additionally, the efficacy of monophasic and biphasic waveforms was compared. It was shown that a 3/3-ms biphasic shock delivered between the right atrium and the coronary sinus had the lowest defibrillation threshold (1.3 ± 0.4 J). The remarkably low amount of energy to convert atrial fibrillation in animals prompted several centers to investigate the use of intracardiac shocks in patients with atrial fibrillation.

Technique

Similar to external cardioversion, evaluation of patients undergoing elective internal cardioversion of atrial fibrillation includes a clinical history, a physical examination, routine laboratory and thyroid function tests, and a 12-lead electrocardiogram. The same oral anticoagulation recommendations should be used as discussed previously for external cardioversion, except that the anticoagulant needs to be interrupted before the procedure to perform a safe venous puncture. Patients are cardioverted in a fasting state, and whenever needed, conscious sedation is provided. Although several techniques are used for internal cardioversion, the following is the most frequently used. Three temporary catheters are inserted in the venous system and positioned under fluoroscopic guidance. Two large-surface-area catheters are used for shock delivery, and a third quadripolar catheter is used for R-wave synchronization and temporary ventricular postshock pacing. In case no ventricular catheter is inserted, the surface electrocardiogram is used for R-wave synchronization. Improperly synchronized shocks, also of low energy, induce ventricular fibrillation (see Fig. 29B-1). The first defibrillation catheter is advanced in the distal coronary sinus, and the second preferably is positioned in the right atrium appendix or, otherwise, in the lateral wall of the right atrium (Fig. 29B-4*A*). The defibrillation catheters are connected to an external defibrillator delivering biphasic shocks. The quadripolar catheter is placed in the apex of the right ventricle and is also connected to an external pacemaker. The right

atrial and right ventricular catheters usually are introduced via a femoral approach. The coronary sinus catheter can be inserted through a femoral, subclavian, jugular, or brachial vein. Alternative positions for the defibrillation catheters are the left pulmonary artery (see Fig. 29B-4*B*) or the left atrium through a patent foramen ovale (see Fig. 29B-4*C*).

Internal cardioversion of atrial fibrillation has several clinical applications such as the treatment of patients resistant to external cardioversion or in whom general anesthesia is contraindicated or hazardous, the conversion to sinus rhythm of inadvertently induced atrial fibrillation during an electrophysiologic study, and the evaluation of patients with recurrent symptomatic atrial fibrillation, resistant to antiarrhythmic drugs, for treatment with an implantable atrial defibrillator. A comparison of the reported success rates and energy requirements for catheter-based restoration of sinus rhythm is not only difficult because of the variable use of a preestablished energy limit for termination of the procedure but also because of the heterogeneous populations treated, the evaluation of several technological improvements of the defibrillation system, and the differences in lead configurations.

Between December of 1995 and February of 1999, 120 patients (89 men, mean age 59 ± 12 years) with a mixture of heart disease seen in the general population with atrial fibrillation underwent 141 internal cardioversions in our hospital. Most of the patients were taking antiarrhythmic drugs at the time of the procedure. The left atrial size ranged from 42 to 70 (53 ± 6) mm and the left ventricular ejection fraction from 21 to 72 (55 ± 12) percent. Atrial fibrillation was induced in 16 patients, and in the other 125 patients the average duration of the treated spontaneous episode was 306 ± 564 (0.1-3650) days. In all procedures, a right atrium to coronary sinus defibrillation vector was used. Shocks were delivered using a 0.5-J start, a 0.5-J step-up protocol until 3 J, followed by 1.0-J steps until cardioversion of atrial fibrillation occurred. All 141 atrial fibrillation episodes were cardioverted successfully with a mean energy of 5.6 ± 4.7 (0.4-35) J. In patients with long-standing atrial fibrillation, the atrial defibrillation threshold is higher than in patients with induced or paroxysmal atrial fibrillation. Although internal cardioversion has a higher acute efficacy in restoring sinus rhythm as compared with external cardioversion, the long-term outcome seems to be independent of the method of cardioversion.

An intriguing phenomenon after internal and external cardioversion of atrial fibrillation is the immediate reinitiation of the arrhythmia occurring within minutes of successful shock delivery (Fig. 29B-5). Because the intracardiac electrograms following an internal cardioversion are frequently monitored, immediate resumption of atrial fibrillation is detected more often as compared with external cardioversion.[36] Complications of internal cardioversion are rare and, if they occur, are related to the invasive nature of the procedure, improper synchronization, and inadequate anticoagulation.

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Chapter 29B: CLINICAL APPLICATION OF EXTERNAL AND INTERNAL CARDIOVERSION AND DEFIBRILLATION

IMPLANTABLE ATRIAL DEFIBRILLATOR

Antiarrhythmic drugs and external defibrillation are presently the primary modes of treatment of patients with atrial fibrillation. Due to the limited efficacy and safety of antiarrhythmic drugs and the repeated hospitalizations for external cardioversion requiring anesthesia, several non-pharmacologic options have been developed, especially for patients with recurrent atrial fibrillation. One of them, the implantable atrial defibrillator, only recently has been evaluated clinically. At present, a stand-alone atrial defibrillator and an atrioventricular cardioverter-defibrillator with dual-chamber pacemaker facilities are available. Because these devices are intended for use outside the hospital, ventricular tachyarrhythmia induced by atrial shocks, especially from a stand-alone atrial defibrillator, could have disastrous consequences. Prior experimental animal studies[37] resulted in programming the atrial shock synchronized to a QRS complex that occurs at least 500 ms after the preceding QRS complex, in the absence of a long-short sequence, to avoid the potential ventricular proarrhythmia risk in a stand-alone atrial defibrillator.

In selected patients with recurrent atrial fibrillation, a stand-alone atrial defibrillator was able to restore sinus rhythm promptly and safely with low amounts of energy.[38] Ambulatory therapy with the stand-alone atrial defibrillator is feasible because the device can terminate most of the episodes of atrial fibrillation in the patient's ambient setting without induction of ventricular proarrhythmia. Interestingly, in the majority of patients, atrial fibrillation can be treated with the device without sedation. The need for sedation is related to the number of shocks delivered to treat an atrial fibrillation episode.[39] A clinical study for the evaluation of a dual-chamber cardioverter-defibrillator for termination of spontaneous atrial fibrillation episodes in patients without indication for implantation of a ventricular defibrillator is presently ongoing. Whether an implantable atrial defibrillator modifies the natural history of atrial fibrillation, improves quality of life, and is cost-effective needs to be defined.

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 30:

THE IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

Authors: Peter A. O'Callaghan, Jeremy N. Ruskin

HISTORICAL PERSPECTIVE

Sudden and unexpected cardiac death (SCD) is estimated to claim 300,000 lives annually in the United States.[1] Despite a significant reduction in total cardiac mortality rates in recent years, the proportion of deaths that are sudden has remained unchanged. In-field electrocardiogram monitoring has demonstrated that the principal cause of SCD in victims of out-of-hospital cardiac arrest is ventricular fibrillation (VF).[2] In more than 80 percent of cases, sudden death is caused by the abrupt onset of ventricular tachycardia (VT) that progresses to VF.[3] Since self-termination of VF is exceedingly rare, the single most important factor determining survival is the time between event onset and first defibrillation attempt.[4] Overall mortality rates associated with out-of-hospital cardiac arrest are unacceptably high, mainly because of the delay in providing effective therapy.[5] In Seattle, Washington, only 10 percent of all out-of-hospital SCD victims are discharged from the hospital neurologically intact, despite good emergency medical response times, prompt cardiopulmonary resuscitation, and the use of automatic external defibrillators.[6]

As originally conceived by Mirowski, the implantable cardioverter defibrillator (ICD) was designed to circumvent the delay in providing definitive therapy to ambulatory individuals with life-threatening ventricular tachyarrhythmias.[7] The internal defibrillator responds by delivering an internal electrical shock within 10 to 20 s of arrhythmia onset, a time frame in which the potential for arrhythmia reversal approaches 100 percent. The first experimental model was successfully tested in 1969 in a dog.[8] After 10 years of research and development, Mirowski and coworkers implanted the first ICD in a human at the Johns Hopkins University Medical Center in 1980.[9] In the original article, the authors state, "It is intended to protect patients at particularly high risk of sudden death whenever and wherever they are stricken by these lethal arrhythmias (...) the only purpose of this device is to achieve defibrillation automatically, before the victim of a lethal arrhythmia can be reached by a cardiac resuscitation team." In 1985, the ICD received approval from the U.S. Food and Drug Administration for market release. Since then, the indications for ICD implantation have greatly expanded, and the number of devices implanted annually has steadily increased, reaching 50,000 new implants worldwide in 1999.

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Chapter 30: THE IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

FUNCTIONAL CHARACTERISTICS

The ICD system consists of two basic components: a pulse generator and a lead electrode or electrodes for arrhythmia detection and for therapy delivery. In addition to internal defibrillation, ICDs also provide pacing (antitachycardia and antibradycardia), synchronized cardioversion, telemetry, and diagnostics (event electrograms and history logs). The pulse generator is essentially a self-powered computer within a hermetically sealed titanium can.[10] Lithium vanadium oxide batteries and defibrillator capacitors occupy the bulk of the space. The operational circuitry-including resistors, capacitors, transformers, and microprocessors-occupies the remaining space and is separated into low-power circuit components (sensing and pacing) and high-power circuit components (defibrillation). A header made of epoxy provides an electrical interface between the internal circuitry and the lead electrode as well as electrical insulation from the surrounding tissues. Since the 1990s, designs have focused on a progressive increase in device functions combined with a gradual reduction in pulse generator size.

Sensing Ventricular Depolarizations

Reliable sensing of ventricular depolarizations is essential for proper functioning of the ICD. Sensing electrodes transmit raw (unfiltered) electrograms to the sense amplifier of the ICD. The sense amplifer amplifies, filters, and rectifies the incoming signals. It then compares them to a sensing threshold and produces a set of RR intervals for the detection algorithm to use (Fig. 30-1*A*). Intracardiac electrogram amplitude can vary markedly among rhythms, such as sinus rhythm, VT, and VF, or even during the same rhythm (e.g., VF). Fixed gain and sensitivity, as used in pacemaker technology, would result in either undersensing or oversensing, depending on the settings chosen. Therefore, all ICDs utilize some form of automatically adjusting signal amplifier (Fig. 30-1*B*). Automatic gain control automatically and continuously varies the gain so that the amplitude of the processed signal is constant. Autoadjusting sensitivity threshold sets the sensitivity to a proportion of the amplitude of the last sensed event, and the sensitivity then gradually increases until the next event is sensed. Sensed events are then analyzed using a detection algorithm. The range of all possible ventricular cycle lengths is divided into rate zones that do not overlap, including a VF zone, VT zones (between 0 and 3 programmable), a normal rate zone, and a bradycardia zone.

Ventricular Fibrillation Detection

Devices employ rate criteria as the sole method of detecting VF. An *X/Y* detector triggers when *X* out of the previous *Y* sensed intervals (typical setting 8/12 intervals) are shorter than the VF detection interval. This approach is very good at ignoring the effect of a small number of undersensed events due to small-amplitude signals during VF. The utilization of rate detection in an *X/Y* detection algorithm results in maximal sensitivity at the expense of specificity. Any tachycardia with a cycle length less than the tachycardia detection interval will be detected as VF by the device, and VF therapy will be initiated. At the end of capacitor charging and prior to the delivery of therapy, a reconfirmation algorithm must be fulfilled (noncommitted device). This prevents inappropriate shock therapy for self-terminating events, such as nonsustained VT.

Ventricular Tachycardia Detection

ICDs have multiple programmable tachyarrhythmia detection zones. Although rate is the principal detection criterion, the VT detection algorithm is different from that in the VF zone. In contrast to VF detection, most VT detection algorithms require a programmable number of consecutive intervals shorter than the VT detection interval. An interval longer than the detection interval (e.g., due to RR variability in atrial fibrillation) would reset the counters.

In certain patients, both ventricular and supraventricular tachycardias (e.g., sinus tachycardia, atrial fibrillation, or atrial flutter) may result in ventricular rates within the VT zone or zones. Up to 25 percent of ICD discharges are inappropriate when rate is employed as the sole criterion for VT therapy.[12] These inappropriate discharges are poorly tolerated by patients and constitute a major clinical problem.

To increase specificity, optional VT detection enhancements are programmable. This approach should be limited to tachycardia rates that are hemodynamically tolerated by the patient. Detection enhancements include sudden onset, rate stability, and electrogram morphologic (QRS width) criteria. These programmable options are not available in the VF zone, where maximal sensitivity is required. The onset criterion is intended to distinguish sinus tachycardia with a gradual rate increase from VT characterized by a sudden rate increase (e.g., greater than 9 percent shortening in cycle length at onset of episode). The rate stability criterion is used to differentiate sustained monomorphic VT with a small variation in cycle length (e.g., less than 40 ms) from atrial fibrillation with large cycle length variability. The electrogram morphologic criterion measures the width of the intracardiac electrogram to differentiate ventricular from supraventricular tachycardias with normal conduction. Although programming these options improves specificity, it does so at the risk of prolonging detection times and of failure to detect an episode of VT. "Sustained-rate duration" is a programmable maximum period of time (e.g., 30 to 120 s) during which therapy is inhibited if the programmed enhancement criteria are not met. At the end of this period, if the tachycardia rate persists above the VT cutoff rate, therapy will be delivered. As a safety feature, sustained-rate duration is nearly always programmed "on" whenever enhancement criteria are employed. In one study, programming stability and onset criteria plus sustained-rate duration significantly reduced inappropriate therapies to 13 percent, compared to 28 percent in patients using a rate criterion only.[13] Addition of an electrogram morphologic criterion can reduce inappropriate detection even further.[14] However, optimal programming of ICD width criterion requires testing during exercise as well as at rest.[15]

The lack of specificity of VT detection despite optional VT detection enhancements is a significant limitation of single-chamber ICDs. Dual-chamber pacemaker-defibrillators, requiring an additional atrial lead, provide not only the hemodynamic benefits of dual-chamber pacing but also dual-chamber detection algorithms.[16] Detection algorithms in these devices employ a stepwise analysis of rate, stability, atrioventricular (AV) association, and onset (ventricular acceleration, atrial acceleration, or nonaccelerated).[17] Again, these programmable options are not available in the VF zone, where maximal sensitivity is required. Preliminary clinical experience is mixed. In one study, all episodes (122) of VT and VF were correctly diagnosed, and 51 of 53 episodes of supraventricular tachyarrhythmias were correctly diagnosed. Only 2 episodes of atrial fibrillation with rapid regular ventricular rates were incorrectly diagnosed as VT.[18] However, a nonrandomized study comparing a dual-chamber ICD with an optimally programmed single-chamber device found that the number of inappropriate therapies for atrial fibrillation was not decreased.[19]

Ventricular Fibrillation Therapy

ICDs employ electrical defibrillation as the sole therapy option for the treatment of VF. In contrast

to cardiac pacing, which requires depolarization during diastole of a small number of cells located very close to the electrode, defibrillation requires depolarization of the majority of ventricular myocardial cells, many of which are relatively refractory and can be up to 10 cm away. Successful defibrillation may require voltages up to 100 times greater than the voltage of the ICD battery (approximately 6.4 V). A capacitor is used to store charge immediately prior to therapy delivery. This energy is then delivered between the high-voltage electrodes and depolarizes the intervening myocardium, thereby restoring baseline rhythm (Fig. 30-2). Reversing electrode polarity during capacitor discharge (biphasic waveform) lowers defibrillation energy requirements and was one of the main factors that facilitated the introduction of smaller, lower-energy pectoral devices.[20,21]

The time interval between VF onset and delivery of defibrillation energy is usually 10 to 15 s, with capacitor charge time accounting for most of the delay. During this time, the subject may experience presyncope or syncope with restoration of consciousness after successful defibrillation and restoration of cardiac output. One study of ICD recipients found that 16 percent of patients who received device therapy experienced syncope. In comparison, 65 percent of these patients had experienced syncope during tachyarrhythmia prior to device implantation.[22]

Ventricular Tachycardia Therapy

In contrast to VF therapy, treatment options in the VT zone or zones include antitachycardia pacing (ATP), cardioversion, and defibrillation. Therapy progresses through a programmable sequence of responses (tiered therapy) until the episode is terminated. Most sustained monomorphic VTs, particularly in patients with coronary artery disease, are due to reentry and can be terminated by a critical pacing sequence.[23] Pacing at faster rates increases the probability of VT termination but also increases the risk of tachycardia acceleration. ATP, with backup defibrillation if acceleration occurs, is an attractive, well-tolerated treatment that avoids high-energy shock therapy, which is painful and diminishes battery life (Fig. 30-3). The most common form of ATP is adaptive-burst pacing, which delivers a train of stimuli at a fixed percentage of the tachycardia cycle length. Repeated and more aggressive pacing trains can be administered, resulting in either termination of the tachycardia or progression to the next treatment modality (cardioversion or defibrillation). ATP is extremely effective, with over 90 percent successful termination of spontaneous VTs.[24,25] Gross et al. reported that the addition of ATP to ICD therapy significantly reduced the cumulative occurrence of first ICD shock from 36 to 28 percent at a mean follow-up of 2 years.[26]

Cardioversion, in contrast to defibrillation, is a synchronized shock, usually of low energy. Compared to high-energy defibrillation, low-energy cardioversion reduces the time to therapy and conserves battery life. Efficacy rates and acceleration rates are similar for these two treatment modalities.[27]

Bradycardia Pacing

Bradycardia ventricular demand pacing is a standard feature of all single-chamber ICDs. Dual-chamber pacemaker-defibrillators provide not only improved diagnostic specificity but also the benefits of dual-chamber pacing, rate-responsiveness, and mode switching. In contrast to single-chamber devices, dual-chamber ICDs have reasonable longevity despite continuous pacing. Approximately 20 percent of ICD recipients need antibradycardia pacing, and most of them would benefit from a dual-chamber device.[28] If one includes patients with poor ejection fraction and patients who would benefit from dual-chamber sensing, it is possible that up to 50 percent of ICD recipients may benefit from implantation of a dual-chamber ICD.[29,30]

Pacing thresholds during VT and after defibrillation are frequently higher than those needed for bradycardia pacing, and the pacing output for these various conditions is separately programmable. Welsh et al. reported that the postshock pacing threshold was on average 2.8 times greater than the diastolic pacing threshold and advised programming postshock pacing outputs to at least 4 times the diastolic pacing threshold to maintain adequate safety margins.[31]

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DEVICE IMPLANTATION

Methods of Implantation

ICDs are implanted in the pectoral region using techniques similar to those for permanent pacemaker implantation (Fig. 30-4). An integrated lead consisting of pace-sense electrodes and either one (right ventricular) or two (right ventricular and superior vena cava) high-energy defibrillation coils is inserted, preferably via the cephalic vein to avoid the risks of subclavian puncture and possibly future subclavian crush syndrome.[32]

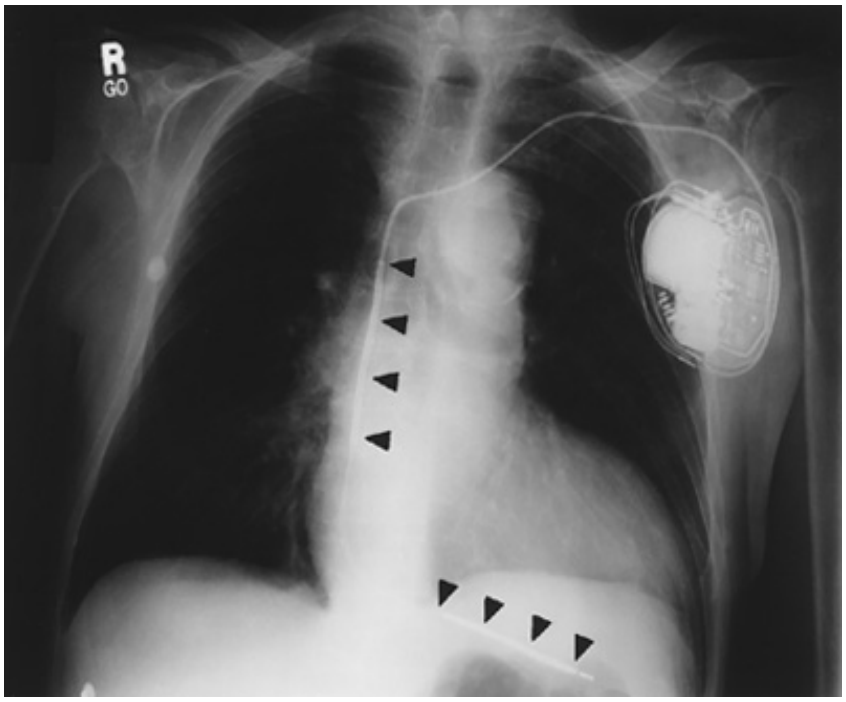

Figure 30-4: Posteroanterior chest x-ray of pectoral ICD device. A single integrated lead is inserted via the cephalic vein and positioned at the right ventricular apex. This is attached to a pulse generator implanted in the left pectoral region. ICDs are implanted using techniques similar to permanent pacemaker implantation. The integrated lead consists of right ventricular and superior vena cava defibrillation coils (*arrows*) and a tip electrode. In addition to the defibrillation coils, the titanium case of the pulse generator acts as a large-surface-area defibrillation electrode (active can). The defibrillation pathway in this patient is right ventricular coil to both superior vena cava coil and active can.

In dual-chamber devices, a separate atrial lead is inserted. Anesthesia may be local or general, with procedures performed under local anesthesia well tolerated in most patients.[33,34] In a retrospective analysis, patients who had their ICD placed under local anesthesia and intravenous sedation had higher intraoperative blood pressures and were discharged from hospital earlier than those who received general anesthesia.[35]

Pulse generator implantation may be prepectoral (subcutaneous) or subpectoral (submuscular). The prepectoral technique can be employed in patients with adequate subcutaneous tissue and the submuscular technique reserved for patients with a thin layer of subcutaneous tissue.[36] Implanting physicians should be familiar with both techniques. Prepectoral (subcutaneous) device implantation avoids deep subpectoral dissection, is associated with a shorter procedure time, may facilitate battery replacement, and has overall complication rates comparable to those for subpectoral implantation.[37]

In unipolar defibrillation systems, the titanium case of the pulse generator acts as a large-surface-area defibrillation electrode ("active can").[38] The defibrillation pathway in pectoral active-can implants is right ventricular coil to active can (with or without a superior vena cava coil). As a result, the position of the pulse generator affects the defibrillation wavefront and should, when possible, be implanted in the left pectoral region. Right-sided implantation results in significantly higher defibrillation thresholds (DFTs) than does left-sided implantation.[39]

Device Testing

The ability to reproducibly defibrillate VF is fundamental to the success of ICD therapy in preventing SCD. Accomplishing this goal requires meticulous testing at the time of implantation. Correct lead positioning usually involves advancing its tip as close as possible to the apex of the right ventricle. During sinus rhythm, R-wave amplitude, rate of change of the signal voltage (slew rate), pacing threshold, and lead impedances are assessed. The minimum acceptable R-wave amplitude is greater than 5 mV, to ensure satisfactory sensing during both sinus rhythm and VF.

VF is induced by the device either by a critically timed T-wave shock or very rapid burst ventricular pacing. The relationship between defibrillation energy and success is best described as a sigmoidal dose-response curve, the probability of success increasing steadily with each increase in energy until a 100 percent success plateau is reached (Fig. 30-5). The measured DFT is defined as the minimum energy producing defibrillation success and may be significantly lower than the lowest energy required for consistent defibrillation success (E_{99}). In clinical practice, various defibrillation threshold testing protocols are described.[41,42] To ensure future efficacy, even if there is a temporary or chronic rise in DFT, an adequate safety margin (at least 10 J) must exist between the measured DFT and the maximum energy output of the device. Today it is relatively uncommon to encounter DFTs so high that implantation criteria are not met. Boriani et al. achieved a safety margin of greater than or equal to 10 J and successfully implanted a single-lead unipolar system with a maximum energy output of only 29 J in 54 of 55 patients (98 percent).[43] If high DFTs are encountered at implantation, repeat testing can be performed after repositioning the lead (usually by attempting to get as close to the right ventricular apex as possible); changing the lead polarity, pulse duration, or waveform; adding additional defibrillation electrodes; or changing to a higher-energy-output device. In addition, in unipolar systems, a pneumothorax can greatly increase the high voltage impedance, resulting in high DFTs.[44] Finally, the role of antiarrhythmic drugs should be considered. When high DFTs are found at the time of implantation in patients who have been taking chronic oral amiodarone, we recommend completing the procedure and repeating DFT testing after a 4-week drug-washout period.

Predischarge Testing and Programming

Prior to discharge, the pace-sense characteristics of the ICD system are assessed in all patients and posteroanterior and lateral chest x-rays are reviewed to rule out lead dislodgment. Modern ICD systems employ integrated lead technology that combine both pace-sense and defibrillation functions. Changes in lead position that can potentially result in failure to detect or terminate VF invariably result in a change in pace-sense variables relative to implant values.[45] It is our practice

to reserve predischarge arrhythmia induction testing for select patients with marginal implant characteristics or in whom routine testing raises the possibility of a device malfunction.

The characteristics of induced VT correlate poorly with those of subsequent spontaneous VT episodes due to the frequent induction of faster, "nonclinical" VTs.[46] Fortunately, empirically programmed ATP successfully terminates VT in over 90 percent of cases.[47] In addition, even in VF survivors, the most common tachyarrhythmia recorded during follow-up is monomorphic VT.[48] Therefore, in the majority of ICD recipients, empiric programming of a VT zone should be considered prior to discharge.

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LONG-TERM FOLLOW-UP

Routine Patient Follow-up

Patients are reviewed routinely every 3 months to assess the pace-sense and impedance characteristics of the ICD system, to assess the charge times, and to diagnose the cause of any delivered therapy. Radiographs of the ICD system are obtained annually. Fortunately, careful regular follow-up will identify the majority of asymptomatic problems. If routine assessment reveals a significant alteration in the pace-sense or impedance characteristics of the system and if no defibrillation shock was recently administered, DFTs are rechecked noninvasively under intravenous sedation to confirm an adequate defibrillation safety margin. Tokano et al. performed serial DFT testing in 31 patients who received biphasic defibrillation systems. After 2 years' follow-up 5 patients, (15 percent) had an increase in defibrillation energy requirements of 10 J or more, and 1 patient (3 percent) required surgical revision of the system.[49]

All patients with an ICD should be considered for pulse generator replacement when there is evidence of battery depletion, since late shocks occurring many years after primary implantation appear to define a continuing need for this therapy in many patients.[50] At the time of elective pulse generator replacement, the pace-sense characteristics of the ICD system are reassessed, and VF is induced in order to confirm satisfactory sensing and ability to defibrillate VF with a safety margin of 10 J or more. Occasionally, a patient's defibrillation energy requirements may be unexpectedly elevated at the time of generator replacement, and appropriate revision of the system or implantation of a new integrated lead is required.

Psychosocial Issues

The ICD is generally well tolerated in the vast majority of patients for whom it is recommended. Quality of life declines in the first 6 months postimplantation but by 12 months has returned to preimplant levels.[51] Depression, anxiety, and reduced sexual function may occur after device implantation. Factors that adversely affect quality of life include frequent or inappropriate shocks, device malfunction, or product recall.[52,53] Since shock delivery has a major impact on quality of life, it is appropriate to consider measures such as concomitant drug therapy, empiric programming of ATP for VT, and use of detection enhancement algorithms to minimize the risk of both appropriate and inappropriate shock delivery during long-term follow-up.[13,14,26] In a prospective, multicenter trial of ICD patients randomized to receive either sotalol or placebo, sotalol significantly reduced the mean annual number of shocks (1.4 shocks) compared to placebo (3.9 shocks) and significantly prolonged the time interval to first shock.[54]

Automobile Driving

A major concern among ICD patients is driving restrictions. Because of the risk of an arrhythmia recurrence or the delivery of high-energy shocks, restrictions on driving should be considered and discussed with all patients prior to device implantation. The period for greatest risk of ICD discharge is within the first 6 months after implantation. Patients receiving implantable defibrillators comprise a heterogeneous population. At one end of the spectrum is the patient with drug-refractory recurrent sustained ventricular tachyarrhythmias causing syncope or cardiac arrest

who is likely to receive more frequent device discharges. At the other end of the spectrum is the asymptomatic high-risk patient who has never experienced a spontaneous episode of life-threatening ventricular tachyarrhythmia. A more restrictive approach to the issue of driving seems appropriate for the former group of patients but is inappropriate for the latter and may make such patients unwilling to accept ICD therapy. Published guidelines from the American Heart Association and the North American Society of Pacing and Electrophysiology recommend that patients who receive an ICD because of a previously documented episode of VT or VF should be prohibited from all driving for the first 6 months after ICD implantation.[55] After 6 months, if an ICD discharge has not occurred, patients may resume driving. Patients who have a prophylactic ICD implant and who have never had a documented episode of spontaneous ventricular tachyarrhythmia should not be prohibited from noncommercial driving. The recommendations make no distinction between patients whose primary treatment is antiarrhythmic drug therapy rather than ICD therapy.

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COMPLICATIONS AND TROUBLESHOOTING

Morbidity and Mortality

ICD therapy is associated with well-known risks (Table 30-1) that must be weighed against the potential benefits of automatic ventricular tachyarrhythmia therapy. The last 10 years have seen a simplification of device implantation from nonthoracotomy transvenous abdominal implantation to single-lead pectoral implantation. A multicenter study of 473 patients implanted with a pectoral unipolar device reported successful device implantation in 98 percent of patients; in 7 percent of patients, implant criteria either were not met or were not fully assessed. No patient died within 24 h of the procedure, and the 1-month (perioperative) mortality rate was 0.9 percent.[57] Patients were followed for a mean of 6 months. Twenty-nine patients (6 percent) has serious procedure- or device-related complications requiring surgical intervention. A study of over 3000 patients who had nonthoracotomy ICD systems implanted in either an abdominal, a prepectoral, or a subpectoral position found that the 1-year cumulative complication-free survival rate was 88 percent and did not differ significantly among the three groups.[58] However, the complication rate depends on the definitions used and the duration of follow-up. If one includes mild device-related complications (e.g., inappropriate therapy delivery), approximately 50 percent of patients experience an adverse event within the first year of ICD implantation.[59] This needs to be considered when recommending device implantation in high-risk asymptomatic patients.

Table 30-1: Complications Associated with Pectoral ICD Implantation

PROCEDURE-RELATED
Short-Term
DFT testing (inability to defibrillate, worsening sys-tolic function, electromechanical dissociation)
Subclavian stick complications (pneumothorax, hemo-thorax, air embolism, subclavian artery puncture)
Venous thromboembolism
Phrenic nerve stimulation
Right ventricular perforation
Pericardial effusion or tamponade
Hematoma (pulse-generator pocket)
Seroma (pulse-generator pocket)
Hypotension
Myocardial infarction
Cerebrovascular accident
Proarrhythmia (atrial fibrillation, increased fre-quency of ventricular tachyarrhythmia: 'electricalstorm')
Long-Term
Infection

Erosion
Migration
Venous thromboembolism
Endocarditis
Shoulder-related problems
SYSTEM-RELATED
Lead dislodgment (Gross-, microdislodgment, Twiddler's syndrome)
Lead conductor fracture
Lead insulation defect
Lead perforation (+/- diaphragmatic pacing)
Loose set screw
Exit block (high pacing threshold)
Inappropriate shock delivery
Premature battery depletion
Device recall

SOURCE: Modified from O'Callaghan and Ruskin,[56] with permission.

Lead-related problems, such as dislodgment, insulation defects, or conductor fracture, which can result in failure to sense, failure to pace, and either inappropriate defibrillation shocks or inability to defibrillate VF, remain a significant problem despite the enormous advances in lead technology. A comparison of abdominal versus pectoral implants followed for a mean of 4 months postimplantation found that pectoral devices were associated with significantly fewer severe lead-related events, the majority of which were dislodgments (5 versus 11 percent).[60]

One of the most devastating complications is infection of the ICD system. Pectoral devices avoid the infection risks associated with tunneling to the abdomen or placement of a subcutaneous patch. Of 950 patients who had a transvenous system implanted, the infection rate was 0.6 percent, compared to 1.9 percent in patients who had a transvenous system plus a subcutaneous patch.[61] Infection resembles that observed with permanent pacemaker implantation. Direct intraoperative contamination is the source of most infections. However, due to the low virulence of some organisms (e.g., *Staphylococcus epidermis*), infections may not become obvious for some considerable time after implantation. In general, explantation of the entire ICD system is required. After a regimen of intense antibiotic therapy and if all clinical evidence of infection is resolved, reimplantation at a different site may be performed, but the risk of reinfection is higher than following a primary implant.

Troubleshooting

The differentiation of appropriate from inappropriate device function in a patient who has received an ICD discharge is a challenging problem. The initial step toward management is device interrogation to determine whether the ICD therapy was appropriate or inappropriate. ICDs have advanced from devices providing basic diagnostic data, such as event counts or RR intervals only, to sophisticated electrocardiographic monitoring units. Analysis of stored intracardiac electrograms recorded during the time interval preceding and following ICD therapy, in addition to marker channels that annotate each sensed event, results in a confident diagnosis of the causes of most ICD therapies (Fig. 30-6). In

general, changes in electrogram morphology compared to sinus rhythm are consistent with ventricular tachyarrhythmias, while an identical electrogram morphology is consistent with supraventricular arrhythmias. Atrial activity can often be identified with far-field electrograms. A distinct change in electrogram morphology can be demonstrated in either the near-field or the far-field electrogram in virtually 100 percent of VTs.[62] In dual-chamber devices, the differentiation of appropriate from inappropriate device function is greatly facilitated by the analysis and retrieval of simultaneously recorded atrial and ventricular electrograms.

In addition to careful analysis of stored electrogram data, real-time measurements (sensing, pacing, and impedance measurements) can be obtained, the ICD system can be x-rayed, and VF may be induced under intravenous sedation to determine the cause of inappropriate device function. Occasionally, problems such as loose connections only become obvious by device manipulation or a patient's movement during real-time telemetry. Accurate diagnosis is essential in order to institute the appropriate action, which may include device reprogramming, activation of VT detection enhancement algorithms, alteration of antiarrhythmic drug therapy, or surgical revision of the ICD system.

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THE EVIDENCE BASE FOR ICD THERAPY

Background

As a therapeutic modality, the ICD is unsurpassed in its ability to prevent SCD (Fig. 30-2). Nevertheless, despite a marked reduction in SCD rates, overall mortality rates in ICD recipients remain high, with nearly a 20 percent 2-year mortality rate in most series.[63] The degree of survival benefit conferred by the defibrillator in a given patient population is dependent on the sudden arrhythmic death rate relative to the nonarrhythmic death rate, a ratio that is largely unknown. Patients with heart failure constitute a large proportion of ICD recipients. There was concern that implantable defibrillators may have little effect on overall survival rates in this population of patients for several reasons. First, as New York Heart Association (NYHA) functional class deteriorates, the proportion of deaths that are sudden and unexpected decreases. Second, successfully terminating an episode of VT or VF will have little effect on overall survival if the patient dies shortly thereafter of progressive pump failure. Because of these concerns, prospective randomized trials were conducted to test the hypothesis that implantable defibrillators significantly improve total survival rates.

Secondary Prevention of Sudden Cardiac Death

The results of three large prospective ICD trials comparing implantable defibrillators to antiarrhythmic drug therapy (mainly amiodarone) in patients with life-threatening ventricular tachyarrhythmias have consistently shown that the implantable defibrillator improves overall survival (Table 30-2). In the Antiarrhythmic Versus Implantable Defibrillator (AVID) trial of over 1000 patients, implantable defibrillators resulted in a 31 percent reduction in total mortality rate at 3 years compared to the antiarrhythmic drug therapy group (25 versus 36 percent; $p < .02$; Fig. 30-7).[64] The Canadian Implantable Defibrillator Study (CIDS) randomized over 600 patients presenting with sustained ventricular tachyarrhythmias to treatment with either the implantable defibrillator or amiodarone.[65] After 3 years' follow-up, patients randomized to receive the implantable defibrillator had a 20 percent reduction in total mortality rate compared to amiodarone-treated patients (25 versus 30 percent; $p = .07$). The Cardiac Arrest Study-Hamburg (CASH) randomized 346 cardiac arrest survivors to one of four treatment groups: amiodarone, metoprolol, propafenone, or the implantable defibrillator.[66] The propafenone arm was stopped in 1993 because of excessive mortality rates with this class I agent. During follow-up, patients randomized to receive the implantable defibrillator had a 37 percent reduction in total mortality rate compared to amiodarone- or metoprolol-treated patients (12 versus 20 percent; $p = .047$).

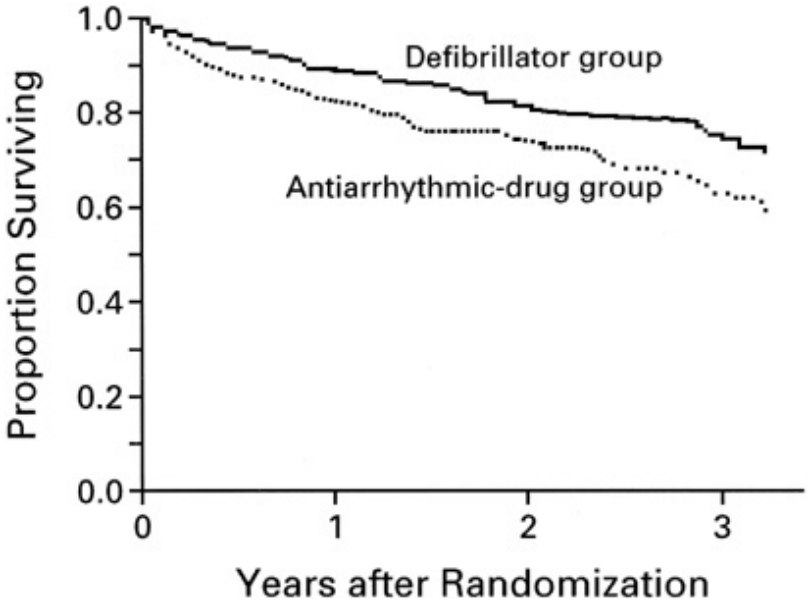

Figure 30-7: The Antiarrhythmic Versus Implantable Defibrillator (AVID) Trial. Overall survival in the defibrillator group and the antiarrhythmic drug group up to 3 years after randomization in the AVID trial. Survival was better among patients treated with the implantable defibrillator ($p < .02$). (From the AVID Investigators,[64] with permission.)

Although each of these three studies found lower total mortality rates in ICD recipients, only the AVID trial reached clear statistical significance. A meta-analysis of these three trials was presented at the North American Society of Pacing and Electrophysiology Annual Scientific Sessions in 1999 (unpublished). In total, there were 200 deaths among patients treated with implantable defibrillators and 255 deaths among patients treated with amiodarone. Compared to amiodarone, the ICD reduced the total mortality rate by 27 percent ($p < .05$). As a result of evidence from these clinical trials, the implantable defibrillator is now accepted as the therapy of first choice in survivors of symptomatic sustained ventricular tachyarrhythmias.

Primary Prevention of Sudden Cardiac Death

The majority of patients at risk of SCD have not previously experienced a sustained ventricular tachyarrhythmia. Primary (prophylactic) ICD implantation involves placing the device in a patient who is considered at high risk but has never had a spontaneous episode of sustained VT or VF, with the aim of effectively treating the first episode and thereby preventing sudden death. Defining populations of patients who are at sufficiently high risk that primary ICD implantation is justified is the focus of several prospective clinical trials (Table 30-3). Included are select patients with left ventricular dysfunction and nonsustained ventricular tachycardia (NSVT), high-risk coronary artery disease patients postsurgical revascularization, and patients with either ischemic or nonischemic dilated cardiomyopathy.

Table 30-3: Multicenter Primary Prevention ICD Trials

Trial	Study Population	Treatment Groups	Sample Size	Primary End Point	Study Period	Outcome
MADIT[67] (Multicenter Automatic Defibrillator Implantation Trial)	Prior MI with LVEF <35%, NSVT, and inducible nonsuppressible VT or VF	ICD vs conventional medical therapy	196 patients	Total mortality rate	1990-1996	Total mortality rate in ICD group significantly less than in conventional group (16 vs 39%, $p < .01$)

MUSTT[68] (Multicenter Unsustained Tachycardia Trial)	CAD with LVEF <40%, NSVT and inducible VT or VF	Antiarrhythmic therapy (ICD or EP-guided antiarrhythmic drug) vs no antiarrhythmic therapy	704 patients	Cardiac arrest or death from arrhythmia	1990-1998	5-year incidence of cardiac arrest or death from arrhythmia significantly less among 'antiarrhythmic therapy' than among 'no antiarrhythmic therapy' patients (25 vs 32% *p* = .04)
CABG-Patch[69] (Coronary Artery Bypass Graft Patch Trial)	CABG with LVEF <36% and positive SAECG	ICD + CABG vs CABG only	900 patients	Total mortality rate	1990-1997	At 4-year follow-up, total actuarial mortality rate in ICD group no different than for control group (27 vs 24%, *p* = .7)
CAT[70] (Cardiomyopathy Trial)	Dilated cardiomyopathy with LVEF <30% and no symptomatic ventricular arrhythmias	ICD vs control group	~720 patients	Total mortality rate	1991-present	No possible benefit from ICD determined at interim analysis (1997)
SCD-HeFT[71] (Sudden Cardiac Death in Heart Failure Trial)	Ischemic or dilated cardiomyopathy with congestive heart failure (NYHA II-III) and LVEF <35%	ICD vs amiodarone vs conventional group	~2500 patients	Total mortality rate	1996-present	Ongoing
MADIT-II[71] (Second Multicenter Automatic Defibrillator Implantation Trial)	Prior myocardial infarction with LVEF <30%	ICD vs conventional group	~1200	Total mortality rate	1998-present	Ongoing

ABBREVIATIONS: CABG = coronary artery bypass graft; CAD = coronary artery disease; EP = electrophysiologic; MI = myocardial infarction; Rx = treatment; SAECG = signal-averaged electrocardiogram.

NSVT in the setting of a previous myocardial infarction and left ventricular dysfunction is associated with a 2-year mortality rate of approximately 20 to 30 percent.[72-74] The Multicenter Automatic Defibrillator Implantation Trial (MADIT) was designed to determine whether prophylactic ICD implantation in patients with prior myocardial infarction, left ventricular ejection fraction (LVEF) less than or equal to 35 percent, NSVT, and inducible, nonsuppressible VT or VF would improve survival rates compared to conventional medical therapy.[67] Amiodarone was used in 74 percent of the conventional therapy group 1 month after

randomization, but by the end of the study only 45 percent of the conventional group were still taking amiodarone. Total mortality rates in the ICD group were significantly less than in the conventional treatment group. The Multicenter UnSustained Tachycardia Trial (MUSTT) was designed to determine whether electrophysiologically guided antiarrhythmic therapy would reduce the risk of sudden death among patients with coronary artery disease, LVEF less than or equal to 40 percent, NSVT, and inducible VT or VF compared to no antiarrhythmic therapy.[68] Patients randomized to antiarrhythmic therapy (ICD or electrophysiologically guided drug therapy) had a significantly reduced arrhythmic mortality rate compared to the conservative treatment group. It is noteworthy that the improvement in outcome was entirely due to the ICD patients; electrophysiologically guided drug therapy (mostly class I agents) did not improve and may have worsened outcome. Although not a primary end point of the trial, Kaplan-Meier estimates of overall mortality rate show significantly fewer deaths in ICD patients than in either of the other two groups (Fig. 30-8). Therefore, the results of the MADIT and MUSTT trials confirm that, in patients with coronary artery disease, depressed LVEF, NSVT, and inducible sustained ventricular tachyarrhythmias who have never had a spontaneous episode of sustained VT or VF, the ICD is effective in significantly reducing the risk of SCD and prolonging overall survival.

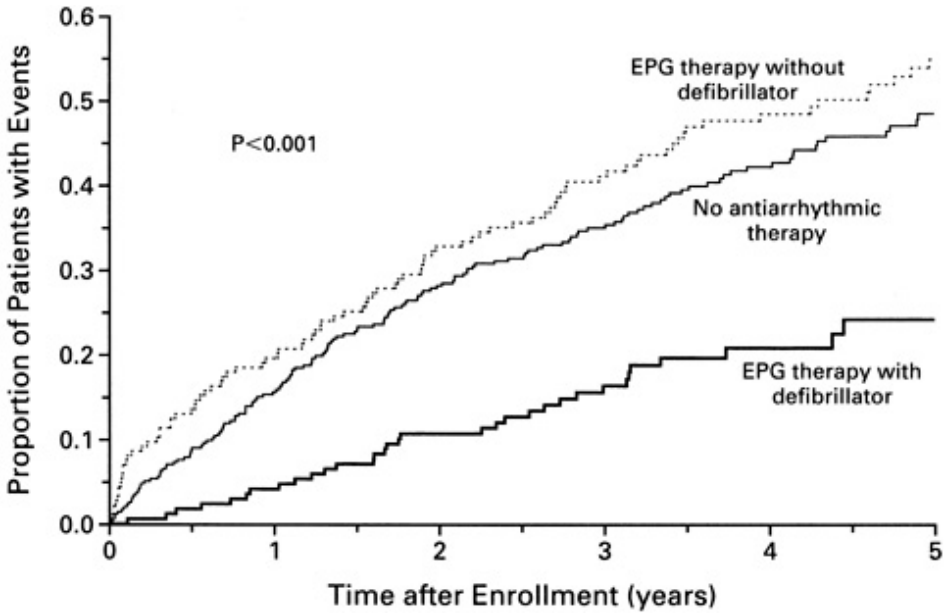

Figure 30-8: The Multicenter Unsustained Tachycardia Trial (MUSTT). Kaplan-Meier estimates of overall mortality rate according to whether the patients received treatment with electrophysiologically guided (EPG) therapy without defibrillator (i.e., antiarrhythmic drug therapy), no antiarrhythmic therapy, or electrophysiologically guided therapy with a defibrillator. Mortality rates were significantly less in the ICD-treated patients than in the other two groups. (From Buxton et al.,[68] with permission.)

The Coronary Artery Bypass Graft (CABG) Patch trial randomized patients with LVEF less than 36 percent and a positive signal-averaged electrocardiogram who were undergoing coronary artery bypass surgery to a prophylactic ICD or no specific antiarrhythmic therapy.[69] There was no survival benefit from prophylactic ICD implantation in this population. This observation reflects the fact that many of the patients enrolled in the CABG-Patch trial would not have demonstrated inducible sustained VT had electrophysiologic testing been performed and therefore were at relatively low risk of arrhythmic death compared with the MADIT or MUSTT populations. The study also underscores the survival benefit of coronary artery revascularization in patients with coronary artery disease and left ventricular dysfunction.

Despite conventional medical therapy, the mortality rate associated with congestive heart failure and left ventricular systolic dysfunction remains unacceptably high, in the range of 5 to 15 percent annually in mild heart failure and increasing to 20 to 50 percent annually in patients with severe heart failure.[75] SCD is responsible for approximately half of all cardiac deaths in patients with heart failure. The Cardiomyopathy

Trial (CAT), the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), and the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) will address the issue of whether the ICD improves survival in a population of cardiomyopathy patients irregardless of the presence or absence of arrhythmia markers (inducibility, NSVT, etc.).[70,71] Preliminary results from the CAT trial suggest that the ICD does not improve overall survival, however our future approach to the management of heart failure patients awaits the results of SCD-HeFT and MADIT-II.

The results of negative ICD trials (CABG-Patch and CAT) emphasize the fact that ICDs prolong survival in a population of patients only if that population has a sufficiently high incidence of life-threatening ventricular tachyarrhythmias and a sufficiently low incidence of death from all other causes. The real challenge over the next few years will be developing means of accurately identifying patients at sufficiently high risk of life-threatening ventricular tachyarrhythmias and sufficiently low risk of death from all other causes in whom ICD therapy is both efficacious and cost effective.[76]

Cost-Effectiveness

The cost of ICD therapy compared to alternative therapies will be the focus of much study and discussion in the next few years. In addition to hardware costs (approximately $20,000 to $25,000), there are implantation costs, hospital admission charges, and the cost of routine follow-up and pulse generator replacement. Treatment strategy is central to the issue of overall costs. In the early 1990s, management of patients with life-threatening ventricular tachyarrhythmia consisted of serial antiarrhythmic drug testing, with ICD therapy reserved for those patients whose arrhythmias were not adequately suppressed. This strategy was characterized by long hospitalizations and frequent progression to late ICD implantation, resulting in substantial costs. In recent years, the strategy of ICD implantation as first-line therapy and the progression from thoracotomy and abdominal implantation to transvenous pectoral implantation has significantly reduced the length of hospital stay and substantially lowered the initial cost of ICD therapy.[77,78]

Long-term costs need to be compared with outcome measures, including total mortality rate and quality of life, in order to assess cost effectiveness. In the AVID trial, the average length of additional life associated with ICD therapy was 2.7 months. The estimated cost per life-year saved was $127,000.[79] In the MADIT trial, the average length of additional life associated with ICD therapy was 10.3 months, and the estimated cost per life-year saved was $27,000.[80] The cost analysis of MADIT, in contrast to AVID, compares favorably with other cardiac interventions. The difference is most likely due to differences in patients' selection. The MADIT patients, all of whom had inducible nonsuppressible ventricular tachyarrhythmias (NSVTs) on electrophysiologic testing, were at higher risk of death than were the AVID patients, as evidenced by the poorer prognosis in the conventional arm of MADIT compared to that in the antiarrhythmic-drug arm of AVID. These results emphasize the fact that the patients' selection largely determines the cost effectiveness of ICD therapy. The most cost-effective use of the ICD is in patients at high risk of death due to ventricular tachyarrhythmia and at low risk of death from all other causes. More accurate risk stratification is necessary to ensure that ICD therapy is applied in an optimally efficient and cost-effective manner.

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ICD THERAPY IN SPECIFIC CLINICAL SETTINGS

The American College of Cardiology (ACC) and the American Heart Association (AHA) advise ICD therapy in cardiac arrest survivors, in patients with spontaneous sustained ventricular tachycardia, in select patients with syncope of undetermined origin, and in select patients with coronary artery disease, left ventricular dysfunction, and NSVT (Table 30-4).[81] In these clinical circumstances, the implantable defibrillator is now regarded as the treatment of first choice. The role of antiarrhythmic therapy in these patients is mainly limited to adjunctive therapy in ICD recipients who have other tachyarrhythmias (e.g., atrial fibrillation) or who are receiving frequent shocks and require suppressive drug therapy. Future drug trials in patients with ICDs may result in the development of new, safer antiarrhythmic drugs.

Cardiac Arrest Survivors

Aborted SCD is, in the majority of cases, caused by life-threatening ventricular tachyarrhythmias (VF and hypotensive VT). Structural heart disease is almost invariably present, which in adult populations is most frequently coronary artery disease.[82] Survivors of cardiac arrest, in the absence of an acute myocardial infarction (first 48 h), are at high risk of future recurrence. Data from the 1970s, which today reflect the natural history of this condition, show a 36 percent 1-year mortality rate in patients who were successfully resuscitated, hospitalized, and discharged home following an out-of-hospital VF arrest.[83]

The role of ischemia in the pathogenesis of SCD is not clearly defined. Only a small proportion of cardiac arrest survivors have clinical evidence of an acute myocardial infarction. Nonetheless, since the majority of cardiac arrest survivors have evidence of significant chronic coronary atherosclerosis, transient ischemia is suspected as the major trigger factor for life-threatening ventricular tachyarrhythmias. Cardiac catheterization identifies those survivors of SCD who have critical obstructive coronary artery disease. It is our practice to revascularize these patients whenever feasible. Cardiac arrest occurring in the setting of acute clinical ischemia or within 48 h of an acute myocardial infarction is, with rare exception, treated in the conventional manner without electrophysiologic workup or ICD implantation. In addition, select patients with significant multivessel coronary artery disease, reversible ischemia on functional assessment, and no obvious arrhythmic substrate (no prior Q-wave infarction, preserved left ventricular function, and negative signal-averaged ECG) usually require revascularization rather than ICD implantation. In this group, we perform an electrophysiologic study following revascularization, and those with no inducible arrhythmias are considered to be a low-risk group, whose treatment usually consists of beta blockade.[84] These two groups (patients with acute clinical ischemia and patients with significant multivessel coronary artery disease, reversible ischemia, and no obvious arrhythmic substrate) account for only a minority of cardiac arrest survivors. The majority of cardiac arrest survivors have an obvious arrhythmic substrate [prior Q-wave infarction, depressed LVEF, positive signal-averaged ECG, or inducible sustained monomorphic VT (SMVT)], and, in addition to revascularization, we advise ICD implantation.

Until now, it has been assumed that ventricular tachyarrhythmias due to a transient or reversible disorder are adequately treated by correcting the underlying cause; this is supported by the current ACC-AHA guidelines. Recent analysis of the AVID trial registry of screened nonrandomized

patients has reported that the overall mortality rate in these patients is as great as in patients with prior cardiac arrest.[85] Determining whether this high mortality rate is due to sudden arrhythmic death or progressive pump failure requires further study and may significantly affect our management of these patients.

Sustained Monomorphic Ventricular Tachycardia

In patients with SMVT that has resulted in a cardiac arrest or syncope, the ICD is usually employed as first-line therapy. In patients with SMVT that is tolerated hemodynamically, other potential therapeutic options include empiric amiodarone therapy, electrophysiologically guided antiarrhythmic drug therapy, transcatheter radiofrequency ablation, and arrhythmia surgery. Empiric amiodarone therapy is associated with high rates of drug discontinuation due to adverse side effects. "Guided" drug therapy using either invasive electrophysiologic study or noninvasive Holter monitoring has failed to adequately protect against arrhythmia recurrence and has largely been abandoned. Catheter ablation, the treatment of choice in patients with VT and structurally normal hearts, is usually only employed as adjunctive therapy in patients with underlying structural heart disease, typically in patients with implanted devices. Catheter ablation is suitable in only about 10 percent of patients with spontaneous sustained ventricular tachycardia.[86] Arrhythmia surgery is the only therapy with SCD rates similar to those for ICD therapy.[87,88] Although this approach can be curative, perioperative mortality rates are much higher than those associated with ICD implantation, ranging from 9 to 15 percent. Combined aneurysmectomy and intraoperative map-guided subendocardial resection yields a low rate of arrhythmia recurrence and is only indicated in highly selected patients who have a discrete left ventricular aneurysm.

In summary, compared to the other available treatments, ICD therapy is widely applicable, well tolerated, and associated with good short-term and long-term results. Today it is the preferred mode of therapy in the vast majority of patients with structural heart disease and SMVT. The various therapeutic options available should be considered as complementary rather than competing therapies. In managing individual patients, more than one therapy or even all therapies may be employed over a period of time.

Syncope of Undetermined Origin

Syncope is a common, usually benign condition. However, when associated with structural heart disease and inducible VT at electrophysiologic study, it carries a high risk of SCD. One representative study reported a sudden death rate of 48 percent at 3 years in patients with syncope of undetermined origin and inducible sustained VT, compared to 9 percent in patients with negative electrophysiologic study results.[89] The risk of death in patients presenting with syncope plus inducible ventricular tachyarrhythmia on electrophysiologic study is similar to that in patients presenting with documented spontaneous VT or VF.[90] The ACC-AHA guidelines recommend ICD therapy in patients with syncope of undetermined origin, structural heart disease, and inducible hypotensive ventricular tachycardia.[81] However, follow-up of small series of such patients have reported a high total mortality rate despite ICD therapy.[91] Whether ICD therapy truly reduces the total mortality rate in this group can only be answered by a prospective, randomized trial. The CIDS trial randomized patients with syncope of undetermined origin and documented or induced sustained VT.[65] Analysis of this subgroup should help resolve this issue.

Patients with idiopathic dilated cardiomyopathy who present with syncope have a high mortality rate, and, in contrast to coronary artery disease patients, the role of electrophysiologic study is ill defined. According to the ACC-AHA guidelines, ICD therapy is contraindicated in patients with syncope of undetermined origin and no inducible ventricular tachyarrhythmia. Knight et al. reported on 14 consecutive patients with nonischemic cardiomyopathy, unexplained syncope, and

a negative electrophysiologic test result who underwent defibrillator implantation.[92] Fifty percent of patients received appropriate shocks during 2 years' follow-up, supporting the use of ICD therapy in these patients. Prospective studies are needed to identify which patients with dilated cardiomyopathy and undetermined syncope may benefit from ICD implantation. Meanwhile, these patients need careful clinical assessment, and select patients may benefit from implantable event loop-recording devices.

Symptomatic Patients with Severe LeftVentricular Dysfunction

Patients with poor left ventricular function who have experienced a spontaneous episode of life-threatening ventricular tachyarrhythmia are a high risk of both SCD and death due to progressive pump failure. Successfully terminating an episode of VT or VF will have little effect on overall survival if the patient dies shortly thereafter of pump failure. In the past, this observation raised the concern that implantable defibrillators may have little effect on overall survival in this patient population. It is somewhat surprising that subgroup analysis of both the AVID and CIDS trials has found that patients with a LVEF less than or equal to 35 percent derive the greatest survival benefit from defibrillator therapy.[93,94] Patients with an LVEF greater than 35 percent had similar survival benefit up to 3 years postrandomization with either empiric amiodarone or device therapy, probably due to a lower arrhythmia recurrence rate. Bocker et al. also assessed the potential benefit of ICD therapy in 603 patients with and without heart failure and concluded that patients with NYHA functional class I to III heart failure benefited in terms of overall survival from ICD implantation.[95] ICD therapy is contraindicated in patients with NYHA class IV heart failure unless they have experienced an episode of life-threatening ventricular tachyarrhythmia and are awaiting cardiac transplantation.

Patients awaiting heart transplantation who have experienced a spontaneous episode of life-threatening ventricular tachyarrhythmia deserve special consideration. Not only are they at risk of sudden tachyarrhythmic death, but they also are at high risk of sudden death due to bradyarrhythmias or electromechanical dissociation and of death due to progressive pump failure.[96] Nevertheless, it has been reported that cardiac transplant candidates who have experienced a spontaneous episode of life-threatening ventricular tachyarrhythmia can be effectively protected against sudden arrhythmic death despite having a high incidence of appropriate shocks early after implantation.[97]

Asymptomatic High-Risk Patients

Since the prognosis associated with a first cardiac arrest is very poor, an effective primary prevention strategy is required to identify and effectively treat patients at high risk of sudden death who have not yet experienced a spontaneous episode of life-threatening ventricular tachyarrhythmia (hypotensive VT or VF). The results of the MADIT and MUSTT trials confirm that, in a clearly defined high-risk group of patients with coronary artery disease, depressed left ventricular function, NSVT, and inducible sustained ventricular tachyarrhythmias, the ICD is effective in significantly reducing the risk of SCD and prolonging overall survival. In clinical practice, however, patients with coronary artery disease, depressed left ventricular function, and NSVT are common, and there is at present no consensus as to which patients should proceed to invasive electrophysiologic study and possible ICD implantation. In addition, the cost effectiveness of screening large numbers of these patients has not been assessed. We do not recommend routine screening of patients with left ventricular dysfunction to detect the presence of NSVT. However, in selected patients with severe left ventricular dysfunction due to who are brought to our attention because of recurrent NSVT, we recommend electrophysiologic testing and, if MADIT or MUSTT criteria are met, ICD implantation.

Primary prevention in many patients with cardiomyopathy is limited by our inability to accurately identify those at risk of SCD. The issue of whether the ICD improves survival in cardiomyopathy patients irregardless of the presence or absence of arrhythmia markers (e.g., inducibility, NSVT, etc.) is at present being addressed by SCD-HeFT and MADIT-II trials (Table 30-3). The ability of noninvasive markers to predict overall mortality rates and arrhythmic events in over 200 patients with idiopathic dilated cardiomyopathy over a 5-year follow-up period is currently being undertaken and should help identify patients who may benefit most from ICD therapy.[98]

Patients awaiting heart transplantation who have never experienced a spontaneous episode of life-threatening ventricular tachyarrhythmia deserve special consideration. Although ICD therapy is contraindicated in patients with NYHA class IV heart failure, due to a high incidence of nontachyarrhythmic deaths, it has been argued that ICD should be implanted in all NYHA class III patients as a "bridge" to transplantation. To date, no prospective randomized trial has been conducted to assess the benefit of such a strategy.

Summary

The ICD is now accepted as first-line therapy in the management of most patients who have experienced a spontaneous episode of life-threatening ventricular tachyarrhythmia. Much work needs to be done to accurately identify those patients at high risk of arrhythmic death who are at relatively low risk of death from all other causes and who would benefit from prophylactic ICD therapy. Prospective randomized trials have identified specific subgroups of patients who benefit from ICD therapy (MADIT and MUSTT patients), but a clear strategy regarding the screening and the investigation of such patients is required.

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FUTURE DIRECTIONS

Implantable cardioverter-defibrillator technology is evolving rapidly. Nonetheless, ICD devices are far from ideal, and many advances can be anticipated in the years ahead.[99] Advances in battery and capacitor technology, improved lead systems, and more efficient defibrillation waveforms will hopefully enable the ICD of the future to more closely approach the size of today's permanent pacemakers. Increased battery longevity is required to reduce the morbidity associated with pulse-generator replacements and to improve the cost-effectiveness of ICD therapy. Integrated arrhythmia management systems incorporating sophisticated dual-chamber pacing, dual-chamber cardioversion, and dual-chamber defibrillation will be employed in patients with paroxysmal supraventricular and ventricular tachyarrhythmias. The incorporation of a reliable hemodynamic sensor to differentiate hemodynamically stable from hypotensive tachyarrhythmias would help identify the most appropriate therapy for each arrhythmia.

More important than technological advances in the next few years will be a clearer understanding of the role of ICD therapy in the primary prevention of SCD. Careful selection of patients to reduce overall mortality rates as well as SCD will ensure that both patients and society benefit.

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Figure 30-4: Posteroanterior chest x-ray of pectoral ICD device. A single integrated lead is inserted via the cephalic vein and positioned at the right ventricular apex. This is attached to a pulse generator implanted in the left pectoral region. ICDs are implanted using techniques similar to permanent pacemaker implantation. The integrated lead consists of right ventricular and superior vena cava defibrillation coils (*arrows*) and a tip electrode. In addition to the defibrillation coils, the titanium case of the pulse generator acts as a large-surface-area defibrillation electrode (active can). The defibrillation pathway in this patient is right ventricular coil to both superior vena cava coil and active can.

Figure 30-5: Percent probability for successful defibrillation versus shock energy. The measured ICD energy margin is the energy difference between the lowest conversion success [defibrillation threshold (DFT)] and the programmed ICD energy: energy margin = E_{ICD} - DFT. The ICD safety margin is the energy difference between the lowest energy required for consistent defibrillation success (E_{99}) and the programmed ICD energy: safety margin = E_{ICD} - E_{99}. (Adapted from Singer and Lang,[40] with permission.)

Figure 30-6: Stored electrogram of inappropriate shock delivery due to atrial fibrillation. The recording is a continuous 32-s strip consisting of a waveform channel and a status channel. Atrial fibrillation is seen throughout the recording. In the first panel, the ICD classifies the shorter intervals as fibrillation (F). In the second panel, before the 12-s mark the detection criterion for VF is met. Device charging (*) and reconfirmation (R) of the arrhythmia begin as recorded in the status channel. In the third panel, a high-voltage shock is delivered inappropriately at the 21-s mark, denoted by a full-scale positive rectangular marker in both the waveform and status channels. Atrial fibrillation persists, and the detection criterion for VF is met a second time, in panel 4 before the 27-s mark. During device charging, the ventricular rate slows, and redetection of "sinus rhythm" (normal rate zone) aborts shock therapy. Sinus redetection is denoted by an arrow in the status channel and a negative deflection in the marker channel. Information regarding the device, date and time of the episode, screen sweep speed, the electrogram number and duration, and the reason the event was stored is located in the oblong box at the top of the page. (Courtesy of Mary Guy RN, ICD Clinic, Massachusetts General Hospital. From O'Callaghan and Ruskin,[56] with permission.)

Figure 30-7: The Antiarrhythmic Versus Implantable Defibrillator (AVID) Trial. Overall survival in the defibrillator group and the antiarrhythmic drug group up to 3 years after randomization in the AVID trial. Survival was better among patients treated with the implantable defibrillator ($p < .02$). (From the AVID Investigators,[64] with permission.)

Figure 30-8: The Multicenter Unsustained Tachycardia Trial (MUSTT). Kaplan-Meier estimates of overall mortality rate according to whether the patients received treatment with electrophysiologically guided (EPG) therapy without defibrillator (i.e., antiarrhythmic drug therapy), no antiarrhythmic therapy, or electrophysiologically guided therapy with a defibrillator. Mortality rates were significantly less in the ICD-treated patients than in the other two groups. (From Buxton et al.,[68] with permission.)

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Part 4: RHYTHM AND CONDUCTION DISCORDERS
Chapter 31:

CARDIAC PACEMAKERS

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The concept for bradycardia pacemakers originated in the 1950s. Over the past 4 decades, cardiac pacing has undergone tremendous growth, while the pacer units themselves have been downsized. Current units are capable of fully programmable dual-chamber pacing, rate response to activity and metabolic changes, have telemetry of pacer function, incorporate algorithms to respond to changes in intrinsic rhythms, and can store a history of patients' arrhythmic events. Besides providing bradycardia support, pacers are an integral part of patients' comprehensive arrhythmia and hemodynamic management strategies. A number of current and comprehensive reviews are available,[1-3] and the reader is referred to these for more detailed discussion of selected topics.

The basic pacemaker system consists of a pulse generator connected to one or two leads attached to the heart. Almost all pacemakers use a lithium-iodide battery. Pacing is accomplished by sending current pulses through the lead to a distal electrode (cathode), which initiates depolarization of the myocardium. Current returning through the anode completes the electrical circuit.

CODES FOR CARDIAC PACING

Pacemakers are coded by a specific abbreviation according to the type of pacemaker and mode of pacing. In common usage, the first three or four letters are used, but a total of five letters have been defined by the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) (Table 31-1).[4]

Table 31-1: The NASPE/BPEG Pacemaker Code

Chamber Paced	Chamber Sensed	Response to Sensed Event	Programmability/Rate Response
O (none)	O	O	O
A (atrium)	A	I (inhibit)	R (rate responsive)
V (ventricle)	V	T (triggered)	P (simple programmable)
D (dual)	D	D (I + T)	M (multiprogrammable)
S (single chamber, A or V)	S		C (communicating)

NOTE: In current terminology, only rate responsiveness (*R*) is indicated by the fourth position. All current pacers have full programmability; therefore, the letters *P*, *M*, and *C* are no longer used.

The first three letters refer to the type of pacemaker or pacing mode that is being employed. The first letter refers to the chamber(s) being paced and the second letter refers to the chamber(s) being sensed. The letter A indicates atrial pacing or sensing, and V refers to ventricular pacing or sensing. If A and V are both being paced and/or sensed, the designation D, dual-chamber pacing or sensing, is used. The third letter refers to the response to a sensed event. The pacemaker can either inhibit (I) pacing output from one or both of its leads, or it can trigger (T) pacing at a programmable interval after the sensed event. The detailed

description and indications for different pacing modes will be described.

The fourth letter designation represents either the type of programmability or whether the pacemaker is capable of providing rate-responsive pacing. Lastly, the fifth letter represents cardiac devices that are capable of treating atrial or ventricular tachyarrhythmias. In common usage, only the rate responsiveness of the pacemaker is noted in the fourth letter designation, and the fifth letter designation is only used for atrial pacers with antitachycardia function.

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Chapter 31: CARDIAC PACEMAKERS

TEMPORARY PACING

Temporary pacing is a modality required to provide patients with heart rate support when they experience intermittent or persistent hemodynamically relevant bradyarrhythmias or to provide standby pacing for patients at increased risk for sudden and complete heart block. Occasionally, temporary pacing is used to control sustained atrial or ventricular tachyarrhythmias. The end point for temporary pacing is either resolution of a temporary indication for pacing or implantation of a permanent pacemaker for a continuing indication. The clinician must decide whether to insert a temporary transvenous pacemaker versus relying on a noninvasive external unit.[5]

Indications

Indications for pacer implant can be divided according to whether there is consensus opinion as to the appropriateness of the indication (Table 31-2). The indications for temporary pacing are listed in Table 31-3. In general, indications for temporary pacing may include patients who are at high risk for developing complete heart block, such as is the case in patients with acute myocardial infarctions and alternating bundle branch blocks. Other indications for temporary pacing include those indications for permanent pacing when patients are symptomatic and cannot wait for the permanent pacemaker. In general, it would be advisable to place the permanent pacemaker as soon as possible to avoid the risks of temporary pacemaker placement.

Table 31-2: Consensus for Appropriateness of Pacer Implant Indication

Class I	Conditions for which there is general agreement that permanent pacemakers should be implanted.
Class IIa	Conditions for which permanent pacemakers are frequently used but there is divergence of opinion with respect to the necessity of their insertion. Weight of evidence/opinion is in favor of pacemaker use.
Class IIb	Conditions for which permanent pacemakers are frequently used but there is divergence of opinion with respect to the necessity of their insertion. Weight of evidence/opinion is in favor of pacemaker use.
Class III	Conditions for which there is general agreement that devices are unnecessary.

Temporary pacing is also indicated when a patient has bradycardia causing symptomatic or hemodynamic compromise. Temporary pacing at rates of 80 to 100 beats per minute can be used to prevent bradycardia-dependent ventricular arrhythmias or those associated with a long QT interval and torsade de pointes. Temporary atrial pacing is occasionally used in patients to restore atrioventricular (AV) synchrony in patients with temporary sinus arrest who have intact AV conduction. Toxic drug effects, such as digitalis toxicity, or metabolic abnormalities, such as hyperkalemia, may produce a temporary symptomatic bradycardia requiring temporary pacing.[6]

Lyme disease is a specific cause of carditis that has been associated with various degrees of AV

block in some patients.[6,7] In the presence of high-degree or complete AV block (see Chap. 23), the escape rhythm consists of a slow wide QRS or there may be a systole. Temporary cardiac pacing is necessary in the more advanced cases, but implantation of a permanent pacemaker is generally not necessary for patients with Lyme disease since the AV block almost always resolves.

Occasionally, temporary pacing is used for management of tachyarrhythmias for overdrive pacing of atrial or ventricular arrhythmias. The most common clinical setting is generally in the postoperative period after major cardiac surgery, when atrial flutter may be pace terminated into sinus rhythm.[8]

Temporary Pacing in Acute Myocardial Infarction

The use of temporary pacing in acute myocardial infarction can be accomplished by transcutaneous systems in those patients without active need for pacing and in those patients at low to moderate risk for developing complete heart block. Because transcutaneous systems are uncomfortable during active pacing for prolonged periods of time, transvenous pacing may be placed in patients requiring active pacing or in those patients at increased risk for developing complete heart block (Table 31-3).[9]

In patients with inferior infarction, any conduction disturbance is likely to be proximal to the His bundle. Therefore, patients with inferior infarction require temporary cardiac pacing only if there are symptoms (angina, hypotension, etc.) associated with the bradycardia or for persistent rates less than 40 beats per minute.

Although patients with inferior myocardial infarction are less likely to require temporary pacing compared with patients with anterior infarction, the recent guidelines on the use of temporary pacing in patients with acute infarction do not differentiate between anterior and inferior infarction.[9] Temporary pacing is indicated in the presence of high-degree (Mobitz type II second-degree AV block) or complete AV block because of the likelihood that these patients will be hemodynamically unstable with their bradyarrhythmia. Any symptomatic bradycardia with hypotension is also an indication for temporary pacing. Additionally, the presence of new bifascicular block generally places patients at increased risk for complete AV block, especially with associated first-degree AV block; therefore, temporary pacing would be reasonable. It is unclear whether patients with new left bundle branch block with normal PR interval or new right bundle branch block (with normal axis) require temporary pacing.

Selected patients with right ventricular infarction or other patients who require AV synchrony may require dual-chamber AV pacing. However, most patients who need temporary transvenous pacing receive a single ventricular lead because of its ease of use.

Techniques for Temporary Pacing

Techniques and clinical competence required to implant temporary pacemakers have been described elsewhere.[1,10,11] Catheters are generally placed into the right heart by percutaneous sheaths placed into the internal jugular, subclavian, brachial, or femoral vein. For temporary VVI pacing, the catheter is advanced under fluoroscopic guidance into the right ventricle. If fluoroscopy is not available, the pacing catheter can be advanced into the right ventricle by using intracardiac electrograms to position the lead.

Alternatively, transcutaneous pacing is a common method for noninvasively pacing patients who require a prophylactic temporary backup pacer or require emergent pacing.[5,12] It can be activated quickly in situations in which emergency ventricular pacing is required. The unit incorporates two

large pads placed in an anterior and posterior position. The main drawback is the high energy requirements (50 to 100 mA at 20 to 40 ms), which cause skeletal muscle stimulation and pain; therefore, this should not be used for extended periods in awake patients.

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Chapter 31: CARDIAC PACEMAKERS

INDICATIONS FOR PERMANENT PACING

The indications for permanent pacemakers can be divided into three classifications (Table 31-2) and are listed in Table 31-4 according to the most recent indications published by a joint task force by the American College of Cardiology and American Heart Association in 1998.[13] These recommendations serve as guidelines, and there are other clinical factors that may affect the decision to implant a pacer. Many indications for pacemaker implantation are predicated by the presence of symptoms. However, many symptoms such as fatigue or subtle symptoms of congestive heart failure may be recognized only in retrospect, after placement of a permanent pacemaker.

Table 31-4: Indications for Permanent Pacemaker

	Class I	Class II	Class III
Acquired AV block	Third-degree AV block with:	*Class IIa*	Asymptomatic first-degree AV block
	Bradycardia and symptoms due to AV block	Asymptomatic complete AV block with average awake ventricular rate >40 bpm	Asymptomatic type I second-degree AV block above the level of the bundle of His
	Requirement of drugs that result in symptomatic bradycardia	Asymptomatic type II second-degree AV block (permanent or intermittent)	AV block expected to resolve
	After catheter ablation of the AV junction or after postoperative AV block not expected to resolve	Asymptomatic type I second-degree AV block at or below the bundle of His (documented by electrophysiologic studies)	
	Neuromuscular diseases with AV block	First degree AV block with symptoms suggestive of pacemaker syndrome and documented alleviation of symptoms with temporary pacing	
	Escape rhythm <40 bpm or asystole >3 s in awake symptom-free patients		
	Second-degree AV block, permanent or intermittent, with symptomatic bradycardia	*Class IIb*	
		Marked first-degree AV block in patients with congestive heart failure	

After myocardial infarction	Persistent second- or third-degree AV block in the His-Purkinje system or Transient advanced infranodal AV block and associated BBB Symptomatic second- or third-degree AV block at any level	*Class IIb* Persistent advanced AV block at the AV node level	Transient AV conduction disturbances without intraventricular conduction defects or with isolated left anterior fascicular block Acquired left anterior fascicular block Persistent first-degree AV block in the presence of old or age-indeterminate BBB
Bifascicular or trifasicular block	Intermittent complete heart block associated with symptoms Type II second-degree AV block	*Class IIa* Bifascicular or trifascicular block with syncope not proven to be due to AV block but other causes of syncope not identifiable HV interval >100 ms or pacing-induced infra-His block	Fascicular block without AV block or symptoms Fascicular block with first-degree AV block without symptoms
Sinus node dysfunction	Sinus node dysfunction with documented symptomatic bradycardia (in some patients, this will occur as a result of long-term essential drug therapy of a type and dose for which there is no acceptable alternative) Symptomatic chronotropic incompetence	*Class IIa* Sinus node dysfunction, occurring spontaneously or as a result of necessary drug therapy, with heart rates <40 bpm without clear association between significant symptoms and bradycardia *Class IIb* In minimally symptomatic patients, chronic heart rate <30 bpm while awake	Sinus node dysfunction in asymptomatic patients, including those in whom substantial sinus bradycardia is a consequence of long-term drug treatment Sinus node dysfunction in patients in whom symptoms suggestive of bradycardia are clearly documented not to be associated with a slow heart rate Sinus node dysfunction with symptomatic bradycardia due to nonessential drug therapy

Hypersensitive carotid sinus and neurocardiac syndromes	Recurrent syncope associated with clear, spontaneous events provoked by carotid sinus stimulation; minimal carotid sinus pressure induces asystole of >3 s duration in the absence of any medication that depresses the sinus node or AV conduction	*Class IIa* Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response *Class IIb* Syncope with associated bradycardia reproduced by head-up tilt (with or without provocative maneuvers or isoproterenol)	A hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of symptoms Vague symptoms (dizziness or light-headedness) with a hyperactive cardioinhibitory response to carotid sinus stimulation Recurrent syncope, light-headedness or dizziness in the absence of a cardioinhibitory response

SOURCE: Adapted from Gregoratos et al., 13 with permission.
See Table 31-2 for definition of classes I, II, and III indications.
ABBREVIATIONS: AV = atrioventricular; BBB = bundle branch blocks; bpm = beats per minute.

Pacing in Acquired Atrioventricular Block

It is generally agreed that complete heart block, permanent or intermittent, at any anatomic level associated with symptoms such as dizziness, lightheadedness, syncope, congestive heart failure, or confusion is an indication for a permanent pacemaker. In the absence of symptoms, pacing is indicated for patients with third-degree AV block, especially with awake heart rates of less than 40 beats per minute or pauses of longer than 3 s.

In the presence of bifascicular or trifascicular block, intermittent third-degree or type II second-degree AV block usually indicates the need for a permanent pacemaker. When patients with these conduction patterns present with syncope, a pacemaker is usually required. However, an electrophysiology study may be useful to rule out other causes of syncope (e.g., ventricular tachycardia) particularly if structural heart disease is present. Additionally, during electrophysiology study, permanent pacing may be indicated if there is a markedly prolonged HV interval (>100 ms)[14] or nonphysiologic pacing or drug-induced infra-His block.[15]

Second-degree AV block associated with symptomatic bradycardia is an indication for pacing. In asymptomatic patients with second-degree AV block, type II, cardiac pacing may be required if the level of block is infranodal, because the progression to complete heart block is common.[16] Although type I second-degree AV block is usually located at the AV nodal level, there are patients with bundle branch block or intraventricular conduction delays in whom type I second-degree AV block is located at an infranodal level. These patients should be approached similar to patients with second-degree type II AV block, since the risk of progression to complete heart block remains high. Lastly, with 2:1 AV block, the level of block may be difficult to determine. In the presence of a bundle branch block or intraventricular conduction delay and 2:1 AV block, the level of block is usually infranodal and therefore may be an indication for pacing.

In asymptomatic and otherwise healthy patients, the presence of intermittent second-degree, type I AV block may be due to enhanced vagal tone.[17,18] In asymptomatic elderly patients with daytime type I second-degree AV block and structural heart disease, however, there is some divergence of opinion as to whether permanent pacing should[19-21] or should not[13,18] be considered. Many patients may become symptomatic during clinical follow-up.[18,19]

Due to the benign prognosis first-degree AV block is not considered an indication for permanent pacing.[13,22] However, with marked first-degree AV block (PR > 0.30 s), inappropriately timed atrial systole that occurs after ventricular systole can lead to symptoms similar to having retrograde ventriculoatrial conduction. This may be of hemodynamic consequence in some patients, particularly with left ventricular systolic or diastolic dysfunction.[23,24] Additionally, because there is not an appropriately timed ventricular systole occurring at the end of atrial systole, end-diastolic mitral regurgitation develops, which may be of clinical significance in patients with left ventricular systolic dysfunction.[25] Therefore, dual-chamber pacing may be indicated in select patients with marked first-degree AV block in whom hemodynamic improvement can be demonstrated by temporary pacing to resynchronize the atrium and ventricles.[13]

Of note, patients with neuromuscular diseases with AV block should be considered for DDD pacing, since progression of conduction system disease is not uncommon.[26-28]

Pacing in Congenital Atrioventricular Block

Congenital heart block is usually due to AV nodal block. Patients tend to be asymptomatic and typically have narrow QRS complex rhythms. However, congenital AV block is associated with serious and possible fatal complications, including syncope and sudden death.[29-32] In one study,[30] a mean daytime heart rate less than 50 beats per minute was associated with sudden death or need for pacemaker. Exercise testing is useful to assess heart rate response at rest and exercise.[30] Other indicators of poor outcome include prolonged QT interval (corrected for heart rate), cardiomegaly, atrial enlargement, decreased left ventricular systolic function, mean ventricular rates lower than median for age, periods of junctional exit block, and mitral regurgitation.[30-32]

Therefore, cardiac pacing is indicated in all symptomatic patients with congenital AV block. Furthermore, cardiac pacing is now recommended even for symptom-free adults. In the largest series published to date, there was reported a 5 percent mortality risk in adults older than 15 years with congenital AV block in the absence of heart disease. Eight of 102 patients whose cases were followed for 7 to 30 years had fatal Stokes-Adams attacks.[31] Syncope, mitral regurgitation, and/or heart failure occurred in 30 percent of this cohort.[31,32]

Pacing in Sinus Nodal Dysfunction

Sinus nodal dysfunction has become the most common indication for pacing in the United States. Pacing therapy has been demonstrated to be superior to medical therapy with theophylline for patients with sinus nodal dysfunction.[33] The guidelines (Table 31-4) stress the importance of correlating symptoms with bradyarrhythmias. Often, it is difficult to correlate ECG findings with symptoms. Furthermore, symptoms may be nebulous. For instance, the presence of fatigue and dyspnea may be due to a bradyarrhythmia but may also be due to lack of conditioning or other cardiac dysfunction.

The presence of the tachycardia/bradycardia syndrome is especially common in patients with paroxysmal atrial arrhythmias (Fig. 31-1). The bradyarrhythmia often occurs at the termination of tachycardia and can lead to pauses of several seconds. Drugs used to suppress tachyarrhythmias may lead to symptomatic bradycardia, in which case a bradycardia pacemaker would be required.

Patients with asymptomatic bradyarrhythmias should be evaluated carefully prior to placing a pacemaker. In general, an absolute heart rate of less than 30 beats per minute is an indication for pacer placement, even in the absence of symptoms. An exercise test can demonstrate intact sinus nodal function in patients with otherwise asymptomatic bradyarrhythmias who do not require pacing therapy. Athletes commonly have physiologic bradycardia, even with heart rates of less than 40 beats per minute, due to enhanced vagal tone. Finally, it should be noted that sleep apnea may cause asymptomatic, nocturnal bradyarrhythmias,[34] in which case pacing therapy is not indicated.

Pacing in Carotid Sinus Syndrome

The diagnosis for carotid sinus syndrome (CSS) is typically made by demonstrating asystolic pauses of longer than 3 s with carotid sinus massage or a vasodepressor response of greater than 50 mmHg associated with clear symptoms provoked by carotid sinus stimulation, such as wearing a tight shirt or turning one's head. Vague symptoms such as dizziness associated with a hyperactive cardioinhibitory response to carotid sinus stimulation do not represent an indication for permanent pacing.

Improvement of symptoms and suppression of syncope have been demonstrated by treating patients with cardiac pacing,[35-38] particularly dual-chamber pacing.[36-38] Single-chamber atrial pacing is contraindicated because of the increased risk of transient AV block. Some studies suggest that hemodynamic evaluation of patients may enable them to be stratified into groups among whom VVI pacing would be sufficient. However, DDD pacing is probably better in most patients with CSS, because of the presence of vasodepressor and cardioinhibitory reflexes.

Cardiac Pacing in Neurocardiogenic Syncope

The role of pacing for neurocardiogenic syncope is controversial. Because these are younger patients who generally respond to medication, pacing is not required in most patients.[39] Cardiac pacing has been shown to prevent the bradycardia and AV block associated with neurocardiogenic syncope, but patients still typically experience hypotension, vasodilatation, and other associated symptoms.[39-41] The Vasovagal Pacemaker Study demonstrated a role for pacing in patients with vasovagal syncope refractory to standard medical therapy.[42] Therefore, patients with refractory neurocardiogenic syncope may benefit from pacing, especially if they have a predominant cardioinhibitory component.[43]

Pacing in Hypertrophic Cardiomyopathy

In patients with hypertrophic cardiomyopathy (HCM) and left ventricular outflow tract (LVOT) gradients, DDD pacing with a programmed short AV interval has been proposed as therapy to reduce LVOT gradient and improve symptoms.[44-47] This concept is based on early studies where it was shown that DDD pacing with short AV interval decreased the LVOT gradient by a mean of 35 mmHg,[44] and there was improvement of symptoms associated with HCM. An observational study involving 84 patients whose cases were followed for a mean of 2.3 years showed improvement of symptoms in nearly all patients, and there was reduction in the left ventricular wall thickness by more than 4 mm in a subgroup of patients.[47] However, 15 percent of the patients required AV junction ablation to allow ventricular preexcitation by the pacer.

The mechanism by which DDD pacing reduces LVOT gradient remains controversial. With ventricular pacing at short AV interval, the right ventricular apex is preexcited by the pacemaker, causing alteration of the left ventricular activation sequence and paradoxical septal motion. This causes the septum to move away from the posterior left ventricular wall in early systole, thereby widening the LVOT during systole. It is also possible that ventricular pacing alters myocardial perfusion, decreases mitral valve systolic anterior motion, and/or decreases inotropy, which may also contribute to the beneficial effects of pacing in this disorder.

Therefore, if DDD pacing is used as therapy for obstructive hypertrophic cardiomyopathy, placement of pacing lead and programming of the AV interval are crucial for a beneficial effect. The AV interval should be programmed to the longest interval that still allows for left ventricular preexcitation, which would decrease but not eliminate the deleterious effects of pacing with very short AV intervals.[46] Echocardiography may help select the optimal pacing AV interval.

The long-term clinical effectiveness of DDD pacing in patients with obstructive HCM remains controversial. Some recent and randomized studies cast some doubt as to the clinical effectiveness of pacing for objectively improving functional capacity, quality of life, and LVOT gradient.[46,48,49] One small randomized study failed to demonstrate improvement in exercise response to DDD pacing.[48] Another study in patients with symptomatic obstructive HCM showed that when patients were randomized to backup AAI pacing versus DDD pacing with short AV interval, there was no difference in subjective improvement.[49] LVOT gradient was reduced by 40 percent in 57 percent of patients and remained unchanged in the other

43 percent of patients. Only 12 percent of patients (all older than age 65) showed improvement in functional capacity after 12 months in the study. Therefore, based on this randomized double-blind study, pacing could not be routinely recommended for drug-refractory patients with obstructive HCM but, rather, may be considered for select patients with medically refractory obstructive HCM as an alternative to surgical myectomy.[50]

Patients with hypertensive cardiac hypertrophy with cavity obliteration may also show clinical improvement with DDD pacing.[51] In contrast to obstructive HCM, patients with nonobstructive symptomatic HCM experience limited symptomatic improvement and no objective evidence of hemodynamic benefit with DDD pacing and short AV interval.[52]

Pacing in Dilated Cardiomyopathy and Congestive Heart Failure

Initial reports suggested that patients with congestive heart failure and dilated cardiomyopathy may benefit from dual-chamber pacing by altering and optimizing timing of left atrial to left ventricular activation or improving left ventricular contractile function. There was initial enthusiasm that pacing with a short AV interval may improve hemodynamic function[24,25] and that the patients with first-degree AV block derived the most benefit.[25] An acute hemodynamic study demonstrated that pacing with a short AV interval could eliminate presystolic mitral regurgitation in patients with first-degree AV block, restore normal AV relationships, and improve hemodynamic function.[25] Subsequent studies showed that standard DDD pacing does not improve hemodynamic function in patients with physiologic PR intervals.[53,54] On this basis, DDD pacing is possibly indicated in patients with dilated cardiomyopathy or marked first-degree AV block and where acute hemodynamic studies demonstrate improvement by dual-chamber pacing.[13]

Whereas pacing the ventricles with short AV interval may have limited benefit, the ability to pace the ventricles in a more synchronous manner to improve mechanical efficiency has also been studied. Ventricular pacing typically is achieved by pacing through a lead placed in the right ventricular apex, which may not produce the most efficient ventricular mechanical function. Pacing through the His-Purkinje system in theory may provide more physiologic ventricular activation patterns but is currently not readily available.[54a] Pacing from the right ventricular septum or outflow track may enable earlier left ventricular activation and, hence, more simultaneous contraction. However the results of hemodynamic improvement using right ventricular outflow tract pacing has shown a trend for improvement in some studies,[55,56] whereas other studies[57-59] show no benefit at all compared with right ventricular apical (RVA) pacing.

It has been proposed that left ventricular or biventricular pacing may optimize hemodynamic function in patients with dilated congestive cardiomyopathy, particularly those patients with intraventricular conduction delay. Left ventricular pacing can be accomplished by either an epicardial lead or a transvenous lead through the coronary sinus venous system. An acute hemodynamic study[58] was performed on patients with severe heart failure, intraventricular conduction delay (usually left bundle branch block), and increased capillary wedge pressure. These patients had measurement of hemodynamic parameters during either right ventricular pacing or biventricular pacing, which was compared with AAI pacing (control values). These results showed improvement of cardiac index and decrease in capillary wedge pressure with either right ventricular pacing or biventricular pacing compared with AAI pacing. Furthermore, biventricular pacing showed more hemodynamic benefit compared with right ventricular pacing. Another study on patients with congestive heart failure and wide QRS duration showed that epicardial left ventricular pacing, with or without concurrent right ventricular pacing, improved hemodynamic function at optimized AV intervals compared with control values.[60] Therefore, left ventricular pacing may evolve as a therapeutic pacing technique in patients with congestive dilated cardiomyopathy and intraventricular conduction delay.

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Chapter 31: CARDIAC PACEMAKERS

PACEMAKER HARDWARE

Implant and Explant

Nearly all pacemakers are implanted through a transvenous approach by either cardiologists or surgeons. The choice of using an operating room or a catheterization laboratory for the implant procedure probably plays little role in procedural-related complications, but a cardiac catheterization laboratory involves lower hospital costs.[61,62]

A full description of the surgical procedure has been reviewed elsewhere.[1,63] Venous access for lead placement generally is through a subclavian venipuncture or a cephalic vein cutdown. The use of subclavian venipuncture is technically easier, and this vein can almost always accommodate two leads. With the subclavian venipuncture, there exists the risk of subclavian artery puncture, pneumothorax, or air embolus. Furthermore, pacing leads placed medially incur an additional long-term risk of being "crushed" by the clavicle and first rib leading to lead insulation breaks or fractures (Fig. 31-2). Lateral puncture of the subclavian or axillary vein using intravenous contrast may allow for safe lateral subclavian venous puncture.[64] A cephalic vein cutdown[65] may also avoid some of the risks associated with subclavian vein puncture; however, this vein is not always accessible and cannot always accommodate two pacing leads.

Explanations of pacemaker generators are routinely performed during pacemaker generator changes. However, removal of pacemaker leads can be difficult due to fibrosis between chronically implanted leads and surrounding cardiac, valvular, and vascular structures. Traditional methods for extraction of chronically implanted leads involve specialized extraction sheaths that are glided over implanted leads to tear and peel away the encapsulating tissue.[66] Recently, a technique using ultraviolet excimer laser light has been introduced to facilitate lead extraction by allowing advancement of sheaths over pacer leads without excessive mechanical tearing of fibrotic tissues.[67,68] Compared with mechanical extraction, laser-assisted extraction demonstrated a greater success rate in lead removal (94 percent versus 64 percent) and less time to remove leads,[67] with no difference in complications.

Hardware

The pacemaker system consists of a pulse generator and the pacing lead(s). Pacemaker system selection should be primarily based on the medical and surgical requirements of the patient. It is unusual that one pacemaker system would be most optimal and cost effective for all patients. An algorithm for choosing a pacemaker system and pacing mode is presented in Fig. 31-3.

Pacemaker leads can be unipolar or bipolar (Figs. 31-4 and 31-5). Unipolar leads use a distal electrode in the catheter as the cathode and the shell of the pacemaker generator as the anode. Therefore, the myocardium and adjacent tissue complete the circuit. A bipolar lead consist of two separate conductors and electrodes within the lead. Since the electrodes for sensing in a bipolar lead are much closer together, bipolar signals are sharper with less extraneous noise (Fig. 31-6).

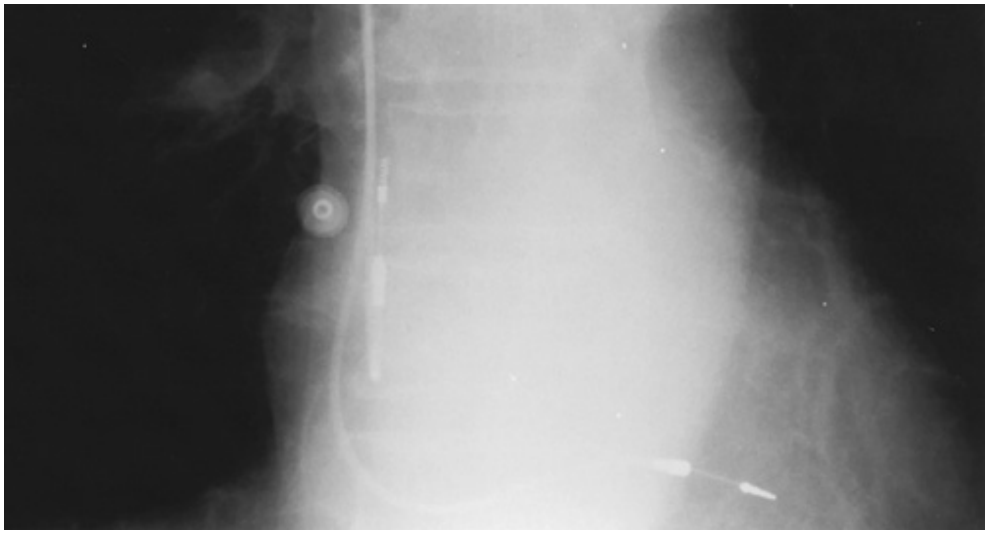
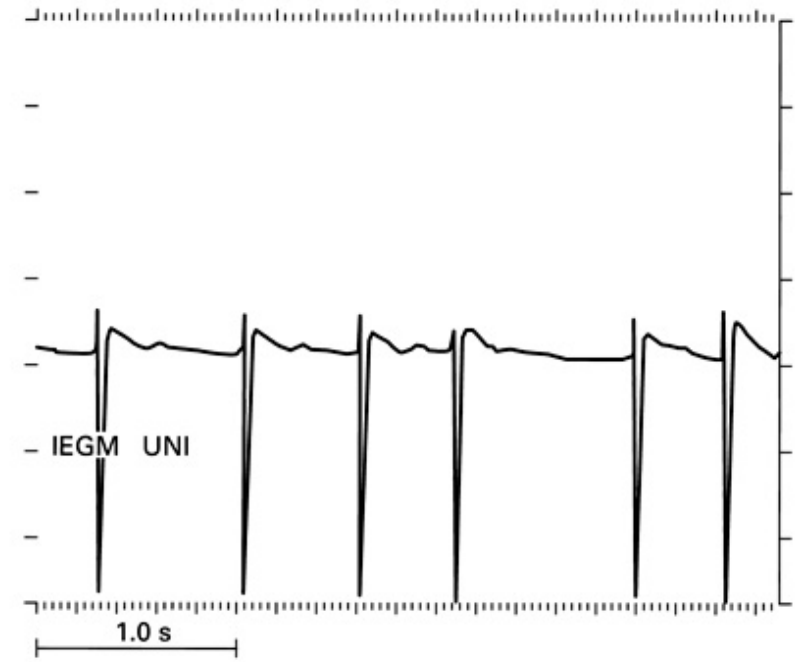


Figure 31-5: Chest x-ray from a patient with a bipolar dual-chamber pacing system. The atrial lead is attached to the right atrial appendage by active fixation (screw-in lead), and the screw is visible on the chest x-ray. The ventricular lead is attached to the ventricle by passive fixation.



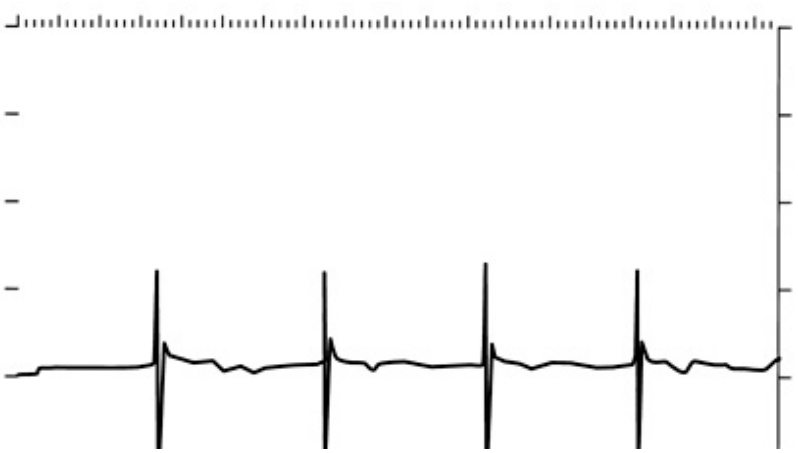


Figure 31-6: Unipolar (*top*) and bipolar (*bottom*) intracardiac electrograms (IEGMs) from a patient with a ventricular pacemaker whose underlying rhythm is atrial fibrillation. Note that the bipolar signal is sharper, with less sensing of far-field ventricular electrical activity or T waves. With either unipolar or bipolar electrograms, direct measurement of the electrogram amplitude is possible. Each division on the left represents 1 mV. Therefore, the unipolar intracardiac electrogram is 2 to 3 mV from baseline to peak. The bipolar electrogram would be expected to be approximately 2 mV.

Unipolar leads are simpler to design, smaller in diameter and, because of their simplicity, probably less likely to fail.[69] Because of their small size, it is easier to pass two unipolar leads through a cephalic venous approach. However, there are several disadvantages to unipolar lead systems. Because the unipolar lead uses body tissue to complete the circuit, there is the possibility of causing muscle stimulation. Most pacemakers avoid this by placing the stimulating surface of the pacemaker anterior such that it interfaces with subcutaneous tissue and not the pectoralis muscle. Unipolar sensing is far more likely to pick up extracardiac signals, including myopotentials (Fig. 31-6), far-field sensing of remote cardiac potentials, and electromagnetic interference. Finally, unipolar pacing is generally contraindicated in patients with a concomitant implantable defibrillator. Therefore, most leads implanted today are bipolar.

Leads are attached to the heart by active or passive fixation. Active fixation involves the use of some type of exposed or retractable screw within the lead system that fixes the lead to the heart (Fig. 31-5). Passive fixation involves the use of tines, which are short protuberances that extend proximal to the distal electrode and interact with myocardial tissue to hold the lead in place. Active fixation leads are used more in the atrium and allow fixation of the leads almost anywhere within the right atrium or ventricle. The use of either type of lead probably has little effect on complication rate or lead dislodgment rate when used by experienced operators.

Lead Placement and Acute Threshold Testing

Atrial and ventricular leads are placed into the appropriate chambers after ensuring adequate pacing and sensing thresholds (Table 31-5). The basic premise in obtaining acute pacing and sensing thresholds during implant is that these thresholds may degenerate over time, and adequate safety margins need to be obtained to ensure safe long-term pacing and sensing. Furthermore, one should be aware of the type of unit implanted, its capabilities for pacing outputs, programmed sensitivities, and pacing modality (bipolar versus unipolar). The indication for pacing may also affect decisions about acceptable pacing thresholds, because of the inverse relationship between current drain and battery life. In patients who only require occasional backup pacing, higher pacing thresholds may be acceptable. Therefore, pacing thresholds should be optimized at the time of implant as influenced by the patient's pacing requirements and pacing capabilities of the pacemaker.

Table 31-5: Acceptable Pacing and Sensing Thresholds During Implant

	Atrial	Ventricular
Pacing threshold at 0.5 ms	<1.2 V	<1.0 V
Sensing threshold (bipolar)	>1.5-2 mV	>5 mV
Sensing threshold (unipolar)	>2-2.5 mV	>5 mV
Impedance*	300-1400 ohm	300-1400 ohm

*New high-impedance leads result in less current drain and improved longevity.

For sensing functions, ventricular electrograms should measure at least 5 mV and frequently measure in excess of 10 to 20 mV. Ventricular sensitivity is generally programmed between 2 to 3 mV so that adequate safety margin exists for sensing intrinsic ventricular depolarization without the risk of oversensing T waves or other artifacts. Atrial electrograms are lower in amplitude than ventricular electrograms; however, a minimum atrial electrogram of 1 to 2 mV should be obtained. In unipolar systems, a larger atrial electrogram is important because of the increased risk of oversensing myopotentials or other artifactual signals if the atrial sensitivity is programmed to less than 1 mV. In patients with paroxysmal atrial fibrillation or flutter, the atrial electrogram during tachycardia might be smaller than during sinus rhythm. Conversely, in patients with marked sinus bradycardia where it is expected that there will be nearly 100 percent atrial pacing, atrial sensing thresholds may not be as important. Finally, the minimum programmed sensitivity available by the pacer (0.15 to 0.5 mV) may influence acceptable sensing thresholds at implant.

Many factors may affect atrial or ventricular pacing and sensing thresholds. There is variation to these thresholds depending on the autonomic tone or the electrolyte status. There is an expected rise in acute thresholds within 1 to 4 weeks following implant due to acute inflammation, which appears to be more exaggerated with active fixation lead systems. Many drugs, particularly antiarrhythmic medications, may affect pacing thresholds. The presence of new myocardial infarction around the leads would be expected to lead to deterioration of pacing and/or sensing thresholds. Leads that are steroid eluting generally limit the acute rise in pacing threshold. Long-term thresholds appear to stabilize sometime after 3 to 6 months.[70]

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Chapter 31: CARDIAC PACEMAKERS

PACEMAKER FOLLOW-UP

The goal for pacemaker follow-up should be to perform a systematic evaluation of the pacemaker as it relates to and functions with the patient and his or her individual needs. These goals are outlined in Table 31-6. Complete guidelines for pacemaker follow-up have been described.[71]

Table 31-6: Goals of Pacemaker Follow-up

TTM or Direct	Direct or indirect measurement of battery voltage and anticipate need for replacement
TTM	Evaluation of pacing and sensing during normal pacer function and during application of magnet
Direct	Lead function: sensing, pacing thresholds, and impedance measurement; telemetry of lead during various arm/chest positions to expose any subtle lead insulation defects
Direct	Optimization of pacing outputs and parameters based on results of pacing tests, patient clinical condition, and medications
Direct	Evaluation of diagnostic information stored in pacemakers and integrate information with overall patient management strategy
Direct	Patient education

ABBREVIATIONS: TTM = transtelephonic monitoring; Direct = direct evaluation of pacemaker using specific programmer.

In the first several months after pacer implant, several evaluations of pacer function may be required in order to optimize pacing outputs, rate responsiveness, and other features. There is a stable period of pacer function starting 6 to 12 months following implant until the expected time for battery depletion. Therefore, direct evaluations of pacer function may be performed once or twice per year during this time, depending on whether the patient is pacer dependent and depending on the pacer type and whether any of the pacer components are under any advisory warnings.

Transtelephonic Monitoring

Technology is available for simple devices used by patients to transmit their ECG by telephone to a receiving station so that their ECG rhythm may be analyzed to detect normal or abnormal pacemaker function.[71,72] In this way, a spontaneous pacing rhythm can be assessed for normal or abnormal pacing function. More importantly, by applying a magnet to the pacemaker and observing the *magnet rate* during the transtelephonic monitoring (TTM), the battery status can be assessed. During TTM, changes in pacing rate or loss of output could always be detected. Ventricular oversensing or atrial pace/sense problems can sometimes be detected during TTM.[72]

Follow-up using TTM should be used to supplement and not replace direct evaluation of pacer function. The frequency of follow-up should be individualized according to the type of pacemaker, whether the patient is pacemaker dependent, age of pulse generator and expected longevity, presence of any pacemaker component under advisory or warning, and patient clinical factors. As depletion of pacer battery occurs, TTM may be used as often as every month to appropriately determine the timing for pacer replacement.

Components for Direct Evaluation of Pacemaker Systems

CHECKING PACING THRESHOLDS AND PROGRAMMING PACING OUTPUTS

Pacemakers should always be programmed for maximal safety particularly in patients who are pacemaker dependent. To understand how to program pacemakers safely and efficiently, some basic principles are reviewed.

Current Drain

Ultimately, the longevity of the battery will be a function of the current drain versus battery capacity. There is nominal current drain for operating pacemaker circuitry, which varies according to the pacer type; however, most current drain results from pacing output. The current delivered per pacing pulse is a function of the voltage divided by the lead impedance ($I = V/R$)-Ohm's law. Therefore, it is desirable to be able to implant leads with low pacing voltage thresholds. Additionally, leads designed to have high impedance appear to decrease long-term current drain.[73]

Strength-Duration Curve

The strength-duration curve (Fig. 31-7) relates voltage and pulse width. This curve is dynamic during the first 2 to 3 months following implant. With an acute rise in threshold, the curve is expected to shift upward two to four times and then subsequently shift back downward at a level greater than the initially obtained values. At pulse widths less than 0.2 ms, the curve is steep; at pulse widths exceeding 1.0 ms, the curve is flat. With this kind of relationship, programming pulse widths greater than 1 ms generally does not add safety margin to the pacing output but does substantially increase battery current drain. Similarly, programming pacing pulse widths less than 0.2 to 0.3 ms may not allow sufficient safety margin at even high voltage amplitudes.

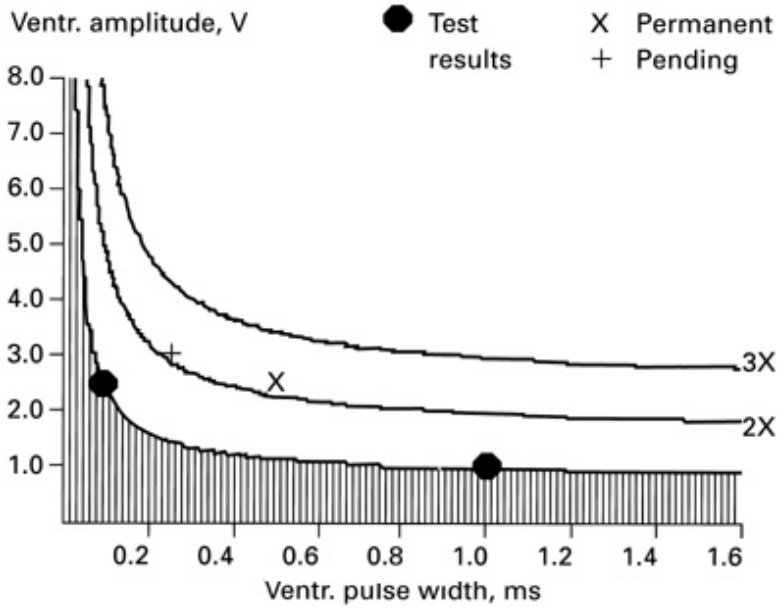

Figure 31-7: A sample of a strength-duration curve. The voltage threshold at 2.5 V was 0.1 ms, and the pulse-width threshold at 1.0 ms was 1.0 V. Sample curves are shown providing for two and three times the safety margin for programming voltage and pulse width. Ventr. = ventricular.

Total Energy Expenditure of the Pacemaker

This is defined as energy = $(\text{voltage})^2$ multiplied by pulse width divided by impedance. According to this

relationship, the energy expenditure has an exponential relationship to voltage output but has a linear relationship to pulse width. Therefore, it is preferable to reduce voltage output rather than pulse width to conserve battery life.

Calculating Pacing Threshold

At implant, it is standard to fix the pulse width at 0.5 ms and reduce the voltage until the lowest voltage that maintains consistent pacing-which is the pacing threshold (Fig. 31-8). One can fix the pulse width at any value, however (usually between 0.3 and 1.0 ms), and calculate a voltage threshold. Similarly, one can fix the voltage at a certain value and reduce the pulse width to the lowest value that maintains consistent pacing, which would also define the pacing threshold. Either method is acceptable to define a pacing threshold.

Safety Margin

The safety margin for pacing outputs can be calculated by multiples of either the pulse width or the voltage threshold. For example, if the voltage threshold at 0.5 ms is 1.5 V, then a pacing output of 0.5 ms and 3.0 V would yield an energy safety margin of fourfold, given the relationship between energy and voltage. Similarly, if the pulse width threshold at 3.0 V is 0.15 ms, then a pacing output of 3.0 V and 0.6 ms would provide an energy safety margin of fourfold.

Acute Pacing Outputs

Because the extent of the acute rise in pacing thresholds may be difficult to predict, it is better to program high pacing outputs at implant and during the first 6 to 24 weeks after implant. A greater safety margin may be desired in patients who are pacemaker dependent. Typically, greater safety margins are also desired in ventricular leads rather than atrial leads. Steroid-eluting leads generally result in blunting of the acute rise in threshold,[74] which may allow for lower pacing outputs early after implant.

Chronic Pacing Outputs

In the time frame of 2 to 6 months, the pacing thresholds stabilize. Therefore, chronic pacing outputs may be programmed (Table 31-7). Almost all pacing batteries consist of lithium-iodide systems, which generate 2.8 V. It is most efficient to pace at the voltage of the battery (2.5 to 2.8 V). Therefore, longevity of pacemakers can be improved if pacing outputs are reduced to 2.5 V with pulse widths programmed 2 to 4 times pulse-width thresholds.

Table 31-7: Recommendations for Pacing Outputs

	Atrial Leads	Ventricular Leads
Pacemaker dependent	2-3 × PW threshold	4 × PW threshold
	1.5-1.8 × V threshold	2 × V threshold
Not pacemaker dependent	2 × PW threshold	2-3 × PW threshold
	1.5 × V threshold	1.5-1.8 × V threshold

ABBREVIATIONS: PW = pulse width; V = voltage.

Finally, some newer pacemakers have the ability to confirm capture on a beat-by-beat basis.[75] Using algorithms to automatically check pacing capture thresholds, these pacers adjust pacing voltages just above the pacing threshold in order to reduce current drain and prolong battery longevity.

OTHER FEATURES

Sensing

Sensing of atrial and ventricular intracardiac electrograms can be evaluated by different algorithms. To test atrial sensing, the pacemaker needs to be programmed temporarily at a programmed atrial rate less than the intrinsic sinus rate. To test ventricular sensing, the pacer can be temporarily reprogrammed to the VVI mode if the programmed rate is less than the intrinsic heart rate. Alternatively, with intact AV conduction, the AV delay can be increased to allow AV conduction and thereby allow for ventricular sensing in the DDD mode. Increasing the programmed sensitivity until the intrinsic P or R wave is no longer sensed (Fig. 31-9) is another method to test sensing threshold. Telemetry of atrial or ventricular electrograms allows for direct measurement of the electrogram amplitude (Fig. 31-6). Lastly, some pacemakers have algorithms whereby the pacemaker automatically measures atrial and ventricular electrograms.

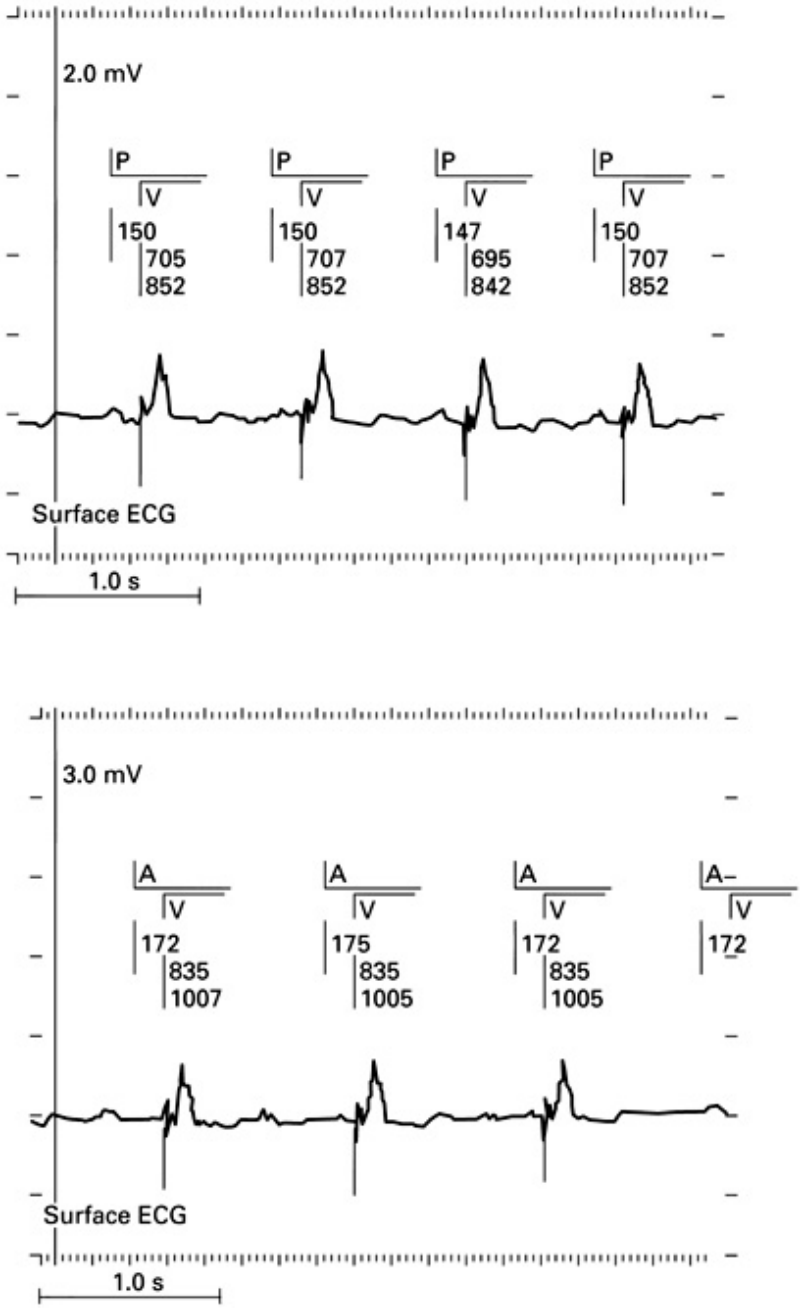

Figure 31-9: *Top*. P-wave synchronous ventricular pacing, with marker channels "P" indicating sensed P

waves and "V" indicating paced ventricular complex. At 2 mV, there was appropriate P-wave sensing. *Bottom*. "A" indicates that the pacemaker is pacing the atrium. At the programmed sensitivity of 3 mV, there was undersensing of the P wave and therefore atrial pacing occurred. Hence, the sensed P-wave amplitude is between 2 and 3 mV.

Lead Function

Lead function is assessed by checking pacing and sensing function and by measuring impedance. Although there is a wide variability of normal lead impedances, chronic lead impedances should not widely vary between outpatient follow-up visits. A fractured lead exhibits a markedly elevated lead impedance. Insulation breaks manifest by reduced lead impedances. Lead fractures or insulation breaks often are intermittent problems. Therefore, normal lead impedances and pacing and sensing thresholds do not rule out these problems. The leads can be stressed by having the patient change position and do various provocative arm movements to facilitate diagnosis of lead-related problems that are not otherwise observed.

Battery Function

Almost all pacemakers use lithium-iodide batteries, which have an initial battery voltage of 2.8 V. Battery voltages can be directly measured and, at a certain level (elective replacement index [ERI]), the pacemaker unit requires elective generator change. At a lower battery voltage (end of life [EOL]), there is potential loss of pacemaker function; therefore, immediate generator change is mandated.

Battery function can also be assessed without formal interrogation. Many pacemakers reset to a VVI mode at a preset pacing rate, or the pacing rate decreases to less than the programmed lower rate of the pacemaker when battery function reaches the ERI or EOL stage. Additionally, the magnet mode causes asynchronous pacing at a preset *magnet* rate for each particular pacemaker model. This magnet rate varies according to whether the battery status is adequate or not.

Rate Responsiveness

Rate-responsive pacemakers require periodic adjustments of the rate-responsive features to optimize clinical responsiveness. The programmable variables include a rate-responsive upper pacing rate, which may be a separate programmable variable than the upper tracking rate. A rate-response slope may be programmed to determine the pacing rate at a certain activity level. Some pacemakers store data with respect to the use of rate responsiveness over a certain period. Otherwise, one can simply have the patient walk briskly for 2 to 3 min and assess the heart rate to determine whether it is appropriate given the patient's age and clinical status. Some pacemakers offer algorithms whereby the physician chooses the appropriate heart rate for "brisk walking," and the pacemaker automatically calculates the optimal rate-responsive programming.

Pacer Diagnostic Function

Modern pacemakers have increased memory capabilities to store diagnostic information. The basic diagnostic feature displays counts or percentages of pacing versus sensing in the atrial and ventricular chambers. If a patient has complete heart block but has intact sinus nodal function, it would be expected that there be 100 percent ventricular pacing with predominant atrial sensing. The breakdown of pacing and sensing in each chamber can be stratified according to the heart rate that can give the clinician some clues as to the presence of chronotropic incompetence or appropriateness of rate responsiveness.

With respect to arrhythmia monitoring, the presence and quantity of premature ventricular and atrial complexes are presented. For patients with mode-switching pacemakers, the number of mode switches probably represents a marker for the number of atrial arrhythmias.[76] However, these data do not provide information with respect to duration and timing of these atrial arrhythmias. One study showed that most of these atrial arrhythmias are very brief, lasting only a few seconds in many cases.[77] More information about the occurrence, timing, and duration of arrhythmias, including stored intracardiac electrograms, is available in some pacers. This type of information may facilitate diagnosis of arrhythmias without the need for ancillary testing (Fig. 31-10). Furthermore, when patients complain of symptoms such as palpitations, these diagnostic features may enablediagnosis of, or rule out, atrial or ventricular tachyarrhythmias.

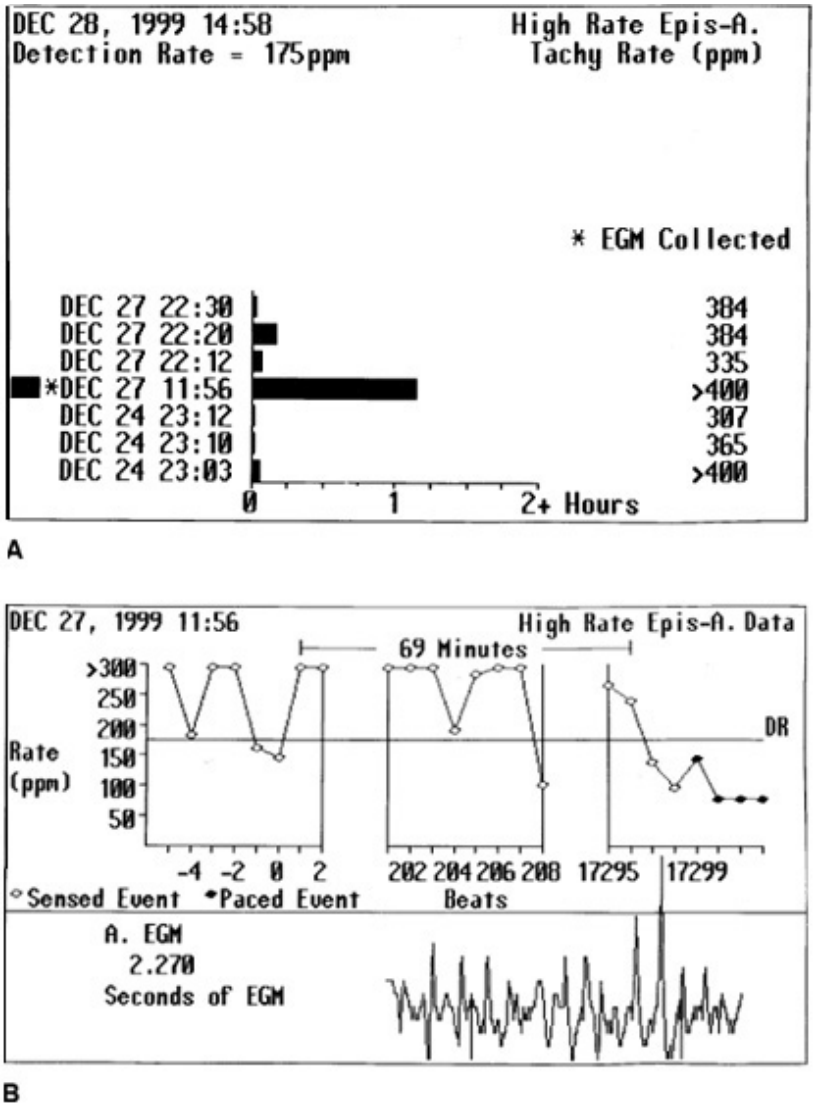

Figure 31-10: *A.* Shown are rate histograms demonstrating seven episodes of atrial fibrillation lasting from a few minutes to an episode lasting over an hour. *B.* This graphic demonstrates the beat-to-beat rate just before onset of the atrial tachyarrhythmia, after 200 beats, and just after termination of the arrhythmia, 69 min later. A snapshot of the stored intraatrial electrograms (A-EGMs) confirms atrial fibrillation as the mechanism. DEC, December; Tachy, tachycardia.

Chest Radiograph (Posteroanterior and Lateral)

A standard chest x-ray (Figs. 34-4 and 34-5) is recommended as part of the predischarge evaluation to ensure appropriate placement of leads, rule out lead migration, and serve as a baseline.

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Chapter 31: CARDIAC PACEMAKERS

PACEMAKER FUNCTION AND MODES

Magnet Mode

Virtually all pacemakers pace in an asynchronous mode when they come into contact with a magnetic field. The response to a magnet varies according to manufacturer, pacemaker model, and sometimes even the mode in which a pacer is programmed. Single-chamber pacers respond to magnets by asynchronous pacing at either the programmed rate or a special magnet rate (Fig. 31-11). This allows a simple noninvasive method to assess pacing at the bedside, office, or by TTM. In patients who are pacemaker dependent and experiencing oversensing thereby inhibiting pacemaker output, a magnet is a convenient short-term method to ensure pacing. Furthermore, pacemakers usually have one magnet rate for a battery that is intact and another one for a battery that is at ERI or at EOL. If these rates are known, applying a magnet to a pacemaker is an easy noninvasive method to assess battery status.

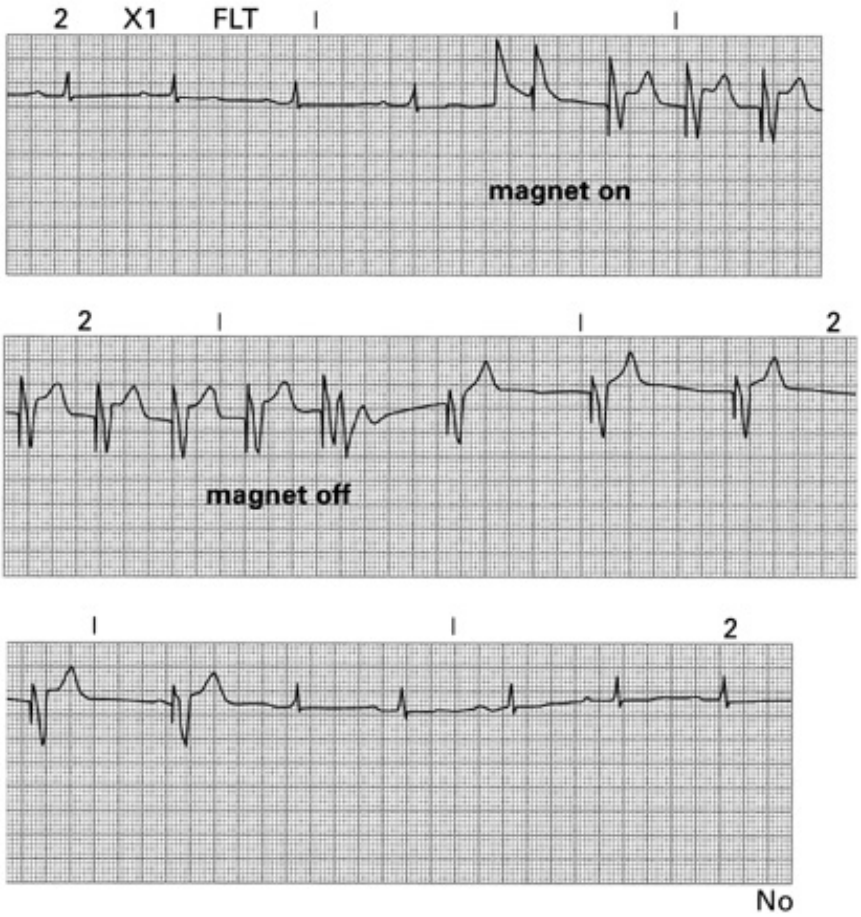

Figure 31-11: An electrocardiogram of a patient with sinus nodal dysfunction and first-degree atrioventricular block who has an implanted VVI pacemaker. Note that application of a magnet causes VVI pacing in the asynchronous mode at a rate of approximately 95 beats per minute. After the magnet is removed, the pacemaker reverts to VVI at 50 beats per minute until the

patient's sinus rhythm inhibits pacemaker function.

VVI Mode

In the VVI mode, a pacemaker operates as shown in Fig. 31-12. The lower rate is converted to an interval (milliseconds). After a paced or sensed ventricular event, a programmable refractory period prevents inappropriate sensing of T waves. After the pacemaker ventricular refractory period, there is an interval extending to the escape interval during which time the pacemaker senses a ventricular event, if one occurs before the end of the interval; otherwise, there is ventricular pacing output.

Hysteresis is a programmable function in which the ventricular escape interval is longer after a sensed ventricular event than after a paced ventricular event. This feature can be used in patients with sinus rhythm so that VVI pacing would not initiate until the sinus rate drops below the hysteresis rate, which is lower than the pacemaker rate (Fig. 31-13).

AAI Pacing

AAIR is an excellent mode of pacing in patients with sinus node dysfunction and normal AV nodal and His-Purkinje function.[78,79] The timing sequences are the same for AAI as for VVI pacing. Atrial sensitivities are programmed at lower values (increased sensitivity) to sense intrinsic P waves safely. This frequently leads to oversensing of far-field ventricular electrograms, which can be avoided by programming a longer refractory period.

Patients with sinus nodal dysfunction may develop AV block, which may be a source of concern when using AAI pacing. However, with careful selection of patients, [78,79] including normal PR intervals, absence of bundle branch block, and AV Wenckebach occurring at atrial pacing rates of more than 120 beats per minute, the risk of development of second- or third-degree AV block is less than 0.6 percent per year.

DDD Pacing

DDD pacing is the most common pacing mode for dual-chamber pacemakers. The timing sequences for DDD pacing are described in Fig. 31-14. This mode is used for patients with AV node and/or sinus node dysfunction.

DDD PACING IN PATIENTS WITH SINUS NODE DYSFUNCTION

Patients with sinus node dysfunction may have intermittent or chronic sinus bradycardia requiring intermittent or continuous atrial pacing. If patients have intact AV conduction, the pacemaker functions as an AAI pacer. Due to medications that slow AV conduction and/or intrinsic AV nodal or His-Purkinje disease, however, patients with DDD pacemakers frequently demonstrate fused ventricular complexes originating from ventricular stimulation and through the AV conduction system. The degree of fusion of the ventricular complex between pacing from a right ventricular lead and conduction down the AV nodal-His-Purkinje system depends in large part on the difference between the programmed AV interval and the intrinsic AV conduction time.

For ventricular output to be inhibited in patients with DDD pacemakers, the pacemaker AV interval must be longer than the conduction time between the sensed or paced atrial complex to the right ventricular lead. A very long AV interval (more than 0.25 s) may decrease the benefit of AV synchrony when AV pacing does occur. It is not uncommon that pacemakers sense the ventricular electrogram late during ventricular depolarization especially with right ventricular

conduction delay or right bundle branch block. Pacemaker *pseudofusion* occurs when there is ventricular pacing within the QRS complex (Fig. 31-15).

PATIENTS WITH ATRIOVENTRICULAR BLOCK AND NORMAL SINUS NODE FUNCTION

In the DDD mode, if the lower rate of the pacer is programmed at a sufficiently low value to permit atrial tracking, the pacemaker stimulates the ventricle synchronous with intrinsic P waves. If a patient does not require atrial pacing, it may be reasonable to implant a dual-chamber pacer with a single tripolar or quadripolar lead that allows atrial sensing and ventricular pacing and sensing (Fig. 31-16). These VDD pacing systems allow for ease of implant and for bipolar atrial sensing. Atrial sensing may not be as reliable compared to a fixed atrial lead, which may lead to occasional atrial undersensing.[80,81] In a recent prospective comparison between single-lead VDD systems to DDD leads, however, there were lower P-wave amplitudes in the group with VDD systems, but no significant clinical differences with respect to atrial undersensing.[82]

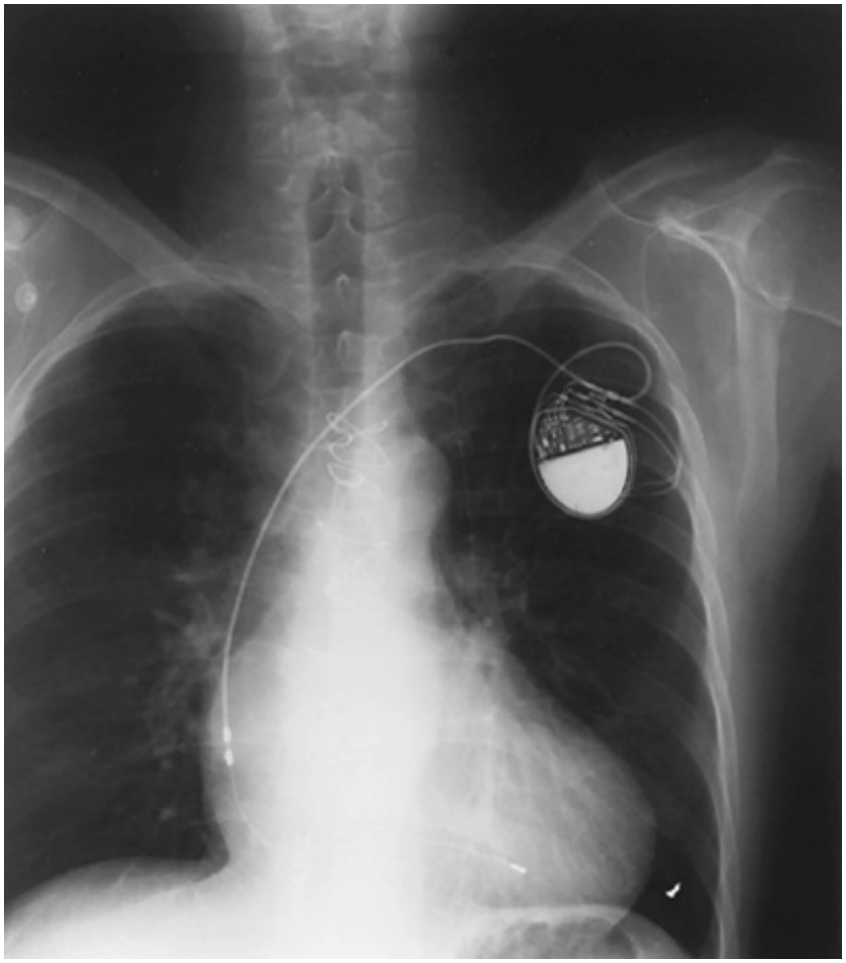

Figure 31-16: Chest x-ray showing a single lead in the heart. Note the bipolar electrodes in the atrium and the single electrode in the ventricle. This pacemaker system is capable of VDD pacing. Therefore, it senses atrial depolarizations and can pace or sense in the ventricle.

DDD versus VVI Pacing

Multiple retrospective and observational studies[83-91] and a few prospective studies[92-94] demonstrate hemodynamic, clinical, and quality-of-life benefits of dual-chamber or atrial-based

pacing versus ventricular pacing. Therefore, it appears prudent to implant DDD pacers in most patients with intact atrial function but not all patients.

In patients with congestive heart failure due to left ventricular systolic dysfunction, the dependence of cardiac output to AV synchrony appears to decrease secondarily to the already increased left ventricular filling pressures. Patients with fixed stroke volume (i.e., left ventricular systolic dysfunction) may depend almost exclusively on heart rate for cardiac output[83] and, therefore, may have limited benefit from AV synchrony. However, any improvement in cardiac output with restoration of AV synchrony may be clinically significant. Additionally, clinical conditions such as left ventricular hypertrophy or diastolic dysfunction generally are dependent on adequate preload to maintain cardiac output. Restoration of AV synchrony appears to be particularly significant for these patients.

Patients with Sick Sinus Syndrome

In patients with sick sinus syndrome, dual-chamber pacing has been shown to be superior to VVI pacing.[9293,95-97] Many studies have demonstrated that atrial-based pacing (DDD) is associated with decreased clinical events, including atrial fibrillation, congestive heart failure, stroke, and death,[88-98] mainly but not exclusively in patients with sick sinus syndrome. Several mechanisms by which atrial-based pacing is beneficial in patients with sick sinus syndrome may not apply to the subset of patients with AV block. Patients with sick sinus syndrome are more likely to have intact VA conduction compared with patients with high-degree or complete AV block. VVI pacing in patients with retrograde VA conduction causes atrial contractions against closed AV valves, leading to atrial distension and transient increases in pulmonary capillary wedge and jugular venous pressures. Increased atrial distension may predispose individuals to atrial fibrillation. This is apt to be more evident in the patients with sick sinus syndrome who already have paroxysmal atrial fibrillation or are at risk for such arrhythmias. Sympathetic activity is elevated during VVI versus dual-chamber pacing, which contributes to increased morbidity and possible mortality.[99] Even in the absence of retrograde conduction, VVI pacing with VA dissociation leads to atrial systoles throughout the cardiac cycle, which can also lead to a similar deleterious effect on atrial size and function. Therefore, dual-chamber pacing appears to reduce the incidence of atrial fibrillation and embolic complications.[88,90,93]

Andersen and colleagues published short- and long-term reports on a randomized study comparing single- and dual-chamber pacing in patients with sick sinus syndrome.[92,93] In their long-term study, they reported a reduction of embolic events, atrial fibrillation, and mortality with use of atrial-based pacing. Additionally, they found progressive benefit from atrial pacing compared with ventricular pacing, which resulted in overall improvement of survival based on total mortality and death from cardiovascular causes. Additionally, many studies have shown that maintenance of AV synchrony improves quality of life particularly at rest.[86,87] In fact, many patients who have VVI pacers may not recognize the extent of their symptoms until they have an upgrade to a DDD system.

Atrioventricular Block

In patients with AV block, the advantage of dual-chamber pacing has been demonstrated by some authors[98,100] but not by others.[91,94] In a retrospective study from the Mayo Clinic[91] on an elderly population, long-term survival was not affected by the mode of pacing. Lamas et al.[94] published a series on 407 elderly patients (older than age 65) who were randomized to have a dual-chamber pacer programmed to either VVI[R] or DDD[R] modes. These authors concluded that the main quality-of-life benefits associated with DDDR pacing were noted in the group of patients with sick sinus syndrome, and there were no quality-of-life benefits noted in the patients with pacers implanted for AV block.[94]

Therefore, there now appear to be adequate data supporting the use of atrial-based pacing (AAI, DDI, and DDD) in patients with sick sinus syndrome. The benefit of dual-chamber versus ventricular pacing in patients with advanced or complete AV block appears to be controversial. In patients with intact sinus node function and AV block, however, it is prudent to at least implant a single-lead VDD system, if not a complete dual-chamber pacing system, to restore AV synchrony in order to restore physiologic pacing.

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Chapter 31: CARDIAC PACEMAKERS

PACING TIMING INTERVALS AND UPPER RATE BEHAVIOR

Atrioventricular Interval

The AV interval is divided into three zones. The first 20 to 40 ms of this interval is the atrial blanking period. The ventricular channel is blanked during this period to prevent inappropriate sensing of atrial output (crosstalk). Crosstalk is a greater problem in unipolar than in bipolar systems. The next part of the AV interval occurs from the end of the blanking period to approximately 100 to 120 ms after the atrial pacing output. If a ventricular sensed event occurred at this point, it would be nonphysiologic because of the short elapsed AV interval. The pacemaker responds with a ventricular output at a short AV interval (100 to 120 ms), which is a safety feature [ventricular safety pacing (Fig. 31-17)]. Ventricular safety pacing is a feature that ensures ventricular pacing in case the sensed event was not a ventricular depolarization; instead, pacing occurs at a short interval so that the pacing output falls before the T wave.

Finally, if there is a sensed event in the latter part of the AV interval, the pacemaker response is to inhibit ventricular pacing output.

Upper Rate Behavior

The total atrial refractory period (TARP) consists of the AV interval and the postventricular atrial refractory period (PVARP). The TARP is a programmable value that can be calculated in milliseconds. Ventricular tracking of atrial events cannot exceed a frequency shorter than the TARP. By dividing 60,000 by the TARP, a rate can be calculated that is the upper rate at which a pacemaker can track atrial events at a 1:1 ratio. At atrial rates exceeding this value, every other atrial event will fall within the pacemaker refractory period (PVARP) and there will be 2:1 pacemaker AV block. Therefore, the rate corresponding to the TARP corresponds to the pacemaker 2:1 rate.

The upper tracking rate is a separate programmable value. The upper tracking rate is generally programmed at a rate less than that corresponding to the TARP. This leads to pacemaker Wenckebach behavior when the patient's atrial rate exceeds the programmed upper rate (Fig. 31-18). The Wenckebach interval is defined as the difference between the programmed upper rate and the rate corresponding to the TARP.

Therefore, when a patient has a sinus or other atrial tachycardia, the pacemaker can track the P waves in a 1:1 fashion up to either the upper programmed rate of the pacer or to the pacemaker 2:1 rate, which ever is lower. If the 2:1 pacemaker rate is lower, there may be deleterious hemodynamic consequences for an exercising patient in whom the ventricular response would abruptly drop by nearly half. For this reason, a Wenckebach interval is preferred by programming the TARP to a sufficiently short interval or the upper rate of the pacemaker to a rate that is less than the 2:1 AV block rate.

Various strategies are available for active patients with DDD pacemakers who require physiologic upper rates. Many pacemakers offer autoadjusting AV intervals that shorten with increasing rates.

By shortening the AV interval, the TARP decreases, which allows greater upper tracking rates before reaching the rate of 2:1 AV block. Another strategy involves sensor-driven rate smoothing.[101] The rate-responsive features are activated, and, in fact, a separate upper sensor-driven rate, different than the upper atrial tracking rate, may be programmed. This enables maintenance of increased ventricular pacing rates driven by the sensor when the pacer would otherwise respond with AV Wenckebach or 2:1 AV block.

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Chapter 31: CARDIAC PACEMAKERS

USE OF PACEMAKERS IN DIFFERENT CLINICAL SITUATIONS

Paroxysmal Atrial Fibrillation, Flutter, and Other Tachyarrhythmias

DDD pacing is problematic in the presence of atrial tachyarrhythmias. During atrial fibrillation, there are so many sensed atrial events occurring at rapid rates that a DDD pacemaker responds with an attempt to track these electrograms up to but not exceeding the upper rate (Figs. 31-19 and 31-20). The ECG hallmark is an irregularly irregular ventricular paced rhythm at a mean rate just below the upper rate. Of course, if the patient has intrinsic AV conduction, the patient's ventricular rate is not controlled by the pacemaker but rather by the intrinsic AV nodal conduction.

There are various strategies for preventing inappropriate upper tracking behavior during atrial tachyarrhythmias. In a patient with intact AV conduction and paroxysmal atrial tachyarrhythmias, DDI or DDIR modes would be appropriate (Fig. 31-19). In this mode of pacing, there is no tracking of atrial events. If there is a sinus or other atrial sensed electrogram, the pacer will inhibit atrial pacing output. Ventricular pacing occurs only at the lower rate interval. For patients with sick sinus syndrome, the clinical problem necessitating a pacemaker is the bradycardia resulting from intrinsic sinus node dysfunction or the bradyarrhythmias resulting from therapy to suppress the tachyarrhythmias. Therefore, DDIR is a very effective pacing mode for patients with sick sinus syndrome who have intrinsic AV conduction.

At the initiation of atrial fibrillation or other atrial tachyarrhythmia, many pacers can automatically switch pacer modes from DDD[R] to VVI[R] or DDI[R] (Fig. 31-20). The automatic mode switch may occur at the upper rate of the pacemaker or at a separate programmable mode switch rate. It may occur with single or multiple sequential premature atrial complexes, depending on the pacemaker model. Mode switching appears to be a clinically effective method of pacing in patients with AV block and paroxysmal atrial arrhythmias.[102-104]

Mode switching reduces symptoms associated with atrial fibrillation only if patients have adequate control of intrinsic AV conduction during atrial fibrillation. For this reason, a strategy of AV junction ablation with implantation of a mode-switching dual-chamber pacemaker can provide symptomatic relief for those patients with medically refractory paroxysmal atrial fibrillation with rapid ventricular response.[103,104]

Prevention of Atrial Fibrillation by Pacing

The initiation and maintenance of atrial fibrillation involve several pathophysiologic mechanisms, the most dominant of which is multiple reentrant pathways (see Chaps. 23 and 24). Pacing therapy may reduce dispersion of refractoriness in the atrium, a feature in reentry, or eliminate pause-dependent initiation of arrhythmias. As discussed above atrial-based pacing (AAI or DDD) reduces the incidence of atrial fibrillation compared with VVI pacing in those patients who require pacing; it is unknown, however, whether atrial pacing in itself may reduce the occurrence of atrial fibrillation. In patients with sick sinus syndrome who require bradycardia pacing support, it has been suggested[105-107] that standard atrial pacing reduces the frequency of atrial fibrillation. These studies examined the arrhythmia-free interval before and after atrial pacing. In another study of

patients who had atrial fibrillation without sinus nodal dysfunction, however, DDD pacers were implanted 3 months prior to planned AV junction ablation, and these pacers were programmed to DDD pacing at 70 beats per minute or to backup DDI pacing at 30 beats per minute.[108] The patients who were actively paced did not have fewer episodes of atrial fibrillation. Therefore, pacing in itself may not reduce the occurrence of atrial fibrillation but may be helpful in the management of those patients who have sinus nodal dysfunction.

It has been reported that dual-site atrial pacing may reduce the occurrence of episodes of atrial fibrillation.[106,107] One lead is placed in the right atrium and a second lead is placed in the coronary sinus ostium or inside the coronary sinus to advance left atrial depolarization. In theory, synchronization of the atria may reduce dispersion of refractoriness and thereby reduce the occurrence of atrial fibrillation.

Pacing in Chronic Atrial Fibrillation or Other Atrial Tachyarrhythmia

Patients with persistent atrial tachyarrhythmias and high-degree or complete AV block generally require a VVIR pacemaker unless their functional status is limited, in which case a VVI pacemaker would suffice. DDD[R] may be implanted in select patients with persistent atrial fibrillation in whom cardioversion to sinus rhythm is expected.

Pacing in Complete or Intermittent Third-Degree Atrioventricular Block

Patients with complete or intermittent third-degree AV block generally receive a DDD pacemaker (Fig. 31-3). If their sinus nodal function is intact, the ventricles are paced synchronous with the P wave after a programmed AV delay. Because some of these patients would not require atrial pacing, some manufacturers offer a single tripolar or quadripolar lead that utilizes a bipole in the atrial cavity for atrial sensing, and the distal electrode(s) are attached to the right ventricle for ventricular pacing and sensing (Fig. 31-16). This mode of pacing, VDD, facilitates implant, since only one lead is required.

Pacing in Carotid Sinus Syndrome and Vasovagal Syncope

Patients with one of the neurally mediated syncope syndromes generally have intact sinus and AV nodal function. Because of combined vasodepressor and cardioinhibitory responses, patients usually require dual-chamber pacing when a pacer is implanted. Additionally, these patients benefit from an interventional pacing rate (80 to 100 pulses per minute) during their vasovagal episodes and only require backup pacing at rates of 40 to 50 pulses per minute during other times. Therefore, one algorithm is to use dual-chamber hysteresis so that when a patient's heart rate drops to the lower rate, pacing is initiated at the interventional rate. This algorithm has limitations, since a patient's heart rate needs to exceed the interventional pacing before inhibiting the pacer. Some pacemakers now offer *rate-drop response* pacing, which involves interventional pacing (80 to 110 pulses per minute with gradual decline in paced rate at 1 to 5 minutes) that is triggered by a steep drop in a patient's intrinsic heart rate. Based on the North American Vasovagal Pacing Study, there was a reduction in syncope from 70 percent in the control group to 22 percent in patients who had pacers implanted with the rate-drop response feature.[42]

Pacing in Cardiac Transplant Patients

After orthotopic cardiac transplant, there is a high incidence of chronotropic incompetence resulting in slow junctional rhythm, sinus arrest, or sinus bradycardia. Bradycardia tends to resolve spontaneously in most patients, but 6 to 21 percent of patients may require permanent pacing.[109] Although symptomatic bradycardia is generally an early finding after transplantation, up to 5 percent of patients following transplant may have symptomatic bradycardia as a late

finding.[110] During the implant, the atrial lead is positioned in the donor atrium. A DDDR or AAIR pacer is placed, depending on whether AV conduction is intact.[111]

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HEMODYNAMICS OF CARDIAC PACING

In theory, a pacemaker optimizes and maintains AV synchrony and optimizes ventricular activation and heart rate to enable cardiac output to meet the metabolic needs of the patient, whether he or she is resting, sleeping, or exercising. There are many variables involved in determining cardiac output through an effect on stroke volume, such as the autonomic tone, physical condition of the patient, left ventricular diastolic and systolic function, and peripheral vascular resistance. As seen in Table 31-8, many variables in pacing systems can affect cardiac hemodynamic function.

Table 31-8: Effects of Cardiac Pacing Variables on Hemodynamic Function

Feature	Effects
AV synchrony	Improves hemodynamic function in patients with diastolic dysfunction
	Required for most patients with one of the neurally mediated syncope syndromes
	Prevents AV valve regurgitation that is observed with ventricular contraction against open AV valves
	Prevents increase in pulmonary venous or central venous pressure seen when atria contract against closed AV valves
AV interval	Short AV interval in patients with hypertrophic cardiomyopathy
	Shorter AV interval after sensed P wave than during AV sequential pacing to have equivalent PR intervals
	In patients with dilated cardiomyopathy, physiologic AV interval may be preferable to markedly prolonged PR interval
Rate responsiveness	Useful in patients with chronotropic incompetence
	Useful as a rate-smoothing feature during upper tracking rate behavior in DDD patients to prevent deleterious effects of pacemaker AV Wenckebach or 2:1 AV block
Pacing site	Right ventricular apex is preferred in patients with hypertrophic cardiomyopathy to have left ventricular apical preexcitation preceding septal activation
	Multisite ventricular pacing is under study in patients with congestive heart failure, dilated cardiomyopathy, and intraventricular conduction delay

ABBREVIATIONS: AV = atrioventricular.

Atrioventricular Interval

The role of the AV interval and the optimal AV interval for improving hemodynamic function has been studied.[112-114] For most patients, the optimal AV interval corresponds to the physiologic range (i.e., an AV interval of approximately 150 ± 50 ms). In clinical practice, however, most patients' quality of life is not significantly different between AV intervals that are *optimized by noninvasive assessment* versus AV

intervals that are *suboptimal*.[114]

There are other considerations when programming AV intervals. With AV sequential pacing, the start of the P wave corresponds to the start of the AV interval while, with P-wave synchronous ventricular pacing, the start of the P wave begins approximately 20 to 70 ms prior to the start of the AV interval, depending on the conduction time from the sinus node to the atrial electrodes. The optimal AV interval for P-wave synchronous ventricular pacing would be shorter than the optimal AV interval for AV sequential pacing.[112] Therefore, to achieve similar hemodynamic effects from ventricular pacing following a sensed or paced P wave, the sensed AV interval should be programmed approximately 40 to 50 ms shorter than the paced AV interval. Additionally, left ventricular cardiac function is more dependent on left atrial to left ventricular relationships rather than right atrial to right ventricular AV interval. For this reason, there is much variability between patients with respect to programming AV intervals.

Pacemaker Syndrome

The pacemaker syndrome is a constellation of signs and symptoms representing adverse reaction to VVI pacing.[115-117] Most of the symptoms relate to loss of AV synchrony and also to retrograde conduction. These include orthostatic hypotension, near syncope, fatigue, exercise intolerance, malaise, weakness, cough, awareness of heartbeat, chest fullness, neck fullness, headache, chest pain, and other symptoms that may be nonspecific. On exam, these patients may have intermittent or persistent cannon A waves and possible liver pulsation. ECG demonstrates VVI pacing present at the time of the symptoms.

The basis for pacemaker syndrome is not only loss of AV synchrony but also the presence of ventricular-atrial conduction. Atrial contraction against closed AV valves leads to increases in jugular and pulmonary venous pressure causing cough and malaise in patients with intact cardiac function and congestive heart failure in other patients with structural heart disease. Distended atria can lead to reflex vasodepressor effects mediated by the autonomic nervous system and diuresis mediated by elevated levels of atrial natriuretic peptide.[118,119] Therefore, if patients have decreased cardiac output and arterial pressure secondary to VVI pacing, autonomic and humoral reflexes can lead to further hypotension and hemodynamic deterioration.

DDI pacing may produce pacemaker syndrome if the sinus rate exceeds the lower rate. DDD pacing can lead to pacemaker syndrome in select patients with severe intraatrial conduction delay who experience inappropriate timing between left atrial systole and left ventricular contraction.[120] This may necessitate the addition of a coronary sinus pacing lead to advance left atrial systole.[121]

The management of pacemaker syndrome usually requires restoration of AV synchrony. In many patients, an upgrade to a dual-chamber pacer is indicated. In some patients with intact sinus and AV conduction, lowering the pacing rate in VVI mode and using the hysteresis mode may promote sinus rhythm, lessening the symptoms associated with pacemaker syndrome. Using the VVIR mode by itself will not prevent or reduce symptoms from the pacemaker syndrome. Many patients may experience mild symptoms of the pacemaker syndrome and not recognize the symptoms until after an upgrade to a dual-chamber pacemaker.[122] Most patients prefer DDD pacing to VVI pacing[117,122,123] in various clinical and hemodynamic studies.

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RATE-RESPONSIVE PACEMAKERS

The ability of a pacemaker to increase the lower rate in response to a physical or physiologic stimulus is termed *rate-responsive*, *rate-adaptive*, or *sensor-driven* pacing. The letter R in the fourth position of the NASPE/BPEG pacing code indicates rateresponsive pacing. Sensor systems that respond to parameters or activities that correlate with physiologic need for increased cardiac pacing rate provide input to the pacer, which increases the pacer lower rate. Numerous sensors have been developed with the goal of providing sensor input into the pacemaker, which can be then used to provide rate-adaptive pacing.[124-133]

Hemodynamic Evaluation of Rate-Adaptive Pacing

Cardiac output is a function of ventricular rate and stroke volume, modified by variables such as AV synchrony, ventricular preload, ventricular afterload, and autonomic state. In normal individuals at rest, pacing-induced increase in ventricular rate usually results in a transient increase in cardiac output followed by decrease in stroke volume, returning cardiac output toward normal. When there is a physiologic need for increased cardiac output, however, such as during exercise, stroke volume is maintained during increased ventricular pacing rate.

The role of the atrium and the need for AV synchrony remain less certain during faster rates compared with heart rates under 100 beats per minute. In patients with AV and ventricular-atrial block, pacing in the VDD mode compared with VVI pacing matched to the atrial rate (without AV synchrony) appears to provide similar cardiac output.[134,135] Multiple studies have shown that the change in work capacity correlates with ventricular rate during exercise whether the ventricular rate is triggered by spontaneous atrial activity or by a pacemaker sensor. Therefore, AV synchrony may be less important in patients during exercise who achieve or require heart rates in excess of 120 beats per minute. Nevertheless, VVIR pacing is not a substitute for DDD pacing.

If a patient has a VVI pacemaker and ventriculoatrial conduction, or a DDD pacing programmed with long AV intervals such that the P wave is closer to the preceding R wave, deleterious hemodynamic consequences may result. In this circumstance, there would be a decrease in cardiac output, since the atrium would consistently pace against closed AV valves, producing increases in the pulmonary and jugular venous pressures. This would also produce symptoms of the pacemaker syndrome. Dual-chamber pacemakers currently available often have options of rate-adaptive AV intervals. This provides the advantage of maintaining normal AV relationships during exercise and prevent retrograde atrial contraction.

RATE-ADAPTIVE SENSORS

Multiple rate adaptive sensors are available or under development.[124-133] Actively based sensors are used most commonly. These are piezoelectric crystal systems that are very sensitive to detection of vibration induced by up-down motion (activity) or acceleration, particularly (forward-backward motion).

The drawback of activity-based pacers is that they do not provide feedback that is proportional to physiologic need. For instance, climbing up stairs requires more work than going down stairs;

however, going down stairs is usually faster and would activate the sensor more than climbing up stairs. This leads to faster-paced rates while going down stairs. Similarly, other activity with little body vibrations may produce ineffective rate adaptation from the pacemaker. Therefore, true physiologic sensors are desirable for rate-responsive pacing. The role of physiologic sensors is to provide some measurable index of activity, exercise, or catecholamine state that can provide a more accurate input to the pacemaker for rate-adaptive pacing. The QT interval is affected by heart rate but also independently by catecholamines. Therefore, pacers can measure the interval from the ventricular stimulus to the end of the sensed T wave and modulate heart rate based on this measurement. The drawback of this technique is that the patient has to be ventricular paced in order to measure the QT, or stimulus-T, interval.

Since there exists a close relationship between respiratory rate or minute ventilation and heart rate, various sensors incorporate measurements of respiratory effort. These systems are based on measurement of transthoracic impedance between the pacemaker lead and the pulse generator. The impedance increases with inspirations and decreases with expiration; the amplitude of the impedance change is proportional to the tidal volume. Minute ventilation is the product of the tidal volume and respiratory rate. Thus, minute ventilation can provide an accurate physiologic estimate of metabolic needs. One of the disadvantages of this system is that energy is required to measure impedance, which increases current drain from the pacemaker.

A number of other sensor systems are available or under development. Many use physiologic parameters, such as pH, oxygen saturation, stroke volume, or temperature. The premise behind all of these are that the measured parameters can provide an accurate measure of a patient's metabolic needs, which can be used to guide rate responsiveness. There are various benefits and drawbacks to the different methods.

DUAL SENSORS

Some sensors systems provide the advantage of more physiologic pacing during steady state but have a slow response time during initiation of exercise. Other sensors, particularly activity sensors, have fast response times at initiation of activity but may not produce physiologic responses during peak or steady-state activity. Pacers with dual sensors can provide patients with rapid responses during the start of exercise to augment the heart rate and a more physiologic sensor (QT, minute ventilation) to provide more proportional heart rate response during steady state.[136,137] The benefit of dual sensors has not been conclusively demonstrated in long-term randomized studies, and, in fact, one acute exercise study demonstrated no clinical advantage of dual sensor over single-sensor rate-responsive pacing.[138]

Programming Rate-Adaptive Parameters

The parameters for programming rate responsiveness include the lower and upper activity rates, which may be separate from the upper tracking rate. A treadmill test may be required to optimize pacemaker programming. In practice, it is often sufficient to have the patient walk for a few minutes and program the rate-responsive features to achieve what would be expected to be a physiologic pacing rate for that patient. Different pacers have different algorithms that can automate the adjustments of the rate responsiveness. In most patients, it is difficult to demonstrate clinical effectiveness of automatic rate-response optimization versus fixed rate-responsive programming in the office or clinic.[139]

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PACEMAKER COMPLICATIONS

Pacemaker complications can occur at the time of implantation[66,140] or, less likely, can occur late after implantation (Table 31-9). Overall, early complications have been reported in the range of 3 to 11 percent,[1,66,140,141] depending on the definition of complication, duration, and intensity of follow-up.

Table 31-9: Complications Related to Pacemakers

Early complications, related to implant	
Pneumothorax	0.5-1.9%
Large hematoma	0.5-1.7%
Cardiac perforation	0.2-1.2%
Lead dislodgment, atrial	1.6-3.8%
Lead dislodgment, ventricular	0.5-1.4%
Venous thrombosis	2-5%
Other complications	
Wound dehiscence	
Infection	
Pain	
High thresholds	
Loose setscrew	
Lead failure	
Pacemaker failure	
Diaphragmatic stimulation	
Skin erosion	
Pacemaker syndrome	

Complications of Pacemaker Implant

Cardiac perforation is a potentially serious and often unrecognized complication of pacemaker

lead insertion. This may be recognized at the time of lead insertion by fluoroscopic position of the lead, a paced QRS complex having right bundle branch block pattern, diaphragmatic stimulation, or hypotension resulting from cardiac tamponade. In the absence of anticoagulation, perforation usually does not lead to tamponade if the lead is withdrawn and repositioned. After implantation, cardiac perforation may be recognized by pericardial pain, friction rub, increasing ventricular pacing threshold, diaphragmatic stimulation, or pericardial effusion. The presence of these signs is not diagnostic of cardiac perforation, and echocardiograms should be performed to examine the lead position. If perforation is suspected, and the patient is hemodynamically stable, clinical observation is often the prudent course.

Other implant-related complications include subclavian arterial puncture, pneumothorax, hemothorax, and air embolus. Rarely, a lead may be introduced into the left ventricle through an inadvertent subclavian arterial puncture or through an unrecognized atrial or ventricular septal defect.[142,143]

Complications of venous leads include venous occlusion with resulting superior vena cava syndrome or thrombosis of the subclavian vein with ipsilateral arm edema.[144-147] Acute thrombosis may be treated with heparin and warfarin and managed conservatively if the patient responds to anticoagulation. Invasive and surgical interventions, including venoplasty and stent placement, have been described.[144,147] Most occlusions, partial or complete, may occur over time and tend to be asymptomatic because of the formation of venous collaterals.[148]

Infections related to pacemaker implantation are rare. The use of prophylactic antibiotics and irrigation of the pacemaker pocket with antibiotic solution may help prevent infection, especially from local flora.[149,150] Early infections may be caused by *Staphylococcus aureus* and can be aggressive. Late infections are commonly related to *Staphylococcus epidermidis* and may have a more indolent course. Occasionally, pacemaker infections are misdiagnosed as pacemaker allergy. Other signs of infection include local inflammation and abscess formation, erosion of the pacer, and fever with positive blood culture without an identifiable focus of infection. Transesophageal echocardiography may help determine whether vegetations are present on the pacemaker lead.[151,152] If the pacemaker is infected, removal of the pacemaker leads and generator is usually required.[153]

Mechanical Complications

During implant, the leads are connected to the pulse generator by a setscrew mechanism. If the setscrew is loose (Fig. 31-4), then pacemaker malfunction may occur, manifested by increased impedance and intermittent or complete failure to capture.

The pacemaker leads are subject to long-term complications. The insulation of the leads may break, leading to problems with oversensing (due to electrical noise), undersensing, and failure to capture (due to current leak). This problem often manifests intermittently and may be difficult to detect during a routine pacer check. The patient may complain of pectoral muscle stimulation due to current leak around an insulation break.[154] An abnormally low impedance with demonstrable lead malfunction is diagnostic for insulation break. Subtle insulation breaks may be detected by having the patient perform provocative maneuvers while monitoring an ECG (and marker channels) and or measuring impedances.

Leads may also fracture over time (Fig. 31-2). Early lead fractures lead to increased impedances associated with failure to capture, oversensing, and undersensing. Some leads use retention wires to preform an atrial lead so that it is more likely to attach and remain within the atrial appendage. Fracture of a retention wire does not cause any pacemaker malfunction, but it can lead to serious complications, including cardiac perforation and death, when it penetrates

through the insulation into the atrial cavity.[155]

Twiddler's syndrome is a term applied to patients who intentionally or unintentionally manipulate their pulse generator, causing twisting of the entire pacemaker system. This leads to lead dislodgment or fracture. This may also result from an excessively large pacemaker pocket allowing rotation of the pacemaker.

Electromagnetic Interference of Pacemaker Function

In general, electromagnetic interference (EMI) can originate from a variety of sources that have the potential to affect pacemaker function adversely. In Table 31-10 are listed some of the more common sources of EMI with potential pacemaker effects.

Unipolar pacemakers are usually more susceptible to EMI interference than are bipolar pacemakers because the sensing circuit encompasses a larger area compared with bipolar sensing. Factors that affect EMI interference have to do with the source of the interference and the proximity to the pacemaker generator. Many of these sources are located in a hospital environment or specialized places such as construction sites. Magnetic resonance imaging scans are contraindicated in patients with pacemakers, although there are case reports of patients with pacers undergoing MRI scans without adverse events.[156] Sources of EMI at home and the office usually do not pose a problem for patients. There is concern, however, that electronic article surveillance devices, found commonly in retail establishments, can interfere with pacemaker function,[157,158] if patients linger by these devices.

The effects of EMI vary according to its source and the type of pacemaker. Inhibition of pacing output can potentially be life threatening for patients who are pacemaker dependent. If the EMI is interpreted as atrial events by the pacemaker, then inappropriate ventricular pacing may occur in patients with DDD pacemakers, since these pacemakers attempt to *track* these events, which are interpreted as atrial. EMI often causes electrical noise that causes the pacemaker to function in a *noise reversion mode*. The actual function of this mode differs among the different pacemakers, but this mode involves switching to an asynchronous pacing mode. After elimination of this interference, pacers generally revert to the previously programmed mode; however, it is possible for EMI to cause pacemakers to revert to a backup pacing mode. Backup pacing in some models is unipolar VVI pacing at a preset rate.

Occasionally, EMI causes permanent damage to the pulse generator. Therapeutic radiation can damage the complementary metal oxide semiconductors (CMOS) that are part of most modern pacemakers. Generally, doses in excess of 5000 rad, but as little as 1000 rad, may induce pacemaker circuitry damage, which in turn can cause pacemaker failure or even induce a runaway pacemaker. If the pacemaker cannot be shielded from the field of radiation, then consideration should be given to reimplanting the pacemaker at a distant site.

In studies[159,160] examining interactions between pacemakers and cellular telephones, it was noted that digital telephones may cause intermittent pacemaker dysfunction. These adverse effects observed included pacemaker inhibition, inappropriate ventricular tracking (in VDD or DDD pacemakers), or resetting the pacemaker to a backup asynchronous mode. Factors associated with interference include unipolar pacing systems, digital cellular phones, increased output by the cellular phone, and close proximity of the cellular phone to the pacer. Because of the diversity of cellular phones and pacemakers that have different shielding capabilities against electromagnetic interference, it is difficult to draw firm conclusions on the use of digital cellular telephones.[159] No consistent problems have been detected with analog telephones. It is advisable that patients use cellular telephones that are analog or to keep digital cellular (with power outputs greater than 3 W) phones 20 cm away from their pacemaker generator.

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PACEMAKER MALFUNCTION

Pacemaker malfunction can be categorized as loss of capture, abnormal pacing rate, undersensing, oversensing, or other erratic behavior. The approach to diagnosing pacemaker malfunction is to inspect the ECG carefully, interrogate the pacemaker; check pacing and sensing thresholds, lead impedances, and battery voltage/magnet rate; and perform a chest x-ray. Many instances of pacemaker malfunction actually represent normal function of the pacemaker (Table 31-11). Usually, causes of pacer malfunction may be diagnosed noninvasively, but, occasionally, surgery is required to diagnose problems.

Table 31-11: Suspected Malfunction Occurring During Normal Pacer Function

Observation	Suspected Problem	Possible Normal Pacer Function
Pacing artifacts delivered in the middle of normal QRS complexes	Pacemaker undersensing	Pseudofusion
Unexplained pauses after sensed but not paced complexes	Pacemaker oversensing	Hysteresis
Pacer rate less than lower rate, which occurs at night	Pacemaker oversensing at night	Different sleep rate/lower rate
Rapid pacing rates	Pacemaker oversensing of EMI in atrial channel or other atrial events causing upper rate tracking	Scanning hysteresis/rate drop response causing an increased 'intervention' pacing rate for vasovagal episodes
	Pacemaker-mediated tachycardia	Activation of rate-response sensors
		Upper rate tracking of unsuspected atrial tachyarrhythmia or sinus tachycardia
DDD pacer operating in VVI mode	Malfunction of pacer	Pacer reset due to EMI or low battery
		Pacer that mode switched due to atrial tachyarrhythmia

ABBREVIATION: EMI = electromagnetic interference.

Abnormal Pacing Rates

Abnormal pacing rates can be due to normal or abnormal pacing function (Table 31-11). Failure of the pacemaker to output is usually due to oversensing. Occasionally, there is pacemaker output that is not visible because of bipolar pacing producing very low amplitude pacing artifacts (artifacts from digital ECG recording are commonly difficult to visualize). Conversely, absence of pacing stimuli may be due to

interruption of current flow from a lead fracture, insulation break, or a loose setscrew.

Abnormally fast pacing rates usually are due to normal pacing function. They may be in response to rate-adaptive sensors. In DDD pacemakers, upper rate pacing may be due to sinus tachycardia, atrial tachyarrhythmias, or pacemaker-mediated tachycardia (Table 31-12). In either case, the pacemaker function is normal and is responding either to a rapid atrial rate or to retrograde atrial activity. Rarely, very rapid ventricular pacing ("runaway pacemakers") can cause life-threatening problems requiring disconnection of the pacemaker. Occasionally, abnormal pacing rates can be due to an unstable lead position where the lead is swinging between heart chambers.

Table 31-12: Causes of Upper Rate Behavior in DDD Pacemakers (and Atrioventricular Block)

	ECG Characteristics	Response to Magnet
Sinus tachycardia	1:1 Atrioventricular pacing, pacemaker Wenckebach or 2:1 block depending on the PVARP, upper rate, and sinus rate	No change in paced rhythm after magnet removed
Atrial fibrillation	Irregularly irregular paced ventricular rhythm up to but not exceeding the upper rate	No change in paced rhythm after magnet removed
Pacemaker-mediated tachycardia	Regular paced ventricular rhythm equal to or less than upper rate	Termination of tachycardia

ABBREVIATION: PVARP = postventricular atrial refractory period.

Loss of Capture

The loss of pacemaker capture occurs when there is a visible pacing stimulus and no atrial or ventricular depolarization. This may be intermittent or persistent. Most problems occur at the pacemaker lead/tissue interface. For instance, lead dislodgment can cause obvious failure to capture. An increase in the pacing threshold above the pacing output can occur as part of the rise above initial threshold within a few weeks following lead placement (Fig. 31-21) or because of drug therapy, electrolytes, myocardial infarction, or ischemia. Fracture of the lead, insulation breaks, and loose setscrews are mechanical problems that can cause failure to capture. Lastly, battery depletion may cause the pacing output to decline sufficiently such that pacing failure occurs.

Loss of capture requires a check of pacing threshold and of pacing lead impedance and a chest x-ray. For instance, if the problem is an elevated pacing threshold, pacing outputs must be increased. Abnormal lead impedances may confirm a lead failure and the need for lead replacement.

Oversensing

This problem leads to abnormal pacing rates with pacemaker pauses. Generally, unipolar lead systems are more susceptible to oversensing. The sources for oversensing can be intracardiac, extracardiac, or due to EMI. Analysis of ECG, especially with pacemaker interrogation and pacemaker marker channels, may help to determine the cause. If the oversensing is regular, analysis of the pauses may suggest T-wave or P-wave oversensing. T-wave oversensing usually can be eliminated by decreasing the sensitivity (increasing the millivoltage required to sense electrical activity) or increasing the ventricular refractory period.

Oversensing due to lead fracture, insulation break, or other electrode problems will usually be random and erratic (Fig. 31-22). With early lead problems, the malfunction is intermittent and may be

exacerbated by certain body positions or motions. In later stages, the combination of oversensing, undersensing, and failure to capture is almost always diagnostic of a lead-related problem. Programming to an asynchronous mode may temporarily control this problem while awaiting a lead replacement, which should be carried out as promptly as possible.

Crosstalk inhibition is a phenomena usually seen in unipolar pacers. It is due to ventricular sensing of atrial output. This is currently a rare problem because of blanking periods and ventricular safety pacing.

Myopotential oversensing is usually a problem in unipolar but not bipolar systems. These skeletal myopotentials generate interference, which tends to correspond to certain activity. The optimal solution is reprogramming the sensitivity to a level high enough to avoid myopotential sensing while preserving adequate safety margin to sense intrinsic cardiac depolarizations.

Undersensing

An inadequate intracardiac signal can lead to undersensing ( Fig. 31-17). The intracardiac electrograms can deteriorate due to inflammation or scar formation at the tissue lead interface. Additionally, certain drugs, electrolyte abnormalities, infarction, ischemia, lead fracture, or insulation breaks can lead to undersensing. Cardioversion or defibrillation can also cause attenuation of intracardiac electrograms. Usually, undersensing is a greater problem in the atrium than in the ventricle. The optimal solution is to program an enhanced sensitivity (decrease sensing level). With bipolar systems, the programmed sensitivity can usually be reduced to 0.18 mV in the atrium, without oversensing of myopotentials or other extraneous signals.

Other etiologies for undersensing occur when intrinsic atrial or ventricular complexes fall within one of the programmed refractory periods. Undersensing can also result from a pacer that was inadvertently programmed to an asynchronous mode (occasionally occurring with battery depletion or pacemaker generator reset).

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Figure 31-10: *A.* Shown are rate histograms demonstrating seven episodes of atrial fibrillation lasting from a few minutes to an episode lasting over an hour. *B.* This graphic demonstrates the beat-to-beat rate just before onset of the atrial tachyarrhythmia, after 200 beats, and just after termination of the arrhythmia, 69 min later. A snapshot of the stored intraatrial electrograms (A-EGMs) confirms atrial fibrillation as the mechanism. DEC, December; Tachy, tachycardia.

Figure 31-11: An electrocardiogram of a patient with sinus nodal dysfunction and first-degree atrioventricular block who has an implanted VVI pacemaker. Note that application of a magnet causes VVI pacing in the asynchronous mode at a rate of approximately 95 beats per minute. After the magnet is removed, the pacemaker reverts to VVI at 50 beats per minute until the patient's sinus rhythm inhibits pacemaker function.

Figure 31-12: Schematic diagram of the pacemaker timing cycles during VVI pacing. After a ventricular paced or ventricular sensed event, the pacemaker begins a ventricular refractory period (VRP). This is a programmable value usually between 250 and 400 ms. During this time, a sensed ventricular event will not initiate a new timing interval and will not reset the pacemaker. The lower rate interval (LRI) of the pacemaker corresponds to the programmed lower rate. If this interval expires and there is no sensed ventricular event following the end of the ventricular refractory period, the pacemaker stimulates the ventricle (second and fourth complex) and the VRP and LRI begin anew. If there is an intrinsic ventricular depolarization between the end of the VRP and during the LRI, then ventricular output is inhibited and the VRP and LRI begin anew.

Figure 31-13: A patient with atrial fibrillation and the VVI pacemaker with lower rate of 70 pulses per minute (857 ms) and hysteresis rate of 50 beats per minute (1200 ms). The square pulses in the bottom line represent pacing output. This tracing (two leads recorded simultaneously) represents normal hysteresis function. See the text for discussion.

Figure 31-14: Schematic diagram of DDD pacing with selected timing cycles and refractory periods. After a paced atrial complex, the paced atrioventricular interval (PAV) begins. If there is no ventricular depolarization before this interval expires, the pacemaker response is to output a ventricular impulse. After a paced ventricular output, several refractory periods and timing cycles are initiated. The ventricular refractory period (VRP) is the time during which a ventricular event will not reset the timing intervals. The postventricular refractory period (PVARP) represents the time during which an atrial event will not be sensed or will not reset the timing intervals. The upper rate interval represents the shortest interval (maximum rate) that a pacemaker will ventricular pace corresponding to the programmed upper tracking rate. The ventricular-atrial escape interval (VA) represents the time during which, if there is no sensed atrial electrogram, atrial pacing occurs. The programmed lower rate corresponds to the AV interval and the VA interval. During the first two complexes, there were no sensed atrial complexes; therefore, the VA interval expired and atrial pacing occurred. During the third and fourth complexes, there were sensed atrial electrograms following the PVARP and before the VA interval expired (shaded area in the VA bar). Note that atrial sensing usually occurs after the start of the P wave, representing the atrial conduction time to the atrial electrodes. The programmed AV interval following a sensed atrial complex (SAV) may be programmed at a value lower than the PAV to obtain equivalent PR intervals.

Figure 31-15: Surface electrocardiogram with marker channels of a patient with a dual-chamber pacemaker in the DDD mode. Note atrial pacing of all complexes. The first, second, and last complexes have paced ventricular outputs in the middle of the QRS complex. Compared to the third, fourth, and fifth complexes, which do not have these ventricular pacing spikes, there is no change in the QRS complex. This is consistent with "pseudofusion" of the QRS complex. This is due to the fact that the ventricular depolarization is not sensed by the pacemaker until the middle or end of the QRS complex in this particular patient. Subtle variations in the conducted PR interval account for the fact that some of the complexes have a paced ventricular complex and some do not.

Figure 31-16: Chest x-ray showing a single lead in the heart. Note the bipolar electrodes in the atrium and the single electrode in the ventricle. This pacemaker system is capable of VDD pacing. Therefore, it senses atrial depolarizations and can pace or sense in the ventricle.

Figure 31-17: Surface leads I, II, and III are shown at paper speed of 50 mm/s. Note that there is complete undersensing of the P wave. The pacemaker therefore tends to pace at the lower rate interval, which corresponds with an intrinsic QRS complex. This QRS complex is sensed within the ventricular safety period, triggering ventricular safety pacing. For this particular pacemaker, ventricular safety pacing occurs at 110 ms after atrial pacing in order to avoid ventricular pacing during the T wave.

Figure 31-18: *Top*. Sinus tachycardia in a patient with atrioventricular block and a DDD pacemaker with a programmed upper rate of 100 beats per minute, which is less than the intrinsic sinus rate. Note that the interval between the sensed P wave and the paced ventricular complex lengthens progressively, until there is a P wave (within the T wave) following the first, fourth, and seventh paced ventricular complexes without subsequent ventricular pacing, consistent with pacemaker Wenckebach. *Bottom*. The pacemaker is programmed in the DDDR mode with upper rate of 100 beats per minute. The presence of rate response, during activity, acts to smooth the upper rate, preventing the longer pauses during pacemaker Wenckebach.

Figure 31-19: Tracings of a patient with a dual-chamber pacemaker who has underlying atrial fibrillation. Electrocardiograms and corresponding marker channels are shown for pacing modes DDD, DDI, and DVI, respectively. Note that during DDD the pacemaker rhythm is an irregularly irregular paced ventricular rhythm at, but not exceeding, the upper rate of the pacemaker. In the DDI mode, there is no tracking of the atrial fibrillation; therefore, it functions effectively as a VVI pacemaker so long as the patient is in atrial fibrillation. In the last tracing, the mode is DVI; therefore, there is no sensing of atrial electrograms, which accounts for the AV sequential pacing pattern. This mode is generally not used when the DDI mode is available. AR = sensed atrial electrogram in the pacemaker refractory period; AS = sensed atrial electrogram; VP = ventricular paced complex.

Figure 31-20: Electrocardiogram, marker channels, and intracardiac atrial electrograms (IEGMs) are shown for a patient with atrial fibrillation. At the left-hand part of the tracing, there is upper track pacing at an irregular rate due to the atrial fibrillation. Automatic mode switch was programmed on (indicated by the triangles), and the pacemaker automatically mode switched (MS) to the DDIR mode. Note the prolonging of ventricular cycle lengths after mode switch was activated.

Figure 31-21: Electrocardiogram marker channels of a patient with a dual-chamber pacemaker. Note that the atrial pacing outputs (APs) are capturing the atrium, and there is appropriate P-wave sensing (AS or AR). However, none of the ventricular outputs are capturing the ventricle. This is a tracing of a patient who had a pacemaker placed 3 weeks prior to acquisition of this ECG, and the pacing threshold had exceeded the tracing output.

Figure 31-22: Electrocardiogram and marker channels are shown for a patient with a ventricular lead impedance break. Note that based on the ECG there is failure to sense, as manifested by the second and fourth pacing outputs coming very shortly after the QRS complex. There is failure to capture, demonstrated by the second and third pacing outputs, which should capture the ventricle. There is also evidence of oversensing, as demonstrated by the long pause between the fourth and fifth pacing outputs during a diastolic period that exceeds the interval between the previous two pacing outputs. In general, when there is evidence of oversensing, undersensing, and failure to capture, then the likely etiology is either a lead insulation break, lead fracture, or other mechanical problem. The marker channels confirm the above ECG findings. There are sensed ventricular events (S or SR) that do not correspond to surface QRS complexes, consistent with oversensing. Additionally, the erratic pattern of sensed ventricular events is consistent with electrical noise. There are also lack-of-sense markers corresponding to QRS complexes; finally, there are ventricular pace markers (P) that fail to capture the ventricle.

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Part 5: SYNCOPE, SUDDEN DEATH, AND CARDIOPULMONARY RESUSCITATION
Chapter 32:

DIAGNOSIS AND MANAGEMENT OF SYNCOPE

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Syncope is a sudden and transient loss of consciousness. The occurrence of syncope in the general population, as reflected in the 26-year surveillance of the Framingham Study, is 3.0 percent in men and 3.5 percent in women in the general population. As a general rule, the incidence of syncope increases with age.[1]

As an initial presentation, syncope denotes a diversity of disorders ranging from a benign episode to sudden death. Studies in recent years have documented the multiple causes and the widely divergent mortality risks associated with an episode of syncope. On the basis of these studies, patients with a transient episode of altered consciousness (presyncope) and those with complete loss of consciousness (syncope) can be classified into three broad categories[2] (Table 32-1): *cardiac syncope, noncardiac syncope,* and *syncope of undetermined cause.* The relative incidence of these categories varies with the clinical site from which the patients are selected. In the emergency room, noncardiac syncope is most common. For patients admitted to the hospital, cardiac syncope is the most common diagnosis.[3]

Table 32-1: Classification of Syncope

I. Noncardiac
II. Cardiac
III. Undetermined cause

Clearly, the highest mortality occurs among those with cardiac syncope. Among all patients with syncope associated with cardiac disease, sudden death is extremely high.

NONCARDIAC SYNCOPE (Table 32-2)

Sudden transient loss or impairment of consciousness occurs under a wide variety of circumstances. The pathophysiologic mechanisms, diagnostic features, and therapy for these disorders are discussed below.

Table 32-2: Classification of Noncardiac Syncope

- Neurocardiogenic
- Orthostatic
- Cerebrovascular
- Seizure disorders
- Carotid sinus hypersensitivity
- Situational
- Cough
- Swallowing
- Valsalva
- Micturition
- Defecation
- Diver's
- Postprandial
- Metabolic, drugs
- Hypoxia
- Hypoglycemia
- Hyperventilation, panic attacks
- Ethanol, other drugs
- Other forms of syncope or conditions mimicking syncope
- Vertigo
- Migraine
- Psychiatric

Neurocardiogenic Syncope

The syndrome of neurocardiogenic syncope, the common faint (also referred to as neurally mediated hypotension, vasovagal syncope, and vasodepressor syncope), is one of the most common causes of syncope. This disorder is considered to be an abnormality in the complex neurocardiovascular interactions responsible for maintaining systemic and cerebral perfusion (Fig. 32-1).[4-10]

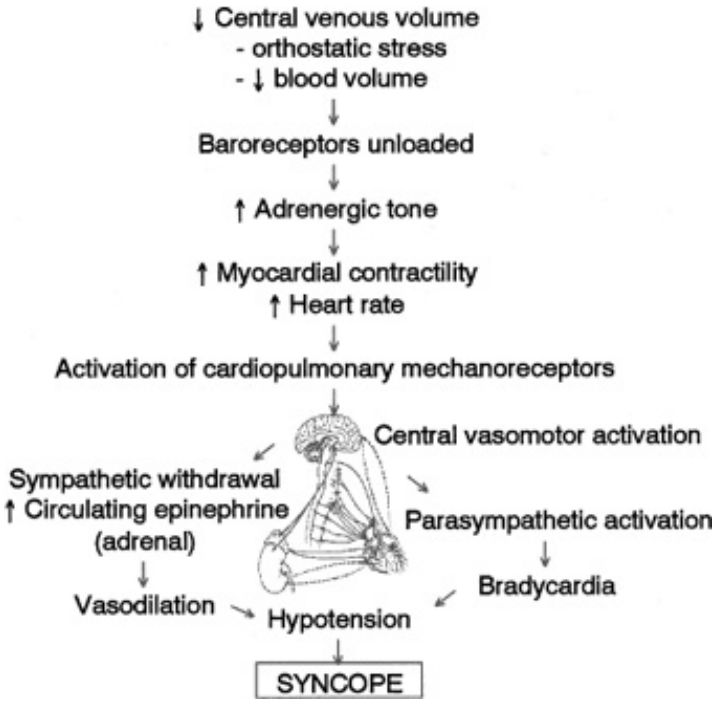

Figure 32-1: Presumed mechanisms of neurocardiogenic syncope. Schematic presentation. ↑ = increase; ↓ = decrease.

PATHOPHYSIOLOGY

The pathophysiology of neurocardiogenic syncope is quite complex and incompletely understood. Under normal circumstances, upright posture causes venous pooling and a transient decrease in arterial pressure, resulting in an unloading of baroreceptors. Reflex augmentation of sympathetic activity and parasympathetic withdrawal result in peripheral arterial vasoconstriction, venoconstriction, and an increase in heart rate and contractility. These adaptive mechanisms serve to maintain normal systemic and cerebral perfusion. Neuroendocrine systems (e.g., renin-angiotensin and vasopressin) may be important modulators of homeostasis during prolonged periods of orthostatic stress.[11]

Individuals susceptible to neurocardiogenic syncope are unable to maintain the adaptive neurocardiovascular responses to upright posture for prolonged periods. These patients tend to have a modest reduction in central blood volume, which is aggravated by upright posture. Increases in circulating catecholamines and cardiac adrenergic tone in response to orthostatic stress result in increased myocardial contractility.[12] Studies in animal models suggest that, under these conditions, cardiopulmonary mechanoreceptors are activated, resulting in increased neural traffic across afferent C fibers leading to the central nervous system vasomotor center; this in turn results in reflex paradoxical vasodilation (vasodepressor response) and bradycardia (cardioinhibitory response).[13] The final result is hypotension, cerebral hypoperfusion, cerebral hypoxia, and syncope. This paradoxical reflex is believed to be a variant of the Bezold-Jarisch reflex and has also been documented during nitrate therapy for acute myocardial ischemia, and during acute hemorrhagic syndromes.[14,15] In addition, vasomotor center activation is believed to cause several of the prodromal symptoms of diaphoresis, nausea, vomiting, and dyspnea that frequently accompany neurocardiogenic syncope. Recent evidence from patients with denervated hearts (i.e., cardiac transplantation patients) and those with neurocardiogenic syncope raises the possibility that other neurohumoral mechanisms, primarily involving the peripheral circulation, may play an important role.[16]

The mechanism of paradoxical vasodilation observed during neurocardiogenic syncope is

incompletely understood. Clinical studies have shown that serum epinephrine concentrations surge prior to the syncopal event with resultant intense β_2 activation, which may cause inappropriate vasodilation and syncope. Withdrawal of peripheral sympathetic neural activity at the time of neurocardiogenic syncope has also been demonstrated by direct recordings of sympathetic neural activity.[17]

The paradoxical bradycardia (cardioinhibitory response) during neurocardiogenic syncope is due to a surge in cardiac parasympathetic tone and usually lags vasodilation by several seconds.[18] The cardioinhibitory response is highly variable, ranging from a relative bradycardia with heart rates in the 40 to 60 beats per minute range to profound periods of asystole. Variable degrees of atrioventricular (AV) block and junctional escape rhythms are observed as well. *Bradycardia aggravates but is not the principal cause of hypotension during neurocardiogenic syncope.* Maintaining heart rate with atropine or cardiac pacing will often reduce, but not prevent, symptomatic hypotension during neurocardiogenic syncope. Elderly patients with neurocardiogenic syncope are likely to have a predominant vasodepressor response without a significant cardioinhibitory component.

CLINICAL CHARACTERISTICS

Predisposition to neurocardiogenic syncope occurs under a wide variety of clinical circumstances. Indeed, the neurocardiogenic reaction per se may be the ultimate cause of most types of syncope. Neurocardiogenic syncope is often noted in individuals receiving sympathetic blocking agents and vasodilator drugs for hypertension, in elderly individuals receiving tranquilizers, in patients with acute or chronic anemia, and in those with transient reductions in blood volume, such as occur following a brisk diuresis or blood donation. Neurocardiogenic syncope complicates acute febrile infections and occurs with prolonged recumbency in chronic illness. Normal individuals at prolonged bed rest have a propensity for fainting, particularly when they arise abruptly from a sitting or recumbent position. Neurocardiogenic syncope is probably the most frequent cause of cardiovascular collapse during dental manipulations (dental syncope).[19] Neurocardiogenic syncope has been noted to follow strenuous exercise and may also occur during rapid acceleration in air flight, particularly when centrifugal force is applied in the head-to-foot position. Neurocardiogenic syncope of an unusual type may occur in pregnancy, being precipitated when the patient is supine and reversed when the patient assumes a lateral decubitus or upright posture (see Chap. 82).

The identification of aggravating factors (*triggers*) is important not only for the diagnosis but also for the prevention of syncope. Situations that decrease central venous volume or increase cardiovascular adrenergic tone are particularly important in the aggravation of neurocardiogenic syncope. The postprandial state, exertion in warm environments, prolonged upright posture, sodium restriction or diuretic use, and emotional or stressful situations are but a few important triggers to consider. Evidence suggests a relationship between chronic fatigue syndrome and neurocardiogenic syncope.[20]

The classic syncopal spell is often preceded by a constellation of prodromal symptoms occurring several seconds prior to the syncopal event. The prodrome may include symptoms of nausea, headache, diaphoresis, dizziness, chest pain, palpitations, dyspnea, and paresthesia. These symptoms may also persist for several minutes to several hours after the syncopal episode has resolved. Patients with sudden loss of consciousness may not report prodromal symptoms. Usually the spell occurs when the patient is upright and is less likely while seated. *Syncope while supine should prompt the search for etiologies other than neurocardiogenic syncope.*

During the syncopal episode, patients typically appear pale and diaphoretic, with a slow, diminished pulse. Occasionally, seizure-like activity may occur during asystolic periods. The syncopal spell classically resolves spontaneously once the patient is in the supine position but may

recur if the patient stands or sits upright soon after the initial spell. The observations of a bystander are particularly helpful. *If the patient experiences a prolonged period of confusion after the syncopal event or is incontinent, etiologies other than neurocardiogenic syncope should be considered.*

Natural History

The frequency and clinical significance of neurocardiogenic syncope are highly variable. Neurocardiogenic syncope may occur as a single isolated event or as a cluster of spells over weeks to months, or it may be a recurrent lifetime problem. The overall prognosis in patients with neurocardiogenic syncope is quite favorable compared with arrhythmic or left ventricular outflow obstructive forms of cardiac syncope. A very small subset of patients has been described as having *malignant* neurocardiogenic syncope.[21,22] This form of syncope is characterized by profound periods of asystole with sudden loss of consciousness, potentially leading to severe trauma and a theoretically increased risk of ischemia-mediated ventricular tachyarrhythmias. This risk is greatest in patients with underlying structural heart disease.

DIAGNOSTIC EVALUATION

Head-up tilt (HUT) testing has become a useful diagnostic study for the identification of patients with neurocardiogenic syncope.[23-25] The sensitivity, specificity, and reproducibility of HUT testing depend on the patient population studied and the HUT protocol employed.[23-30] HUT at an angle of 60° to 90° for a time period of 20 to 60 min has been found to yield a sensitivity ranging from 20 to 74 percent. Longer durations of HUT (45 to 60 min) lead to improved sensitivity without a significant increase in false-positive responses. Recent studies suggest that the optimal HUT angle should be between 60° and 80°. Tilt angles less than 45° sacrifice sensitivity, whereas angles greater than 80° can result in more false-positive results.[24] An average of 63 percent of patients studied with HUT after a negative electrophysiologic study were found to have a positive HUT response, suggesting that a significant proportion of patients with unexplained syncope have neurocardiogenic syncope. Isoproterenol infusion during HUT testing has been shown to improve sensitivity.[23] Low-dose isoproterenol infusion (<2 μg/min) has been shown to nearly double the number of positive responses compared with baseline (short-duration HUT), with an acceptable specificity of 93 percent and reproducibility of 83 percent.[28] High doses of isoproterenol, especially at HUT angles of greater than 80°, markedly increase the incidence of false-positive responses.[29] High-dose intravenous isoproterenol, intravenous adenosine, and sublingual nitroglycerin during HUT have all been shown to increase sensitivity with some reduction in specificity and significant reduction in the time required to perform the test.[31-33]

MANAGEMENT

The management of recurrent neurocardiogenic syncope is challenging and sometimes unsatisfactory. The choice of therapy should be based on an understanding of the neurocardiovascular cascade that eventually culminates in neurocardiogenic syncope. First-line therapy includes counseling the patient to avoid dehydration, prolonged periods of standing motionless, and situations known to trigger syncope. Increased salt intake may be beneficial, if not contraindicated. Patients should be educated to recognize premonitory symptoms and, if they are present, to assume a recumbent position and cough in order to maintain cerebral perfusion. Data suggest that tilt training may improve outcome.[34]

The severity and frequency of recurrence of neurocardiogenic syncope are highly variable. As a result, its pharmacologic management must be highly individualized. Patients with infrequent, near-syncopal spells may respond to general measures alone. Frequent syncopal spells, especially if trauma occurs, usually necessitate pharmacologic interventions.

Therapeutic options include volume expansion, beta-adrenergic receptor blockade, anticholinergic agents, serotonin reuptake inhibitors, methylxanthines, alpha-agonists, and dualchamber cardiac pacing. A stepped approach to pharmacologic therapy is advisable, starting with low initial doses, as these patients seem to be more prone to adverse reactions than the general population. The dose can be gradually titrated until the frequency and severity of spells are diminished. If one class of drug is ineffective, a combination of drugs, each acting on different limbs responsible for the neurocardiogenic syncope, may be beneficial. Several centers report the use of HUT testing to predict the clinical outcome of therapy. This approach has been questioned by two placebo-controlled trials that showed no significant difference in HUT response during treatment with active drug versus placebo.[35,36]

Volume Expansion

A significant proportion of patients with neurocardiogenic syncope have evidence of mild reduction in central plasma volume, and plasma volume expansion can prevent recurrence. Simple measures such as liberalizing salt and fluid intake may suffice.[37] Custom-fitted, counterpressure support garments that extend from the ankle to the waist may be of benefit in highly motivated individuals. In some instances, fludrocortisone acetate may be helpful in augmenting salt retention and volume expansion. The initial dose is 0.1 mg daily; this may be increased by increments of 0.1 mg every 5 to 7 days. The maintenance dose varies from 0.1 to 1.0 mg daily.[38] Potential side effects include recumbent hypertension, marked fluid retention, congestive heart failure, and hypokalemia.

Beta Blockers

Increased adrenergic stimulation with resultant activation of cardiac mechanoreceptors is believed to be an important mechanism in the pathophysiologic cascade that culminates in neurocardiogenic syncope. The negative inotropic effect of beta blockers may theoretically prevent activation of the ventricular mechanoreceptors or block the peripheral vasodilator effects of beta-adrenergic receptor stimulation. Oral metoprolol has been shown to prevent symptom recurrence in patients with neurocardiogenic syncope. In addition, intravenous metoprolol can blunt the hypotension and bradycardia during HUT testing. Recent studies suggest that patients who require isoproterenol infusion during tilt to elicit neurocardiogenic syncope are more likely to respond to beta blockers than are patients who are tilt positive without isoproterenol provocation.

Anticholinergic Agents

During neurocardiogenic syncope, certain subsets of patients experience profound bradycardia that can aggravate the hypotension associated with vasodilation. This subset is believed to have a sudden surge in vagal activity because the bradyarrhythmia, but not the vasodilation, can be prevented by intravenous atropine. The profound bradyarrhythmias are primarily observed in the young and presumably healthy age group. Despite the unimpressive response of neurocardiogenic syncope to atropine, certain other anticholinergic drugs may be of benefit, if tolerated. The anticholenergic activity of propantheline bromide may be an effective treatment.[39]

Transdermal scopolamine has been shown to be a useful preventive agent in certain subsets of patients with recurrent neurocardiogenic syncope. Its mechanism of action is poorly understood but is probably related to its peripheral anticholinergic actions, as well as a depressant effect on the central nervous system transmission to the autonomic nervous system. These central actions of scopolamine are believed to be important for the prevention of the nausea of motion sickness, which may incidentally involve neuropathways common to the vasovagal pathways.[40]

The class 1A antiarrhythmic drug, disopyramide, has known anticholinergic and negative inotropic properties. These properties, which are considered undesirable effects of disopyramide in the therapy of tachyarrhythmias, may prevent the activation of cardiopulmonary mechanoreceptors and the neurogenic reflex observed in neurocardiogenic syncope. Disopyramide has been shown to prevent tilt-induced syncope and to prevent spontaneous syncopal spells. Disopyramide, however, must be used with caution because of its potential for proarrhythmia. In addition, the noncardiovascular anticholinergic side effects of disopyramide may be intolerable for some patients.

Serotonin Reuptake Inhibitors

Serotonin may be an important mediator of inappropriate vasodilation and bradycardia in animal models of hemorrhagic shock. Blockade of serotonin receptors with methysergide can block this event. Nonrandomized studies suggest that the serotonin reuptake inhibitors fluoxetine hydrochloride (Prozac) and sertraline hydrochloride (Zoloft) may both be beneficial in the prevention of neurocardiogenic syncope after 4 to 6 weeks of therapy in approximately 55 percent of patients with severe, recurrent neurocardiogenic syncope.[41] A randomized, double-blinded, placebo-controlled trial showed that paroxetine hydrochloride-treated patients had an 18 percent incidence of recurrence versus a 53 percent recurrence rate in the placebo group.[42]

Methylxanthines

Theophylline appears to reduce the frequency of neurocardiogenic syncope in patients who can tolerate this durg. Two separate clinical studies have shown that theophylline can prevent recurrences in greater than 70 percent of patients.[43] Even low doses of theophylline (6 to 12 mg/kg per day) appear to have benefit in those patients who cannot tolerate higher doses. Unfortunately, side effects such as nervousness, anxiety, and gastrointestinal abnormalities limit the usefulness of theophylline in this setting. Methylxanthines, such as theophylline, appear to have three different pharmacologic effects that may be beneficial therapeutically. In low concentrations, methylxanthines are potent adenosine receptor antagonists. At *therapeutic* serum concentrations, theophylline acts as a phosphodiesterase inhibitor and as a calcium transport inhibitor, both of which may be important in maintaining peripheral vascular tone.

Alpha-Agonists

Nonrandomized studies in a small number of patients have suggested that alpha-agonists may prevent neurocardiogenic syncope due to a patent vasoconstrictor effect that may reduce venous pooling and concomitant reflex arteriolar vasodilation. However, two double-blinded, randomized placebo-controlled trials have yielded mixed results. Etilefrine was no better than placebo in the prevention of syncope. In contrast, the alpha-agonist medodrine reduced the incidence of HUT-induced syncope and improved quality of life compared with placebo control.[44,45]

Cardiac Pacing

Similar to the use of anticholinergics, pacing is valuable in preventing the component of hypotension that is due to bradycardia; however, peripheral vasodilation may still occur despite heart rate control as noted. *Cardiac pacing should be reserved for those patients who have documented episodes of prolonged bradycardia associated with the syncopal spell.* Pacing may be especially beneficial in those rare patients with malignant neurocardiogenic syncope due to cardiac asystole.[46,47] These patients typically require pharmacologic therapy in addition to cardiac pacing to prevent the vasodepressor component. Dual-chamber pacing with rate-drop response is the preferred mode of pacing. The North American Vasovagal Pacemaker Study was the first randomized trial to confirm the effectiveness of pacing in patients with frequent syncope, positive head-up tilt, and relative bradycardia.[48]

Orthostatic Syncope (Orthostatic Hypotension)

Orthostatic hypotension is a disorder in which assumption of the upright posture is associated with a fall in arterial pressure associated with light-headedness, blurring of vision, and a sense of weakness and unsteadiness.[2,49-55] Hypotension is progressive over a period of seconds to minutes, depending on the degree of loss in reflex adaptation. If the fall in perfusion pressure to the brain is profound, syncope occurs. If the individual assumes the recumbent posture, arterial pressure rapidly normalizes and consciousness is restored.

From the diagnostic viewpoint, orthostatic hypotension is conveniently classified under three major causes:[2] *venous pooling and/or blood volume depletion, pharmacologic agents,* and *neurogenic causes* (Table 32-3). In certain cases, circulating endogenous vasodilators may result in orthostatic hypotension and syncope.

Table 32-3: Causes of Orthostatic Syncope

Venous pooling or volume depletion
❍ Prolonged bed rest ❍ Prolonged standing ❍ Pregnancy ❍ Venous varicosities ❍ Blood loss ❍ Dehydration
Pharmacologic agents
❍ Antihypertensive ❍ Sympathetic blocking agents ❍ Calcium channel blockers ❍ Converting enzyme inhibitors ❍ Nitrates ❍ Diuretics ❍ Antidepressants, antipsychotic ❍ Phenothiazides ❍ Tranquilizers ❍ Antiparkinsonian ❍ Central nervous system depressants
Neurogenic

- Diabetes mellitus
- Alcoholic neuropathy
- Spinal cord disease
- Amyloidosis
- Multiple sclerosis
- Multiple cerebral infarcts
- Parkinsonism
- Tabes dorsalis
- Syringomyelia
- Idiopathic orthostatic hypotension
- Shy-Drager syndrome (multiple system atrophy)

Circulating endogenous vasodilators

- Hyperbradykinism
- Mastocytosis
- Carcinoid syndrome

VENOUS POOLING AND/OR BLOOD VOLUME DEPLETION

Excessive venous pooling accounts for the postural hypotension accompanying sustained bed rest, prolonged standing, pregnancy, and marked venous varicosities. Tall, asthenic individuals with poorly developed musculature are particularly prone to this form of postural hypotension. Deconditioning of normal autonomic reflex vasoconstriction may contribute to the orthostatic hypotension associated with prolonged bed rest and following extended periods of weightlessness in astronauts.[2] Blood volume depletion accounts for the orthostatic hypotension associated with dehydration, excessive diuresis, anemia, hemorrhage, excessive gastrointestinal fluid loss, third-space sequestration, prolonged fever, renal dialysis, excessive perspiration, adrenal insufficiency, pheochromocytoma, and diabetes insipidus.[56-60]

PHARMACOLOGIC AGENTS

Pharmacologically induced postural hypotension is a side effect in the administration of several classes of drugs, including antihypertensives, sympathetic blocking agents, diuretics, nitrates, calcium channel blockers, converting enzyme inhibitors, antidepressants, phenothiazines, tranquilizers, antipsychotic drugs, antiparkinsonian drugs, and central nervous system depressants.

NEUROGENIC CAUSES

Neurogenic postural hypotension has been observed in a wide variety of diseases affecting the autonomic nervous system. Specific entities include diabetes mellitus, alcoholic neuropathy, spinal cord injury, idiopathic orthostatic hypotension, and Shy-Drager syndrome (Table 32-3).[57-62] Administration of adrenergic blocking drugs and vasodilators may accentuate the predisposition to orthostatic hypotension in patients with primary neurogenic postural hypotension.

In the idiopathic form of orthostatic hypotension, postural hypotension is accompanied by relatively fixed heart rate, heat intolerance, anhidrosis, nocturnal polyuria, urinary and anal sphincter dysfunction, and impotency.[59,60] In the Shy-Drager syndrome, orthostatic hypotension is accompanied by multiple central nervous system manifestations and is referred to as *multiple*

system atrophy.[57,61]

The central nervous system manifestations in multiple system atrophy may be indistinguishable from those of idiopathic Parkinson's disease and may precede or follow the onset of orthostatic hypotension. The prognosis appears to be worse in patients with multiple system atrophy than in those with idiopathic orthostatic hypotension, with death often resulting from general debilitation and its complications. Severe supine hypertension may complicate the presence of orthostatic hypotension.

When the total or central blood volume is depleted in the presence of an intact autonomic nervous system, pallor, coldness of the extremities, tachycardia, and sweating are evident. Relative bradycardia may occur at the time of syncope, and the clinical presentation may be identical to that of neurocardiogenic syncope. When orthostatic hypotension is due to loss or severe impairment of autonomic reflexes, the syncope is associated with little or no change in heart rate, and there is an absence of the pallor, sweating, and other manifestations observed in patients with intact autonomic reflexes.

THERAPY

Effective therapy in postural hypotension is closely linked to an accurate diagnosis. Primary emphasis must be based on treatable causes, in particular, pharmacologically induced postural hypotension, blood volume loss, venous pooling, and reversible disease entities. A summary of treatment modalities currently applied among patients with chronic orthostatic hypotension is presented in Table 32-4.[2] The wide variety of recommended approaches reflects the frequently disappointing therapeutic response to each of these modalities. Commonly, multiple maneuvers are necessary to achieve optimum control of postural hypotension. Of singular importance is the need to have the patient avoid experiences, such as dehydration, that accentuate postural hypotension and to restrict the use of pharmacologic agents that induce blood volume depletion, vasodilation, and sympathetic blockade. *Patients should be instructed about simple adaptive maneuvers, including slow rising from a recumbent or sitting position, flexing of the calf muscles during assumption of the upright posture, and avoidance of prolonged immobility during standing*.[63,64] Erythropoietin administration to expand red blood cell mass and blood volume has been used to maintain pressure in the upright posture in certain cases of orthostatic hypotension.[65]

Table 32-4: Treatment of Chronic Orthostatic Hypotension

- Evaluation for reversible and accentuating disease entities
- Specific modalities for irreversible orthostatic hypotension
  - Mechanical measures
    - Head-up position of bed
    - Lower body compression garment
    - Slow motion and calf muscle flexing on arising
  - Volume expansion
    - High-salt diet
    - Fludrocortisone acetate
  - Pharmacologic agents
    - Sympathomimetics
    - Vasoconstrictors

Cerebrovascular Syncope

In patients with extensive occlusive disease of the origins of the brachiocephalic vessels, such as pulseless disease (e.g., aortic arch syndrome and Takayasu's arteritis), syncope is not uncommon.[2,66] With lesser degrees of cerebral occlusive disease, as with atherosclerotic narrowing, transient lowering of arterial pressure such as that immediately following assumption of the upright posture may be followed by vague symptoms suggesting impaired cerebral blood flow. In patients with cerebrovascular occlusive disease, a transient decrease in cardiac output and arterial pressure may provoke syncope at levels of arterial pressure that would otherwise be tolerated (see below, "Multifactorial Syncope").

Impairment or loss of consciousness in relation to changing positions of the head, particularly hyperextension and lateral rotation, has been attributed to mechanical narrowing of the vertebral arteries by skeletal deformities of the cervical spine. Such symptoms have been observed in patients with Klippel-Feil deformity, cervical spondylosis, and severe cervical osteoarthritis. Altered consciousness is often preceded by vestibular symptoms. When vertigo is a predominant symptom, the syndrome of benign postural vertigo must be considered.

Among patients with major occlusive disease of the carotid-vertebrobasilar arterial system, manual compression of the carotid artery as a test for carotid sinus hypersensitivity may induce syncope, at times associated with focal neurologic signs. The occurrence of syncope under such circumstances may be misdiagnosed as carotid sinus syndrome. The occurrence of a cerebrovascular accident following manual compression of the carotid sinus has been reported in patients with carotid disease, and *carotid sinus massage should be avoided in patients with symptomatic or suspected occlusive carotid vascular disease.*

Syncope in the *subclavian steal syndrome* is caused by major occlusive disease of the subclavian artery proximal to the origin of the vertebral artery. During upper extremity exercise, blood flow is shunted retrograde, by the circle of Willis, to the distal subclavian artery. The consequent decrease in cerebral circulation induces cerebral ischemia.[2,66] This syndrome is suggested by the findings of diminished brachial arterial pressure on the affected side, a bruit that is maximal over the supraclavicular area adjacent to the origin of the vertebral artery, and the induction of symptoms by exercise of the involved extremity.

Although focal neurologic symptoms and signs are the usual neurologic manifestations of cerebral emboli, transient loss of consciousness can be a primary presenting symptom. *Syncopal episodes are more likely to occur when atherosclerotic occlusive disease involves the vertebrobasilar system, with compromised perfusion to the medullary arousal center.* In vertebrobasilar vascular insufficiency, syncope or presyncope is nearly always preceded by symptoms of vertigo, diplopia, dysarthria, and ataxia. The episodes are generally attributed to microemboli arising from an atherosclerotic plaque, although vasospasm or postural hypotension may contribute (see Chap. 89).

THERAPY

The treatment of recurrent syncope in cerebrovascular disease is predicated on an accurate diagnosis. In this regard, it is essential to segregate the potential contribution of cardiac and vascular factors and their interplay. Anticoagulants and/or platelet antiaggregant agents are recommended for the prevention of embolic disease from the heart or central vessels (see Chap. 44). Surgical endarterectomy should be considered in carotid arterial occlusive disease.

Seizure Disorders

The various forms of syncope from the loss of consciousness during a generalized convulsive seizure are often differentiated on the basis of history alone.[67,68] Grand mal epilepsy as a cause of

sudden loss of consciousness is suggested by the dramatic nature of the onset of the attack, which is often preceded by an aura. Other observations that aid in distinguishing epilepsy are the absence of hypotension and cardiac arrhythmia (other than sinus tachycardia); the presence of sustained tonic-clonic convulsive movements with upturning of the eyes; prolonged unconsciousness; urinary incontinence; and postictal drowsiness, headache, and confusion. While any of these findings occasionally occur in episodes of syncope, the frequent association of these several events generally allows differentiation of epilepsy as its cause. In fact, it is common for patients with true syncope to be incorrectly diagnosed as having a seizure disorder. Akinetic seizures and absence (petite mal) seizures may be difficult to differentiate from syncope. The occurrence in childhood, a past history of recurrent episodes, and the absence of pallor in witnessed episodes are helpful diagnostic findings. *Temporal lobe seizures are the most likely form of epilepsy to masquerade as syncope.*

An abnormal electroencephalogram (EEG) between episodes of altered consciousness can aid in distinguishing a seizure disorder when clinical observations are not definitive, and in some instances continuous EEG and electrocardiogram (ECG) monitoring are required.

Carotid Sinus Hypersensitivity

Compression of the carotid sinus in normal persons is often associated with transient slowing of the heart rate and mild hypotension. In some patients, such stimulation is followed by a profound slowing of heart rate and/or a marked diminution of arterial pressure. This disorder is referred to as *carotid sinus hypersensitivity.*

There are three forms of carotid sinus syncope, as originally described by Weiss and Baker:[69] cardioinhibitory, vasodepressor, and mixed type.

CARDIOINHIBITORY TYPE

The cardioinhibitory type of carotid sinus syncope which is the most common, is associated with slowing of the heart rate secondary to marked sinus bradycardia, sinoatrial block, and/or high-degree AV block. Syncope in this instance is related to the prolonged asystole rather than to a fall in peripheral vascular resistance.

VASODEPRESSOR TYPE

The vasodepressor type of carotid sinus syncope is that form of the syndrome in which syncope occurs as a result of a primary decrease in arterial pressure in the absence of profound bradycardia. Presyncopal signs, such as nausea, sweating, and pallor, are usually not observed, and the fall in arterial pressure may be precipitous.

MIXED FORM

In the mixed form of carotid sinus syncope with bradycardia and hypotension, the vasodepressor component may not be evident until after atropine blockade or during cardiac pacing. Under such circumstances, carotid sinus massage uncovers the hypotension in the absence of bradycardia.

Carotid sinus syncope and presyncope are commonly found in elderly patients in whom symptoms of light-headedness and impaired consciousness may be initiated by relatively minor stimulation of the carotid sinus.[2] Carotid sinus hypersensitivity in the elderly is often associated with generalized atherosclerosis.

Manual carotid sinus compression in elderly persons enjoins caution whenever this maneuver is

attempted. Digital carotid massage should first be attempted with a very gentle and brief (2 to 4 s) compression, always when the patient is supine and with monitoring of the heart rate and blood pressure.[70-73] *The presence of carotid artery bruits is a relative contraindication to carotid massage.*

Carotid sinus syncope has been observed in patients with neoplasms, inflammatory masses, and lymph nodes in the neck adjacent to the carotid sinus.[74] Carotid sinus syncope is well established as a complication of carotid body and parotid tumors. In certain patients, carotid sinus hypersensitivity may be documented only when carotid sinus massage is performed in the upright position or during HUT studies with careful attention to the blood pressure response.

THERAPY

Thorough patient education concerning avoidance of carotid sinus pressure may be effective in preventing syncopal episodes. Anticholinergic and sympathomimetic agents may be tried, but inadequacy of drug therapy and the occurrence of side effects usually necessitate pacemaker therapy. AV sequential pacing appears to minimize the hypotensive effect of cardiac pacing and, hence, is the preferred form of pacemaker therapy in the mixed form of carotid sinus syncope. It is important that pacemaker effectiveness be verified objectively through observation of the effect of carotid sinus stimulation on cardiac rhythm and arterial pressure following pacemaker insertion.

Situational Syncope

The term *situational syncope* has been applied to a group of syndromes that is defined by the circumstances that precipitate the event. In the past, the syncope in these disorders has been attributed mainly to mechanical factors. Recent observations suggest that, at least in part, neurocardiogenic factors contribute to the syncope.[75]

COUGH SYNCOPE

Also called laryngeal vertigo, tussive syncope, and posttussive syncope, cough syncope is associated with loss of consciousness following a paroxysm of vigorous coughing. It is often seen in robust men and children but rarely in women. Cerebral blood flow is impaired by the marked increase in cerebrospinal fluid pressure during coughing, which increases cerebrovascular resistance. There is also a *concussive effect* transmitted via the cerebrospinal fluid. Reflex-induced sinus bradycardia, sinus arrest, and AV block have been observed in patients with cough syncope.[76]

In the treatment of cough syncope, the patient should be informed of the deleterious effects of vigorous coughing. Cessation of smoking and initiation of bronchodilator and anti-inflammatory therapy for associated bronchitis are mandatory for the prevention of cough-induced syncope.

SWALLOWING, OR DEGLUTITION, SYNCOPE

Deglutition syncope has been reported in association with tumor, diverticulum, achalasia, stricture, and spasm of the esophagus. In some patients, no abnormality can be identified radiologically or endoscopically. Syncope is usually associated with sinus bradycardia, sinus arrest, or high-degree AV block.[77]

Similar mechanisms have been implicated in syncope following distension of the viscera, glossopharyngeal neuralgia, fainting associated with irritation of the pleura or peritoneum, and cardiac asystole associated with esophagoscopy or bronchoscopy.[78]

VALSALVA SYNCOPE

Valsalva syncope is related to prolonged increases in intrathoracic pressure that may be observed during a sustained Valsalva maneuver. With prolonged exhalation against a closed glottis, there is a progressive fall in venous return, arterial pressure, and cardiac output.[2] These hemodynamic changes may be sufficient to impair cerebral circulation. An episode of Valsalva syncope may be the first indication of the presence of a disorder predisposing an individual to syncope (e.g., cerebrovascular occlusive disease or sick sinus syndrome). Instruction to the patient regarding avoidance of sustained Valsalva maneuvers is essential in preventing recurring episodes.

MICTURITION SYNCOPE

Micturition syncope is often seen in adult men with nocturia. During or immediately following voiding, there is a loss of consciousness, often without premonitory symptoms. The ingestion of large quantities of alcoholic beverages before retiring is common.[2,79] A similar type of syncope may be observed following drainage of the distended bladder or after removal of large quantities of ascitic fluid. The loss of consciousness in these circumstances may be related to bradycardia and a sudden reflex decrease in peripheral arterial resistance induced by the precipitous fall of intraabdominal volume. The loss of consciousness of typical micturition syncope is precipitated by such factors as the Valsalva maneuver in the upright posture and the peripheral vasodilation associated with a warm bed and recent alcohol consumption.

DEFECATION SYNCOPE

Defecation syncope occurs most commonly in the elderly, usually after arising from bed at night or during manual disimpaction of the rectum.[2,80] It has been attributed to sudden decompression of the rectum. Valsalva-related syncope could also explain some instances of this form of syncope. Many patients with defecation syncope have underlying gastrointestinal or cardiovascular disease.

DIVER'S SYNCOPE

Diver's syncope is an unusual and poorly understood form of loss of consciousness or even sudden death that may occur in underwater diving. In some instances diver's syncope may represent a form of neurocardiogenic syncope. Hypoxia and bradycardia of the diving reflex may be contributing factors.

POSTPRANDIAL SYNCOPE

Hypotension postprandially may result in presyncope and/or syncope and is most common in the elderly. The mechanisms of postprandial hypotension and syncope are not fully understood. Possible contributing factors include inadequate sympathetic nervous system compensation for meal-induced splanchnic blood pooling, impairments in baroreflex function, inadequate postprandial increase in cardiac output, impairment of peripheral vasoconstriction, and release of gastrointestinal peptides.[81,82]

TREATMENT

Therapy of situational syncope should be individualized and should be addressed to the specific circumstance associated with it. Episodes of syncope may be prevented by anticholinergic drugs such as atropine if they are administered prior to a procedure. Other measures include avoidance of vasodilators before meals and/or resting in a supine position after meals for patients with postprandial hypotension and sitting while urinating for men with micturition syncope. Octreotide, a somatostatin analog, has been shown to be effective in patients with postprandial hypotension,

but it is expensive and must be given parenterally.[81,82]

Metabolic Syncope

HYPOXIA-RELATED SYNCOPE

Hypoxia may induce syncope that is related directly to a lack of oxygen or to an episode of neurocardiogenic syncope initiated during a period of oxygen lack. In the presence of cardiovascular disease, pulmonary insufficiency, and anemia, symptoms of hypoxia occur at lesser levels of oxygen deprivation. The impairment of consciousness due to hypoxia is accompanied by sinus tachycardia, while arterial pressure is usually normal. Short-term exposure to moderate altitude may be related to otherwise unexplained syncope in healthy, young adults. The environmental setting in which impaired consciousness due to hypoxia occurs usually leaves little difficulty in its differentiation from other forms of syncope.

HYPOGLYCEMIA-RELATED SYNCOPE

This form of syncope may be associated with weakness, sweating, a sensation of hunger, confusion, and altered consciousness. The symptoms are unrelated to posture and usually respond promptly to food ingestion or intravenous glucose administration. Impaired consciousness is usually associated with sinus tachycardia and is rarely accompanied by hypotension. In contrast to syncope of circulatory origin, it is gradual in onset. Hypoglycemia has been implicated as a possible factor that may trigger neurocardiogenic syncope.

HYPERVENTILATION, PANIC ATTACKS, AND SYNCOPE

In normal persons, anxiety is accompanied by varying degrees of hyperventilation. In the hyperventilation syndrome or in a panic episode, anxiety is associated with an inordinate degree of hyperventilation. Symptoms of hypocapnia and alkalosis may dominate the clinical picture. During the episode, the patient may complain of a tightness in the chest and a feeling of suffocation. These symptoms may be followed by confusion, a sense of unreality, bewilderment, light-headedness, and a feeling of panic. Symptoms of palpitation, precordial oppression, and dyspnea may suggest an acute cardiac or pulmonary catastrophe. Digital and circumoral paresthesias may develop and, in severe cases, may be accompanied by carpopedal spasm, which is probably related to alkalosis-induced decreases in serum ionized calcium. The symptoms may be protracted and persist while the subject is sitting or recumbent. During hyperventilation, there is slight hypotension but no profound fall in arterial pressure, while the heart rate is rapid. Although mentation is impaired, complete loss of consciousness rarely occurs. Typical neurocardiogenic syncope may be superimposed, making identification of the syndrome more difficult. *The induction of a typical episode by voluntary hyperventilation is helpful in distinguishing this syndrome and aids in educating the patient regarding the prevention and control of attacks.*

Other Forms of Syncope or Conditions Mimicking Syncope

MIGRAINE-RELATED SYNCOPE

Symptoms suggesting syncope are unusual in ordinary types of migraine. In rare instances in which the basilar arterial system is involved (as opposed to the more usually affected carotid system), the premonitory aura of migraine terminates in a period of unconsciousness of several minutes' duration. The unconsciousness is slow in onset and may be preceded by a dreamlike state. When the patient awakens, there is severe headache, typically in the occipital area. This form of migraine usually afflicts young women and has a strong menstrual association. The symptoms in syncopal migraine may suggest hyperventilation and/or hysterical syncope.

HYSTERICAL SYNCOPE

Altered consciousness of circulatory origin may be mimicked by hysteria. Hysterical episodes occur most frequently in young adults, often with severe emotional illness, and generally in the presence of an audience.[83] The individual slumps gently, even gracefully, to the floor or in a convenient chair or sofa, typically without injury or awkwardness. The patient may be motionless or may exhibit symbolic restrictive movements. Episodes are of varying duration and may last an hour or more. Although the patient is unresponsive to verbal stimulation, there is evidence, such as eyelid movement, that consciousness is well preserved, and no abnormalities in pulse, arterial pressure, or skin color are evident.

NEXT

Chapter 32: DIAGNOSIS AND MANAGEMENT OF SYNCOPE

CARDIAC SYNCOPE

Either severe obstruction of cardiac output or disturbances of cardiac rhythm can produce syncope of cardiac origin.[2,84-95] Obstructive lesions and arrhythmias frequently coexist; indeed, one abnormality may accentuate the other. Common disorders associated with cardiac syncope are listed in Table 32-5.

Table 32-5: Common Disorders Associated with Cardiac Syncope

○ Left-sided heart
○ Aortic stenosis
○ Hypertrophic cardiomyopathy
○ Prosthetic valve malfunction
○ Mitral stenosis
○ Left atrial myxoma (rare)
○ Right-sided heart
○ Eisenmenger syndrome
○ Tetralogy of Fallot
○ Pulmonary embolism
○ Pulmonary stenosis
○ Primary pulmonary hypertension
○ Cardiac tamponade
○ Cardiac arrhythmia
○ Sinoatrial disease
○ Atrioventricular block
○ Supraventricular tachycardia
○ Ventricular tachycardia/fibrillation
Pacemaker related

Syncope Related to Obstruction of Cardiac Output

Obstruction to cardiac output sufficient to cause syncope may occur on the left or right side of the heart. Syncope, particularly that occurring with effort, is a major symptom of aortic stenosis and is often the initial presentation. The mechanisms are unclear, but studies suggest a reflex fall in peripheral vascular resistance as the usual cause. Failure of cardiac output to increase adequately during exercise, while peripheral resistance decreases, may play a role (see also Chap. 56). Transient arrhythmias can also induce syncope in aortic stenosis. Syncope associated with effort (often occurring immediately after effort) is observed in patients with hypertrophic

cardiomyopathy as well. Nonexertional syncope related to acute decreases in preload or afterload, to inotropic stimulation, or to transient arrhythmias may also occur in hypertrophic cardiomyopathy (see also Chap. 67). Left-sided heart prosthetic valve malfunction can produce transient and at times profound obstruction to blood flow with syncope (see Chap. 60). A left atrial myxoma may obstruct left ventricular filling, leading to low cardiac output and syncope. The obstruction of left ventricular inflow in atrial myxoma may be posturally induced (see also Chap. 77). Mitral stenosis can produce cardiac syncope but usually does so only when tachycardia or other arrhythmias supervene (see also Chap. 57).

Primary pulmonary hypertension and pulmonary hypertension secondary to congenital heart disease may both be complicated by syncope, particularly effort-related syncope. In these conditions, limitation of right ventricular outflow markedly inhibits the cardiac output during increased peripheral demand. The fall in peripheral resistance in the presence of an inability to increase cardiac output may result in profound hypotension. A reflex fall in peripheral resistance similar to that which occurs with aortic stenosis may play a role. In a young patient without a cardiac murmur who presents with syncope during or shortly after exertion, primary pulmonary hypertension should be considered (see also Chap. 52). In pulmonary stenosis and pulmonary embolism, similar mechanisms may account for syncope. Pulmonary embolism as a cause of syncope should also be suspected in paraplegic patients.[96] In tetralogy of Fallot, the magnitude of flow through the right-to-left shunt increases when systemic resistance falls with effort, since the right ventricular outflow obstruction is usually fixed. This shunting results in marked arterial hypoxia, which may precipitate a syncopal episode (see also Chap. 63).

Cardiac tamponade, which affects both the right side and the left side of the heart, can produce syncope, but this is extremely rare. The likelihood of syncope is increased by concomitant arrhythmias.

Syncope Related to Cardiac Arrhythmia

Arrhythmias are a common cause of syncope and must be considered in any patient, particularly when cardiac disease is present. Either extreme of ventricular rate-bradycardia or tachycardia-can depress cardiac output to the point of critical hypotension with cerebral hypoperfusion and syncope. As noted earlier for other forms of syncope, a neurocardiogenic reaction may be precipitated by the hemodynamic effects of arrhythmias (see also Chaps. 23 and 24). The most common arrhythmias producing syncope or presyncope are profound sinus bradycardia, sinoatrial exit block or sinus pause, high-grade AV block, supraventricular tachycardia and ventricular tachycardia/fibrillation. Although arrhythmias occur in the absence of demonstrable underlying cardiac disease, they are usually secondary to such disorders as ischemic heart disease, cardiomyopathy, valvular heart disease (including mitral valve prolapse), and primary conduction system disease.

Primary degenerative disease of the sinus node and the specialized conduction tissue is the most common cause of sinoatrial disease (*sick sinus syndrome;* see Chap. 24). The sick sinus syndrome may be manifested by persistent or episodic sinus bradycardia or sinoatrial exit block, often with impaired junctional escape rhythm. The presence of alternating sinus bradycardia or sinoatrial block with paroxysmal supraventricular tachycardia of diverse types is quite common and is referred to as the *bradycardia-tachycardia syndrome. Syncope often occurs with asystole or bradycardia at the termination of tachycardia, when overdrive suppression of the sinoatrial or junctional pacemakers is present.*[2] A high incidence of associated AV and intraventricular conduction defects occurs in the sick sinus syndrome. AV block, impaired junctional escape rhythm, or ventricular arrhythmias may actually be responsible for syncope in the setting of sick sinus syndrome.

High-grade AV block may be due to disease of either the AV node or the His-Purkinje system. Block of the AV node is usually associated with a functional junctional pacemaker and a normal QRS complex, whereas AV block due to disease of the His-Purkinje system is usually associated with a wide complex idioventricular escape rhythm, which may be quite slow. Bifascicular block associated with a prolonged PR interval is associated with a substantial risk of developing high-grade AV block and syncope. Progression to high-grade AV block in patients with bifascicular block and a normal PR interval is less common. Ventricular tachycardia can cause syncope in patients with AV block or other bradycardic rhythms (see Chap. 24).

Sinus bradycardia, AV block, or cardiac asystole may be mediated by reflex vagal mechanisms and have been observed in a variety of disease states or during diagnostic procedures. Ventricular asystole (usually sinus arrest, although AV block can occasionally be noted) is most commonly due to neurocardiogenic syncope. Transient sinus bradycardia or AV block can also occur in apparently healthy young individuals; certain of these patients may have mitral valve prolapse.[93] Paroxysmal supraventricular tachycardias usually do not produce syncope in young individuals. Syncope, however, may occur in individuals who have accessory AV pathways due to the Wolff-Parkinson-White (WPW) syndrome, wherein supraventricular tachycardia is associated with a very rapid ventricular response. Studies have shown, though, that syncope during supraventricular tachycardia may be related to vasomotor factors and not be due solely to heart rate (Fig. 32-2).[97,98] AV node reentry, atrial fibrillation, or atrial flutter may be associated with a rapid ventricular rate in the setting of baseline short PR interval, or tachycardia occurring during or after exercise may cause syncope. Patients with cardiac disease, particularly obstructive outflow disorders, and older individuals may more commonly have hypotension significant enough to cause cerebral hypoperfusion and syncope.

Paroxysmal ventricular tachycardia may produce syncope at any age. The tachycardia is usually a manifestation of cardiac disease in which there are structural abnormalities and/or ischemia. Ventricular tachycardia is the most common arrhythmic cause of syncope in most series. In some patients, ventricular and supraventricular tachycardia may coexist (see Chap. 24).

Syncope may occur with ventricular tachycardia in the setting of the long QT syndrome. The long QT interval syndrome may be congenital or acquired (see Chaps. 11 and 24). The recognition of the long QT syndromes depends on demonstration of QT prolongation and of recurrent syncope, which is almost always due to ventricular arrhythmia. The ventricular arrhythmia is usually torsades de pointes. Ventricular tachycardia in the long QT syndromes is often triggered by exercise or stress reaction. A pause preceding the onset of tachycardia is common since the early after-depolarizations thought responsible for torsades are bradycardia dependent.[94,99]

It is particularly important to recognize the polymorphic ventricular tachycardia associated with acquired long QT syndromes, because it is a potentially life-threatening side effect of many drugs and metabolic abnormalities. The most frequent causes of acquired long QT syndromes are antiarrhythmic drugs and electrolyte disorders (hypokalemia and hypomagnesemia).

A variety of other drugs may produce arrhythmias or arrhythmia aggravation, resulting in syncope or presyncope. Beta-blocking drugs, calcium-channel-blocking agents, sotalol, and amiodarone are some of the more common agents that may cause significant sinus bradycardia or AV block. Digitalis may occasionally cause sinoatrial exit block or AV block, particularly in patients with sinoatrial or AV node disease. Supraventricular and ventricular tachycardias can be a result of digitalis therapy, particularly in patients with organic heart disease and hypokalemia. Theophylline and beta agonists, used for therapy of chronic obstructive pulmonary disease, may precipitate ventricular or supraventricular arrhythmias. Therapy with diuretics often causes hypokalemia and hypomagnesemia, which predispose individuals to supraventricular and ventricular arrhythmias. Both caffeine and alcohol may precipitate either atrial or ventricular

tachycardia.

In patients with an artificial ventricular pacemaker, syncope may be secondary to pacemaker malfunction or to the pacemaker syndrome (see Chap. 31). Dual-chamber pacemakers can produce pacemaker-mediated tachycardias when there is retrograde conduction of the ventricular impulse to the atria. Improvements in technology have reduced the incidence of this complication.[100,101]

DIAGNOSTIC EVALUATION OF SYNCOPE ASSOCIATED WITH CARDIAC DISEASE

While the history and physical examination often establish the diagnosis of obstructive cardiac syncope, laboratory studies are usually required for the determination of the severity of the disorder. Cardiac catheterization is required when corrective cardiac surgery is contemplated.

By far, the most challenging diagnostic evaluation occurs when arrhythmic cardiac syncope is suspected. Such patients often have evidence of underlying cardiovascular disease, which, when present, portends a poor prognosis. Thus, diagnostic studies directed to the nature and severity of the underlying cardiac disease must be pursued in addition to the arrhythmia evaluation.[102]

The various diagnostic tests used for the evaluation of arrhythmic syncope are listed in Fig. 32-3. Because of the transient nature of most arrhythmias, the routine ECG is generally of limited value. It is, however, very useful in identifying patients with abnormalities that may predispose individuals to syncope, such as prior infarction, WPW pattern, and AV or bundle branch block.

The technique of signal-averaged ECG for detecting late potentials can be used as a noninvasive screening test for detecting a high-risk subset of patients prone to lethal ventricular arrhythmias. The accuracy of the signal-averaged ECG in predicting the induction of sustained monomorphic ventricular tachycardia in high-risk patients with coronary artery disease who undergo electrophysiologic studies is good. The signal-averaged ECG may be helpful in some instances of other myocardial disease such as right ventricular dysplasia.[103-107]

Exercise testing can directly provoke arrhythmias in patients with a history suggesting exercise-induced arrhythmias. It should be performed when exertional arrhythmias are suspected but not documented by ambulatory monitoring or when ischemia is suspected (see also Chap. 14).[108,109] Continuous ECG monitoring is a widely used screening test for suspected arrhythmic syncope. It has low yield in unselected patients. *It is important to recognize that one 24-h monitoring period may not be sufficient for detecting transient rhythm disturbances. The diagnostic yield, moreover, increases only slightly with more prolonged monitoring* (see also Chap. 25).[108-110]

When ambulatory monitoring does not document an arrhythmia, a patient-activated electrocardiographic device (event recorder) may prove efficacious. This type of monitoring is effective in documenting infrequent arrhythmia. It should not be used in patients with suspected life-threatening arrhythmias.[111-113] Extended monitoring with an implantable loop recorder has been demonstrated to provide diagnostic ability in approximately two-thirds of patients with syncope of undetermined cause.[114,115]

When noninvasive testing is inconclusive for the diagnosis of suspected arrhythmic syncope, an electrophysiologic study should be performed on high-risk patients (i.e., those with underlying heart disease, suspicious arrhythmia by ECG monitoring, or recurrent syncope). Patients without identifiable heart disease are less likely to have the cause of syncope identified by electrophysiologic study. The cause of syncope most commonly identified by electrophysiologic study is ventricular tachycardia.

Electrophysiologic studies are useful in stratifying risk among symptomatic patients with bundle branch block or patients with bifascicular block. Patients with normal electrophysiologic study results have a favorable prognosis even without treatment. Patients undergoing permanent pacing on the basis of electrophysiologic testing also have a favorable prognosis, with a low rate of symptom recurrence.[116-121]

The prognosis in patients with syncope due to supraventricular tachycardia is usually good, since therapeutic approaches are available (i.e., drugs and radiofrequency ablation). The prognosis in patients with inducible ventricular tachycardia is less favorable but is improved when specific therapy can be demonstrated to inhibit the inducibility of ventricular tachycardia or with the use of an implantable cardioverter-defibrillator.

TREATMENT OF CARDIAC SYNCOPE

Obstructive Heart Disease

For patients with syncope caused by obstructive heart disease, cardiac surgery is often the treatment of choice.[2] Patients with hypertrophic cardiomyopathy and syncope may respond well to pharmacologic therapy. Recent studies have suggested that an AV sequential pacemaker might control symptoms in certain patients with hypertrophic cardiomyopathy.[122-130] In rare cases with severe obstruction and persistent symptoms, surgery must be considered (see Chap. 67). Among all patients with obstructive heart disease and recurrent syncope, the diagnosis of fixed pulmonary hypertension is most difficult to treat because effective therapeutic options are limited (see Chap. 52).

Arrhythmic Syncope

A detailed discussion of therapy for cardiac arrhythmias is presented in Chap. 24. Some general principles of arrhythmia management as they apply to patients with syncope are summarized here. Treatment of arrhythmic syncope requires accurate definition of the arrhythmia associated with syncope or presyncope.

The bradycardic rhythm disturbances responsible for syncope, primarily AV and sinoatrial pauses or exit block, usually require the implantation of a pacemaker. Patients receiving drugs that cause or contribute to the bradyarrhythmia, however, may benefit from withdrawal or substitution of the offending agent. Patients with bradycardia-tachycardia syndrome usually require pacemaker therapy, because the antiarrhythmic agents required for control of the tachycardia will often further suppress sinoatrial function.

Implicit in the approach to the tachycardias causing syncope is the accurate diagnosis of a specific tachycardia. The definition of the tachycardia and the response to antiarrhythmic therapy are often best achieved in the electrophysiologic laboratory. Patients with syncope due to supraventricular tachycardia associated with an accessory pathway are most often approached with catheter ablation of the accessory pathway.[131,132] Catheter ablation is also a successful mode of therapy in patients with AV nodal reentry supraventricular tachycardia or other supraventricular tachycardias associated with a rapid heart rate (see Chap. 28).

Therapy of paroxysmal ventricular tachycardia responsible for syncope is best guided by pharmacologic testing in the electrophysiologic laboratory.[133-139] Predictive accuracy of therapeutic effectiveness due to antiarrhythmic agents is higher with electrophysiologic testing than with ambulatory monitoring or exercise testing. Empiric drug therapy, except for amiodarone, for ventricular tachycardia causing syncope appears to offer no benefit. Other

modalities of therapy for ventricular tachyarrhythmias include surgical ablative techniques guided by catheter mapping, antitachycardia pacing, automatic internal cardioverter-defibrillator (see Chap. 30), and catheter ablation (see Chap. 28). The operative risk is quite high with surgical ablation of tachycardia, although the success rate is also high. Antitachycardia pacing with defibrillation capability is an effective approach to tachycardia termination and prevention of sudden death.

Polymorphic ventricular tachycardia in the setting of a long QT interval (torsades de pointes) is often secondary to drug therapy, particularly antiarrhythmic drug use. The potential offending drug should be stopped. Acute therapy includes intravenous magnesium and measures to increase the heart rate and shorten electrical diastole (intravenous isoproterenol or cardiac pacing). Treatment of polymorphic ventricular tachycardia associated with a congenitally prolonged QT interval is discussed in Chap. 24.

Pacemaker-induced hypotension and syncope are rectified by changing from ventricular pacing to AV sequential pacing when hypotension due to loss of atrial transport or neurocardiogenic response is responsible for symptoms. Identification of pacemaker-mediated tachycardia usually requires only pacemaker programming changes. Pacemaker malfunction or myopotential inhibition requires a change in programming or replacement of the defective part of the system.

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SYNCOPE OF UNDETERMINED CAUSE

Despite careful diagnostic evaluation, the cause of syncope often cannot be defined. Unexplained syncope probably has a broad spectrum of etiologies. The varying mortality rate among patients with syncope of undetermined cause probably reflects the varying incidence of undetected cardiac syncope. A certain number of these patients probably have experienced syncope of multiple causes.

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SPECIAL PROBLEMS IN SYNCOPE

Syncope in the Elderly

Elderly persons are particularly prone to develop syncope or presyncope. The aging process can result in diminished cerebral oxygen delivery by a variety of physiologic mechanisms, including decreased cerebral blood flow from low cardiac output, cerebral vascular disease, decreased hemoglobin, and lower arterial P_{O_2} . In addition, cerebral arteriolar sclerosis may be present and may necessitate a normal arterial perfusion pressure. Thus, many older patients have only marginal cerebral oxygen delivery at rest.[140-143] Physiologic defenses against a fall in blood pressure may also be impaired as discussed previously.

The aged may also suffer from multiple sensory deficits (e.g., in vision, vestibular function, and peripheral sensory nerve function), variable degrees of dementia, bradykinesis, arthritis, and muscle weakness, all of which enhance the likelihood of a fall when cerebral perfusion is marginal. *Drop* attacks, in which muscle tone in the lower extremities is lost, are frequent in the elderly and must be distinguished from syncope. Carotid sinus hypersensitivity also is relatively common in the elderly, as is postprandial syncope; these entities should be evaluated as discussed previously. *The elderly frequently have multisystem disease and are likely to be taking several medications, sometimes in excessive amounts, that may aggravate the tendency to syncope* (*e.g., antihypertensive drugs, diuretics, vasodilators, antiarrhythmic drugs, or psychoactive drugs*).

Arrhythmias are common in elderly individuals, especially in those presenting with syncope. Syncope is a significant contributor to unexplained automobile accidents among the elderly and should be suspected when external causes are not apparent.[144-146]

In the elderly, syncope may be the presenting complaint for common disorders such as pneumonia, viral illness, acute myocardial infarction, or occult hemorrhage. Thus, the management of syncope in the aged often requires initial management of underlying diseases, with subsequent evaluation to determine whether such therapy controls syncope.

Multifactorial Syncope

In many instances, syncope requires that a constellation of events occur, either simultaneously or in sequence. Without the full complex, the patient may note only light-headedness or perhaps no definable symptoms. A carefully recorded history is required to elucidate such complex presentations.

Transient abnormalities such as fever, fatigue, hypoglycemia, or drug ingestion may increase the likelihood of syncope. Coexisting diseases may decrease the patient's physiologic defenses for maintaining adequate cerebral perfusion to sustain consciousness. A cardiac arrhythmia that ordinarily would not produce syncope may become a contributory factor when other predisposing factors are present (Fig. 32-4). With respect to combined causes of syncope, it is notable that, in the original description of Adams-Stokes syncope, the patients exhibited a permanently slow pulse rate accompanied by aortic stenosis.

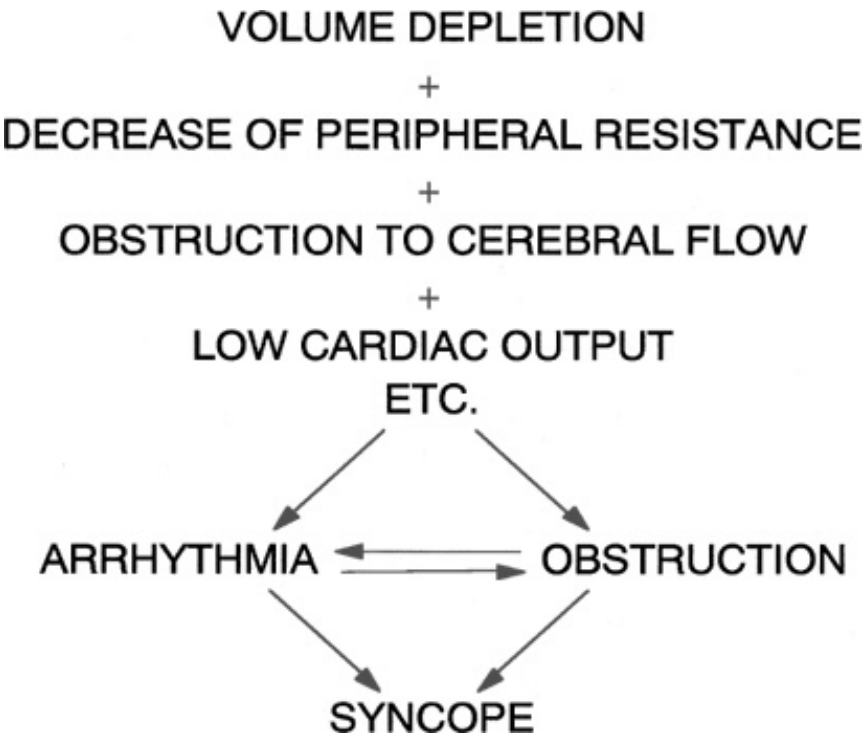

Figure 32-4: Frequently, multiple factors must be present simultaneously or in sequence for syncope to occur as a result of an arrhythmia or obstruction to cardiac output. (From Boudoulas H and Lewis RP.[159] Reproduced with permission from the publisher and authors.)

The development of the neurocardiogenic reaction may determine whether a given stimulus initiates syncope. This relationship has been shown in such diverse causes of syncope as aortic stenosis, vasodilator drug therapy, volume loss, pulmonary embolism, tachyarrhythmias, pacemaker syndrome, postprandial state in the elderly, and after exercise. A common pathophysiologic mechanism that may trigger neurocardiogenic syncope is diminished venous return to the right side of the heart.

Syncope and Sudden Death

Sudden death is common among those with known cardiac syncope (both obstructive and arrhythmic), but occasionally sudden death may also occur in presumptive noncardiac syncope and syncope of unknown cause. It would appear therefore that, in some patients, syncope is a harbinger of sudden death. Patients with advanced heart failure and syncope are at especially high risk for sudden death regardless of the etiology.[147-149] Syncope is also associated with a high mortality rate in patients with hypertrophic cardiomyopathy. It is not always clear to what extent the occurrence of syncope per se is a risk factor for sudden death or whether the risk is more related to the underlying disease.

Recurrent Syncope

In up to one-third of all patients with syncope, it is a recurring event. For most patients, the persistence of syncope increases morbidity from trauma but does not increase mortality. Such recurrences most often reflect a lack of effective therapy and/or a failure to establish the correct diagnosis.

Unexplained syncope in patients with negative initial diagnostic studies has a broad spectrum of etiologies, the most common of which is bradycardia. An implantable long-term monitoring device is useful for establishing a diagnosis when symptoms are recurrent but too infrequent for

conventional monitoring techniques.[114,115,150] Recurrent syncope is particularly common in a subset of patients with mitral valve prolapse in whom dysautonomia, arrhythmia, and hypovolemia all play a role.[93] In certain patients with unexplained recurrent syncope, especially in individuals with multiple physical symptoms, screening for psychiatric disorder may be necessary. In patients with recurrent syncope, advice regarding the avoidance of certain activities, such as working with dangerous equipment, is needed and, in some cases in which public safety is involved, a change in jobs is required (e.g., pilots or bus drivers).

Exercise and Syncope

Individuals with a history of syncope associated with activity and who participate in physical activities or competitive athletics constitute a special problem. Since exercise syncope may be a manifestation of serious underlying cardiac disease, complete evaluation is indicated to define the cause of syncope prior to recommendation for participation in sports. *Identification of myocardial abnormalities by physical examination and echocardiogram is paramount to the prevention of potential sudden cardiac death.*[151-158]

Syncope may occur during or immediately after exercise. The most common causes of exercise-induced syncope are shown in Fig. 32-5. Neurocardiogenic syncope is not uncommon in highly trained individuals with high resting vagal tone, but caution should be used in making this diagnosis without first excluding underlying structural myocardial abnormality. HUT studies can be used to assess patients at risk for neurocardiogenic syncope, but this test may lack sensitivity and specificity in highly trained individuals. Exercise testing is useful, especially if the syncope is exercise induced. Exercise-induced ventricular ectopy, sustained ventricular tachycardia, or rapid supraventricular tachycardia requires electrophysiologic evaluation and general cardiologic evaluation.

Final recommendation and advice to participate in sports with high, moderate, or low intensity should be individualized. Recommendations should be balanced between restricting activity unduly and reducing chance of death or injury from the participation in sports.

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DIAGNOSTIC EVALUATION OF SYNCOPE: AN OVERVIEW

In the initial approach to the diagnosis of syncope, it is essential to distinguish the underlying cause in terms of the three basic categories outlined in Table 32-1. This differentiation is accomplished in a majority of patients by a history (Fig. 32-6), physical examination (Fig. 32-7), and ECG (Fig. 32-8) and is supplemented by routine laboratory studies, including echocardiography (Fig. 32-9). Further, Figs. 32-5 and 32-10 provide a useful framework for initiating a diagnostic evaluation of syncope based on age and in situations when syncope is induced with physical activities.[159-164]

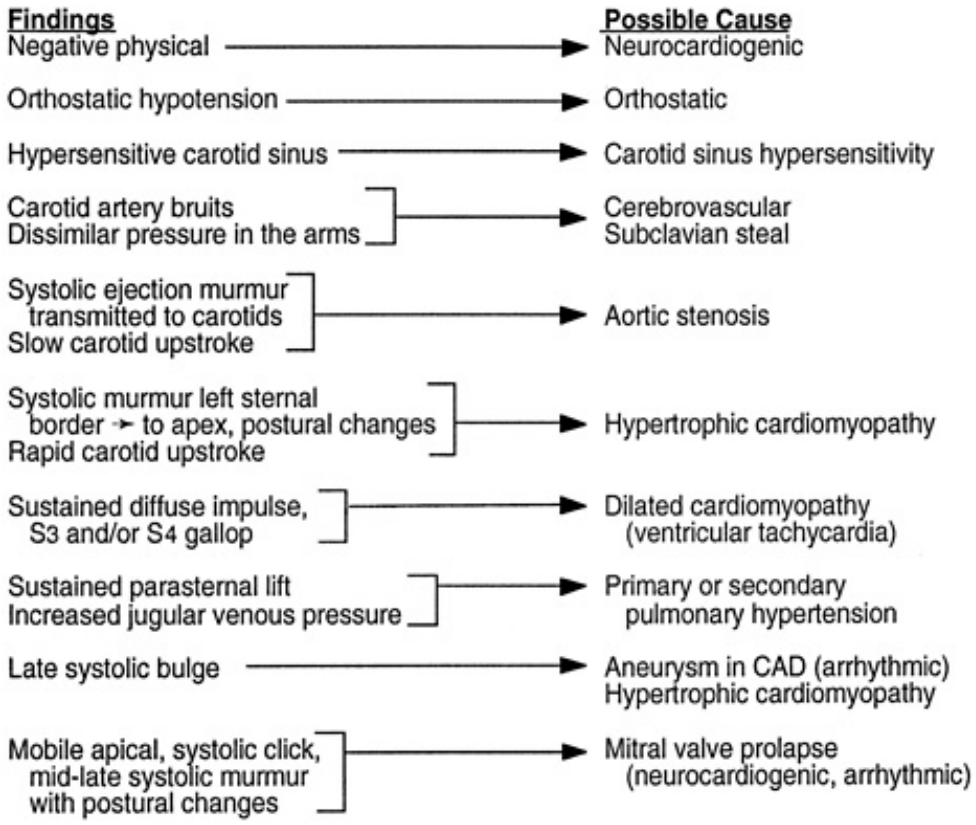

Figure 32-7: Differential diagnosis of syncope based on physical examination. CAD = coronary artery disease.

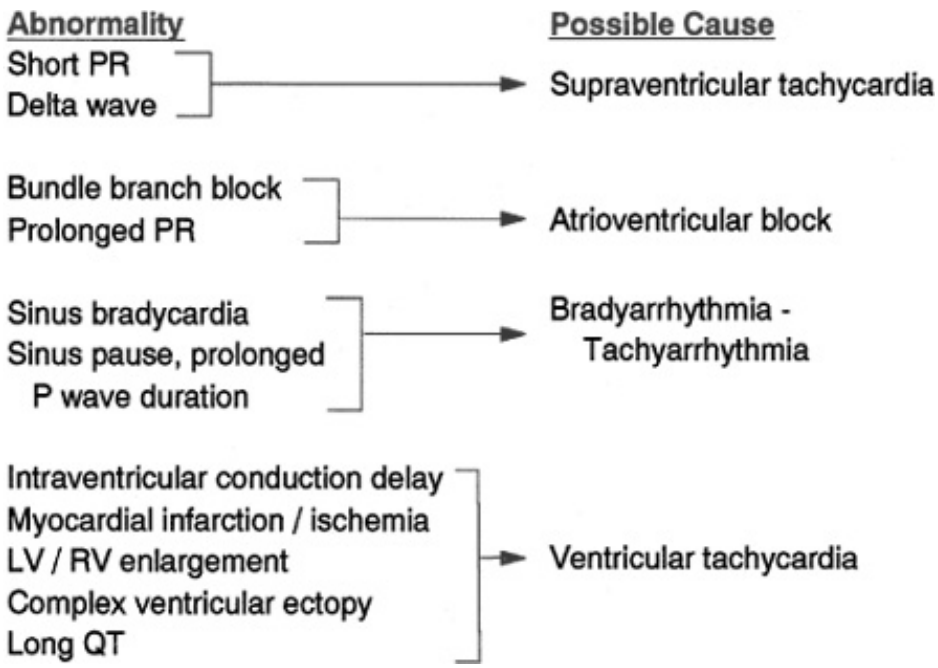

Figure 32-8: Differential diagnosis of syncope based on the electrocardiogram. LV/RV = left ventricular/right ventricular.

The extent of evaluation should initially be predicated on the estimation of mortality and morbidity risk, which is high in cardiac syncope or syncope associated with cardiac disease and low in syncope without structural heart disease. Although cost effectiveness in diagnostic testing should be practiced, the need for an assiduous search should not be dismissed when lethal disease is suspected.

Complete evaluation of syncope is required for the elderly and for patients with suspected arrhythmic syncope (Fig. 32-11). When patients in such a selected group undergo a thorough evaluation, including an electrophysiologic study, an arrhythmic basis for syncope can be found in the majority of patients. *Negative results are often as important as actual identification of an arrhythmia, since the negative evaluation usually denotes a favorable long-term prognosis.* Long-term follow-up suggests that both morbidity and mortality risks can be reduced by therapy guided by electrophysiologic study results. Unfortunately, no controlled studies exist (or are likely to be done) to establish these benefits conclusively.

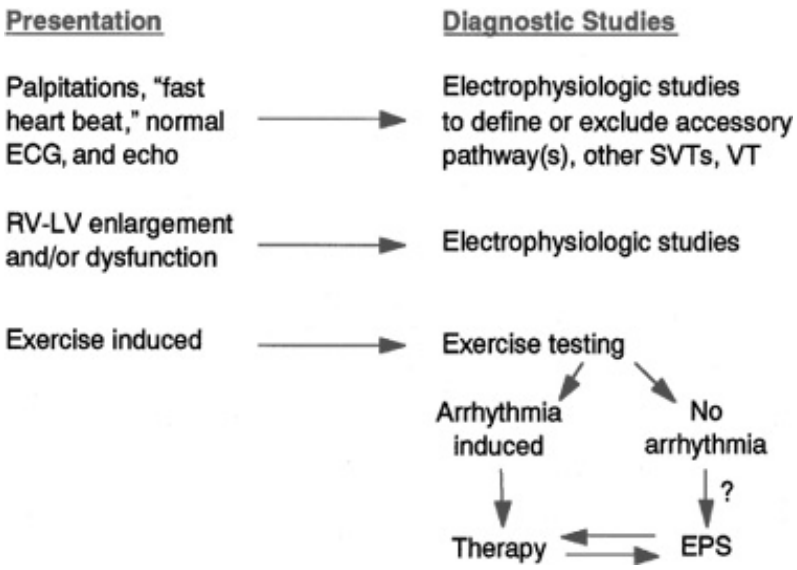

Figure 32-11: Diagnostic evaluation of patients with suspected arrhythmic syncope. RV-LV = right ventricular/left ventricular; SVT = supraventricular tachycardia; VT = ventricular tachycardia; ECG = electrocardiogram; ECHO = echocardiography; EPS = electrophysiologic studies.

The diagnostic evaluation of patients with syncope of unknown cause presents a perplexing problem, particularly when syncope occurs repeatedly and because it may be a harbinger of sudden death. As the understanding of the mechanisms and the breadth of causes of syncope improves (particularly the role of multiple causes), it is reasonable to suspect that the incidence of patients with syncope of unknown cause will be further diminished in the future. In certain cases, devices with extended monitoring capabilities can be used.

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Part 5: SYNCOPE, SUDDEN DEATH, AND CARDIOPULMONARY RESUSCITATION
Chapter 33:

SUDDEN CARDIAC DEATH

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DEFINITION OF SUDDEN CARDIAC DEATH

Sudden cardiac death describes the unexpected natural death due to a cardiac cause within a short time period from the onset of symptoms in a person without any prior condition that would appear fatal. It is most often due to a sustained ventricular tachyarrhythmia. Disparities in definitions have led to differences in the classification of deaths and have influenced the outcomes of studies looking at the incidence of sudden cardiac death.[1-11] The definition of sudden cardiac death should include the time interval from onset of the symptoms leading to collapse and then to death, the unexpected nature of the event, and the specific cause of death. Although many cardiovascular disorders increase the risk of sudden cardiac death, the presence or absence of preexisting cardiovascular disease is not necessary. More recent definitions have focused on time intervals of 1 h or less, which normally identify sudden cardiac death populations having a high proportion (up to 91 percent) of arrhythmic death.[12,13] The information necessary to establish a diagnosis of sudden cardiac death is often not available. For instance, up to 40 percent of sudden deaths are not witnessed, making a determination of the time of onset of symptoms to loss of consciousness impossible.[14-16] Prodromal symptoms such as palpitations, chest pain, and dyspnea may suggest a cardiovascular etiology such as arrhythmia, ischemia, or congestive heart failure but are not specific.[11,17]

Advances in emergency medical services, technological advances such as automatic external defibrillators, and community-based interventions have resulted in a contradiction in terms. Biologic death is an absolute and irreversible event, while patients can survive a cardiac arrest that would lead to sudden cardiac death if left untreated. Processes such as malignant arrhythmias, pump failure, and coronary ischemia that initiate the cascade of events leading to cardiovascular collapse can be modified, and the episode of sudden cardiac death can be averted. Ultimately, though, the distinction between sudden cardiac death, nonsudden cardiac death, and noncardiac death is relevant more from a historical perspective, and total mortality rate is a more definitive end point in assessing the efficacy of an intervention aimed at improving survival.

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Chapter 33: SUDDEN CARDIAC DEATH

EPIDEMIOLOGY

Incidence

Sudden cardiac death accounts for approximately 300,000 to 400,000 deaths yearly in the United States, depending on the definition used (Table 33-1).[1-11] When its definition is restricted to death less than 2 h from onset of symptoms, 12 percent of all natural deaths were sudden, and 88 percent of those were due to cardiac disease. In autopsy-based studies, a cardiac etiology of sudden death has been reported in 60 to 70 percent of sudden death victims.[15,16] Sudden cardiac death is the most common and often the first manifestation of coronary heart disease (CHD) and is responsible for half the deaths from cardiovascular disease, which remains the main cause of death in this country. In the Framingham Study,[1-3] a 26-year survey of 5128 subjects (age 30 to 62) without evidence of cardiac disease at entry, 13 percent of all natural deaths were sudden, accounting for 50 percent of the deaths from CHD. Fifty percent of sudden cardiac deaths in men and 64 percent in women occurred in people without known CHD. The proportion of sudden cardiac death was lower (20 to 34 percent) in patients with known CHD. Sudden cardiac death was the first symptom of CHD in 10 percent of all coronary events in men and 8 percent of those in women.

Table 33-1: Incidence of Sudden Cardiac Death in Selected Regional Population Studies

Study	Patient Population	Definition of Sudden Cardiac Death	SCD (CHD Deaths)	Annual Incidence of SCD (per 1000 population)	Known CHD, %	Proportion of CHD Deaths, %	Comments
Framingham,[1-3] 1948–1974	5128 M + F 30–62 years; no prior CHD	<1 h	M: 160 (350) F: 73 (196)	*Age:* *45–54* *55–64* *65–74* M: 1.1 2.7 2.6 F: 0.3 0.4 1.2	M: 50 F: 36	M: 46 F: 35	18% M (24% F) had SCD as first symptom of CHD
Tecumseh,[4] 1959–1965	M + F ≥30 years	<1 h		2.0	40	46	
Baltimore,[5,6] 1964–1965	M + F 40–64 years	<24 h, witnessed	661 (1098)	*<2 h* *2–24 h* M: 2.02 1.14 F: 0.39 0.34	51	60	
Allegheny,[7] 1970–1981	White M 35–44 years	<24 h, OOH, no disability	433		43	78	50% decline in CHD mortality, 77% due to decrease in SCD mortality
Worcester,[8] 1975–1988	M + F ≥25 years	OOH + ER		*1975* *1978* *1981* *1984* 2.65 1.74 1.70 1.48			
Minnesota,[9] 1970–1980	M + F 30–74 years	OOH + ER		*Year:* *1970* *1980* M: 3.11 2.44 F: 0.96 0.7	M: 26[a] F: 16	M: 67 F: 60	
40 U.S. states,[10] 1980–1985	M + F 35–74 years	OOH + ER	223,864 (399,324)	M: 1.91[b] F: 0.57	56	M: 60 F: 50	
Denmark,[11] 1982	M + F ≥25 years	<24 h	166	*Age:* *25–50* *50–69* *≥70* M: 1.1 2.7 2.6 F: 0.3 0.4 1.2	75	13% of all deaths (1309)	19% had no prodrome or known heart disease

[a]Acute myocardial infarction only.
[b]White population only.
ABBREVIATIONS: CHD = coronary heart disease; ER = emergency room; F = female; M = male; OOH = out-of-hospital; SCD = sudden cardiac death.

The overall annual incidence of sudden cardiac death in the United States is probably best estimated with data derived from the National Center for Health Statistics.[10] This data base from 40 states represents 71 percent of the U.S. population. Based on a combination of the place of death (out of hospital or emergency room) and diagnosis of CHD as an estimate of sudden cardiac death, the sudden cardiac death incidence in 1985 was 1.9 in men and 0.6 in women, resulting in 223,864 deaths of a total of 399,324 deaths from ischemic heart disease. Sudden cardiac death rates in developed countries outside the United States are comparable to those inside the United States. Using methods similar to those of the National Center for Health Statistics study,[10] the World Health Organization reported an annual incidence of sudden cardiac death of 1.9 in men and 0.6 in women, again accounting for nearly half the deaths from CHD in a surveillance study of 3.5 million men and women aged 20 to 64 years.[17] Sudden cardiac death rates in developing countries are considerably lower, paralleling the rates of ischemic heart disease as a whole (Fig. 33-1). In the United States, several populations-based studies have documented a decline (15 to 19 percent) in the incidence of sudden cardiac deaths caused by CHD since the early 1980s.[7,18]

Influence of Age, Race, and Gender

AGE

The incidence of sudden cardiac death increases with age in men and women as well as whites and nonwhites because of the higher prevalence of ischemic heart disease at older ages (Fig. 33-2).[3] Among sudden natural deaths, the proportion of cardiac causes increases with advancing age. Among patients with CHD, however, the proportion of coronary deaths that are sudden decreases with age.[1,3]

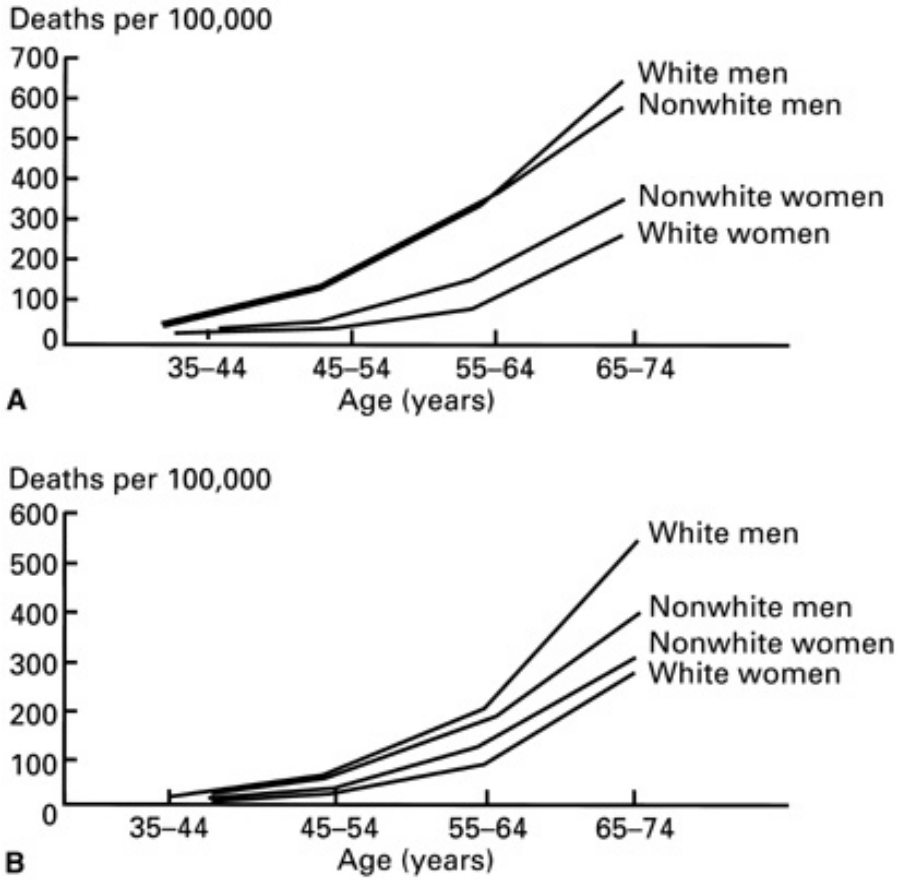

Figure 33-2: Plots of mortality rates (deaths per 100,000) for ischemic heart disease occurring (*A*) out of hospital or in emergency room (an estimate for sudden cardiac death rate) and (*B*) in the hospital, by age, gender, and race in 40 states during 1985. (From the National Center for Health Statistics. Reproduced from Gillum,[10] with permission.)

RACIAL DIFFERENCES

An analysis of cardiac death rates from 40 U.S. states between 1980 and 1985 showed that the rate of sudden coronary death is higher in blacks than in whites (men, 66 versus 61 percent; women, 56 versus 50 percent).[10] The annual age-adjusted incidence of sudden cardiac death in a cohort of 860 white and 117 black cardiac arrest victims in Seattle between 1984 and 1986 was also higher in blacks than in whites: 3.4 percent versus 1.6 percent per 1000 population (p <.001).[19] A similar difference was reported in an analysis of 6451 cardiac arrest victims in Chicago.[20] Not only was the sudden cardiac death rate higher, but the overall survival was also lower in blacks than in whites (10.2 percent versus 16.7 percent, p <.07, in Seattle, and 0.8 percent versus 2.6 percent, p <.001, in Chicago). In both studies, blacks were less likely to receive bystander cardiopulmonary resuscitation (CPR); however, differences in outcome could not be accounted for by differences in emergency medical team response time or administration of advanced cardiac life support. Possible explanations for these findings include limitations in access to preventive care, prehospital delays in patient activation of emergency medical services, and denial or self-treatment of prodromal symptoms. Blacks are also prescribed diuretics more often than whites, leading to an increased risk of hypokalemia and possibly sudden cardiac death.[2] These issues warrant further investigation.

GENDER

Sudden cardiac death has a much higher incidence in men than in women, reflecting gender differences in the incidence of CHD.[1-3] Between 70 and 89 percent of sudden cardiac deaths occur in men, and the annual incidence of sudden cardiac death in men is overall three to four times higher than in women. As is the case with coronary disease, however, this disparity decreases with advancing age, with a male-female ratio for sudden cardiac death of 7:1 in 45- to 64-year-olds and 2:1 in 65- to 74-year-olds.

A higher percentage (64 percent) of sudden cardiac death in women than in men (50 percent) occurs in patients without prior evidence of coronary heart disease.[3] Among survivors of cardiac arrest, women are more likely than men to have other forms of structural heart disease (valvular heart disease, 13 percent versus 5 percent; idiopathic dilated cardiomyopathy, 19 percent versus 10 percent) or a "normal" heart (10 percent versus 3 percent).[21]

SUDDEN CARDIAC DEATH IN THE YOUNG

Sudden cardiac death accounts for 19 percent of sudden deaths in children between 1 and 13 years of age and 30 percent between 14 and 21 years.[22] The overall incidence is low, 600 cases per year, compared with approximately 300,000 per year in the adult population. Structural cardiac abnormalities can be identified in over 90 percent of young victims of sudden cardiac death (Table 33-2).[22-34] About 40 percent of sudden cardiac deaths in the pediatric population occur in patients with surgically treated congenital cardiac abnormalities; in the majority of young victims, however, sudden cardiac death is often the first manifestation of underlying cardiac disease in otherwise healthy-appearing individuals.[35] The most common underlying pathologic conditions in people who die of sudden cardiac death in the first three decades of life are myocarditis, hypertrophic cardiomyopathy, congenital coronary artery anomalies, atherosclerotic coronary heart disease, conduction system abnormalities, congenital arrhythmogenic disorders, arrhythmias associated with mitral valve prolapse, and aortic dissection.

Among young people with sudden death and known congenital disease, aortic stenosis and primary or secondary pulmonary vascular obstruction were most common in patients without prior cardiac surgery, while tetralogy of Fallot and transposition of the great vessels were more common in postoperative patients.[35,36] Both ventricular arrhythmias and supraventricular tachyarrhythmias play important roles, the former being more important in tetralogy of Fallot and the latter, especially atrial flutter, in transposition of the great vessels[37-39] (see below).

Risk Factors for Sudden Cardiac Death

Only a fraction of patients survive an episode of sudden death, and there has been considerable interest in identifying the population at risk for sustained ventricular arrhythmias. More than 80 percent of sudden cardiac deaths occur in patients with underlying coronary disease, and the risk factors for sudden cardiac death largely reflect those for CHD (see Chap. 35). Left ventricular dysfunction and CHD confer the highest risk for sudden cardiac death.[40] In the Framingham Study, a multivariate model based on risk factors such as age, systolic blood pressure, left ventricular hypertrophy, intraventricular block or nonspecific abnormalities on the electrocardiogram (ECG), elevated serum cholesterol level, glucose intolerance, decreased vital capacity, smoking, relative weight, and heart rate found that 53 percent of men and 42 percent of women who were at risk for sudden death were in the upper decile of this analysis (Fig. 33-3).[1-3]

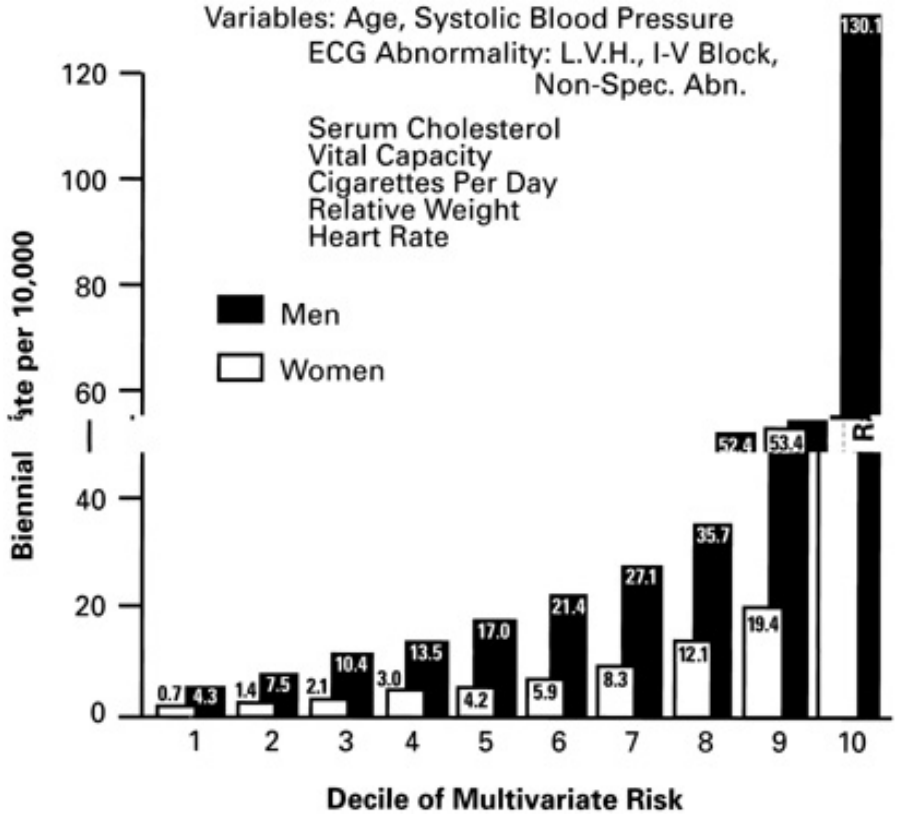

Figure 33-3: Risk of sudden cardiac death by decile of multivariate risk: 26-year follow-up, the Framingham Study. ECG, electrocardiographic; I-V, intraventricular; LVH, left ventricular hypertrophy; Non-Spec. Abn., nonspecific abnormality. (Reproduced from Kannel and Schatzkin,[2] with permission.)

Despite the fact that numerous population-based studies have shown a strong relationship between risk factors for CHD and sudden cardiac death, none of them has identified a single set of risk factors that are specific for sudden cardiac death (Table 33-3).[1,2,40-43] The inability to determine a profile based on coronary risk factors that is specific for sudden cardiac death reflects the fact that these factors are manifestations of chronic disease processes that create the structural basis for sustained arrhythmia. These structural abnormalities may be necessary but are not sufficient to cause an episode of sudden cardiac death. Triggers such as acute ischemia, alterations in hemodynamic status, electrolyte abnormalities, transient drug or toxin effects, or circadian variations in vasoconstriction, plaque stability, and thrombosis may precipitate an event.[44-46] A challenge for the future will be to identify these triggers so that patients at risk for malignant arrhythmias can be targeted for intervention.

LIFESTYLE FACTORS

Observations suggest that changes in lifestyle factors can be of potential importance in protecting patients with CHD from

dying suddenly.[1,2,47-57]

Alcohol

Individuals who consume high amounts of alcohol (more than 5 drinks per day) have increased risks of ventricular arrhythmia and sudden cardiac death. The relationship is less clear for drinkers of light to moderate amounts. A recent prospective analysis of 21,537 males in the Physicians Health Study demonstrated a decreased risk of sudden cardiac death. Men who consumed light to moderate amounts of alcohol (2 to 6 drinks per week) had a significantly reduced risk of sudden cardiac death compared with those who rarely or never consumed alcohol.[47,48]

Cigarette Smoking

Smoking is one of the few coronary risk factors that has been associated with a disproportionate number of sudden deaths as compared to coronary deaths. Smoking has been shown to induce physiologic changes that predispose to sudden cardiac death, such as increases in platelet adhesiveness, decreases in ventricular fibrillation threshold, acceleration of heart rate, increases in blood pressure, induction of coronary spasm, decreases in oxygen-carrying capacity of the circulation by accumulation of carboxyhemoglobin and impairment of myoglobin utilization, and short-term nicotine-induced catecholamine release.[49] A postmortem study linked smoking and the presence of acute coronary thrombus. Fresh thrombus was found in 59 of 113 men who died suddenly, and cigarette smoking was a risk factor in 75 percent of these men, compared with 41 percent of the men with stable plaques ($p < .001$).[50] In the Framingham Study, the annual incidence of sudden cardiac deaths increased from 13 per 1000 in nonsmokers to 31 per 1000 in those smoking more than 20 cigarettes per day.[1,2,49] People who stopped smoking had a prompt reduction in CHD mortality rate compared with those who continued to smoke, irrespective of the duration of previous smoking habits.[51]

Stress and Socioeconomic Status

There are many reports linking stress, particularly emotional stress, to sudden cardiac death.[52-54] For instance, in the hours following the Northridge earthquake in California in 1994, there was a more than fourfold increase in sudden cardiac death in patients with known or unknown CHD, illustrating the role of emotional stress as trigger for sudden cardiac death in this population.[55] Based on the difference of average and actual daily sudden cardiac death rates in that period, it was estimated that as many as 40 percent of sudden cardiac deaths are precipitated by emotional stress.

Socioeconomic factors, presumably associated with higher levels of stress, can also contribute to sudden cardiac death. For instance, a more than threefold increase of sudden cardiac death following myocardial infarction was reported in men with low levels of education and complex ventricular ectopy compared with better-educated men with the same arrhythmias.[56] In a study of sudden cardiac death in women, those who died suddenly were less often married, had fewer children, and had greater educational discrepancies with their spouses than did age-matched controls in the same neighborhood.[57]

Physical Activity

There is increasing evidence that regular physical activity may help prevent CHD and its complications.[2,58-62] On the other hand, the value of vigorous exercise in patients with known CHD is controversial, and several clinical and autopsy-based studies have reported triggering of sudden cardiac death and acute myocardial infarction by vigorous exercise.[63-66] Emergency medical records show that in adults, 11 to 17 percent of cardiac arrest victims collapsed during or immediately after exertion, although the amount of exertion is rarely quantified.[59] The increased risk of cardiac arrest due to ventricular fibrillation during or after exercise is also evident from cardiac rehabilitation programs and exercise stress testing in patients with heart disease. These studies are of selected patients with known heart disease who are already at risk for sudden death, but in these situations, cardiac arrests rates of 1 in 12,000 to 15,000 (rehabilitation) and 1 per 2000 (stress testing) have been reported. This rate is at least six times higher than the general incidence of sudden cardiac death for patients known to have heart disease.[59] Because of immediate and successful defibrillation in most cases, these reported cases of cardiac arrest have rarely been fatal. These observations, however, do support the concept that vigorous physical activity can trigger cardiac arrest due to ventricular fibrillation. On the other hand, there is increasing experimental evidence that regular exercise may prevent ischemia-induced ventricular fibrillation and death.[60,65] Thus, it appears that regular participation in moderate-intensity activities is associated with reduced rates of cardiovascular morbidity and mortality, while the risks of sudden cardiac death and myocardial infarction are transiently increased during acute bouts of high-intensity activity.

Sudden Cardiac Death in Competitive Athletes

Sudden cardiac death in competitive athletes is an extremely rare event. Between 10 and 25 sports-related sudden deaths from cardiac causes occur annually in the United States.[23] The annual incidence of sudden cardiac death during exercise is 1 per 200,000 in competitive high school athletes[29] and 1 per 250,000 among unscreened young runners.[67] Collapse usually occurs during or shortly after exercise, either in training or during competition. Although, unfortunately, sudden cardiac death is often the first manifestation of their disease, the majority of sudden cardiac deaths in athletes occur in persons with underlying cardiac disease.[24,68-70] Age has been shown to be the most useful variable in predicting the underlying cardiac disease (Fig. 33-4). In athletes below 35 years of age, the vast majority of sudden cardiac deaths arise from a variety of congenital cardiovascular diseases, most commonly hypertrophic cardiomyopathy (36 percent) and congenital coronary artery anomalies (19 percent).[69] Arrhythmogenic right ventricular dysplasia, myocarditis, arrhythmias associated with mitral valve prolapse, the Wolff-Parkinson-White syndrome, and aortic dissection are much less common. Coronary artery disease was present in 10 percent, compared with 80 percent in those older than 35 years.[68] Arrhythmogenic right ventricular dysplasia was the most common finding in a cohort from northern Italy, accounting for 22 percent.[71] Hypertrophic cardiomyopathy accounted for only 2 percent of sudden cardiac deaths in this population.[72]

Screening programs for identifying relatively rare cardiac abnormalities in a large population of asymptomatic athletes are often costly and inefficient.[73] Guidelines for such screening have therefore been published. They are based mainly on detailed personal and family history, physical examination, and ECG, with echocardiography and other noninvasive tests reserved for those with any positive finding during the initial evaluation.[74] Guidelines have also been published outlining which athletes with cardiac arrhythmias can participate in competitive athletics[74] (see also Chap. 85).

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Chapter 33: SUDDEN CARDIAC DEATH

MECHANISM OF SUDDEN CARDIAC DEATH

Relationship between Structure and Function in Sudden Cardiac Death

A vast majority of patients who have experienced sudden cardiac death have cardiac structural abnormalities. In the adult population, these consist predominantly of coronary heart disease, cardiomyopathies, valvular heart disease, and abnormalities of the conduction system. These structural changes provide the substrate for ventricular tachyarrhythmias that are the cause of sudden cardiac death in most cases. It is important to recognize the role of triggering factors, such as fluctuations in the autonomic nervous system, electrolyte abnormalities, and proarrhythmic effects of drugs in the initiation of ventricular arrhythmias resulting in sudden cardiac death (Fig. 33-5).[75,76] Strategies aimed at eliminating or reducing the triggers of arrhythmias may prove to be efficient short- and midterm solutions, since many of the structural abnormalities cannot be cured or require long-term risk-factor modification to prevent their development.

Tachyarrhythmias versus Bradyarrhythmias in Sudden Cardiac Death

Ventricular fibrillation is the first recorded rhythm in approximately 70 percent of patients who have cardiac arrest.[77,78] Sustained ventricular tachycardia is only rarely (less than 2 percent) documented as the initial rhythm, but it is unknown how often it precedes and precipitates ventricular fibrillation. In a series of 157 ambulatory patients who were wearing an ECG monitor at the time of their cardiac arrest, primary ventricular fibrillation was documented in 8 percent, ventricular tachycardia degenerating into ventricular fibrillation in 62 percent, and torsades de pointes in 13 percent.[79]

Electromechanical dissociation and asystole are found in about 30 percent of patients experiencing cardiac arrest, and this finding is usually related to the time interval from collapse to first monitoring of the rhythm, suggesting that it is a later manifestation of cardiac arrest.[77,78] The incidence of bradycardia as the first documented rhythm varies according to the population studied. In patients who have died suddenly while wearing an ambulatory ECG monitor, bradyarrhythmias as the initial rhythm were documented in 17 percent (26 of 231), but even in patients with preexisting atrioventricular or intraventricular conduction defects, ventricular tachyarrhythmias are most often the mode of recurrent cardiac arrest.[79,80] In a group of 21 patients with severe congestive heart failure awaiting cardiac transplantation, bradycardia or electromechanical dissociation was associated with 62 percent of sudden cardiac deaths.[81]

We believe that bradycardias reflect the failing heart and are not a significant cause of sudden death unless the bradyarrhythmia allows for the development of a tachyarrhythmia. Therefore, treatment of bradycardia may prevent the onset of tachyarrhythmias and is an important consideration in the prevention of sudden cardiac death. Since ventricular fibrillation is the most frequent cause of sudden cardiac death, understanding the mechanisms responsible for this arrhythmia is essential in its prevention and treatment. A complete discussion is beyond the scope of this chapter (see Chaps. 23 and 24).

Electrophysiologic Effects of Ischemia

The electrophysiologic effects of acute ischemia lead to a loss of membrane integrity, with efflux of potassium, influx of calcium, decrease in amplitude and upstroke velocity of the cardiac action potential, depolarization of the resting membrane potential, and shortening of action potential duration.[82] Within minutes of the onset of ischemia, the resting membrane depolarizes. This depolarization is inhomogenuous and is largely caused by local abnormalities in extracellular potassium levels and acidosis. Refractory periods in the ischemic zone and action potential duration shorten. Despite shortening of the action potential duration, fast sodium and slow calcium channels in partially depolarized fibers may remain inactive, thereby prolonging refractoriness, even after completion of repolarization. This postrepolarization refractoriness may further contribute to inhomogeneities in the electrophysiologic properties within and around the ischemic zone, causing significant conduction delays, unidirectional block, and reentrant arrhythmias. Subsequently, cellular uncoupling occurs after 20 to 25 min of ischemia, causing conduction to become slow and discontinuous.[83]

Ventricular arrhythmias during experimental acute ischemia occur in two peaks, one between 2 and 10 min following coronary occlusion and the second at 15 to 20 min. Rapid polymorphic ventricular tachycardias and ventricular fibrillation are the characteristic arrhythmias during the early stages of ischemia and are the cause of sudden cardiac death.[84] Activation mapping during ventricular fibrillation has demonstrated that the initial arrhythmias are due to reentry, which is facilitated by the inhomogeneous conduction velocities and refractory periods in and around the ischemic zone. The second peak of ventricular arrhythmias coincides with a peak in catecholamine release. Automatic and triggered rhythms have also been implicated in these arrhythmias. Ventricular arrhythmias can be a sign of reperfusion after thrombolysis, percutaneous revascularization, or spontaneous reperfusion. In addition, it appears that the rate, time, and degree of reperfusion influence the incidence, rate, and duration of these arrhythmias. More work is needed to further define these relationships.[85]

In the subacute phase of myocardial infarction (within the first 3 days), sudden cardiac death may occur due to ventricular fibrillation initiated by early, frequent premature ventricular complexes (PVCs). Such PVCs have been shown, in experimental models, to be predominantly due to abnormal impulse initiation consistent with abnormal automaticity. Other manifestations of abnormal automaticity are accelerated idioventricular rhythm and idioventricular tachycardia. These arrhythmias appear to arise, for the most part, from surviving Purkinje fibers in the subendocardial border zone of a transmural infarction. They have no prognostic significance for development of late arrhythmias and usually subside after 2 to 3 days at about the same time that the resting membrane potential and action potential duration of Purkinje fibers normalize.[82]

In the late phases following myocardial infarction, when the infarction is healed, reentrant excitation appears to be the principal mechanism of ventricular arrhythmias. Critical areas of the reentrant circuit are formed by surviving myocardial cells in the epicardial and endocardial border zone of a healed infarction as well as surviving intramural fibers within the infarct zone[84] (see also Chap. 23).

Mechanoelectrical Feedback

Left ventricular dysfunction has been identified as the strongest independent predictor of sudden cardiac death. Despite the clinical recognition that acute heart failure can precipitate ventricular tachyarrhythmias, the mechanism by which this occurs is incompletely understood. Besides mechanisms related to acute and chronic ischemia, it has been shown that acute changes in the mechanical state of the heart related to altered preload and contractility can have direct electrophysiologic effects that may precipitate arrhythmias; this relationship is usually referred to as mechanoelectrical feedback.[86] An increase in both left ventricular preload and contractility has been shown to shorten action potential duration in the canine ventricle.[86] An increase in right ventricular pressure has been shown to shorten action potential duration in humans.[87] The cellular

mechanism by which this occurs is unknown, but there is some evidence that these changes might be mediated by fluctuation of intracellular calcium levels.[86]

Role of the Autonomic Nervous System in the Genesis of Arrhythmias

There is increasing evidence that cardiac abnormalities associated with a high risk of sudden cardiac death are accompanied by changes in autonomic innervation of the heart. Myocardial infarction, for instance, has been shown to cause regional cardiac sympathetic and parasympathetic denervation.[88] The denervated areas show supersensitivity to catecholamine infusion, with disproportionate shortening of action potential duration and refractoriness.[89] This autonomic heterogeneity may predispose to arrhythmia development by creating dispersion of refractoriness and/or conduction.

Sensitivity to sympathetic activation favors the onset of life-threatening cardiac arrhythmias, while vagal activation has been shown to have a protective effect in the presence of tonic sympathetic stimulation.[90] This is thought to be due, at least in part, to the antiadrenergic effects of vagal stimulation via reduction of norepinephrine release and inhibition of adenylate cyclase via inhibitory G proteins. Because it is difficult to study the effects of vagal activity on ventricular electrophysiologic properties directly, the behavior of the sinus node has been used as a surrogate by measuring indices of heart rate variability (reflecting primarily tonic vagal activity) and evaluating baroreflex sensitivity (a measure of reflex vagal activity). In dogs, decreased baroreflex sensitivity is associated with an increased susceptibility to ventricular fibrillation and sudden cardiac death provoked by ischemia in a chronic (4-week) infarct model.[65] Myocardial infarction reduced baroreflex sensitivity 4 weeks after myocardial infarction in 73 percent of animals studied compared to control animals. A transient (less than 3 months) decrease in baroreflex sensitivity following myocardial infarction has also been demonstrated in humans.[91] The prognostic value of baroreflex sensitivity in humans has been suggested in several studies.[92,93]

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Chapter 33: SUDDEN CARDIAC DEATH

CARDIAC DISEASES ASSOCIATED WITH SUDDEN CARDIAC DEATH

Table 33-4 summarizes cardiac abnormalities associated with sudden death.

Ischemic Heart Disease

CORONARY ATHEROSCLEROSIS

In survivors of cardiac arrest, CHD is present in 40 to 86 percent of patients, depending on age and gender of the population.[94] There is ample evidence to support the concept that the electrical instability caused by acute ischemia is more important than infarction in the pathogenesis of sudden cardiac death. Although the majority of patients who suffer sudden cardiac death have severe multivessel coronary disease, fewer than half of the patients resuscitated from ventricular fibrillation evolve evidence of myocardial infarction by elevated cardiac enzymes, and less than 20 percent have Q-wave myocardial infarction.[77] Holter monitoring at the time of arrest has infrequently shown evidence of ischemic ECG changes before the event.[95-97] In postmortem examinations and in catheterization studies, there was a significant (75 to 85 percent) stenosis in at least two major coronary arteries in as many as 76 percent of patients. Detailed pathologic studies have confirmed the presence of acute coronary arterial lesions (plaque fissure, plaque hemorrhage, and thrombosis) in up to 95 percent of patients dying suddenly, but only a fraction had total occlusion.[50,66,98-100] Thus, the important observation is that sudden cardiac death can occur in the absence of infarction but is usually in the presence of diffuse coronary disease.[101]

Coronary collateralization may play an important role in the presentation of coronary artery disease as sudden cardiac death. Studies looking at occluded arteries demonstrated that minimally stenosed coronary arteries were a weaker stimulus for development of collaterals than were high-grade lesions.[102] This mitigating effect of coronary collateralization is further supported by a study of exercise testing in 894 healthy men followed for a mean of 12.7 years. In this study, the initial coronary event was acute myocardial infarction or sudden cardiac death in 73 percent of those with a normal stress test result, as opposed to 20 percent of those with an abnormal stress test result.[103] It has been hypothesized that chronic ischemia may be a stimulus for development of coronary collaterals, which in turn could have a protective effect during acute coronary occlusion. It should be noted that patients with silent ischemia during exercise testing have the same likelihood of developing an acute myocardial infarction or sudden cardiac death as do symptomatic patients.[104]

Since coronary artery disease is the major substrate of sudden cardiac death, risk stratification following myocardial infarction is an important step in the prevention of sudden cardiac death. Few variables, mainly, frequent PVCs (more than 10 per hour), nonsustained ventricular tachycardia, reduced left ventricular ejection fraction (less than 40 percent), and use of digitalis are independent risk factors for sudden versus nonsudden cardiac death following myocardial infarction.[105-109] The incidence of sudden cardiac death in the first 2 years after myocardial infarction ranged from 11 to 18 percent in these studies. Patients with both nonsustained ventricular tachycardia and left ventricular dysfunction have the worst prognosis.[109]

The variables identified to predict sudden cardiac death following myocardial infarction in these

studies are better in selecting a low-risk population for sudden cardiac death than in predicting who will go on to die suddenly. In the absence of frequent PVCs and with a normal left ventricular ejection fraction following myocardial infarction, the risk of sudden cardiac death is low (less than 2 percent in the first year).[110] Even when all clinical risk factors for sudden cardiac death are present following myocardial infarction, the reported risk varies between 10 and 40 percent and generally does not warrant prophylactic antiarrhythmic therapy. It is hoped that risk-stratification models incorporating other methods (e.g., heart rate variability, baroreflex sensitivity, nonlinear dynamics, T-wave alternans, and imaging of the cardiac autonomic innervation) of assessing such triggers of sudden cardiac death as autonomic fluctuations and electrical instability will enhance their positive predictive value (see also Chap. 42).

NONATHEROSCLEROTIC DISEASE OF THE CORONARY ARTERIES

Several nonatherosclerotic diseases of the coronary arteries are associated with increased risk of sudden cardiac death precipitated by cardiac ischemia. Congenital coronary artery anomalies, found in approximately 1 percent of all patients undergoing angiography and in 0.3 percent of patients undergoing autopsy, have been complicated by sudden cardiac death, often exercise-related, in up to about 30 percent of patients.[111] Origin of the left main coronary artery from the right aortic sinus or origin of the right coronary artery from the left coronary sinus were most frequently the cause. It has been postulated that acute ischemia is due to compression of the anomalous coronary artery between the pulmonary artery and aorta during exercise-induced expansion of these vessels and to diminished coronary flow reserve due to the slitlike orifice and acute takeoff angle of the anomalous vessel.[111]

Life-threatening ventricular arrhythmias and sudden cardiac death have been described in patients with coronary artery spasm (Prinzmetal's angina or variant angina). In a series of 81 patients with coronary artery spasm, 13 patients (16 percent) had at least one episode of cardiac arrest due to ventricular fibrillation.[112,113] Significant arrhythmias during attacks of variant angina were documented in 41 percent of these patients and appeared to be associated with a higher risk of sudden cardiac death. Calcium channel blockers are effective in many patients in preventing coronary spasm and appear also to protect from malignant ventricular arrhythmias if the attacks can be completely abolished.[112,113]

Sudden cardiac death has been described as a rare complication of coronary artery dissection in Marfan's syndrome, after labor and delivery, secondary to trauma or coronary catheterization, as a consequence of syphilitic aortitis, or as an extension of aortic dissection. Myocardial bridges have been reported in association with sudden cardiac death during exercise, but they are also an incidental finding at autopsy in up to 25 percent of patients dying of other causes.[114] Coronary arteritis and subsequent infarction have been reported in Kawasaki's disease, giant-cell arteritis, Beçhet's disease, systemic lupus erythematosus, and Churg-Strauss syndrome.[115-120]

Cardiomyopathies

IDIOPATHIC DILATED CARDIOMYOPATHY

Idiopathic dilated cardiomyopathy is the substrate for approximately 10 percent of sudden cardiac deaths in the adult population. The mortality rate for idiopathic dilated cardiomyopathy is high, reaching 10 to 50 percent annually, and seems most closely tied to the severity of pump dysfunction.[121] Mortality rates are higher among patients with advanced heart failure, but the proportion of sudden cardiac deaths is not increased.[122] In an overview of 14 studies including 1432 patients with idiopathic dilated cardiomyopathy, the mean mortality rate after a follow-up of 4 years was 42 percent, with 28 percent of deaths classified as sudden.[121] Sudden cardiac death in idiopathic dilated cardiomyopathy is usually attributed to both polymorphic and monomorphic

ventricular tachyarrhythmias occurring in the setting of a high frequency of complex ventricular ectopy.[123] The terminal event may, however, also be asystole or electromechanical dissociation, especially in patients with advanced left ventricular dysfunction.[81] Factors potentially contributing to the generation of arrhythmias in idiopathic dilated cardiomyopathy are mechanoelectrical feedback, electrolyte depletion due to chronic diuretic therapy, excessive activation of the sympathetic nervous and renin-angiotensin systems, and proarrhythmic effects of antiarrhythmic drugs.[124]

Risk stratification of patients with idiopathic dilated cardiomyopathy is difficult because there are few clinical predictors specific for sudden cardiac death.[125] The only clinical variable that identifies patients with a higher risk of sudden cardiac death is unexplained syncope, and these patients should undergo further evaluation.[121,126] A recent study looked at patients with implantable defibrillators, nonischemic dilated cardiomyopathy, and unexplained syncope with negative electrophysiologic test results. Fifty percent of the patients received appropriate shocks for ventricular arrhythmias within a mean of 10 ± 14 months from implantation.[127] Patients with idiopathic dilated cardiomyopathy have a very high incidence of ventricular ectopy, with simple PVCs, complex PVCs, and nonsustained ventricular tachycardia present in 94 percent, 76 percent, and 40 percent, respectively, thus limiting their prognostic value by a low specificity.[123] The prognostic value of intraventricular conduction delays on ECG, which are associated with decreased survival rates, is, again, not specific for sudden cardiac death, and late potentials recorded by signal-averaged ECGs can be detected only in a minority of patients with idiopathic dilated cardiomyopathy.[128] It is clear that induction of polymorphic ventricular tachycardia or fibrillation during electrophysiologic testing is nonspecific and that the absence of inducible ventricular tachyarrhythmias in this population does not accurately predict a low risk for sudden cardiac death[129] (see Chap. 66). In up to 40 percent of patients with nonischemic dilated cardiomyopathy, inducible monomorphic ventricular tachycardia can be due to a macro-reentry circuit, such as bundle-branch reentry, that is readily amenable to catheter ablation.[130]

HYPERTROPHIC CARDIOMYOPATHY

The incidence of sudden cardiac death in patients with hypertrophic cardiomyopathy (HCM) is 2 to 4 percent per year in adults and 4 to 6 percent per year in children and adolescents.[131] A review of 78 patients with HCM who died suddenly or survived a cardiac arrest episode showed that 71 percent were younger than 30 years of age, 54 percent were without functional limitation, and 61 percent were performing sedentary or minimal physical activity at the time of cardiac arrest.[132] The mechanism of sudden cardiac death in HCM is not clear. Primary arrhythmias, hemodynamic events with diminished stroke volume, and/or ischemia have been implicated.[131,133] It must be emphasized that atrial arrhythmias can lead to ischemia and hemodynamic compromise leading to sudden death in these patients. Assessment of autonomic function in patients with HCM revealed abnormal responses of heart rate and blood pressure to exercise in two-thirds, which was associated with a more malignant clinical course, suggesting that autonomic imbalance may be important in the genesis of sudden cardiac death in these patients.[134]

There are few predictors of sudden cardiac death in patients with HCM. A clinical history of spontaneous, sustained monomorphic VT or sudden death in family members indicates a worse prognosis, as does onset of symptoms in childhood.[132] Hemodynamic and echocardiographic variables such as left ventricular wall thickness or the presence of outflow tract obstruction are not useful in identifying patients at high risk for sudden cardiac death. Ambulatory ECG monitoring has been reported to be of some value in identifying patients with HCM at risk for sudden cardiac death.[135] The prognostic value of electrophysiologic study in the absence of spontaneous, sustained ventricular tachycardia is limited, and in fact the study itself may be dangerous. Sustained ventricular tachyarrhythmias, predominantly rapid polymorphic ventricular tachycardia,

have been induced in 27 to 43 percent of patients with HCM at electrophysiologic study, but their prognostic significance is controversial.[135] The predictive value of asymptomatic nonsustained ventricular tachycardia is also limited.[136] Paced electrogram fractionation in hypertrophic cardiomyopathy may be helpful in determining which patients are at risk for ventricular fibrillation.[137] The absence of inducible, sustained monomorphic ventricular tachyarrhythmias, absence of nonsustained ventricular tachycardia on ambulatory ECG, and no history of "impaired consciousness" (i.e., cardiac arrest or syncope) identified a subset (22 percent) of patients with HCM with a low (less than 1 percent) risk for sudden cardiac death.[136] A large number of mutations in genes coding for the β-myosin heavy chain, cardiac troponin T, cardiac troponin I, α-tropomyosin, myosin-binding protein C, and myosin light chains 1 and 2 in patients with HCM have been identified. Genotype-phenotype correlation studies have shown that mutations carry prognostic significance. Some mutations of the β-myosin heavy chain are associated with a benign prognosis, while other mutations are associated with a high incidence of sudden cardiac death. Mutations in cardiac troponin T are associated with a mild degree of hypertrophy but a high incidence of sudden cardiac death[139,140] (see Chaps. 62 and 67). As with most genetic disorders, the phenotypic expression of the same genetic abnormality is highly variable.

HYPERTENSIVE CARDIOMYOPATHY

Left ventricular hypertrophy has been identified as one of the strongest blood pressure-independent risk factors for sudden death, acute myocardial infarction, congestive heart failure, and other cardiovascular disease and deaths.[141-143] Hypertensive patients with left ventricular hypertrophy have a significantly greater prevalence of PVCs and complex ventricular arrhythmias than do patients without left ventricular hypertrophy or normotensive patients. In the Framingham Study, ECG evidence of left ventricular hypertrophy doubled the risk of sudden cardiac death. Echocardiographic studies showed an incremental risk for cardiovascular deaths of 1.73 in men and 2.12 in women for each 50 g increment in the index of left ventricular mass.[144] A possible mechanism for the increased mortality rate in patients with left ventricular hypertrophy is ventricular tachyarrhythmia.[141] Decreased coronary blood flow, flow reserve, and endothelial dysfunction may all be factors favoring the development of transient ischemia,[142] and long-term, repeated transient ischemic episodes could lead to interstitial fibrosis, which may underlie the arrhythmias in this population.[145] Other potential contributing factors to the increased risk of sudden cardiac death in hypertensive cardiomyopathy are the electrolyte disturbances associated with diuretic therapy of hypertension.[146,147] It remains to be shown that the reduction of hypertrophy or concomitant ventricular ectopy confers a clinical benefit that exceeds the one from the reduction of arterial pressure alone[143,148] (see also Chap. 51).

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

Arrhythmogenic right ventricular dysplasia (ARVD) is predominantly right ventricular cardiomyopathy characterized by fatty or fibrofatty replacement of myocardium. It is a rare cause of sudden cardiac death except in a few endemic regions.[31] Recurrent ventricular tachycardia with multiple left bundle-branch block morphologies typifies this disorder. It is a familial disorder in approximately 30 percent of cases, with an autosomal dominant mode of inheritance. The gene defect has been localized to chromosomes 1, 3, and 14.[149-152] In the fibrofatty variety, patchy myocarditis, programmed cell death, and/or congenital abnormalities of development appear to lead to myocardial atrophy and repair by fibrofatty replacement, which may become the basis for reentrant ventricular arrhythmia. The left ventricle and ventricular septum can be involved in 50 to 67 percent of cases, especially later in the course of the disease, and such involvement confers a poor prognosis.[153,154]

The electrocardiographic manifestations in sinus rhythm include T-wave inversion in V_1-V_3 or

complete or incomplete right bundle-branch block. Intraventricular conduction delay may produce a terminal notch on the QRS complex called an epsilon wave in approximately 50 percent of patients. The ventricular ectopy is usually of a left bundle-branch pattern, with a QRS axis between -90° and +110°, and generally arises from one of three sites of fatty degeneration. Called the triangle of dysplasia, these sites are the right ventricular outflow and inflow tract and apex. Any patient with frequent premature beats of a left bundle-branch morphology and left-axis deviation should be evaluated for this disorder.

In patients with ARVD, particularly at early stages of the disease, ventricular tachycardia is often precipitated by exercise, and its induction is usually found to be catecholamine sensitive at electrophysiologic study.[31,155] The course and prognosis of ARVD are highly variable and difficult to predict. The annual incidence of sudden cardiac death in ARVD has been estimated to be about 2 percent despite various treatments[156,157] (see Chap. 24).

Valvular Heart Disease

The risk of sudden cardiac death in asymptomatic patients with aortic stenosis or regurgitation appears to be low.[158,159] In contrast, in the presurgical era, sudden cardiac death was one of the three most common types of death in symptomatic patients with aortic stenosis, the other two being bacterial endocarditis and congestive heart failure.[160] There appears to be an increased risk of sudden cardiac death following aortic valve replacement for aortic stenosis or regurgitation.[161,162] In 831 patients receiving a Björk-Shiley prosthesis in the aortic (341 patients), mitral (345 patients), or double-valve (145 patients) position, the incidence of sudden cardiac death in the subgroups was 1.8 percent, 3.5 percent, and 4 percent, respectively, over a follow-up period of 7 years.[162] Malignant tachyarrhythmias have been suggested as the cause of sudden cardiac death in such patients, since the presence of PVCs is more frequent in patients who die suddenly than in those who die of other causes. Transient complete heart block is relatively common following both aortic (17.6 percent) and mitral (13 percent) valve replacement, pointing to bradyarrhythmias as the potential precipitating factor for sudden cardiac death[163] (see also Chap. 56).

MITRAL VALVE PROLAPSE

Whether or not mitral valve prolapse (MVP) is a cause of sudden cardiac death is controversial. The prevalence of MVP is so high (4 to 5 percent of the general population and up to 17 percent of young women) that its presence may just be a coincidental finding in victims of sudden cardiac death and not causally related.[164,165] The overall 8-year probability of survival in a group of 237 asymptomatic or minimally symptomatic patients with echocardiographically documented MVP who were prospectively followed was not significantly different from that for a matched control population.[165] On the other hand, MVP may not always be benign. MVP is the only structural cardiac disease found in a significant number of victims of sudden cardiac death, especially in the young female population.[28,166] Of course, they may have had a primary electrical disease unrelated to mitral valve prolapse.[167] Patients with MVP associated with mitral regurgitation and left ventricular dysfunction are clearly at higher risk for such complications as infective endocarditis, cerebroembolic events, and sudden cardiac death.[168,169] Some victims of sudden cardiac death with MVP, mild mitral regurgitation, and normal left ventricular function have been treated with antiarrhythmic agents, raising the possibility of proarrhythmia as the cause of death.

Ambulatory electrocardiography in patients with mitral valve prolapse who experienced sudden cardiac death suggests that, based on the increased incidence of complex ventricular ectopy, the cause of sudden cardiac death in patients with MVP is a ventricular tachyarrhythmia.[167] A prolonged QTc interval and changes in autonomic tone have also been related to sudden cardiac

death in patients with MVP.[170] Several risk factors for sudden cardiac death have been identified in asymptomatic or mildly symptomatic MVP patients without significant mitral regurgitation, including mitral valve annular circumference, thickness of the anterior and posterior mitral valve leaflets, presence and extent of endocardial plaque, and presence or absence of redundant mitral valve leaflets on M-mode echocardiography[165,170] (see Chap. 58).

Inflammatory and Infiltrative Myocardial Disease

Any inflammatory disease can cause sudden cardiac death due to either ventricular tachyarrhythmias or complete heart block. Histologic findings suggestive of myocarditis have been reported in 10 to 44 percent of young victims of sudden cardiac death (Table 33-2).[23] In adults, the diagnosis of myocarditis is made much less frequently, perhaps because of concurrent structural heart disease or because the late manifestations of the disease are indistinguishable from idiopathic dilated cardiomyopathy (see Chap. 69). In South America, however, myocarditis due to specific pathogens, such as Chagas' disease, is the most frequent cause of cardiomyopathy and related sudden cardiac death.[171] Patients with infective endocarditis may also be at risk for sudden cardiac death due to coronary emboli from valvular vegetations. More often, sudden cardiac death is caused by acute hemodynamic deterioration due to valvular failure. Intramyocardial abscesses can also precipitate ventricular tachycardia and lead to sudden cardiac death.

Infiltrative cardiomyopathies, such as primary or secondary amyloidosis, hemochromatosis, or sarcoidosis, have been associated with predominantly cardiac conduction defects but also ventricular tachyarrhythmias and sudden cardiac death. Ventricular tachycardia is sometimes the mode of presentation of sarcoidosis, can usually be reproduced by programmed electrical stimulation, and is associated with a high rate of recurrent arrhythmia and sudden cardiac death[172] (see also Chap. 68).

Congenital Heart Disease

An increased risk of sudden cardiac death due to an arrhythmia has been found predominantly in four congenital conditions: tetralogy of Fallot, transposition of the great vessels, aortic stenosis, and pulmonary vascular obstruction.[35] Patients who have undergone reparative surgery for tetralogy of Fallot have a reported risk of sudden cardiac death of 6 percent before age 20.[37,173,174] A QRS duration of 180 ms or more was found to be the most sensitive predictor of sudden cardiac death and ventricular tachyarrhythmias in 178 adults after repair of tetralogy of Fallot and correlated with other parameters of right ventricular volume overload.[174] Transposition of the great vessels (post-Mustard-Senning) is associated with a 2 to 8 percent rate of late sudden cardiac death, which is due in some cases to sinus node dysfunction and in others to ventricular tachyarrhythmias[38,39] (see Chap. 63). Sudden cardiac death is often (45 to 60 percent) the mode of death in patients with primary or secondary pulmonary hypertension (see Chap. 52). Death is often precipitated by general anesthesia, dehydration, exertion, or pregnancy. Any process that decreases systemic vascular resistance increases right-to-left shunting and decreases pulmonary flow. The resultant peripheral desaturation may trigger lethal arrhythmias and sudden cardiac death.[175] The sudden cardiac death risk in congenital aortic stenosis is estimated to be 1 percent and occurs predominantly in symptomatic patients with severe left ventricular hypertrophy. Ebstein's anomaly is frequently (up to 25 percent) associated with the presence of accessory pathways and the Wolff-Parkinson-White syndrome, which carries a small risk of sudden cardiac death (see below). Congenital heart block without associated structural heart disease occurs in 1 of 20,000 infants, and a moderate decrease in heart rate is usually well tolerated. A maternal risk factor is systemic lupus erythematosus. As previously noted, patients with severe bradycardia, however, have a tendency to develop ventricular arrhythmias. Pacemaker therapy has virtually eliminated the risk of sudden cardiac death in this population.[175]

Primary Electrical Abnormalities

LONG-QT SYNDROME

Sudden cardiac death is one of the hallmarks of the idiopathic long-QT syndrome (LQTS), a group of genetically distinct disorders each resulting from a mutation in one of six genes encoding cardiac ion channels or auxiliary ion-channel subunits.[176-178,341] The prolonged QT interval reflects abnormal prolongation of repolarization. Other characteristics of this disorder, in addition to prolonged (greater than 460 ms) QT interval, include abnormal T-wave contours, relative sinus bradycardia, a family history of early sudden death, a propensity for recurrent syncope, and sudden cardiac death due to polymorphic ventricular tachycardia (torsades de pointes) and ventricular fibrillation. Over 90 percent of the congenital forms of LQTS have been linked to six specific chromosomal defects, resulting in a genetically based classification (LQTS 1 through 6) with important functional and prognostic implications.[178]

The six defects have been mapped to chromosome *11p15.5* (LQTS1), chromosome *7q35-36* (LQTS2), chromosome *3p21-24* (LQTS3), chromosome *4q25-27* (LQT4), and chromosome *21* (LQTS5 and LQTS6). Several mutations have been identified in each gene, and this locus heterogeneity appears to be important prognostically. Defects in outward currents (potassium) or impaired inactivation of inward currents (sodium) can cause abnormal prolongation of the action potential repolarization, enhancing the propensity to develop early afterdepolarizations that may initiate arrhythmias[178] (see Chaps. 23 and 24). Recent data suggest that reentry due to transventricular heterogeneity is responsible for sustaining the arrhythmia.[179]

Five of these genes have been identified as encoding ion-channel proteins (LQTS1, LQTS2, LQTS3, LQTS5, and LQTS6). Four of them (LQTS1, LQTS2, LQTS5, and LQTS6) encode potassium channels. The gene products of LQTS1 and LQTS5 combine to form the slow delayed-rectifier potassium current, I_{K_S}. LQTS1, also referred to as KVLQT1, encodes the alpha subunit of the channel, and LQTS5, or KCNE1, encodes the beta subunit, called minK. Similarly, the products of LQTS2, known as HERG, and LQTS6, or KCNE2, combine to form the rapid delayed-rectifier potassium current, I_{K_r}. LQTS3, or SCN5A, encodes the cardiac sodium channel. The protein encoded by LQTS4 remains unknown.[180-183] Mutations in KVLQT1 account for approximately 50 percent of all cases of the LQTS. The congenital LQTS associated with deafness, or Jervell-Lange-Nielsen syndrome, appears to be caused by homozygous mutations of the KVLQT1 gene.[184]

Carriers of the LQT gene have been reported to have a 5 percent incidence of aborted sudden cardiac death and a 63 percent incidence of recurrent syncope.[177] The mean age at presentation was 24 years, and the annual incidences of sudden cardiac death and recurrent syncope were 1.3 percent and 8.6 percent, respectively, in a series of 196 patients enrolled in an international registry.[176] Multivariate analysis in the registry population identified female gender, congenital deafness, history of syncope, and a documented episode of torsades de pointes or ventricular fibrillation as independent risk factors for postenrollment syncope or sudden cardiac death.[176] Exercise-related cardiac events dominate the clinical picture of LQTS1 patients, and auditory stimuli tend to be a trigger for arrhythmic events in LQTS2 patients.[185] Echocardiographic studies have also been reported to reveal specific wall motion abnormalities associated with an increased risk (relative risk 2.75) of syncope and sudden cardiac death.[186] Genetic typing in the future may facilitate risk stratification, providing valuable information not only about the underlying abnormality but also about the expected severity of the disease and preferred therapy.[178]

WOLFF-PARKINSON-WHITE SYNDROME

The risk of sudden cardiac death in patients with Wolff-Parkinson-White syndrome is less than 1 per 1000 patient-years of follow-up.[187] Although a rare event, it is an important one to consider, since it usually occurs in otherwise healthy individuals and, in the era of catheter ablation of accessory pathways, is a curable cause of sudden cardiac death.[188] Almost all survivors of sudden cardiac death with Wolff-Parkinson-White syndrome have had symptomatic arrhythmias prior to the event, but up to 10 percent had sudden cardiac death as their first manifestation of the disease.[189-193] The mechanism of sudden cardiac death in most patients with this syndrome is presumably the development of atrial fibrillation with rapid ventricular rates due to conduction over an accessory pathway and subsequent degeneration into ventricular fibrillation. Sudden cardiac death survivors tend to have a higher prevalence of atrial fibrillation, multiple bypass tracts, and Atrioventricular Nodal Reentrant Tachycardia (AVNRT). There are no good predictors during sinus rhythm for the development of sudden death in these patients. Spontaneous or exercise-induced intermittent loss of preexitation is helpful in identifying patients who will have a slower ventricular response in atrial fibrillation. Loss of preexitation due to enhanced conduction through the atrioventricular node or other causes of antegrade block in the accessory pathway must be excluded for this finding to be reliable. The best predictor for development of ventricular fibrillation during atrial fibrillation is the spontaneous occurrence of a rapid ventricular response over the accessory pathway, with the shortest interval between preexcited ventricular beats (i.e., those conducted over the accessory pathway) being less than 220 ms.[188-192] Although this short RR interval is a highly sensitive marker, identifying virtually 100 percent of patients at high risk for ventricular fibrillation, its specificity is low, since this finding is present in approximately 20 percent of asymptomatic patients with Wolff-Parkinson-White syndrome[189] and 50 percent of those with mild to moderate symptoms due to atrioventricular reentrant tachycardia.[190] In symptomatic patients, an electrophysiologic study offers the opportunity to assess conduction properties of the accessory pathways, the propensity to develop tachyarrhythmias, and the possibility of curing the patient with catheter ablation at minimal risk. There is no proof that refractory period measurements predict sudden death in asymptomatic or symptomatic patients.

IDIOPATHIC VENTRICULAR TACHYCARDIA

Several distinct clinical or electrophysiologic patterns in patients with idiopathic monomorphic ventricular tachycardia have been described. Sudden cardiac death rarely occurs in these populations.[194] They include a reentrant form, known as verapamil-sensitive ventricular tachycardia or idiopathic left ventricular tachycardia, typically located in the region of the left posterior fascicle, an automatic form that may originate from either ventricle and paroxysmal or repetitive forms that originate from the right ventricular outflow tract. Eighty percent of cases of idiopathic ventricular tachycardias originate from the right ventricular outflow tract and typically have a left bundle-branch block with inferior axis pattern. These arrhythmias are sensitive to vagal maneuvers, such as administration of adenosine, and can be provoked by isoproterenol.[195] Ventricular tachycardia originating from the left ventricular outflow tract is uncommon. The reentrant form generally arises from the left inferior septum posteriorly and has a right bundle-branch block pattern with left-axis deviation but can arise more apically, in which case the axis is right and superior. Calcium channel blockers are effective in suppressing this arrhythmia, and vagal maneuvers, β-blockers, and lidocaine are usually ineffective.

In contrast, several types of idiopathic polymorphic ventricular tachycardias have been described and are associated with an unfavorable prognosis. These arrhythmias include idiopathic ventricular fibrillation (see below), torsades de pointes with a short coupling interval, and catecholaminergic polymorphic ventricular tachycardia. They can occur in sporadic or familial forms and are frequently but not uniformly associated with catecholamine release during physical or emotional stress. Patients with catecholaminergic polymorphous ventricular tachycardia have a favorable response to β-blocker therapy, while those with idiopathic ventricular fibrillation and

short-coupled torsades de pointes may not.[196]

Idiopathic Ventricular Fibrillation

Although the list of potential causes of sudden cardiac death continues to grow, a definite cause of sudden cardiac death cannot be established in approximately 1 percent of patients dying suddenly or after successful resuscitation from cardiac arrest.[197] These instances of sudden cardiac death without evident cause are presumed to be due to idiopathic ventricular fibrillation. The incidence of idiopathic ventricular fibrillation is higher in selected populations, such as younger patients (up to 14 percent in patients below 40 years of age) who had sudden cardiac death[198] or female survivors of sudden cardiac death unrelated to myocardial infarction (10 percent).[21] The risk of recurrent ventricular fibrillation in this young and otherwise healthy patient population ranges between 22 and 37 percent at 2 to 4 years.[197,199,200] In survivors of cardiac arrest due to idiopathic ventricular fibrillation, the diagnosis is made by exclusion if extensive cardiac workup (including physical examination, laboratory tests for acute myocardial infarction and electrolyte abnormalities, ECG, exercise test, echocardiographic study, cardiac catheterization, and electrophysiologic study to exclude significant conduction system abnormalities or accessory pathways) reveals no abnormality that is thought to account for the ventricular fibrillation episode. In a review of 54 published cases of presumed idiopathic ventricular fibrillation, patients were younger (mean age 36 ± 16 years) than those who had sudden cardiac death associated with structural heart disease, and there was a relatively higher proportion of women.[197] Noninvasive evaluation, including exercise testing and ambulatory ECG monitoring, may help confirm the diagnosis of idiopathic ventricular fibrillation in selected patients in whom rapid, nonsustained runs of polymorphic ventricular tachycardia can be documented. Unfortunately, such markers are present in fewer than half the patients with this disorder.[197,201] The prognostic role of electrophysiologic evaluation in these patients is controversial: sustained rapid polymorphic ventricular tachycardia or ventricular fibrillation is inducible in 38 to 75 percent of patients studied[197,200-202]; however, these arrhythmias are generally considered a nonspecific finding,[203,204] and noninducibility of ventricular fibrillation in this patient population did not predict a more favorable outcome.[200]

The syndrome of sudden cardiac death associated with right bundle-branch block and persistent ST-segment elevation in ECG leads V_1-V_3 in patients without demonstrable structural heart disease is known as the Brugada syndrome.[205] Symptomatic patients and those in whom ventricular tachycardia or ventricular fibrillation are inducible at the time of electrophysiologic study have a high incidence of sudden death.[206,207] This syndrome is genetically determined, and three mutations of the gene for the sodium channel SCN5A have been found in chromosome 3. These mutations are distinct from those identified in the LQTS and in right ventricular dysplasia.[208]

A sudden unexpected nocturnal death syndrome is described in young, apparently healthy males from Southeast Asia.[209] This syndrome is known among Asian-Pacific populations and has several names. The Thai describe it as *Lai Tai* (death during sleep). In the Philippines, it is known as *Bangungut* (to rise and moan in sleep followed by death) and as *Pokkuri* (unexpected sudden death at night) by the Japanese.[210] A majority of these patients have been found to have the electrocardiographic manifestations of the Brugada syndrome.[211,212]

In any case, it should be kept in mind that the diagnosis of "idiopathic" ventricular fibrillation is made by exclusion and therefore depends on the sensitivity of the diagnostic tests used. With the development and validation of new diagnostic tools, many forms of "idiopathic" sudden cardiac death in "structurally normal" hearts may have to be reclassified.

Drugs and Other Toxic Agents

PROARRHYTHMIA

The apparent paradox that antiarrhythmic agents can cause arrhythmias has been recognized since the introduction of quinidine in 1918.[213] The results of the Cardiac Arrhythmia Suppression Trial (CAST) showed an increased mortality rate in postinfarction patients treated with encainide, flecainide, and moricizine compared with placebo, despite effective antiarrhythmic efficacy as documented by the suppression of PVCs.[214] Besides antiarrhythmic drugs, many other agents with diverse actions have been implicated in the induction of tachyarrhythmias.[215] Among commonly used drugs associated with the risk of producing ventricular arrhythmias leading to sudden cardiac death are erythromycin, terfenadine, hismanal, pentamidine, and certain psychotropic drugs, such as tricyclic antidepressants and chlorpromazine, which generally affect repolarization. Phosphodiesterase inhibitors and other positive inotropic agents that increase intracellular calcium loading have also been shown to be proarrhythmic and to increase the risk of sudden cardiac death, despite their beneficial effects on hemodynamic parameters.[216] Suggested proarrhythmia mechanisms of classes Ia and III antiarrhythmic drugs-as well as psychotropic drugs, erythromycin, and pentamidine-include increased prolongation of refractoriness (QT interval of the ECG) and development of early afterdepolarizations[217] (Table 33-4). The initiation of the arrhythmia is often triggered by bradycardia or a characteristic "long-short" coupling interval that initiates a pause-dependent prolongation of the QT interval. The ventricular tachycardia in this setting has commonly a typical torsades de pointes morphology. This form of proarrhythmia may be facilitated by electrolyte abnormalities such as hypokalemia or hypomagnesemia. It is usually an early event during drug therapy (within 3 days), and concomitant therapy with digitalis and diuretic agents may predispose patients to this complication.[218] Since it is not possible to predict who will develop proarrhythmic effects, initiation of antiarrhythmic therapy in a telemetry unit is recommended (see Chaps. 23, 24, and 27).

A second mechanism of proarrhythmia, observed predominantly with class IC antiarrhythmic drugs such as flecainide and propafenone, appears to be associated with acute ischemic events and occurs more frequently in patients with ischemic cardiomyopathy.[219] It is believed that the antiarrhythmic drug exacerbates ischemia-induced myocardial conduction delays in an heterogeneous fashion and promotes reentrant ventricular tachycardias.[219]

COCAINE AND ALCOHOL

The increasingly widespread use of cocaine in the United States has led to the realization that this drug can precipitate life-threatening cardiac events, including sudden cardiac death. In a series of 41 survivors of cardiac arrest due to ventricular fibrillation in patients 18 to 35 years of age, one-third had ingested alcohol or drugs (cocaine, heroin, or tricyclic agents).[220] The combination of alcohol and cocaine is especially dangerous due to the generation of a unique metabolite, cocaethylene, that has enhanced cardiotoxicity.[221] Cocaine causes coronary vasoconstriction, increases cardiac sympathetic effects, and precipitates cardiac arrhythmias irrespective of the amount ingested, prior use, or whether there is an underlying cardiac abnormality.[222] The combination of increased oxygen demand due to sympathetic stimulation and diminished coronary flow due to vasoconstriction may precipitate ischemia-induced arrhythmias and sudden cardiac death (see Chap. 71).

ELECTROLYTE ABNORMALITIES

Hypokalemia is often found in patients during and following resuscitation from a cardiac arrest. Although it is often a secondary phenomenon due to catecholamine-induced potassium shift into the cells, primary hypokalemia can also be arrhythmogenic. There is an almost linear inverse

relationship between serum potassium concentration and the probability of ventricular tachycardia in patients with acute myocardial infarction.[223] A decrease in the extracellular potassium level hypopolarizes the resting membrane potential, shortens the plateau duration, prolongs the phase of rapid repolarization in ventricular fibers, and causes an increase in pacemaker activity in Purkinje cells, triggering ventricular arrhythmias.[224] These changes in repolarization may increase the dispersion of the recovery of excitability and facilitate reentrant ventricular arrhythmias.[224] Many of the electrophysiologic effects of hypokalemia are similar to those caused by digitalis and catecholamine stimulation, explaining the high risk of ventricular arrhythmias when a combination of these factors is present.

An association between magnesium deficiency and sudden cardiac death has been reported in humans, especially as a cofactor in drug-induced torsades de pointes.[225] Hypomagnesemia in humans is generally associated with congestive heart failure, digitalis use, chronic diuretic use, hypokalemia, and hypocalcemia, making it difficult to establish whether the hypomagnesemia alone caused the sudden cardiac death. Acute administration of magnesium has been successfully used in the treatment of drug-induced torsades de pointes, although hypomagnesemia is not usually documented in this situation.

Changes in intracellular concentration of calcium may also be arrhythmogenic.[224] An increase in intracellular calcium concentration causes oscillatory release of calcium from the sarcoplasmic reticulum and gives rise to delayed afterdepolarizations, which may lead subsequently to ventricular arrhythmias due to triggered activity. Increases in intracellular calcium are believed to play a significant role in arrhythmias associated with digitalis glycosides, catecholamine-induced ventricular tachycardia, reperfusion arrhythmias, and the proarrhythmic effect seen with phosphodiesterase inhibitors and other positive inotropic agents.

Several studies in patients with hypertension who received treatment with diuretics suggested an increased risk of sudden cardiac death due to therapy with non-potassium-sparing diuretics.[226] Drug-induced potassium or magnesium depletion leading to cardiac arrhythmias has been suggested as the underlying mechanism (see also Chap. 23).

Electrolyte abnormalities are thought to be the cause of sudden cardiac death in patients with severe eating disorders, such as anorexia nervosa and bulimia, or patients who are on liquid protein diets. Sudden cardiac death due to ventricular tachycardia related to prolongation of the QT interval has been reported in a few patients with anorexia nervosa and bulimia.[227] It is thought to account partially for the high fatality rate of this eating disorder.

PREVIOUS | NEXT

Chapter 33: SUDDEN CARDIAC DEATH

CLINICAL PRESENTATION AND MANAGEMENT OF THE PATIENT WITH CARDIAC ARREST

Out-of-Hospital Cardiac Arrest

Cardiac arrest is characterized by abrupt loss of consciousness that would uniformly lead to death in the absence of an acute intervention, although spontaneous reversions rarely occur. About 75 percent of cardiac arrests occur at home, and about two-thirds are witnessed.[14,228,229] Individuals who live alone and women appear more likely to have unwitnessed deaths.[230] The average age of cardiac arrest victims is around 65 years, and 70 to 80 percent are men.[229]

As discussed above, the most common mechanisms of cardiac arrest are ventricular tachyarrhythmias, followed by bradyarrhythmias, or asystole. The most important determinant of successful resuscitation is the time interval from cardiovascular collapse to initial intervention. Since most patients are found in ventricular fibrillation, the time to successful defibrillation is a key element in the acute management of the cardiac arrest victim (see also Chap. 34). The importance of early intervention is reflected in the "chain of survival" concept of emergency cardiac care systems: early access, early CPR, early defibrillation, and early advanced cardiac life support.[231] This concept has led to the development of tiered medical emergency systems in most urban areas. Following activation of the emergency call (911) system, the first response consists of the nearest emergency medical technicians or fire departments who are trained to provide basic CPR and defibrillation. The second response is by paramedics who are trained in advanced cardiac life support, including endotracheal intubation, intravenous medications, and additional defibrillation if necessary.

Initiation of bystander CPR by people trained in basic cardiac life support is another important element of early intervention and improves the chances of successful resuscitation. In an overview of 17 controlled studies of survival from out-of-hospital cardiac arrest, bystander CPR was associated with a greater than twofold odds ratio of survival (28 ± 16 percent of 5565 patients receiving bystander CPR versus 12 ± 11 percent of 8329 patients who did not).[231] The association between early CPR and improved survival appears to be related to the beneficial effects of CPR on ventricular fibrillation. The earlier CPR is performed, the greater the proportion of patients who are found in ventricular fibrillation as opposed to bradycardia or asystole.[78] Further, successful defibrillation is more likely when early CPR is performed. Community-based CPR training programs, such as those implemented in Seattle and Minneapolis, resulted in training of 20 to 25 percent of the adult population and have led to a higher likelihood of bystander CPR being administered in out-of-hospital cardiac arrest. The percentage of patients receiving bystander CPR varies in the communities studied between 8 and 54 percent, with an average around 30 percent.[229] A more efficient approach is targeted CPR training for persons who have an increased likelihood of having to perform CPR. It has been suggested that learning CPR be a mandatory course in high school, much like learning how to drive a car.[232]

In order to improve the time to initial defibrillation, early defibrillation by nonmedical personnel has been advocated. The widespread use of automatic external defibrillators has the potential to improve significantly the availability of early defibrillation.[231,233] These are relatively simple and inexpensive devices that have an automatic detection and treatment algorithm for ventricular

tachyarrhythmias, but whether widespread use of these devices will translate into improved overall mortality rates and quality of life remains to be determined. The addition of interposed abdominal compression to standard CPR techniques has been reported to improve the outcome, particularly in patients found in asystole or electromechanical dissociation.[234]

Although duration of arrest is the most important determinant of successful ventricular defibrillation, other factors should be kept in mind. It has been estimated that in humans only about 4 percent of the transthoracic current actually traverses the heart, the rest being shunted by the thoracic cage and lungs.[235] The transthoracic impedance is inversely proportional to the size of defibrillator patches and the force applied on the paddles. It also depends on the location of the paddles and the paddle-skin coupling material, and it decreases with the number of shocks applied.[236] To improve defibrillation efficacy, especially in individuals with large chests and expected high transthoracic impedance, the operator should use a gel, cream, or saline-soaked gauze between the paddles and the skin and press firmly on the largest hand-held paddles available; several successive shocks may be necessary.[237] Recent experimental evidence suggests that ischemia-triggered release of endogenous adenosine may have deleterious effects on the success of defibrillation.[238] Development of specific adenosine antagonists and their administration during CPR in patients found in ventricular fibrillation might further improve defibrillation success.

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Chapter 33: SUDDEN CARDIAC DEATH

SURVIVAL AND PROGNOSIS AFTER CARDIAC ARREST

Survival to hospital discharge after cardiac arrest varies from 1.4 to 28 percent.[77,78,229,239,240] Marked differences in survival rates following out-of-hospital cardiac arrest have been reported in different communities, being lowest in large cities such as New York (1.4 percent) and Chicago (4 percent)[196] and highest (28 percent) in Seattle, an urban community where many of the early intervention concepts have been pioneered.[241] The in-hospital mortality rate following successful resuscitation outside the hospital remains high, in the range of 30 to 50 percent[77,78,242] (Fig. 33-6). The most important factors associated with increased in-hospital mortality rates after out-of-hospital cardiac arrest are cardiogenic shock after defibrillation, age 60 years or greater, requirement of four or more shocks for defibrillation, absence of an acute myocardial infarction, and coma on admission to the hospital.[77,242]

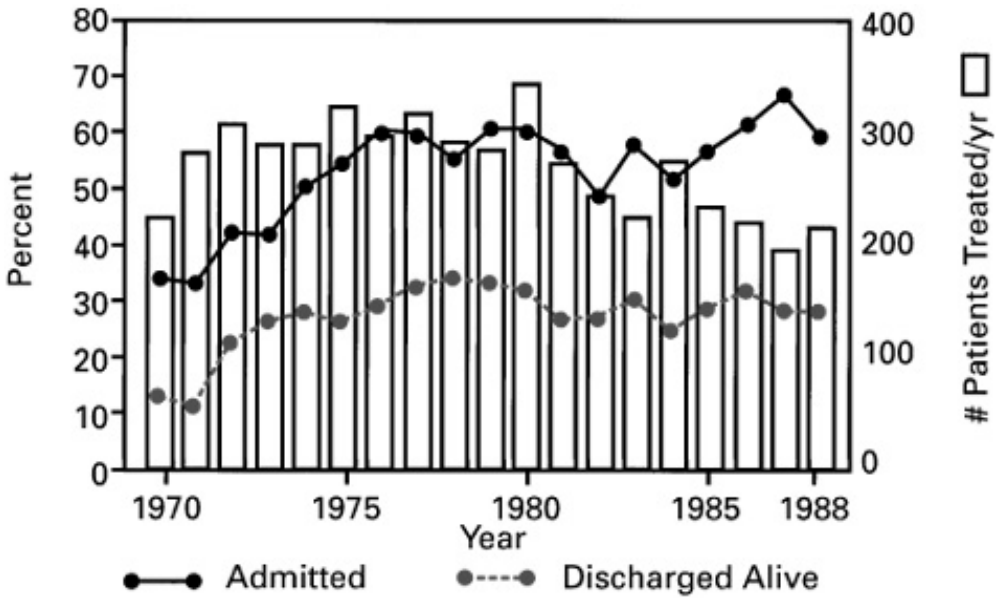

Figure 33-6: Percentage of out-of-hospital cardiac arrest victims admitted to the hospital by emergency medical service personnel and subsequently discharged alive during the period from 1970 to 1988. (From Cobb LA et al. Community-based interventions for sudden cardiac death: Impact, limitations, and changes. *Circulation* 1992; 85:I98-I102. Reproduced with permission from the publisher and authors.)

Survival depends largely on the initial recorded rhythm.[77,78,229,239,240] Some 40 to 60 percent of patients who are found in ventricular fibrillation are successfully resuscitated, but only about one-fourth of patients survive to be discharged from the hospital. The outcome is much better in the small (less than 7 percent) group of patients in whom ventricular tachycardia is the initial documented rhythm: 88 percent survive to the hospital and 76 percent are discharged alive. Bradycardias and electromechanical dissociation as the presenting rhythms are associated with the worst prognosis, and very few (less than 5 percent) of these patients survive to discharge from the hospital.[78] Other factors associated with improved survival are a low "comorbidity index,"

reflecting chronic conditions such as history of heart failure, diabetes, hypertension, and gastrointestinal disorders as well as recent symptoms prior to the event.[243]

An important consideration in the treatment of the cardiac arrest victim is the appropriateness of CPR and the use of life-sustaining therapies in patients with a low likelihood of survival, such as chronically ill people found in asystole or electromechanical dissociation. Their chances of surviving until hospital discharge are less than 1 percent. Further, many older people prefer to die suddenly rather than experience chronic suffering.[244] Advance directives, when available, and consultation with family members and personal physicians might aid in the difficult decision process of when to administer supportive care rather than aggressive management.

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Chapter 33: SUDDEN CARDIAC DEATH

MANAGEMENT OF CARDIAC ARREST SURVIVORS AND RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH

Establishing the Underlying Cardiac Pathology

The initial management following successful resuscitation from cardiac arrest consists of allowing a period of hemodynamic and respiratory stabilization, after which every effort should be made to establish the cause of cardiac arrest and likelihood of recurrence. For this, the underlying cardiac disease should first be determined. History and physical examination may provide the first clues. Myocardial infarction must be excluded by serial enzyme and electrocardiographic studies. Echocardiographic studies can determine left ventricular function, regional wall motion abnormalities, valvular heart disease, or cardiomyopathies. Stress-imaging studies can demonstrate inducible ischemia. Cardiac catheterization is often recommended to evaluate the coronary anatomy and right and left ventricular hemodynamic parameters. Other tests, such as radionuclide studies, magnetic resonance imaging, or cardiac biopsy, may be necessary in selected patients. As discussed above, an underlying cardiac disease can be found in nearly all patients.

PRIMARY VERSUS SECONDARY CARDIAC ARREST

One of the important questions following cardiac arrest is whether it was primarily due to acute circulatory or respiratory failure or to an arrhythmia. Although all these events are usually present during the arrest, it is important to distinguish whether the arrhythmia preceded or followed the hemodynamic collapse. While several clinical and historical clues help to answer this question (Table 33-5), the distinction sometimes cannot be made with certainty. Separating primary from secondary cardiac arrest has important prognostic and therapeutic consequences. In 142 survivors of cardiac arrest with coronary artery disease, the 1-year survival rate was 89 percent, 80 percent, and 71 percent in the patients classified as having had cardiac arrest secondary to acute myocardial infarction (44 percent of patients), secondary to an ischemic event (34 percent), or due to a primary arrhythmic event (22 percent), respectively.[96] Patients who present with cardiac arrest secondary (and within 48 h) to an acute transmural myocardial infarction have a prognosis similar to that of those who have an acute myocardial infarction without an arrhythmia.[77] Specific antiarrhythmic therapy is therefore usually not recommended if cardiac arrest occurs during or within 2 days of an acute Q-wave myocardial infarction. In contrast, if the arrhythmia is the primary event and myocardial infarction developed secondary to the acute hemodynamic deterioration during the arrhythmia, then antiarrhythmic therapy with a drug or device is recommended unless a transient or reversible cause is identified.[96]

Table 33-5: Differences in Clinical Status Immediately before Death in Patients Dying Primarily of Arrhythmia versus Circulatory Failure

Clinical Status Immediately before Death	Arrhythmic Deaths *n* = 82	Circulatory Failure Deaths *n* = 59
Comatose	0/82 (0%)	56/59 (95%)
Standing or actively moving	39/82 (48%)	0/59 (0%)
Terminal arrhythmia		
Ventricular fibrillation	15/18 (83%)	3/9 (33%)

Asystole	3/18 (17%)	6/9 (67%)
Duration of terminal illness		
<1 h	53/82 (65%)	4/59 (7%)
>24 h	17/82 (21%)	48/59 (81%)
Nature of terminal illness		
Acute cardiac events	80/82 (98%)	8/59 (14%)
Noncardiac events	1/82 (1%)	51/59 (86%)

SOURCE: Modified with permission from Hinkle et al.[13]

Every effort should be made to exclude potentially reversible causes of sudden cardiac death (Table 33-6), including transient ischemic episodes in patients who are candidates for complete revascularization and in whom the onset of the arrhythmia is clearly preceded by ischemic ECG changes or symptoms.

Table 33-6: Potentially Reversible Causes of Cardiac Arrest Due to Ventricular Fibrillation

Myocardial ischemia	Electrolyte abnormalities
Prinzmetal's angina	Hypoxia
Proarrhythmia	Acute congestive heart failure
Antiarrhythmic agents	
Other drugs	

Other reversible etiologies for cardiac arrest include transient severe electrolyte disturbances and proarrhythmic effects of antiarrhythmic drugs and other pharmacologic agents. It can be difficult to establish a causal relationship between the proarrhythmic agent and the malignant ventricular arrhythmia, as opposed to its being a coincidental finding. A pathologic prolongation of the QT_c interval preceding initiation of the arrhythmia and return of the QT_c interval to normal following discontinuation of the presumed proarrhythmic agent is strongly suggestive of a cause-effect relationship. Occasionally, especially when type IA agents are implicated in the cardiac arrest event, electrophysiologic evaluation, with programmed stimulation after washout and following reexposure to these agents, is necessary to confirm proarrhythmia as the sole cause of the episode of cardiac arrest. Another setting in which a reversible etiology for cardiac arrest is often present is in the hemodynamically unstable patient in the early postoperative period following cardiac surgery. Infusion of positive inotropic agents, electrolyte imbalances, and hypoxia are often precipitating factors.

Risk Stratification for Sudden Cardiac Death

Several clinical, noninvasive, and invasive strategies can aid in the risk stratification of patients for sudden cardiac death. The underlying cardiac disease largely determines the choice of appropriate testing.

CLINICAL HISTORY

Four independent prognostic variables for sudden cardiac death related to clinical history were identified in a study of 200 patients who suffered from ventricular fibrillation or sustained ventricular tachycardia following myocardial infarction: (1) cardiac arrest at the time of the first documented episode of arrhythmia, (2) New York Heart Association (NYHA) class III or IV, (3) ventricular fibrillation or ventricular tachycardia occurring early after myocardial infarction (3 days to 2 months), and (4) history of multiple previous myocardial infarctions.[245] Risk stratification for sudden cardiac death using these four variables can identify subgroups with a sudden cardiac death incidence ranging from 0 to 28 percent. It is noteworthy that patients with hemodynamically tolerated ventricular tachycardia occurring more than 2 months after myocardial infarction, a subgroup that constituted 40 percent of the study population, were reported to have a 0 percent incidence of sudden cardiac death at 26 months. Syncope in patients with a left ventricular ejection fraction below 30 percent is associated with increased risk of sudden cardiac death (about 50 percent at 3 years) irrespective of finding an arrhythmic cause.[246]

LEFT VENTRICULAR FUNCTION

Depressed left ventricular function is a major independent predictor of total and sudden cardiac mortality rates in patients with ischemic as well as nonischemic cardiomyopathy.[247-250] In survivors of cardiac arrest who have a left ventricular ejection fraction below 30 percent, the risk of sudden cardiac death exceeds 30 percent over 1 to 3 years if the patients do not have inducible ventricular tachycardia; it ranges between 15 and 50 percent in those who have inducible ventricular tachyarrhythmias despite therapy with drugs that suppressed the inducible arrhythmias or with empiric amiodarone.[251-253] Assessment of left ventricular function by clinical history (e.g., a history of congestive heart failure) and by other noninvasive methods (echocardiographic or radionuclide studies) or invasive means (angiography) is therefore essential in the evaluation of a patient at risk for sudden cardiac death.[248] Unfortunately, detection of severe left ventricular dysfunction serves to predict the total cardiac mortality rate but does not distinguish patients who will die suddenly from those who will die of progressive congestive heart failure.[124,248,249]

ELECTROCARDIOGRAPHIC ABNORMALITIES

In survivors of out-of-hospital cardiac arrest, the presence of atrioventricular block or intraventricular conduction defects on ambulatory ECG (72 h) is associated with a higher recurrence rate of cardiac arrest (10 of 14 patients versus 1 of 28 patients without).[78] Other ECG parameters that have been reported to be associated independently with an increased risk of sudden cardiac death are prolongation of the QT interval (in the absence of inherited or acquired long-QT syndrome),[254] increased dispersion of the QT interval,[255,256] and an increase in resting heart rate above 90, particularly in men without a history of coronary artery disease.[257]

Detection of nonsustained ventricular arrhythmias by ambulatory ECG monitoring has been reported to be of value in the risk stratification of patients for sudden cardiac death.[247,258-261] The incidence of sudden cardiac death in the 2 years following myocardial infarction in 766 patients enrolled in the Multicenter Post-Infarction Research Group increased with the frequency of PVCs detected during 24-h ECG monitoring from 3 percent for less than 1 per hour to 14 percent for more than 30 per hour; similarly, patients with nonsustained ventricular tachycardia runs had a higher (17 percent) incidence of sudden cardiac death than did those with single PVCs (6 percent).[247] The prognostic value of ambulatory ECG monitoring in patients with congestive heart failure is limited by the high incidence of these arrhythmias (up to 88 percent) in this population, resulting in a low specificity of this parameter.[262]

BAROREFLEX SENSITIVITY

Reduced baroreflex sensitivity, reflecting mainly an impairment in the vagal efferent component of the baroreceptor reflex, may help to predict cardiovascular mortality rates and arrhythmic events, particularly in patients following myocardial infarction.[91-93] In two prospective studies including a total of 200 patients following myocardial infarction, baroreflex sensitivity was significantly reduced in the 14 patients with sudden cardiac death or life-threatening arrhythmias compared to those without (less than 3 ms/mmHg

versus 8 ms/mmHg).[95,263] The prognostic significance of baroreflex sensitivity was not diminished in patients with reduced left ventricular function and carried the highest relative risk for arrhythmic events, superior to that of other prognostic variables, including left ventricular function.

HEART RATE VARIABILITY

Another noninvasive measure of sympathovagal balance is heart rate variability, beat-to-beat variations of RR intervals and their mathematically derived parameter. Several measures of heart rate variability have been reported to be associated with an increased risk of sudden and total cardiac death following myocardial infarction, underscoring the importance of the autonomic nervous system in the evolution of life-threatening arrhythmias.[261,264-266] In a study of 808 survivors of myocardial infarction, heart rate variability of less than 50 ms carried a 5.3 relative risk of death compared with the group with a heart rate variability of greater than 100 ms.[264] In a prospective study of 6693 nonselected and consecutive patients who underwent 24-h ambulatory ECG monitoring, those with a heart rate variability of less than 25 ms had a fourfold higher risk of sudden cardiac death than did patients with higher variability.[266] The sensitivity, specificity, positive predictive value, and relative risk in the prediction of arrhythmic events following myocardial infarction have been reported to be 60, 94, 55, and 10.4 for reduced heart rate variability [standard deviation of RR intervals (SDNN), less than 50 ms] and 80, 91, 44, and 23.1, respectively, for decreased baroreflex sensitivity (less than 3.0 ms/mmHg).[267] A prospective international study is in progress to assess the prognostic significance of diminished baroreflex sensitivity and heart rate variability 20 days after myocardial infarction in a large population.[268]

NONLINEAR DYNAMICS

According to the chaos theory, apparently irregular events such as ventricular ectopy are nonrandomly distributed in time, and their clustering can be quantified by fractal geometric analysis.[269] Fractal clustering of ventricular ectopy has been associated with sudden cardiac death in patients with mitral regurgitation and has also been demonstrated in other patients with life-threatening ventricular arrhythmias. The physiologic correlate for a low fractal dimension appears to be transient increases in cardiac sympathetic tone.[270]

T-WAVE ALTERNANS

Macroscopic T-wave changes with an alternating pattern have been observed in patients with long-QT syndrome prior to onset of ventricular fibrillation as well as in the setting of mechanical alternans, as is sometimes present during cardiac tamponade. Recent studies have indicated that T-wave alternans that is discernible only by computer-averaging techniques may be a more ubiquitous phenomenon that can identify patients at risk for ventricular arrhythmias.[271] Techniques for computer-assisted analysis of T-wave alternans are being developed and may provide a quantitative, noninvasive method for assessing susceptibility to ventricular fibrillation. T-wave alternans assessed by computer analysis has been shown to predict arrhythmia-free survival over 20 months, with a nearly 90 percent sensitivity and specificity in a small cohort of 66 patients[272] (see Chaps. 23 and 24). The positive predictive accuracy of this test appears to be similar to that of others with a very high negative predictive value.

LATE POTENTIALS

Late potentials, microvolt waveforms extending the duration of a filtered QRS complex detected by signal-averaging electrocardiography (SAECG), have been shown to be helpful in the risk stratification of patients following myocardial infarction. The prognostic significance of late potentials has been demonstrated in several studies, which reported a 17 to 29 percent incidence of sudden cardiac death, ventricular fibrillation, or sustained ventricular tachycardia in patients with an abnormal SAECG, in contrast to 0.8 to 3.5 percent in those without.[273] Although the negative predictive value of a normal SAECG is good, the application of SAECG in risk stratification for sudden cardiac death is limited by a low positive predictive value in patients following myocardial infarction as well as by its low sensitivity in patients with nonischemic cardiomyopathies[130,274,275] (see also Chap. 23). The sensitivity, specificity, and positive predictive value of SAECG are all improved when used in patients with known left ventricular dysfunction after myocardial infarction and/or nonsustained ventricular tachycardia.[275]

ELECTROPHYSIOLOGIC STUDIES

Electrophysiologic studies have advanced our understanding of life-threatening ventricular arrhythmias and facilitated the development of new therapies for their prevention and treatment. Induction of sustained monomorphic ventricular tachycardia is the generally accepted end point for programmed stimulation, while induction of nonsustained ventricular arrhythmias, polymorphic ventricular tachycardia, or ventricular fibrillation may be a nonspecific finding, depending on the aggressiveness of the stimulation protocol.[204,276] Information obtained during the electrophysiologic study-such as ventricular tachycardia rate, morphology, origin, mechanism, and hemodynamic stability-is crucial to determining whether the patient is a candidate for serial drug testing, catheter ablation therapy, surgical therapy, or an implantable defibrillator. In patients who present with sustained monomorphic ventricular tachycardia, ventricular tachycardia is reproducibly inducible in the vast majority, especially in those with coronary artery disease.[276] Electrophysiologic testing is also useful in patients with structural heart disease presenting with unexplained syncope. Ventricular tachycardia is the most common abnormal finding in these patients, but demonstration of His-Purkinje conduction disease or hemodynamically unstable supraventricular tachycardia can also be important. In patients with CHD, reduced left ventricular function, and documented nonsustained ventricular tachycardia, electrophysiologic studies can help select patients who would benefit from antiarrhythmic therapy. In survivors of cardiac arrest due to ventricular fibrillation, the prognostic value of electrophysiologic testing is less clear. Since sustained ventricular tachycardia or ventricular fibrillation is inducible in fewer than half the patients, suppression of induction of ventricular fibrillation by antiarrhythmic therapy is an unreliable end point, and even patients with no inducible ventricular arrhythmias remain at a high risk for recurrent cardiac arrest.[277,278] Nevertheless, in survivors of cardiac arrest, electrophysiologic study may reveal the mechanism of arrest, have prognostic significance, and help select an appropriate therapy.[279,280] The routine use of electrophysiologic testing following myocardial infarction and in patients with nonischemic cardiomyopathy is controversial, and the appropriate end points are unclear[277,281] (see Chap. 26).

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Chapter 33: SUDDEN CARDIAC DEATH

TREATMENT OPTIONS FOR PATIENTS AT RISK FOR SUDDEN CARDIAC DEATH

General Considerations

There are few direct and randomized comparisons of various treatment strategies to prevent sudden cardiac death. Since reduction of sudden cardiac death rates does not necessarily parallel a reduction in total mortality rate, reduction in total mortality rate is a more appropriate end point in assessing antiarrhythmic efficacy. Patient selection affects the outcome of different treatment strategies. For example, in patients at low risk of sudden cardiac death, proarrhythmia or procedural mortality rates may outweigh the benefits achieved with an antiarrhythmic intervention. On the other hand, in patients at high risk for recurrent cardiac arrest, the risk-benefit profile of antiarrhythmic treatment strategies may be more favorable. Selection of therapy is further limited by the patient's baseline characteristics. For instance, only patients with inducible sustained ventricular arrhythmias are good candidates for electrophysiologically guided antiarrhythmic drug therapy, and radiofrequency ablation of ventricular tachycardia is an option only in patients with hemodynamically stable monomorphic ventricular tachycardia or bundle-branch reentry. In an era of limited health care resources, the cost-effectiveness of different treatment strategies is another element to be considered in choosing therapy. Last but not least, quality of life is an important aspect in the selection of the most appropriate therapy.

Pharmacologic Therapy

BETA BLOCKERS

Of all the therapies currently available for the prevention of sudden cardiac death, none is more established or more effective in patients with coronary heart disease than beta blockers.[282,283] Although beta blockers are less effective in suppressing spontaneous or induced ventricular ectopy when compared with other membrane-active antiarrhythmic agents, both nonselective beta blockers (timolol and propranolol) and cardioselective agents (e.g., metoprolol) have been shown in placebo-controlled, randomized trials to reduce total mortality rates by 20 to 36 percent, in large part because of a reduction of sudden cardiac death.[283-286] The benefits of beta blockade are additive to those of standard treatment for congestive heart failure. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial demonstrated a 34 percent decrease in the mortality rate due to all causes, a 38 percent decrease in the cardiovascular mortality rate, and a 41 percent decrease in sudden death in 3991 patients who were randomized to beta blockers or placebo while being treated with standard medical therapy, including angiotensin-converting enzyme (ACE) inhibition, digitalis, and diuretics.[287]

In a review of 19,000 post-myocardial infarction patients who were randomized to beta blockers or placebo, active treatment was associated with a decrease in total mortality rate of 20 percent, of sudden cardiac death rate of 30 percent, and of reinfarction of 35 to 40 percent.[288] Beta blockers are effective in the setting of ventricular arrhythmias provoked by a high sympathetic tone, as in patients with congenital long-QT syndrome,[176] arrhythmogenic right ventricular dysplasia,[157] or congestive heart failure.[289] It is important to note that the beneficial effects of beta blockers on cardiac mortality rate are most pronounced in patients who are at higher risk for sudden cardiac death, such as patients with congestive heart failure, atrial and ventricular arrhythmias post-myocardial infarction, and diabetes[282] (see also Chaps. 23 and 42).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Vasodilator therapy is an effective treatment in patients with congestive heart failure and has been shown to reduce mortality rates by up to 40 percent in the first year.[290-292] The effect of ACE inhibitors on sudden cardiac death in established heart failure is less clear. In studies of patients with class I through IV congestive heart failure treated with ACE inhibitors or placebo, approximately 20 percent of patients died suddenly, without a significant difference in the sudden death mortality rate.[290-292] The situation is somewhat different in patients without heart failure in the post-myocardial infarction setting. Several trials have demonstrated a significant reduction in overall deaths in post-myocardial infarction patients (ejection fraction less than 35 percent) with or without mild heart failure. These studies have demonstrated a significant or trend toward a significant decrease in sudden cardiac death.[293-296] A recent metaanalysis analyzed 15 trials that included 15,104 post-myocardial infarction patients treated with ACE inhibitors. There were 900 sudden cardiac deaths in these studies, and a significant or trend toward significant reduction in sudden cardiac death in all of the larger (*n* >500) trials.[297]

CLASS I ANTIARRHYTHMIC DRUGS

The role of antiarrhythmic drug therapy in the prevention of sudden cardiac death has changed considerably since placebo-controlled trials such as Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that suppression of spontaneous nonsustained ventricular arrhythmias with certain drugs does not necessarily result in improved survival rates.[214] In CAST, type IC antiarrhythmic drugs, such as encainide, flecainide, and moricizine, were associated with excess deaths from arrhythmias in asymptomatic post-infarction patients with frequent ventricular ectopy despite effective suppression of spontaneous ventricular ectopy[214] (Table 33-7). These results were interpreted as being due to an excessive proarrhythmic effect, which outweighed the lower mortality risk of these patients. Whether the risk-benefit ratio between pro- and antiarrhythmic effect of antiarrhythmic drugs is different in other patient populations or with other antiarrhythmic drugs is not clear, since there are very few placebo-controlled, randomized trials with total mortality rate as an end point.

There is no evidence that other class I antiarrhythmic drugs can prolong survival in any patient group studied, and they may even be harmful. Results of a meta-analysis of empiric long-term antiarrhythmic therapy after myocardial infarction with mostly class I antiarrhythmic agents (mexiletine, phenytoin, tocainide, flecainide, encainide, procainamide, aprindine, imipramine, and moricizine) showed either no beneficial effects or detrimental effects on mortality rate despite effective reduction of PVCs.[298,299] A meta-analysis of lidocaine in acute myocardial infarction suggested an increase in in-hospital mortality rate despite a reduction in the prevalence of ventricular fibrillation.[300] Empiric use of these drugs in patients with sustained ventricular arrhythmias has been associated with a very high rate of sudden cardiac death, between 30 and 70 percent at 2 years.[301] In a randomized trial between electrophysiologically guided conventional (i.e., class I drugs) therapy versus empiric amiodarone in survivors of cardiac arrest (CASCADE), overall survival rates were lower in the conventional arm (78, 62, and 32 percent at 2, 4, and 6 years, respectively).[302] The propafenone arm was stopped early in the Cardiac Arrest Study-Hamburg (CASH) because of excess mortality rates in cardiac arrest survivors compared with amiodarone, beta blockers, and implantable defibrillators[303] (see also Chap. 24).

SOTALOL

Sotalol, in the currently marketed form of a racemic mixture of the *d*- and *l*-stereoisomers, is a potent class III antiarrhythmic agent with nonselective beta-blocking effects.[304] Sotalol has been reported to suppress inducible ventricular tachycardia in 30 to 40 percent of patients who present

with sustained ventricular arrhythmias. In a randomized trial of sotalol and other antiarrhythmic agents in patients with sustained ventricular tachycardia, the arrhythmia recurrence rate (21 percent at 1 year) and the arrhythmic death rate (12 percent at 4 years) was half of that achieved with class I agents.[305] However, since most patients receiving sotalol had failed other antiarrhythmic agents, the results were biased in favor of sotalol. The beta-blocking effect of sotalol seems to be essential for its benefit. The Survivor With Oral *d*-Sotalol (SWORD) trial of the *d*-isomer (class III antiarrhythmic effect only, devoid of beta-blocking effect) in patients with prior myocardial infarction was associated with increased mortality rates[306] (Table 33-7). The most serious side effect encountered with sotalol is proarrhythmia (mostly torsades de pointes), which has been reported to occur in up to 8 percent of treated patients.[303] In survivors of cardiac arrest, sotalol therapy was less effective than implantable cardioverter defibrillators.[307]

AMIODARONE

Amiodarone is widely considered the most effective antiarrhythmic agent for therapy of supraventricular and ventricular arrhythmias. It is a class III antiarrhythmic agent with additional class I, II, and IV properties and has unusual pharmacokinetics with a delayed onset of action and an elimination half-life of up to 53 days after chronic therapy[308] (see Chap. 27). In contrast to that of other antiarrhythmic agents, the long-term clinical efficacy of amiodarone is poorly predicted by the results of electrophysiologic evaluation.[252,253] Uncontrolled trials in patients with sustained ventricular tachycardia or ventricular fibrillation demonstrated a relatively low incidence of sudden cardiac death in patients treated with amiodarone, despite a high recurrence rate of ventricular arrhythmias. The sudden cardiac death rates at 1, 3, and 5 years in two series of 462 and 589 patients with mostly sustained ventricular arrhythmias were 9 percent, 15 to 16 percent, and 21 to 22 percent, respectively, whereas the arrhythmia recurrence rates were approximately 20 percent, 30 percent, and 40 percent during the same time period.[252,253] Again, the most important predictor of sudden cardiac death in patients treated with amiodarone for sustained ventricular tachycardia or ventricular fibrillation is left ventricular ejection fraction. In a series of 122 such patients with mostly coronary artery disease, the actuarial probability of sudden cardiac death at 5 years was 5 percent when the ejection fraction was greater than or equal to 40 percent and 49 percent when the ejection fraction was less than 40 percent.[309]

Amiodarone has been shown to reduce significantly sudden cardiac death rates following myocardial infarction in several placebo-controlled randomized studies, but its effects on the total mortality rate are inconsistent.[310] The Basel Antiarrhythmic Study of Infarct Survival (BASIS), a prospective randomized trial of empiric amiodarone, ambulatory ECG-guided conventional antiarrhythmic therapy, or placebo in 312 patients with complex ventricular ectopy following myocardial infarction showed that amiodarone significantly reduced the total mortality rate at 1 year from 13 percent in the placebo group to 5 percent in amiodarone-treated patients ($p < .05$).[311] On the other hand, amiodarone therapy did not reduce the total mortality rate compared with placebo in nearly 2700 post-myocardial infarction patients enrolled in the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[312] and the European Myocardial Infarction Amiodarone Trial (EMIAT),[313] despite a 50 percent risk reduction in the arrhythmic mortality rate (Table 33-7).

In patients with congestive heart failure who are at high risk for sudden cardiac death, prophylactic therapy with amiodarone was shown to decrease the mortality rate (by 28 percent) in the Argentinean Grupo de Estudio de la Sobrevida en la Insufficiencia Cardiaca en Argentina (GESICA) trial[314] but not in the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (STAT-CHF).[315] Comparison of the two patient populations and subgroup analysis suggested that prophylactic amiodarone may be more beneficial in patients with nonischemic cardiomyopathy, found in greater number in the GESICA study (Table 33-7). The consequence of these amiodarone trials is that this drug can be used safely in patients with left

ventricular dysfunction, and, in contrast to some class I agents, it does not increase mortality rates. Therefore, amiodarone is the drug of choice when antiarrhythmic drug treatment is indicated in patients with left ventricular dysfunction.

In patients who survived cardiac arrest not associated with myocardial infarction, empiric amiodarone therapy has been shown to be superior to electrophysiologically guided conventional therapy.[302] Rates for survival free of cardiac death, resuscitated cardiac arrest, and defibrillator shocks associated with syncope at 1, 3, and 5 years was 91 percent, 76 percent, and 63 percent, respectively, in the amiodarone-treated patients, compared with 77 percent, 56 percent, and 46 percent in the conventionally treated patients. The efficacy of amiodarone in reducing total mortality rates in patients with ventricular fibrillation or hemodynamically unstable ventricular tachycardia compared to implantable cardioverter-defibrillator (ICD) treatment has been evaluated prospectively in the randomized Amiodarone versus Implantable Defibrillator (AVID) study, which reported a survival benefit in the patients randomized to ICD therapy.[307] Prospective, randomized trials addressed a similar question in cardiac arrest survivors in the Canadian Implantable Defibrillator Study (CIDS)[316,317] and CASH[303,318] (see below).

Intravenous Amiodarone

Intravenous amiodarone in the United States remains a powerful parenteral drug for the acute treatment of patients with life-threatening ventricular arrhythmias.[319] The efficacy of intravenous amiodarone in patients with recurrent, hemodynamically unstable ventricular tachycardia refractory to lidocaine, procainamide, and bretylium is approximately 40 percent in prospective studies, and about 80 percent of the arrhythmias are suppressed within the first 48 h. A loading dose of 5 mg/kg over the first 30 min and a total dose of 1000 mg in the first 24 h is recommended. Additional boluses of 150 mg may be necessary for arrhythmia control.[320] Compared with bretylium, intravenous amiodarone was at least as effective and caused significantly less hypotension than did bretylium in 302 patients with recurrent or incessant ventricular arrhythmias refractory to lidocaine and procainamide[321] (see also Chaps. 24 and 27).

The use of intravenous amiodarone in out-of-hospital cardiac arrest was recently studied. Intravenous amiodarone was compared to placebo in 504 patients suffering out-of-hospital cardiac arrest that was refractory to three or more precordial shocks. Patients receiving 300 mg of intravenous amiodarone had an improved rate of survival to admission to the hospital as compared to placebo. Whether use of intravenous amiodarone confers a survival benefit remains to be determined.[322]

Device Therapy

AUTOMATIC IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

The ICD was initially developed to recognize ventricular fibrillation or rapid ventricular tachycardia and terminate it automatically by delivering one or more high-energy shocks.[323] Newer-generation defibrillators have the additional ability to deliver low-energy cardioversion, antitachycardia pacing for ventricular tachycardia, and antibradycardia pacing. In addition, the extended storage capabilities of new defibrillator systems permit retrospective analysis of the stored electrograms during arrhythmia detection, allowing more accurate conclusions about the type of arrhythmia recognized by the device (supraventricular or ventricular), their mode of initiation, and effects of additional antiarrhythmic therapy.

The first generation of epicardial defibrillators required a thoracotomy to place the sensing and defibrillator leads epicardially, and the generator size mandated implantation of the device in an abdominal pocket. The development of biphasic waveforms, "active cans" (the generator case

itself serves as a defibrillator electrode), and more efficient capacitors has made it possible to reduce the size of the defibrillators, which can now be implanted subpectorally with a transvenous endocardial lead system that integrates both pace-sense and high-voltage defibrillation abilities. Endocardial placement has reduced the perioperative mortality rate associated with defibrillator implants from 4 to 5 to less than 1.0 percent.[324]

ICDs are very effective in terminating ventricular tachyarrhythmias. In a large data base of 2834 epicardial and endocardial defibrillators implanted in 2807 patients between 1989 and 1993, 98.8 percent of 7470 ventricular fibrillation episodes were detected, and 97.9 percent of 42,132 ventricular tachycardia episodes were successfully terminated by the device.[324] The long-term outcome of patients with implantable defibrillators is also favorable, considering that virtually all patients receiving such devices are at high risk for sudden cardiac death, since they had either cardiac arrest or recurrent ventricular tachycardia refractory to medical therapy prior to implantation of the device. Defibrillator therapy has been shown to effectively reduce the annual incidence of sudden cardiac death in patients with severe underlying cardiac disease (less than 5 percent)[325,326] as well as in patients without significant structural heart disease (0 percent).[327] Despite effective reduction of the mortality rate from sudden cardiac death, however, long-term survival in patients with severely depressed left ventricular function is still poor despite defibrillatory therapy, and the overall cardiac mortality rate does not appear to be reduced in direct proportion to the reduction in sudden cardiac death.[328]

To investigate the potential benefit of ICD therapy compared with antiarrhythmic drug treatment in secondary prevention, the AVID, CASH, and CIDS studies randomized patients with documented sustained ventricular arrhythmia to one of these two treatment strategies. AVID and CIDS enrolled patients with ventricular fibrillation or poorly tolerated ventricular tachycardia and left ventricular dysfunction. In the AVID trial, which enrolled 1016 such patients, the ICD group had 38 and 25 percent reductions in the overall mortality rate at 1 and 3 years, respectively, compared to the group of patients taking amiodarone or sotalol.[307] CIDS enrolled 659 patients. Preliminary results after 1 year of follow-up were recently reported, and a 20 percent reduction in mortality rate with ICD was demonstrated.[317] CASH enrolled patients with cardiac arrest secondary to a ventricular arrhythmia regardless of the underlying disease or ventricular function. The final results have not yet been published, although a 2-year 39 percent reduction of the mortality rate due to all causes in the ICD arm compared with the drug arm (metoprolol or amiodarone) has been reported by the investigators.[318] These studies show that, compared to the best currently available antiarrhythmic drug therapy, ICDs improve survival rates in patients with a history of ventricular fibrillation or ventricular tachycardia (Table 33-7).

Several studies looking at the primary prevention or prophylactic use of defibrillators in high-risk populations have been completed (Table 33-7). The Multicenter Automatic Defibrillator Implantation Trial (MADIT)[329] demonstrated a survival benefit of defibrillator therapy compared with conventional therapy in patients who are post-myocardial infarction with nonsustained ventricular tachycardia, left ventricular dysfunction, and inducible sustained ventricular tachycardia that was not suppressed by procainamide. It has led to the approval of prophylactic implantation of defibrillators in this narrowly defined patient population. The Multicenter Unsustained Tachycardia Trial (MUSTT) was a randomized, controlled trial to test the hypothesis that electrophysiologically guided antiarrhythmic therapy would reduce the risk of sudden death among patients with coronary artery disease, a left ventricular ejection fraction of 40 percent or less, and asymptomatic, nonsustained ventricular tachycardia. Patients in whom sustained ventricular tachyarrhythmias were induced by programmed stimulation were assigned to receive either antiarrhythmic therapy, including drugs and implantable defibrillators, as indicated by the results of electrophysiologic testing, or no antiarrhythmic therapy. Electrophysiologically guided antiarrhythmic therapy with implantable defibrillators, but not with antiarrhythmic drugs, reduced the risk of sudden death in high-risk patients with coronary disease[330] (Fig. 33-7). The

Coronary Artery Bypass Graft (CABG) Patch trial enrolled patients with coronary artery disease scheduled for elective coronary artery bypass grafting (CABG) who also had a left ventricular ejection fraction of less than 30 percent and an abnormal SAECG. Nine hundred patients were randomized to receive either an ICD at the time of CABG or usual care and followed for a mean of 32 months. This study found no significant difference in the primary end point of total mortality at 30 days and a mean of 32 months.[331] The findings were not surprising in view of the known benefit of revascularization in preventing sudden cardiac death (see below) and the poor positive predictive value of the SAECG (Table 33-7).

The number of patients who could benefit from an ICD implant is increasingly larger due to the lower mortality and morbidity rates associated with the implantation of newer endocardial devices, which can be implanted with techniques similar to those of bradycardia pacemaker insertion. ICDs can effectively protect against both tachycardic and bradycardic sudden cardiac death regardless of the underlying heart disease or various triggers of arrhythmias. Since their mode of action is therapeutic rather than preventive, ICD therapy might effectively be combined with other antiarrhythmic strategies, such as drugs or catheter ablation, to prevent frequent recurrences of tachyarrhythmias. Despite the undisputed efficacy of implantable defibrillators in preventing sudden cardiac death, there are several major questions that remain to be answered: (1) Which patients will benefit most from defibrillator therapy?, (2) Do ICDs improve quality of life?, (3) Are ICDs cost-effective compared with antiarrhythmic drug therapy?, and (4) Will adjunctive antiarrhythmic drug therapy add to the efficacy of ICDs? (see also Chap. 30).

PERMANENT PACEMAKER

Permanent pacing appears to have a beneficial effect on survival in patients with congenital long-QT syndrome.[332,333] The beneficial effects of permanent pacing may be related to prevention of bradycardia and pauses, potentially contributing to a more homogeneous repolarization, as well as rate-dependent shortening of the QT_c interval in patients with mutation in the sodium channel gene (*SCN5A*)[178] (see Chap. 24). This is an unreliable approach and is unlikely to be used in the future due to the development of small, dual-chambered ICDs.

Patients with obstructive hypertrophic cardiomyopathy are at increased risk for sudden cardiac death may also benefit from pacemaker implantation. In a series of 84 patients with this condition who had severe, drug-refractory symptoms and a history of syncope in half the patients, only two sudden cardiac deaths occurred during the 2.5-year follow-up period after pacemaker implantation.[334] This approximately 1 percent annual mortality rate compares favorably with the annual incidence of sudden cardiac death in hypertrophic cardiomyopathy of 2 to 4 percent per year in adults and 4 to 6 percent per year in children and adolescents[134] demonstrated in previous studies. Most studies have shown a decrease in left ventricular outflow tract gradient, however, pacing may have deleterious effects on other hemodynamic parameters, and there are no controlled trials demonstrating improved survival[334,335] (see Chap. 67).

Role of Surgery

REVASCULARIZATION

There is a reduced prevalence of sudden cardiac death after CABG.[336,337] Among the 13,476 patients in the Coronary Artery Surgical Study (CASS) registry, all of whom had significant coronary artery disease, operable vessels, and no significant valvular disease, the mean incidence of sudden cardiac death during the 4.6-year average follow-up was 5.2 percent in patients treated medically and 1.8 percent in those treated surgically.[336] The beneficial effect of CABG was even more pronounced in the subgroup of patients with reduced left ventricular ejection fraction and

multivessel disease, where the survival rate free from sudden cardiac death at 5 years was 91 percent for the surgical group versus 69 percent in the medical group. CABG also seems to be beneficial in patients with cardiac arrest prior to hospitalization. In an uncontrolled study of 265 survivors of cardiac arrest, 32 percent underwent CABG and 68 percent were treated medically.[338] After adjusting for differences in baseline variables between the two treatment groups, the use of CABG was associated with a significant risk reduction in recurrent cardiac arrest (risk ratio 0.48, confidence interval 0.24 to 0.97). The protective effect of CABG against recurrent cardiac arrest appears to be best in patients with reversible ischemia as the major pathophysiologic factor in sudden cardiac death. These patients are characterized by critical coronary artery disease, significant regions of myocardium at risk for ischemia, and no inducible monomorphic ventricular arrhythmias at electrophysiologic study.[251,338] Despite the encouraging results of CABG in survivors of cardiac arrest, it should be noted that only a minority of these patients are candidates for operative revascularization and that monomorphic ventricular tachycardia, which is often associated with ventricular scars from healed myocardial infarctions, is usually not controlled by myocardial revascularization alone.[339]

ANTIARRHYTHMIA SURGERY

Electrophysiologically guided subendocardial resection and cryoablation are potentially curative surgical options in patients with recurrent monomorphic ventricular tachycardia in whom areas of slow conduction around myocardial scars are critical for sustaining ventricular tachycardia. Long-term follow-up of this operative technique has yielded a clinical success rate of nearly 90 percent in eliminating the presenting ventricular tachycardia in patients who survive surgery. The technique is limited, however, by the high surgical mortality rate of 10 to 15 percent.[340] These data, gathered in the 1980s, may exaggerate the operative risk, since current myocardial preservation is improved. We believe that the use of this therapy should be revisited. The best candidates for electrophysiologically guided subendocardial resection are patients who require coronary revascularization and have a well-defined left ventricular aneurysm.

Another surgical technique aimed at reducing sudden cardiac death rates in high-risk patients is left cardiac sympathetic denervation in the therapy of congenital long-QT syndrome.[341] The goal of this surgery is selective partial sympathetic denervation of the heart. In a review of 85 long-QT patients who continued to have recurrent syncope and cardiac arrest despite beta-blocker therapy and subsequently underwent left sympathectomy, the cardiac event rate was reduced from 22 ± 32 to 1 ± 3 per patient, and the number of patients with cardiac events decreased from 99 to 45 percent.[341] The rate of sudden cardiac death over a follow-up period of nearly 6 years was 8 percent (see also Chap. 24). This therapy, which, when successful, is almost always associated with development of Horner's syndrome, has fallen out of favor as a result of the evolution of ICD therapy.

CATHETER ABLATION THERAPY

Catheter ablation of arrhythmias has emerged as a curative approach for many supraventricular arrhythmias and a few specific forms of ventricular tachycardias.[188] The role of catheter ablation in the prevention of sudden cardiac death is less well established, but this therapy form has been successfully employed in selected cases. Rarely, supraventricular tachycardias with a rapid ventricular response may degenerate into fatal ventricular tachyarrhythmias and cardiac arrest.[342] Radiofrequency catheter ablation can eliminate the risk of a rapid ventricular response by abolishing conduction over an accessory pathway in patients with Wolff-Parkinson-White syndrome, or it can slow or completely block conduction over the atrioventricular node in patients with atrial arrhythmias and rapid, medically uncontrolled atrioventricular conduction.

Radiofrequency catheter ablation can potentially prevent sudden cardiac death in patients with

documented and inducible bundle-branch reentrant ventricular tachycardia as the only mechanism of cardiac arrest.[343] The role of catheter ablation in other forms of ventricular tachycardia is less well established. Catheter ablation of ventricular tachycardia in patients with structural heart disease is currently feasible in only a small subset of patients who present with a hemodynamically relatively well-tolerated monomorphic ventricular tachycardia.[344] Although the acute success rate in eliminating the index arrhythmia in a few specialized centers is near 60 percent, these patients often have extensive coronary heart disease, and other ventricular tachycardia morphologies recur frequently during follow-up, necessitating additional therapies.[345] Improved mapping techniques of the ventricular tachycardia circuit, better catheters, and perhaps other energy sources may help improve the efficacy of catheter ablation for ventricular tachycardia and potentially expand its role in the prevention of sudden cardiac death (see also Chap. 28).

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Chapter 33: SUDDEN CARDIAC DEATH

SUMMARY

Sudden cardiac death affects more than 300,000 individuals in the United States annually and accounts for half the mortality rate due to coronary heart disease. The vast majority of people who have experienced sudden cardiac death have underlying structural heart disease, which in the adult population is most frequently coronary heart disease, but a variety of other cardiac disorders can cause sudden cardiac death as well. Ventricular tachycardia and fibrillation and, less often, bradycardia and asystole are responsible for sudden cardiac death. Enhanced sympathetic tone appears to be important in triggering or predisposing to sudden cardiac death. Long-term survival following a cardiac arrest episode is still poor (less than 30 percent). The time delay to defibrillation and/or bystander administration of CPR directly influences survival. ICDs appear to be the most effective therapeutic option for treating survivors of cardiac arrest. Beta blockers and ACE inhibitors are helpful in the prevention of sudden cardiac death, in part through a reduction in the incidence of myocardial infarction. Proof for the use of other prophylactic medications, including antiarrhythmics, to prevent sudden cardiac death is inadequate. The most important factor limiting our ability to alter the incidence of sudden cardiac death is our inability to identify with acceptable sensitivity and specificity a large percentage of the individuals who experience sudden cardiac death. Short-term efforts to improve the survival of sudden cardiac death victims should be directed toward delivering CPR and electrical therapy as soon as possible after the onset of an arrest.[232] Long-term goals should be focused on the prevention of sudden cardiac death and encompass basically four interrelated, stepwise objectives:[232] (1) more accurate and specific identification of the patients at risk, (2) identification and characterization of mechanisms responsible for ventricular tachycardia-ventricular fibrillation, and bradycardia-asystole, (3) identification of interventions that prevent these arrhythmias, and (4) testing of these interventions in the individuals at risk.

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Part 5: SYNCOPE, SUDDEN DEATH, AND CARDIOPULMONARY RESUSCITATION
Chapter 34:

CARDIOPULMONARY RESUSCITATION AND THE SUBSEQUENT MANAGEMENT OF THE PATIENT

Authors: Nisha Chandra-Strobos, Myron L. Weisfeldt

INTRODUCTION: HISTORICAL ISSUES

Since biblical times, humans have attempted to restore life to the dead or nearly dead individual. The modern era of resuscitation began in the 1930s, when Wiggers pioneered the study of the mechanisms and treatment of ventricular fibrillation.[1] Major developments occurred in 1954, when Elam and colleagues showed that mouth-to-mouth or mouth-to-nose resuscitation was superior to the Schafer prone method of resuscitation in terms of efficacy of ventilation.[2,3] The importance of the circulation of blood was also recognized, and direct or internal cardiac massage became an accepted technique as early as 1916. Largely due to its complication rates and limited practical usefulness, it was replaced by noninvasive techniques of resuscitation.[4,5] In 1960, Kouwenhoven and coworkers developed the present technique of external chest compression in the supine position and coupled this with artificial respiration.[6] This technique of cardiopulmonary resuscitation (CPR) gained rapid popularity and was shown to be effective.[7] Only recently has the importance of prompt defibrillation taken a primary position in resuscitation efforts. Studies in large populations have confirmed that survival from prehospital cardiac arrest is dependent upon both prompt CPR and prompt defibrillation.

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MECHANISMS OF MOVEMENT OF BLOOD DURING CARDIOPULMONARY RESUSCITATION

The original hypothesis suggested that blood flow to the periphery during external chest compression resulted from direct compression of the heart between the sternum and the vertebral column.[6] According to this concept, chest compression ("systole"), similar to internal cardiac massage, resulted in blood being squeezed from both ventricles into the great arteries as the pulmonary and aortic valves opened.

Retrograde flow of blood was prevented by closure of the mitral and tricuspid valves. During the release phase of chest compression ("diastole"), the ventricles recoiled to their original shape and filled by a suction effect, while elevated arterial pressure was thought to close both the pulmonic and aortic valves.

This widely held concept is not, however, consistent with a number of observations in animal models[8] and humans[9]; these suggest a correlation between the rise in intrathoracic pressure during chest compression and the apparent magnitude of carotid flow and pressure. The importance of fluctuations in intrathoracic pressure as a means for generating blood flow is further supported by the observations of Criley et al. that, by the continuous and early initiation of coughing, patients in ventricular fibrillation can maintain consciousness as long as cough is continued.[10] The critical ingredient of the cough is clearly a rise in intrathoracic pressure, probably with no cardiac compression. Criley's observations strongly suggest that following cardiac arrest, a rise in intrathoracic pressure is a potent mechanism for the movement of blood to the brain in humans.[10]

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EXPERIMENTAL OBSERVATIONS

For brain blood flow to occur during CPR, a carotid arterial-to-jugular pressure gradient must be present during chest compression. In large animals, chest compression during CPR results in an essentially equal rise in central venous, right atrial, pulmonary artery, aortic, esophageal, and lateral pleural space pressures with no transcardiac gradient being developed (Fig. 34-1).[11]

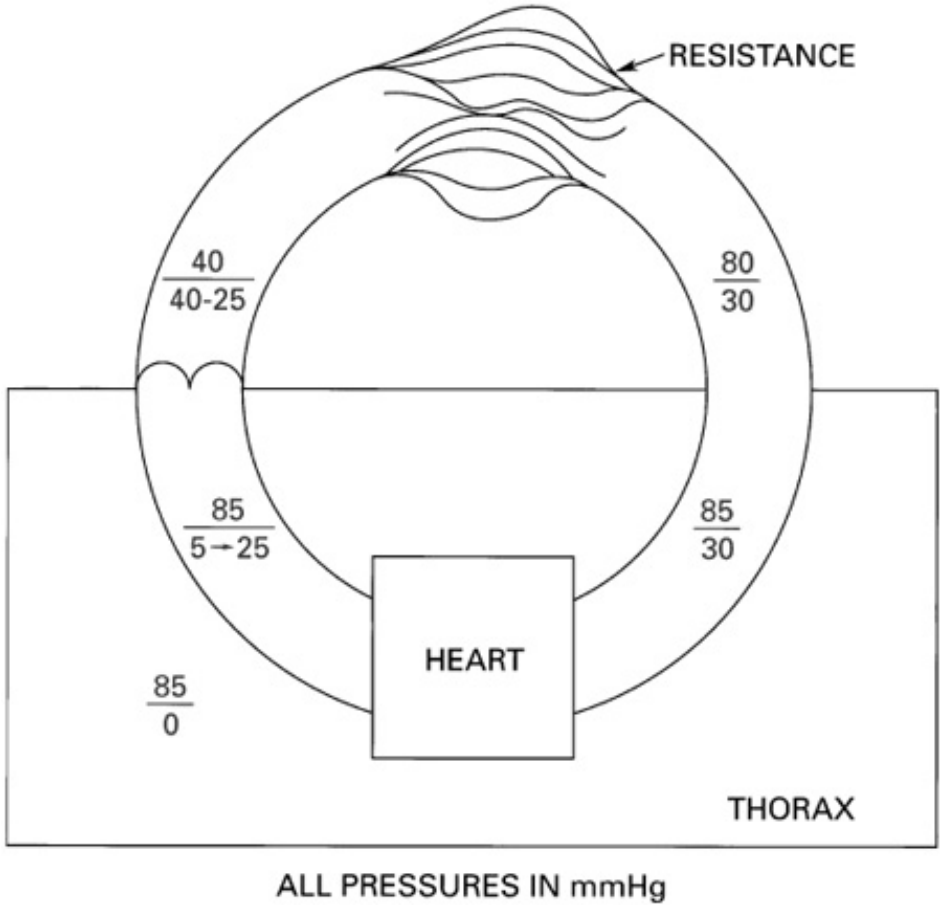

Figure 34-1: Representative pressures recorded during conventional cardiopulmonary resuscitation with forward carotid flow. Pressures are those recorded during compression. Intrathoracic pressures were indexed from esophageal pressures. There is no significant pressure gradient across the heart. The extrathoracic arterial pressure is similar to the intrathoracic aortic pressure. The extrathoracic venous pressure is markedly lower than the intrathoracic venous (right atrial) pressure. There is an extrathoracic arteriovenous pressure gradient that results in forward flow.

In large animals, aortic pressure is transmitted directly to the carotid arteries, but retrograde transmission of intrathoracic venous pressure into the jugular veins is prevented by valves at the thoracic inlet. Thus, during chest compression ("systole"), a peripheral arteriovenous pressure

gradient appears, and blood flow occurs consequent to this gradient. During compression, there is no pressure gradient across the heart; therefore, the heart cannot be the pump responsible for generating blood flow during CPR. In fact, the heart functions merely as a passive conduit. When chest compression is released ("diastole"), intrathoracic pressures fall toward zero, and venous flow into the right side of the heart and lungs occurs.

During diastole, a modest gradient also develops between the intrathoracic aorta and the right atrium and determines myocardial flow. Limited retrograde flow occurs into the aorta from extrathoracic arteries, raising aortic diastolic pressure and increasing coronary flow. The rise in intrathoracic pressure during chest compression is likely a consequence of airway collapse, which occurs at the level of the small bronchioles and results in air trapping. With the release of chest compression, this airway collapse is relieved.[12]

Unlike the hemodynamic pattern described above, in some animals intrathoracic vascular pressures during vigorous chest compression are much higher than pleural pressure.[13] In such animals, the rise in vascular pressures probably results from compression of the heart during chest compression, and the classic mechanism of direct cardiac compression is probably operating in these animals. Even during cardiac compression, however, venous valves at the thoracic inlet remain essential for establishing a peripheral arteriovenous pressure gradient, which facilitates peripheral flow. It is likely that flow produced by the two mechanisms operating simultaneously can occur, and in such situations the resultant flow is additive.

The position of the mitral valve during chest compression came to be regarded as a marker for the mechanism of blood flow during CPR, with mitral valve closure suggesting direct cardiac compression.[14] Some investigators, using transesophageal echocardiography, have demonstrated mitral valve closure during CPR in humans.[15] Others have reported that the mitral valve remains open during chest compression.[16] Animal studies have demonstrated that mitral valve closure or position cannot be used to identify the primary mechanism for blood flow during CPR.[17]

Studies of the perfusion of vital organs indicate that during CPR (irrespective of the primary mechanism for blood flow), cerebral flow is dependent on the gradient between the carotid artery and the intracranial pressure during systole, with myocardial flow being dependent on the gradient between the aorta and right atrium during diastole.[18]

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OBSERVATIONS IN HUMANS

Unfortunately, at this point we can draw no final conclusion as to the frequency or importance of the two mechanisms (cardiac compression or generalized increase in intrathoracic pressure) during conventional cardiopulmonary resuscitation in humans. Published studies, however, suggest that manipulation of intrathoracic pressure is probably the dominant mechanism.[19] In a number of patients, comparable arterial and right atrial pressures have been observed as well as the presence of a pressure gradient at the thoracic inlet upon withdrawing an intravascular catheter from the superior vena cava to the extrathoracic internal jugular vein.[11,20,21] This hemodynamic pattern favors the concept of forward flow of blood through manipulation of intrathoracic pressure. This concept is further strengthened by the observation that maneuvers designed to increase intrathoracic pressure during chest compression-such as prolonged compression or vest CPR-are rewarded by a significant increase in peripheral arterial pressure. Recent studies have also shown increased peripheral arterial pressures in man during CPR with the use of an inspiratory airflow resistance valve. Inspiratory resistance is designed to reduce "diastolic" intrathoracic pressure (during the release phase of chest compression) and thereby increase net intrathoracic pressure fluctuations.[23] Perhaps the strongest evidence supporting the theory of manipulation of intrathoracic pressure as a mechanism for blood flow in humans is found in the documented efficacy of "cough CPR."[10] In some patients, who are usually thin-chested, with cardiomegaly, extremely high arterial pressures are generated with conventional CPR. In a few of these patients, central venous pressure was found to be lower than arterial pressure. This hemodynamic picture suggests cardiac compression. In other patients, however, this higher arterial pressure may reflect higher generalized intrathoracic pressure during chest compression. This may be a result of functional airway obstruction due to airway collapse, pulmonary congestion, and/or bronchospasm.[12] In the majority of the patients in whom radial artery pressure has been measured during CPR, the arterial pressure has been relatively low and similar to that seen in the dog during conventional CPR.[19,20]

In human beings (and also in animals), it is not essential to think about the mechanisms of blood flow during CPR in an exclusive fashion. As the force of chest compression changes or as chest wall anatomy and chest compliance change during prolonged resuscitation, the dominant mechanism for blood flow (during resuscitation) may also change.

Building on these concepts, several experimental maneuvers and techniques have been developed to increase arterial pressure during chest compression. Following clinical evaluation, some are now being considered for limited clinical use. Some of these techniques require special equipment, whereas others can be performed by unequipped health care providers.

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EXPERIMENTAL AND ALTERNATIVE TECHNIQUES OF CARDIOPULMONARY RESUSCITATION

"High-impulse CPR" requires no special equipment and has been shown to improve vascular pressures.[13] It incorporates high-force, rapid down-thrust chest compression. However, clinical experience with this technique is limited.

Interposed abdominal compression (IAC) CPR can be performed by three unequipped health care providers. In this technique, the upper abdomen is compressed when the chest is released. The mechanism of benefit with IAC CPR in humans is unclear but may relate to improved venous return, decreased arterial runoff, or greater rise in intrathoracic pressure (with the diaphragm pushed up before chest compression). This technique increases carotid flow and improves survival in animals. Human clinical trials during in-hospital IAC CPR have also shown improved survival as compared with conventional CPR.[24] Based on these results, the 2000 American Heart Association (AHA) Guidelines for CPR suggest that IAC CPR be considered an alternative to conventional in-hospital CPR (class 2A recommendation).[25] The clinical value of this technique in the prehospital arrest patient, however, remains unproven.

Recently, the technique of phased chest and abdominal compression-decompression has also undergone animal and clinical testing. This technique is a mechanized IAC CPR in which the rescuer uses a special chest-abdomen manual compression device (the Lifestick Resuscitator); the chest and abdomen are thus compressed alternately. Its originators suggest that this technique, although similar to IAC CPR, is safer and more effective. Clinical studies are presently ongoing.[26]

The technique of perithoracic high-pressure vest inflation without airway manipulation (vest CPR) requires special equipment and allows cyclic increments in intrathoracic pressure to 100 to 150 mmHg during external chest compression. It has been shown to significantly increase cerebral and myocardial blood flow during CPR in animals. This technique employs a special computer-controlled pneumatic vest device positioned around the chest. Initial human data confirm higher vascular pressures during vest CPR as compared with conventional resuscitation.[22] Survival studies are lacking. A multicenter randomized survival trial was terminated prior to target patient enrollment. Data suggests that this technique may be of value as an alternative to standard CPR for short-term hemodynamic support.[26]

Active compression-decompression CPR (ACD CPR) requires a special suction-cup plunger-type device that can be readily deployed by first responders. It incorporates a negative pressure "pull" on the thorax during the release phase of chest compression and slightly improves vascular pressures and air exchange during CPR.[27] The mechanism of benefit from this technique of resuscitation may relate to improved venous return and/or increased intrathoracic pressure during chest compression as a consequence of changes in the bony thorax. Except for one 500-patient French study, all other recent, large, in-hospital and out-of-hospital studies in cardiac arrest patients have shown no survival benefit of ACD CPR.[28,29] It may, however, be of some value in improving short-term resuscitation outcomes. Lurie et al. have reported on the hemodynamic benefits of an inspiratory impedance valve attached to the endotracheal tube during resuscitation.

Preliminary human data suggests that this device, coupled with ACD CPR, increases coronary perfusion pressures and improves end-tidal CO_2.[23] Larger clinical studies are necessary before the clinical usefulness of this technique is assessed.

In cardiac arrest in animals, aortic infusion during CPR (via catheters placed retrograde) has been shown to improve coronary flow and survival. However, human experience with this technique is limited. Emergency cardiopulmonary bypass and hypothermia during cardiac arrest is also undergoing clinical evaluation following promising animal studies. The initial clinical experience is favorable and a multicenter trial is ongoing. In summary, recent data suggest that several experimental CPR techniques may offer short-term survival benefit-i.e., survival to hospital admission-but the data on long-term improved outcome as compared to conventional CPR is less compelling for all strategies studied.

Although such experimental techniques lend themselves to limited clinical use, their study has resulted in a better understanding of physiology, which, in turn, allows several aspects of conventional external chest compression to be manipulated in order to optimize vital-organ perfusion pressures.[30] First, greater sternal force augments myocardial and cerebral perfusion but can also result in greater tissue injury. Second, adequate duration of compression during each chest compression-release cycle is critical for maintaining maximal myocardial and cerebral blood flow during resuscitation. At higher rates of chest compression, more time per minute is spent in chest compression. Based on these data, changes in the AHA recommendations regarding chest compression rate have evolved. The 2000 standards recommend that chest compressions be performed at a rate of approximately 100/min.[25]

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DIAGNOSIS AND IDENTIFICATION OF CARDIAC ARREST

Cardiac arrest is defined as the sudden cessation of effective cardiac pumping function as a result of either ventricular asystole (electrical or mechanical) or ventricular fibrillation. Rapid diagnosis and treatment are essential because (1) more than a few minutes of total cardiac arrest result in permanent cerebral anoxic damage and (2) the success of resuscitative measures is related to the rapidity with which they are instituted following arrest. Based on these and other observations, the concept of early activation of emergency medical systems (EMS) has evolved for victims of out-of-hospital cardiac arrest[25] (see also Chap. 36).

Preliminary Patient Evaluation and Triage

Cardiac arrest should be considered in the differential diagnosis of sudden collapse in any patient. It can be clinically confirmed by pulseless major vessels and absent heart sounds.

Although respirations (agonal respirations) may continue for a minute or two, the patient with cardiac arrest rapidly becomes cyanotic and unconscious.

Once the diagnosis of cardiac arrest is made and no trauma is suspected, the unconscious patient should be positioned supine on a firm surface and the airway opened using the head tilt-chin lift technique or alternative strategies, as described below (in the discussion of ventilation during CPR). The patient should immediately receive rescue breathing either with a bag-valve mask device or with mouth-to-mouth breathing. Simple airway barrier devices, which are easily deployed, can be used to minimize direct patient contact and are preceived as being more hygienic during mouth-to-mouth resuscitation. Following airway opening and rescue breathing, chest compressions should be promptly initiated at approximately 100/min. Recent animal data suggests that ventilation can be deferred for several minutes in witnessed cardiac arrest without changing survival if chest compressions are initiated promptly. In addition, a recent study that randomized patients receiving dispatcher-assisted CPR to ventilation or no ventilation failed to demonstrate any benefit of early ventilation.[31] These and other data have raised several questions regarding the need and benefit for early ventilation in patients in cardiac arrest. Nevertheless, the AHA continues to recommend early ventilation for all patients.[25]

If available, an electrocardiogram (ECG) can confirm the diagnosis and identify asystole, ventricular fibrillation, or electromechanical dissociation as the mechanism of arrest. However, cardiopulmonary resuscitation (CPR) should be initiated immediately, as described above, once the clinical diagnosis is made without delaying to obtain this information. If a defibrillator but not an ECG is immediately available, a 200-J countershock should be administered without delay. Prehospital CPR studies in several patients have confirmed that, early in cardiac arrest, the mechanism of arrest is usually ventricular fibrillation and that survival is critically dependent on the time to defibrillation.[32] Most hospitals and paramedics are now equipped with defibrillators with "quick look" paddles that simultaneously allow the ECG rhythm to be analyzed. On the basis of the rhythm, an etiology for the arrest can then be explored in a more focused way and appropriate therapy initiated. A recent debate has emerged prompted by animal data from Niemann et al. showing that animals receiving CPR prior to early defibrillation did better than

those in whom no CPR preceded defibrillation.[33] This observation is further supported by recent data from Cobb et al. showing that 90 s of "high-quality" CPR prior to defibrillation improved outcome in patients receiving bystander CPR.[34] The current recommendation is that if defibrillation is delayed, CPR should be performed immediately. However, if a defibrillator is available, the value of "predefibrillation CPR" is unclear. Clearly, if defibrillation fails to restore circulation, CPR should be performed immediately. Also, if collapse time without CPR is known to be more than 2 to 4 min, 90 s of initial CPR will likely be of value.

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AUTOMATIC EXTERNAL DEFIBRILLATORS

Given the value of early defibrillation, automatic external defibrillators (AEDs) were developed for use by first (minimally trained) professional responders, and were shown to dramatically improve survival after prehospital arrest.[35,36] AEDs have an approximately 90 percent sensitivity and specificity for successfully recognized ventricular fibrillation. They are designed for use by first responders or persons with little medical training (e.g., fire fighters, EMS technicians). These devices have varying degrees of automation and can deliver several successive defibrillatory shocks via two self-adhesive electrodes placed by the user directly on the left anterior and left lateral chest. Most manual physician- or paramedic-operated waveform defibrillators deliver monophasic shocks. In recent years commercially available AEDs deliver a biphasic waveform shock. Recent research has focused on the relative efficacy of these two waveforms. Data suggests that biphasic-waveform defibrillation using shocks <200 J are safe and as effective as (if not more so) higher-energy monophasic shocks. Also, animal data suggests less postshock myocardial dysfunction following biphasic-waveform defibrillation. Various modifications of the biphasic waveform (sawtooth pattern, etc.) are being evaluated. Current recommendations do not clearly rank one defibrillatory waveform over the other; both are acceptable.

AEDs have been successfully used by nontraditional health care professionals (airline crews, police, and security guards) with dramatic improvement in patient survival. This program has been termed *public-access defibrillation.* All such AED defibrillation programs have been under strict physician-guided training and supervision. Perhaps the most compelling results of this strategy of emergency care were reported recently by White et al. in Rochester, Minnesota, where police-initiated AED defibrillation and resuscitation resulted in a survival to hospital discharge of approximately 50 percent (Fig. 34-2).[31] The value of training the on-site nontraditional health care provider was further tested and ratified when Valenzuela et al. trained casino security guards and demonstrated significant increases in resuscitation rates. They have demonstrated the compelling benefit of early defibrillation (Fig. 34-3).[37] Some authors have questioned the cost effectiveness of deploying first responder AEDs. A treatment should be considered economically attractive if it is associated with an incremental cost effectiveness ratio of less than twice the average annual income per life year (i.e., approximately $50,000 per life year). Modeling studies and clinical trials have demonstrated that the cost effectiveness of first responder AED programs is well within the cost of programs deemed to be clinically appropriate, if achieved by a low intensity intervention such as police or lay responder defibrillation (estimated cost $29,000 to $46,700 per year). Available data suggests that time to defibrillation is not cost-effectively reduced by adding to existing EMS systems.[38] In a dramatic move to test the value of early AED deployment, several AEDs have been prominently positioned at O'Hare Airport and have been successfully used by airport patrons. Recent state and federal legislation that endorses early AED deployment by trained supervised persons and indemnifies users, trainers, and other owners of AEDs has paved the way to evaluate public-access defibrillation.

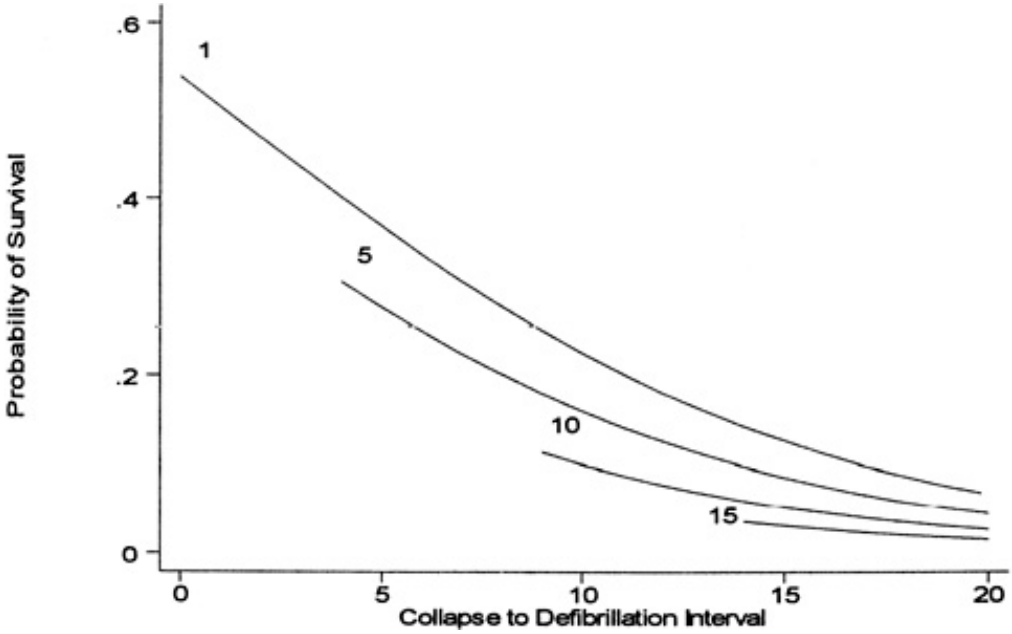

Figure 34-3: Relationship of collapse to CPR and defibrillation to survival: simplified model. Graphical representation of simplified (includes collapse to CPR and collapse to defibrillation only) predictive model of survival after witnessed out-of-hospital cardiac arrest due to VF. Each curve represents change in probability of survival as delay (minutes) to defibrillation increases for a given collapse-to-CPR interval (minutes). (From Valenzuela et al.,[37] with permission.)

The use of AEDs by nontraditional health care professionals and possibly by trained lay persons is currently the focus of intense research. It is highly recommended that all first-responder EMS units be equipped with AEDs. Several agencies have developed training programs that incorporate AEDs and basic CPR training. However, the duration of training needed to correctly teach the use of an AED is likely much less than that currently used by most training agencies (i.e., only 3 or less hours appear to be needed).

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RESPIRATORY ARREST

Respiratory arrest is the cessation of effective respiratory effort. It can result from airway obstruction (due to a foreign body or other causes), drowning, smoke inhalation, drug overdose, head trauma, cerebrovascular accident, or suffocation. When respiratory arrest occurs suddenly (as with foreign-body obstruction), the patient rapidly becomes cyanotic, though a palpable pulse with blood pressure, consciousness, and ineffective respiratory efforts may be maintained for several minutes. Opening the airway and/or rescue breathing may be all that is necessary to resuscitate such a patient.

The Heimlich maneuver is recommended for relieving foreign-body airway obstruction. It is implemented by standing behind the victim and delivering a series of sharp thrusts to the upper abdomen with a closed fist.[39] Abdominal thrusts can also be used directly in the unconscious, supine patient by the trained health care provider to help dislodge a foreign body mechanically. The Heimlich maneuver can also be self-administered by placing the fist between the navel and the xiphoid process and delivering a series of quick upward thrusts. If incorrectly administered, this maneuver can lead to visceral damage.[40] When properly used, however, the technique is both safe and effective.

Manual removal of a foreign body in the unconscious victim should be done only by trained health care providers. This can be achieved by opening the victim's mouth and attempting to dislodge any obvious foreign body with a finger. As a single method, back blows may not be as effective as the Heimlich maneuver in adults.

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VENTILATION AND CHEST COMPRESSION DURING CARDIOPULMONARY RESUSCITATION

The 1980s defined the physiology of circulation during CPR. In the last 5 years, several investigators have focused on understanding the physiology of ventilation during CPR (see below). Although several questions remain unanswered, recent research has served to challenge several "dogmas," as discussed below.

Clearing the airway is of the utmost importance. Foreign bodies, loose dentures, or any other oral obstruction should be removed. Next, the head tilt-chin lift technique, which causes the tongue to move anteriorly, is used to open the airway. The chin is lifted forward, with the fingers of one hand supporting the jaw, and the head is tilted back by the other hand, which rests on the patient's forehead.[35] The head tilt-neck lift method of opening the airway is also commonly employed and is an acceptable technique for use by the skilled rescuer. Here, the rescuer tilts the head back with one hand on the patient's forehead; the other hand is placed behind the patient's neck, lifting it upward to open the airway. If no spontaneous respirations are present, mouth-to-mouth (or mouth-to-nose) ventilation is immediately initiated, with adequacy being judged by the rise and fall of the patient's chest with each breath. To minimize gastric distention, it is necessary to deliver slow (2-s) ventilatory breaths.

Equipped rescuers will use a barrier device or a bag-valve mask technique of ventilation together with a small plastic oral "airway," which moves the tongue anteriorly. Adequate ventilation is difficult with the bag-valve mask technique, since a single rescuer often has difficulty maintaining an adequate seal on the face, and rapid bag deflation commonly results in gastric distention and aspiration. Slow (2-s) ventilation must be employed if the bag-mask technique is used.

Several invasive airway adjuncts have also been developed for use by nonphysician health care providers in prehospital situations, and several newer devices have been shown to be superior to the bag-valve mask technique of ventilation.[41] The esophageal obturator airway (EOA), esophageal gastric tube airway (EGTA), the Combitube, the laryngeal tracheal mask airway (LMA), and the pharyngotracheal lumen airway are among those that have been used in the prehospital setting. Considerable training and skill are needed in placing and using these devices properly. Serious, life-threatening complications have been reported following the use of the EOA or EGTA. As a consequence, their use has generally been abandoned in favor of other more safe and effective devices. Recent data suggest that the Combitube and LMA are attractive alternatives to endotracheal intubation with proven field success and ease of training.[42] Although endotracheal intubation remains a class I recommendation by the AHA (to achieve ventilation and secure the airway), these other devices do have a clinical role and are considered to be class IIA alternatives when compared to bag-valve mask ventilation.

Endotracheal intubation is considered the ideal technique for ensuring adequate ventilation during CPR. Whenever possible, a nasogastric tube should be inserted following intubation to drain the stomach and thus decrease the chances of aspiration. Intubation can be rapidly implemented, but much valuable time can be wasted by repeated unskilled attempts at intubation. If this technique is used, CPR should be discontinued for no more than 20 to 30 s while the tube is being passed into the airway. If more than 20 to 30 s elapse without successful intubation, the laryngoscope should

be withdrawn and CPR reinstituted. The concern of delaying resuscitation during intubation was supported by a recent study in a pediatric population that compared bag-valve mask ventilation to endotracheal intubation and failed to demonstrate any benefit of endotracheal intubation, likely due to the delay in intubating patients.

The optimal requirements for ventilation during CPR in human beings remain unknown. No study has clearly identified the optimal timing, sequence in relation to chest compression, or tidal volume needed during CPR. During the first few minutes of cardiac arrest without prior hypoxia, as noted above, animal studies suggest that ventilation is less important relative to chest compression and defibrillation. Airflow from chest compression alone and air in the lungs at the time of arrest may be initially sufficient to sustain ventilation.[43,44] Recent human data from Seattle tend to support this observation, since dispatcher-assisted CPR with or without ventilation resulted in similar outcomes.[31] The value of expired air ventilation has further been called into question based on animal studies that show that expired air, when used for ventilation, actually worsens outcome in a ventricular fibrillation cardiac arrest model. The value of immediate expired air ventilation for victims of witnessed cardiac arrest has thus clearly been called into question. There are few data on the value (or lack thereof) of ventilation in the victim of an unwitnessed arrest. Based on these data, the new AHA guidelines for resuscitation recommend 100 chest compressions per minute with a 15:2 compression-ventilation ratio (for both single and two rescuer CPR) and ventilation with two breaths slowly delivered over 2 s with a tidal volume sufficient to achieve obvious chest rise (10 to 12 mL/kg) or if a bag-valve mask is used, 400 to 600 mL per breath.

In addition to these recommendations, it is critical, in performing chest compression, to use sufficient force to depress the sternum by approximately 2 in. (5 to 6 cm). As this is usually difficult to gauge, sufficient chest compression force should be used to generate a palpable femoral or carotid arterial pulse.

Airway, breathing, chest compression (ABC) is the specific sequence used to initiate CPR in the United States, with survival rates as high as 35 percent in cities with advanced EMS systems[32,36] (see Chap. 36). ABC is also used in many other countries. However, in the Netherlands, CAB (chest compression first followed by airway opening and breathing) is the common technique for CPR implementation, with resuscitation outcomes similar to those reported for ABC in the United States. Despite its proven efficacy, the recently perceived risk of infectious disease transmission during CPR has reduced the willingness of both lay and medical personnel to initiate mouth-to-mouth ventilation and CPR in unknown victims of cardiac arrest. In an effort to respond to these concerns and encourage the lay administration of CPR, some cities have mandated the public availability and use of barrier devices during mouth-to-mouth ventilation. The effectiveness of such barrier devices is, however, unknown. To overcome this limitation, potential rescuers who are reluctant to initiate CPR because of the perceived risk of infection should be encouraged to activate the EMS system immediately, open the victim's airway, and then initiate and continue chest compressions only until paramedics arrive (i.e., C-A). The paramedics can then initiate ventilation with the necessary protective equipment. It is important to note that a randomized comparison with CAB (chest compression, airway, breathing) or CAD (chest compression, airway opening, defibrillation) has never been done.

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DEFINITIVE THERAPY

The AHA's *2000 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care* adopted a new classification for therapeutic recommendations.[25] This classification allows a relative therapeutic value to be assigned to a given strategy of treatment based on scientific data. It is as follows:

1. Class I: Definitely helpful
2. Class IIA: Acceptable, probably helpful
3. Class IIB: Acceptable, possibly helpful, probably not harmful
4. Class III: Not indicated, may be harmful
5. Indeterminate: clinical data too preliminary or insufficient to allow classification into the other four categories

During cardiac arrest, the ECG will usually show rapid ventricular tachycardia or fibrillation, asystole, or heart block-or it may be near normal.

Ventricular Tachycardia or Fibrillation

With ventricular fibrillation, an attempt at electrical defibrillation should be made as quickly as possible. Successful defibrillation is accomplished by the passage of adequate electrical current (amperes) through the heart (see also Chap. 32). Current flow is dependent on the energy chosen (joules) and the transthoracic impedance (ohms), or resistance to current flow. Factors that affect transthoracic impedance include the energy selected, electrode size, skin-paddle coupling material, the number and time interval of previous shocks, the distance between the electrodes (size of the chest), phase of ventilation, and paddle electrode pressure.[45] Human transthoracic impedance ranges from 15 to 150 ohms, with the average adult impedance being 70 to 80 ohms. If transthoracic impedance is high, low-energy shocks are ineffective in generating enough current to achieve successful defibrillation. Transthoracic impedance can be reduced by firm pressure on hand-held electrode paddles and a gel/cream or saline-soaked gauze pads between the electrode and the skin.[45] In addition, proper electrode/paddle placement is essential; one electrode should be placed to the right of the upper sternum below the clavicle and the other to the left of the nipple, with the center of the electrode in the midaxillary line. An acceptable alternative is one electrode anteriorly over the left precordium and the other posteriorly behind the heart in the right infrascapular location. The latter positioning is best achieved by using preadhesive rather than hand-held electrodes. In female patients with large breasts, the electrodes are best placed to the right of the upper sternum and either under or lateral to the left breast. Direct current is employed during defibrillation. The paddles, coated with low-resistance gel, are applied firmly to the chest and then for monophasic defibrillations discharged with 200 J, which is repeated at 200 to 300 J if the first shock is unsuccessful. The current AHA standards suggest that a third 360-J shock should be delivered if ventricular fibrillation persists.[25] These three shocks should be delivered in rapid succession. Prospective studies by Adgey and others have shown 85 to 90 percent successful defibrillation using only 200 J in patients weighing up to 90 kg.[46,47] Some advocate higher-energy defibrillation, but few currently use more than 400 J.[48] High-energy defibrillation likely causes more cardiac injury, and increases postshock myocardial dysfunction; there is no clear evidence that it increases the frequency of successful resuscitation.[49] As mentioned above, several

defibrillators have biphasic defibrillatory shock-wave forms. Most conventional manual defibrillators use the monophasic exponential wave form, whereas several AEDs deliver a biphasic defibrillatory shock wave at lower energy levels with equal if not greater success.

When the ECG shows fine fibrillation waves, defibrillation efforts are often unsuccessful. Although commonly practiced, the early use of epinephrine in such situations is not supported by improved survival in clinical trials. Nevertheless, it is suggested that the administration of epinephrine (5 to 10 mL of 1:10,000) intravenously (IV) may result in a more vigorous and coarse fibrillation that is more responsive to defibrillation. This effect is possibly due to improved coronary flow following epinephrine administration (see below), although recent data raise the question of epinephrine-induced deleterious myocardial effects, especially at higher doses.[50] If defibrillation fails, it is likely that marked acidosis or hypoxemia is present. Emphasis should be on modest hyperventilation with supplemental oxygen to correct both hypoxemia and metabolic acidosis.[51] Sodium bicarbonate might then be administered (1 meq/kg) to aid in the management of acidosis, and defibrillation should be repeated with 360 J. By using instantaneous Fourier transformation analysis, Brown et al. have demonstrated that the coarseness of the waveform of ventricular fibrillation may be highly predictive of subsequent survival and appears to correlate with coronary flow.[52] Preliminary human data to confirm these observations are limited.

In a recent study, the value of intravenous amiodarone in shock-refractory ventricular fibrillation/ventricular tachycardia (VF/VT) was tested in patients who had experienced prehospital cardiac arrest. Athough it improved survival to hospital admission, there was no difference in survival to hospital discharge between those who did and did not receive amiodarone.[53] Although often given, there are few data to support the use of lidocaine, bretylium, procainamide, or magnesium in such patients-i.e., those with shock refractory VF/FT (class of recommendation indeterminate).[54-56] Based on these data, it appears that amiodarone may be of some short-term benefit in patients with recurrent VT/VF. Amiodarone is usually dosed as a bolus of 150 to 300 mg over 10 min, 1.0 to 2.0 mg/min for 6 h, then 0.5 to 1.0 mg/min for 6 to 24 h. For recurrent VF in the setting of ischemia, intravenous propranolol or other intravenous beta blockers or amiodarone may be effective.[54] Beta blockers seem particularly helpful in the setting of primary ventricular fibrillation complicating acute myocardial infarction.[54] In fact, the early benefit of amiodarone has been ascribed by some to its beta blocking properties.

Hyperkalemia is a readily treated condition that can cause atrioventricular (AV) block, impaired intraatrial and intraventricular conduction, and occasionally ventricular fibrillation or, less commonly, asystole. It can be recognized by the development of tall, peaked T waves with a normal QT interval and sine wave-like ventricular tachycardia. Life-threatening hyperkalemia responds most readily to calcium infusion; 10 to 30 mL of 10% calcium gluconate is infused intravenously over 1 to 5 min under constant ECG monitoring. Calcium counteracts the adverse effects of potassium on the neuromuscular membranes but does not alter plasma potassium. Its effect, though immediate, is transient. Hyperkalemia should subsequently be treated by glucose-insulin or ion-exchange resins (Chap. 31). Sodium bicarbonate is also used as an agent to lower potassium.

With VT in an alert and responsive patient, cough may reverse the arrhythmia without defibrillation, and repeated cough may maintain the conscious state as a result of the rise in intrathoracic pressure.[10,57] It is an appropriate strategy for immediate use pending more definitive drug or electrical intervention. It is commonly used in the cath lab. The efficacy of the precordial thump (precordial chest blows) has been variably reported in patients with VT. A thump is generally ineffective for terminating prehospital VF. Hence, it should never be used in the patient with VT and a pulse unless a defibrillator is immediately available.

Asystole or Heart Block

For patients with prehospital cardiac arrest, asystole has been shown to be an ominous rhythm with a very low likelihood of successful resuscitation.[32] On the other hand, asystole due to vagal stimulation is the commonest cause of cardiac arrest associated with anesthesia induction and surgical procedures. Asystole also occurs as a result of heart block or sinus node disease (see Chap. 34). Atropine (0.5 mg) given intravenously and repeated in 5 min can be used acutely to prevent or reverse severe bradycardia in many of these settings.

If asystole is witnessed or of short duration, vigorous blows to the precordium may sometimes restart the heart. Rhythmic chest blows may maintain limited perfusion and can be continued if needed while palpating the femoral or carotid pulse until other treatment is available. If the chest blow fails, CPR should be initiated and intravenous epinephrine (5 to 10 mL of 1:10,000) administered. Possible treatable causes of asystole-such as acidosis, hypoxemia, hyper- or hypokalemia, and hypothermia-should be considered and treated appropriately if suspected. If an overdose of calcium channel blocker is suspected, calcium chloride, 1 g given as an intravenous bolus, may be very effective (class IIA recommendation). Resuscitation measures may result in the return of a slow ventricular rhythm, which can subsequently be supported with atropine (1 to 2 mg IV) until a temporary pacemaker is placed. Temporary pacing is the optimal treatment for true asystole or profound bradycardia. Obviously, considerable skill and training are required for temporary transvenous pacemaker placement (see Chap. 31). Transcutaneous pacing has been developed as a noninvasive and simple technique that can be implemented rapidly. It uses external surface electrodes with a high-voltage pacing source. Higher voltages are required to overcome transthoracic resistance, but they are painful and are therefore used mainly on unconscious patients. The energy delivered to the heart by this technique is variable, as is its efficacy. Recently, pacing sources with longer pacing stimulus duration have been developed and may offer less painful and more effective pacing. Prehospital studies of transcutaneous pacing for asystole have not confirmed an improvement in survival.[58] It may, however, be of some benefit for patients early in asystole (class IIB intervention). Clinical evidence does not support its routine use in all patients with asystole.

In rare instances, very fine VF may result in an almost straight line on a single-lead ECG and thus be mistaken for asystole. In such cases, where the diagnosis of asystole is in question, it is suggested that a perpendicular ECG lead be viewed. Rotation of "quick look" ECG paddles by 90 degrees easily achieves this. If ventricular fibrillation is present, the perpendicular ECG lead will demonstrate a typical fibrillation pattern; whereas in true asystole, a straight line will be seen in all ECG leads. If VF is diagnosed, the initial treatment should be according to the outline above-i.e, three successive countershocks. There is little value in defibrillating true asystole.

Electromechanical Dissociation

In *electromechanical dissociation* (EMD), there is evidence of organized electrical activity on the ECG at a reasonable rate, but failure of effective perfusion (no pulse or blood pressure). The most treatable causes of this condition are hypovolemia due to severe hemorrhage, pericardial tamponade, tension pneumothorax, hypoxia, hypothermia, acidosis, hyperkalemia, and massive pulmonary embolism. Signs of these problems should be sought and definitive therapy undertaken with fluids and/or blood replacement, pericardiocentesis, placement of a pleural needle or tube, endotracheal intubation, and other maneuvers as deemed necessary. These conditions should also be strongly considered if CPR results in no palpable pulse or evidence of perfusion. Unfortunately, many patients with electromechanical dissociation have primary myocardial failure. Following diagnosis, ventilation should be optimized and epinephrine administered. Calcium chloride has been used for EMD, but prospective studies have not shown it to improve survival.[59] In acute myocardial infarction, sudden electromechanical dissociation is a sign of myocardial rupture. In such cases, pericardiocentesis and surgical repair can rarely result in survival.

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ESTABLISHMENT OF AN INTRAVENOUS ROUTE

While external chest compression and artificial ventilation are continued, a plastic catheter should be inserted into a large peripheral vein. Drug administration during CPR should be preferentially accomplished only from a source above the diaphragm, since there is little cephalad flow from veins below the diaphragm. If a peripheral vein cannot be cannulated, a cutdown should be attempted or a central venous line placed by a percutaneous route. If CPR is properly performed, drugs administered through a peripheral line will often reach the arterial circulation within 15 to 30 s.[51] Recent data suggest that a 20-mL fluid bolus significantly improves peripheral drug delivery to the central compartment. Larger amounts of fluids should be used if drugs are given via a femoral line. Intracardiac injections are unnecessary except when there is no intravenous access. If an intravenous route is unavailable, epinephrine (1 to 2 mg in 10 mL of sterile distilled water) and lidocaine (50 to 100 mg in 10 mL of sterile distilled water) can be administered by way of the endotracheal tube into the bronchial tree. The drug should be injected through a long catheter passed beyond the tip of the endotracheal tube. Cardiac compression should be withheld, and several insufflations with an Ambu bag should immediately follow drug administration to aid drug absorption through aerosolization.

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MAJOR DRUGS USED DURING CARDIOPULMONARY RESUSCITATION

Drugs that are used for the treatment of various arrhythmias are mentioned above. Catecholamines are used in cardiac arrest to (1) increase arterial and coronary perfusion during and following CPR, (2) stimulate spontaneous contraction during asystole, (3) make fine VF more responsive to defibrillation, and (4) act as an inotropic agent.

Epinephrine was among the earliest pressors evaluated during resuscitation. It is effective in achieving several of these goals, although recent data have highlighted its possible deleterious effects on postresuscitation left ventricular function. Both animal and clinical studies have extensively evaluated the hemodynamic effects of epinephrine during resuscitation. Animal studies show that during conventional CPR, cerebral and myocardial perfusion pressures are low. Epinephrine increases brain and heart flow by two mechanisms: (1) It prevents carotid artery collapse and raises arterial pressure during both chest compression and the release phase of chest compression (i.e., "systole" and "diastole," respectively). This results in higher carotid arterial systolic and aortic diastolic pressures, which, in turn, are reflected in higher cerebral perfusion and myocardial perfusion pressures and flow. (2) It preferentially reduces blood flow to the external carotid, renal, and splanchnic beds, thereby redirecting flow toward the brain and heart.[60,61]

Arterial collapse at the thoracic inlet has been shown to be the critical limiting factor for cerebral perfusion pressure and flow during prolonged CPR. Arterial collapse results from high extravascular intrathoracic pressures, low intravascular volumes, and loss of arterial tone. Collapse results in a precipitous fall in carotid arterial and hence cerebral perfusion pressure. Epinephrine during CPR can not only reverse arterial collapse but also prevent it from developing. With the administration of epinephrine during conventional manual CPR in the dog, cerebral blood flow can be maintained at approximately 15 percent and myocardial flow at approximately 5 percent of prearrest values for 20 min.

These data strongly support the early and frequent use of epinephrine during CPR in an effort to optimize the perfusion of vital organs. The recommended dose of epinephrine (1 mg IV every 3 to 5 min) is comparable to a 0.007 to 0.014 mg/kg dose in a 70-kg person. This dose has been questioned, since animal studies using higher doses of epinephrine have shown improved blood flow to vital organs and improved survival.[61] Other studies of higher doses of epinephrine, however, have shown increased myocardial oxygen demand despite this improved blood flow.[62] Higher than recommended doses of epinephrine have been reported to increase arterial pressure and coronary perfusion pressure in a small number of human studies. These studies spawned an intense interest in the use of higher doses of epinephrine during CPR. Results from several prospective randomized out-of-hospital clinical trials of more than 2400 adult cardiac arrest victims, however, have shown no statistically significant improvement in survival to hospital admission or discharge or improved neurologic survival when higher doses of epinephrine (0.1 to 0.2 mg/kg) were compared with standard doses.[63,64] On the other hand, these trials did not demonstrate any obvious deleterious effect of the higher doses of epinephrine.

Recent retrospective studies suggest that higher cumulative doses of epinephrine are associated with worse hemodynamic and neurologic outcome event when duration of cardiac arrest are

accounted for. Hence, most experts would use 1 mg IV uniformly. Higher doses worsen postresuscitation myocardial dysfunction, hence its use is not routinely recommended.[25] The recommended dose is 0.5 to 1 mg IV, and this dose should be repeated at approximately 3- to 5-min intervals unless effective cardiac activity is restored. If an intravenous route is not available, epinephrine can be administered down the endotracheal tube; 10 mL of a 1:10,000 solution should be used, and this can also be repeated every 3 to 5 min.

The benefits of epinephrine are principally due to the alpha vasoconstriction induced by this agent. The inotropic effects of the drug may not be helpful, since these effects increase myocardial oxygen demand, even during ventricular fibrillation, when supply or blood flow is limited.[62] Consequently, there is some interest in using a pure vasoconstrictor during CPR rather than epinephrine. Animal studies of vital organ perfusion and human survival studies comparing epinephrine and phenylepinephrine (a pure alpha vasoconstrictor) have yielded similar results. Vasopressin has recently been evaluated as an alternative pressor agent, with promising results.[64a] Animal studies have demonstrated it to be as effective as pressor but with less resultant myocardial dysfunction as compared to epinephrine. Initial human data has been encouraging. However, a large prospective randomized out-of-hospital study of vasopressin versus epinephrine failed to confirm any survival benefit of this agent.[64b] It may be considered an alternative pressor to epinephrine for patients in shock-refractory VF (class IIB).

Norepinephrine is a potent vasoconstrictor and generally produces a rise in blood pressure; it is also an inotropic agent. Its disadvantage is renal and mesenteric vasoconstriction, and it should not be used in the initial phase of resuscitation. This agent is most useful where severe hypotension is present but where the chronotropic effects of epinephrine are not desirable (as in acute myocardial infarction or severe ischemia). This agent should be administered cautiously, since severe tissue injury results from extravasation around an intravenous site. A large prehospital trial failed to identify any differences in survival following treatments with norepinephrine, high-dose epinephrine, or standard epinephrine.[63]

Similarly, dopamine (a chemical precursor of norepinephrine) and dobutamine (a synthetic catecholamine) are preferred for use as inotropic agents because of their lesser chronotropic effect. Recent animal data suggests that dobutamine may be particularly effective in reducing postresuscitation left ventricular dysfunction. Isoproterenol (a synthetic catecholamine) is a pure adrenergic agonist and effective vasodilator. Therefore, its use during CPR is contraindicated since it can significantly decrease vital organ perfusion pressures. In patients with a palpable pulse, however, it is useful for treatment of bradycardia due to heart block or asystole until a temporary pacemaker is placed (see also Chap. 31).

Sodium Bicarbonate

The recent AHA recommendations deemphasize the role of sodium bicarbonate and suggest that much less sodium bicarbonate should be used than previously advocated for acid-base control during cardiac arrest. As with other types of metabolic acidosis, if adequate alveolar ventilation is achieved, the metabolic acidosis of arrest is partially corrected through P_{CO_2} excretion.[51] Recent clinical trials failed to demonstrate improved outcome from cardiac arrest with buffer therapy.[65] Rather, several deleterious effects of bicarbonate administration including respiratory acidosis, hypernatremia, and hyperosmolality have been reported. Ideally, sodium bicarbonate should be given according to the results of measurement of arterial blood pH, P_{CO_2} determination, and calculation of the base deficit. Bicarbonate should be used, if at all, only after more established interventions such as defibrillation, ventilation with endotracheal intubation, and pharmacologic therapies (epinephrine and antiarrhythmic drugs) have been tried.[25] If needed, 1 meq/kg of sodium bicarbonate should be administered; then no more than half this dose may be repeated every 15 min. Excessive use of sodium bicarbonate can result in metabolic alkalosis, hypernatremia, and

hyperosmolality. Some benefit of the usual bicarbonate solution (7.2 percent) may occur as a result of the hyperosmolality of the solution temporarily drawing fluid into the intravascular compartment.

On the other hand, bicarbonate may be most useful during the immediate postresuscitation period, when a profound metabolic acidosis occurs. In most instances during CPR, its use should be considered as a class IIB recommendation.[30]

Calcium Chloride

Calcium chloride (5 to 7 mg/kg) enhances the contractile state of the heart and is indicated in treating severe hypotension due to an overdose of calcium channel blocker or hyperkalemia. It is no longer recommended for use in asystole or electromechanical dissociation.

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TERMINATION OF CARDIOPULMONARY RESUSCITATION

Despite resuscitative efforts, the patient in cardiac arrest may not regain spontaneous circulation. The decision to end (or even initiate) CPR should be based on a physician's assessment of the patient's prior advance directives (if known) and the cerebral, cardiovascular, and general status of the patient.[66,67] Recent prospective and retrospective data confirm that survival is unlikely in patients who have no return of spontaneous circulation after 30 min of ACLS care.[68] Recent studies have demonstrated that continued in-hospital CPR efforts (in patients failing prehospital advanced cardiac life support) are not only expensive but also unsuccessful.[69] Persistent deep unconsciousness and absence of respiration, reflex response, or pupillary reaction suggest cerebral death, and resuscitative efforts are usually unproductive. These guidelines, however, should be altered in patients with hypothermia, barbiturate overdose, and perhaps following electrocution, where recovery has been seen even after hours of resuscitation.[70]

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POSTARREST CARE

Patients who have been successfully resuscitated usually require monitoring in an intensive care setting. These patients are prone to develop cardiac arrhythmias, hemodynamic and ventilatory instability, and ischemic encephalopathy. Ventilatory support with a respirator may well be necessary initially. Serial arterial blood-gas determinations should be made to identify hypoxemia and assess the rapidly changing acid-base status. Commonly, hyperventilation was employed postresuscitation to not only treat acidosis but also help reduce CNS edema. Recent studies raise the possibility of worsening cerebral ischemia with low P_{CO_2} levels after brain ischemia. Based on these observations, normal ventilation is preferred in the comatose postresuscitation patient.

Several therapeutic strategies have been employed in animal models to help reduce hypoxic encephalopathy after cardiac arrest. None (including emergency cardiopulmonary bypass, which is currently undergoing clinical testing) have clearly been shown to be beneficial in humans.

The treatment of encephalopathy after cardiac arrest involves the prevention of further hypoxia and hypotension. For cerebral edema after cardiac arrest, methylprednisolone (60 to 100 mg) or dexamethasone sodium phosphate (12 to 20 mg IV every 6 h) has been recommended, but there is no conclusive evidence that these agents are beneficial. High-dose barbiturates or lidoflazine have also been shown to reduce postarrest brain injury in animal studies; the value of this therapy in human beings is negligible. In animals, mild to moderate hypothermia appears to be neuroprotective following an ischemic event. Clinical data are limited but suggestive of benefit. Trials are ongoing. The prognosis of the patient with anoxic encephalopathy is related to the depth and continued duration of cerebral dysfunction (see also Chap. 89). Failure to exhibit neurologic improvement 24-72 h following resuscitation is usually an ominous sign. Clinical and laboratory evaluations (electroencephalography, sensory evoked potentials) are often employed to help define prognosis and thus guide further care in such individuals.

Other potential life-threatening problems in the postarrest period include acute renal failure, bowel infarction, infection, adult respiratory distress syndrome, and sepsis. Patients regaining consciousness may have postarrest amnesia or may develop psychotic behavior.

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OUTCOME OF RESUSCITATION

In their initial study, Kouwenhoven and colleagues reported a 24 percent successful resuscitation and discharge rate from the hospital. Recent studies have shown that with a paramedical response system, a near 40 percent successful out-of-hospital resuscitation rate can be achieved.[32,71] Many of these patients die in hospital, however, with the dominant cause of death being anoxic encephalopathy. Recent data suggest that somatosensory evoked potentials may be useful and highly predictive in identifying patients who are likely to have irreversible brain injury.[72] The critical factors for successful out-of-hospital resuscitation include approximately 7 min total duration of CPR, approximately 4 min from collapse to the initiation of CPR, and approximately 10 min to successful delivery of the first countershock.

It is important to point out, however, that the quality of life for patients surviving to hospital discharge is often quite good, with most discharged patients being able to return to gainful employment.

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CHAIN OF SURVIVAL

The concept of a "chain of survival" has been adopted by several agencies and underscores the importance of an integrated public education and health care system if outcome from prehospital cardiac arrest is to be optimized.[25] Early access (to EMS systems), early CPR (to include bystander CPR), early defibrillation (to include the use of AEDs), and early *advanced cardiac life support* (ACLS) care are the major links in the chain, and any one weak link weakens the whole chain of survival.

This is best exemplified in two recent publications that reported on prehospital cardiac arrest outcomes in New York and Chicago, where survival rates were only 1 to 2 percent. Despite a mature EMS system and considerable public training in CPR, delayed defibrillation-due to traffic, elevators, and other factors-contributed significantly to the poor outcome in these studies.[73,74] Other cities, where prompt defibrillation has been possible, have reported a 20 to 30 percent survival rate.[75] To overcome this tragic limitation, AEDs were developed and have been shown to facilitate prompt defibrillation and thereby improve survival (Fig. 34-3). Hence, the American Heart Association and American College of Cardiology have jointly recommended that all professional first-responder units (especially in rural areas where long transport times are common) be equipped with AEDs.

If mortality from out-of-hospital arrest is to be reduced, public education programs to increase awareness of the warning signs of a heart attack and teach CPR are critical (Fig. 34-3). Despite many years of public education, the incidence of bystander CPR nationwide remains low.[73,74] This may have several explanations, including a lack of training in high-risk populations, poor performance or lack of retention despite training, unnecessarily complex training programs, or a fear of communicable disease during mouth-to-mouth resuscitation. This last issue has become particularly significant in the 1990s. Individuals should be reassured that the likelihood of disease transmission is minimal, 70 percent of arrest victims collapse at home, and if an individual is still unwilling to do mouth-to-mouth CPR, he or she should be taught to at least activate EMS ("call") and start chest compressions ("pump"). Ventilation ("blow") could then be started by suitably equipped trained EMS rescuers. Present data indicate that a refocusing of basic life support (BLS) training programs is essential, with efforts being targeted at simplification of training, with specific education and training penetration into high-risk patient groups (older patients and minority groups). The CPR message must be kept simple (for example, "call-pump-blow"). These goals must be achieved if the first two links in the chain of survival (early access and early CPR) are to be strengthened. Universal 911 would facilitate early and easy access and should be encouraged in all communities. Minimal standards of performance and excellence for EMS systems should be established and monitored. Dispatcher-assisted CPR teaches CPR on the telephone to the person who is calling to report the arrest (while professional help is in transit) and has been shown to be effective. The Seattle-King County EMS system is proof that such efforts directly improve outcome (Fig. 34-3).[75] On the other hand, the Chicago-New York experience is a chilling reminder of the consequence of one weak link in the chain of survival. The outcome from prehospital arrest can be improved only if each community strives to optimize its own chain of survival.

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Part 6: CORONARY HEART DISEASE
Chapter 35:

ATHEROGENESIS AND ITS DETERMINANTS

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INTRODUCTION

Despite steady progress in treatment of cardiovascular diseases, people are still dying of these diseases, although at later ages.[1] In the United States as well as in many other countries, cardiovascular diseases remain by far the number 1 cause of death for both men and women of all ethnic backgrounds and, no less important, cause the greatest disability. By the year 2020, coronary heart disease (CHD) and stroke will hold first and fourth places, respectively, in the World Health Organization's list of leading causes of disability.[2] A worldwide epidemic of cardiovascular diseases is evolving, and atherosclerosis, often with thrombosis superimposed, is by far the most frequent underlying cause.

It has been known for decades that the earliest lesions of atherosclerosis, fatty streaks, are present in the aorta from early childhood, but today we know that atherosclerosis begins already during fetal development, particularly in fetuses of hypercholesterolemic mothers.[3] Therefore, literally, a life-long effort is needed to prevent this disease and its dreadful consequences. Although a genetic predisposition to atherosclerosis may be present, the vast majority of atherosclerosis-related diseases, including CHD, are acquired; that is, the clinical manifestations of atherosclerosis, which usually appear in later life, are largely preventable. This fact is the major challenge to the world of cardiology at the turn of the millennium.

Definition

Atherosclerosis is a complex inflammatory-fibroproliferative response to retention of plasma-derived atherogenic lipoproteins in the arterial intima.[4,5] Literally, both softening (*athére* is Greek for gruel or porridge) and hardening (*skleros* is Greek for hard) need to be present to qualify for the diagnosis atherosclerosis; that is, *atherosclerosis* is not synonymous with *arteriosclerosis*. The latter term is broader, covering all diseases leading to arterial hardening, including native atherosclerosis, restenosis after angioplasty, and transplant vascular disease. These conditions all share some pathologic processes, but the mix of lipid accumulation, smooth muscle proliferation, and immune activation differs markedly.[6] It is important to recognize this distinction between atherosclerosis and arteriosclerosis, particularly when dealing with animal models of arterial diseases, because it is the lipid-related atheromatous component that is dangerous in human atherosclerosis, not the smooth muscle cell-related sclerotic component. The lipid-related component destabilizes plaques and thus is responsible for the great majority of all the life-threatening complications of human atherosclerosis: plaque disruption with superimposed thrombosis.[7]

Susceptibility to Atherosclerosis

Some individuals are more susceptible to atherosclerosis than others (e.g., males compared with females), and the same applies to different arterial segments within an individual. Atherosclerosis is a focal intimal disease of large and medium-sized systemic arteries, including the aorta,

iliofemoral, coronary, carotid (bifurcation) and, to a lesser extent, intracranial arteries. Secondary changes may occur in the underlying media and adventitia, particularly in the more advanced stages of the disease. For unknown reasons, some arteries (such as the internal mammary arteries) are highly resistant to atherosclerosis. Although the epicardial coronary arteries appear to be the most susceptible arteries in the body, intramyocardial arteries are highly resistant to atherosclerosis.

NEXT

Chapter 35: ATHEROGENESIS AND ITS DETERMINANTS

ATHEROGENESIS IN SUSCEPTIBLE MICE

To reproduce in animals a vascular disease resembling human atherosclerosis, atherogenic lipoprotein concentrations need to be above a certain level. Normal wild-type mice do not develop hypercholesterolemia and are thus fundamentally resistant to atherosclerosis, even when fed a high-fat high-cholesterol diet that induces the disease in other species, such as rabbits, pigs, birds, and nonhuman primates. By inactivating and/or overexpressing selected genes, however, hypercholesterolemic atherosclerosis-prone mice have been created, for example, mice deficient in apolipoprotein E (apoE $^{-/-}$)[8,9] or low-density lipoprotein receptor (LDLR $^{-/-}$),[10] or both,[11] double knockouts deficient in both the LDLR and apobec-1 protein,[12] and LDLR $^{-/-}$ mice expressing human apolipoprotein B 100 (apoB100).[13] Among mammals, research using the mouse has several unique advantages, including the extensive knowledge of, and the ability to manipulate, the murine genome. Over the past decade, remarkable progress has been made in our knowledge of vascular biology through the use of genetically engineered mice, and mice are being increasingly used as a model for the study of atherosclerosis and its risk factors.[14-16]

The most commonly used genetically altered murine models for studies of atherosclerosis are mice deficient in apoE and/or LDLR. ApoE is a ligand for receptors that clear chylomicron and very low-density lipoprotein remnant particles. Consequently, apoE $^{-/-}$ mice develop severe hypercholesterolemia and atherosclerosis spontaneously on a normal chow diet, in contrast to LDLR $^{-/-}$ mice, which only do so when fed a high-fat high-cholesterol diet.[17] The atherosclerotic lesions that develop in these atherosclerosis-prone mice are morphologically quite similar to those in humans, which is why the mouse has become the most common experimental animal model for atherosclerosis research. Therefore, a more detailed description of atherogenesis in these mice is appropriate.

Endothelial Dysfunction

Endothelial function is generally similar in blood vessels from normal mice compared with blood vessels from other species.[18] For example, acetylcholine (the classic endothelium-dependent agonist) relaxes the mouse aorta as well as the carotid, coronary, mesenteric, and pulmonary arteries.[18] The relaxation observed in response to acetylcholine in murine blood vessels is endothelium dependent and, thus, similar to that observed in many other species, including humans.[18] In hypercholesterolemic atherosclerosis-prone mice, endothelium-dependent relaxation is impaired, i.e., endothelial dysfunction is present,[19-22] consistent with studies of atherosclerosis in other experimental animals and in humans.[18]

Transfer of the human apolipoprotein A1 (apoA1) gene tends to normalize the impaired endothelial function in these mice,[22] apparently without preventing subendothelial lipid deposition, endothelial activation [vascular cell adhesion molecule 1 (VCAM-1 expression)] or monocyte adherence to the activated endothelium.[23] Nevertheless, lesion formation is dramatically reduced.[24,25] The atheroprotective effect of the mouse's own native apoA1 has been more difficult to prove,[26-28] but clear protective effect has been documented.[29]

Lesion-Prone Areas

In aortas of normocholesterolemic mice, VCAM-1 and intercellular adhesion molecule 1 (ICAM-1), but not E-selection, are expressed by endothelial cells in regions predisposed to atherosclerotic lesion formation.[30] The complex hemodynamics in these lesion-prone areas may also increase the local transendothelial passage of lipoproteins and promote their retention and modification in the subendothelial space.[31] Oxidative modified LDL (oxLDL) has many proinflammatory properties which may explain the local upregulation of these inducible endothelial cell adhesion molecules, even before lesion formation, in hypercholesterolemic atherosclerosis-prone animals.[30]

Injuring Lipoprotein Retention

The first event in the birth of a plaque is the transendothelial passage of atherogenic lipoproteins into the subendothelial space, where they are retained and modified.[4,5,32] In normal mice, the subendothelial space contains an acellular matrix of branching filaments (presumed to be mainly proteoglycans) and numerous collagen fibrils without any visible lipid deposition[4]-normal mice do not spontaneously form an arterial intima.[33] The retention of lipoproteins in the subendothelial space provides a microenvironment where lipoprotein modification and aggregation can occur.[4] Modification, e.g., oxidation, of the retained lipoprotein makes it more atherogenic.[34,35] OxLDL is proinflammatory, cytotoxic, and recognized by the macrophage scavenger receptor promoting intracellular lipid accumulation and foam cell formation. In vitro studies suggest that lipoprotein retention involves interactions between apoB and matrix proteoglycans[36,37] and appears to be an important if not the key step in lesion development.

The concentration of a particular macromolecule within the subendothelial matrix depends on its plasma concentration, molecular size, permeability (the arterial endothelium is permeable to all plasma proteins), degree of retention (trapping) and rate of degradation within intima, and efflux from intima as well as on the location along the arterial tree.[38,39]

Inflammatory/Immune Response

One of the earliest detectable cellular responses in atherogenesis is the focal recruitment of circulating monocytes and, to a lesser extent, T cells into the arterial intima is.[40] The persistence of this cellular response seems to underlie disease progression (Fig. 35-1).[41] A few B cells may also be present,[42] but granulocytes are rare in atherosclerosis. Atherosclerotic lesions develop initially beneath an intact but activated endothelium at lesion-prone sites, preferentially affecting the outer walls of bifurcations and the inner wall of curvatures. The local factors responsible for the focal development of lesions are not well understood, but hemodynamic shear stress, the frictional force acting on the endothelial cell surface as a result of blood flow, is weaker in the susceptible lesion-prone areas.[31,43] Hemodynamic shear stress is an important determinant of endothelial function and phenotype. High shear stress (>15 dyne/cm^2) induces endothelial quies cence and an atheroprotective gene expression profile, whereas low shear stress (<4 dyne/cm^2), which is prevalent at atherosclerosis-prone sites, stimulates an atherogenic phenotype.[31,43] The endothelium mediates the transendothelial trafficking of leukocytes into the intima by expressing specific and inducible adhesion molecules such as VCAM-1 and ICAM-1. These adhesion molecules are upregulated at lesion-prone sites in apoE $^{-/-}$ mice prior to lesion formation and thus probably play an important role in the recruitment of mononuclear cells during atherogenesis.[40] Sites of predilection for lesion development include the aortic root, the lesser curvature of the aortic arch, the principal branches of the aorta (in particular, the coronary arteries and the brachiocephalic trunk), the carotid bifurcations, the aortic bifurcation, the iliac arteries, and the pulmonary arteries. Adhesion of monocytes to the endothelial surface was seen already at 6 weeks, macrophage foam cell lesions (fatty streaks) developed as early as 8 weeks, and, as lesions continued to progress, smooth muscle cells appeared and advanced atherosclerotic plaques were present after 15 weeks. The latter consisted of a fibrous cap containing smooth muscle cells

surrounded by connective tissue matrix that covered a necrotic core with numerous foamy macrophages. Thus, the apoE $^{-/-}$ mouse contains the entire spectrum of lesions observed during atherogenesis and was the first mouse model to develop lesions similar to those in humans.[44]

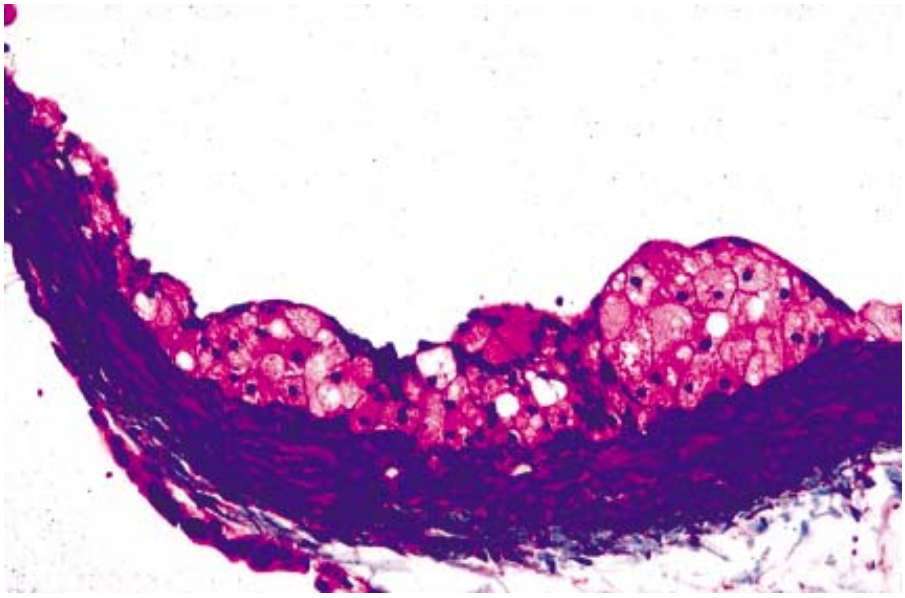

Figure 35-1: (Plate 77) An early atherosclerotic lesion (fatty streak) in the aortic root of a 3-month-old apolipoprotein E-/- mouse fed a high-fat Western-type diet for 6 weeks. The lesion consists of lipid-laden monocyte-derived macrophage foam cells and a few lymphocytes (T cells) beneath an intact endothelium. Elastin trichrome stain.

Leukocyte adhesion to the endothelium alone however, is, not enough to get monocytes and T cells into the intima. They have to pass through the endothelium and, for that, one or more chemokines (chemotactic cytokines) are needed.[45,46] The proinflammatory chemokine monocyte chemoattractant protein 1 (MCP-1) attracts potently both monocytes and T cells, but not neutrophils, eosinophils, and B cells, and plays a fundamental role in the recruitment of these cells.[47] Endothelial cells, smooth muscle cells, and macrophages all contribute to overexpression of MCP-1 in atherosclerosis. Thus, once within the intima, monocytes recruit themselves by secreting MCP-1.[45,48-50] MCP-1 appears to be uniquely essential for monocyte recruitment in several inflammatory diseases,[51] including atherosclerosis.[49,50] Additionally, MCP-1 may induce tissue factor expression in plaque cells and thus increase the risk of atherosclerosis-mediated luminal thrombosis.[52] A prime candidate for upregulation of MCP-1 in the vessel wall is minimally oxidized LDL, linking hypercholesterolemia to fatty-streak formation, plaque progression, and tissue factor expression.[53]

Once within intima and activated, macrophages may secrete a variety of potent cytokines that profoundly influence local cellular accumulation and function. Macrophages can both initiate the oxidation of LDL and take up oxLDL by specific scavenger receptors. Lesion size is reduced in atherosclerosis-prone mice lacking the macrophage-expressed oxygenating enzyme 12/15-lipoxygenase[54] and scavenger receptors, suggesting that lipoprotein oxidation and uptake are key events in atherogenesis.[35]

The humoral and cellular immune system modulates the development of atherosclerosis.[35,55] Plaque T cells and their products [e.g., interferon-γ (IFN-γ)] appear to promote atherosclerosis, whereas nonplaque B cells and their products (e.g., antibodies) are atheroprotective.[56,57]

Hyperimmunization with oxLDL, resulting in high antibody titers, and polyclonal immunoglobulin therapy protect against atherosclerosis, whereas splenectomy (removal of a B cell-enriched immune organ) promotes atherosclerosis in apoE $^{-/-}$ mice.[57] In contrast, all proatherogenic activities of the immune system discovered until now have been associated with inflammatory responses elicited by macrophages and T cells within plaques.[57] Neither B nor T cells, however, are required for the development and growth of plaques, documented in apoE $^{-/-}$ × RAG mice lacking lymphocytes.[58,59] A variety of antigens are formed in developing plaques with immune activation and subsequent modulation, mediated by both cellular and humoral events, of the ongoing atherosclerotic process.[55] Further evidence of immune activation is the upregulated expression of the immune mediator CD40 and its ligand CD154 by all cell types present in advanced atherosclerotic lesions.[60] The interaction of CD40 with CD154 mediates both humoral and cellular immune responses, and blocking this interaction reduces lesion formation in atherosclerosis-prone mice.[61,62]

There are a number of candidate antigens in the lesion that could be responsible for immune activation, including modified LDL,[35] heat-shock proteins,[63-65] β_2-glycoprotein I,[66] and microbial antigens. Of these, the most extensive data support an important role for oxLDL, which is abundantly present in atherosclerotic plaques, where it is recognized by plaque T cells and gives rise to nonplaque B-cell stimulation.[55,57]

Inflammation, but not infection, plays a critical role in atherogenesis.[67] LDL$^{-/-}$ mice fed normal chow do not develop atherosclerosis, even when infected with *Chlamydia pneumoniae* (Cp), but if cholesterol is added to the diet, hypercholesterolemia-induced atherosclerosis develops and Cp infection appears to accelerate its development.[68] Cp infection appears to accelerate atherosclerosis also in the hypercholesterolemic apoE $^{-/-}$ mice;[69] that is, Cp alone is not atherogenic, although it may be causally related to the development of atherosclerosis. Marek's disease in chickens (avian herpesvirus) is the only disease in which an infection alone causes an arterial disease with some morphologic similarities to human atherosclerosis, but full-blown human-like atherosclerosis develops only if the chickens concomitantly are fed a cholesterol-rich diet.[70] This infectious arterial disease in birds is preventable by vaccination.[71]

Fibroproliferative Response

Only endothelial cells, monocyte-derived macrophages, and a few T cells participate in the early inflammatory/immune response, giving rise to early atherosclerotic lesions (fatty streaks) (Fig. 35-1, Plate 77). In disease progression, this pure inflammatory/immune response is accompanied by a fibroproliferative response in which the vascular smooth muscle cell plays a dominant role.[72] Smooth muscle cells are not normally present in the mouse intima, but they are, of course, present in the adjacent tunica media, from which they migrate into intima to become the matrix-synthesizing cell in the developing atherosclerotic plaque.[72] Macrophages and T cells continue to be present throughout plaque development and probably promote rather than retard progression.

Lipids begin to accumulate extracellularly, partly due to di-rect retention of atherogenic lipoproteins in the extracellular matrix and partly due to foam cell necrosis and apoptosis followed by the release of intracellular lipids to the extracellular space.[44] In such a way, a *necrotic* lipid-rich core with foamy macrophages and cholesterol crystals may form, covered by a fibrous cap containing both smooth muscle cells and inflammatory cells[44] (Fig. 35-2, Plate 78).

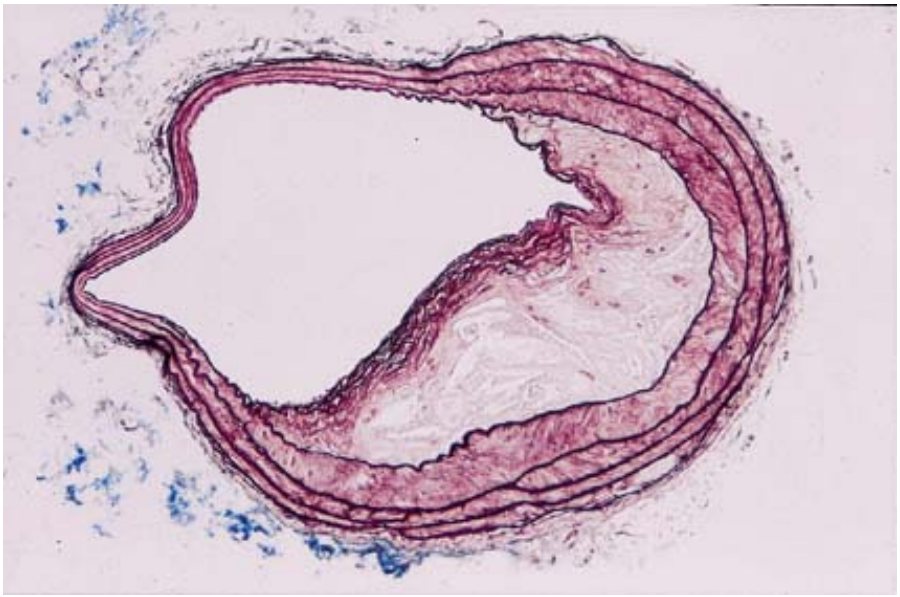

Figure 35-2: (Plate 78) An advanced atherosclerotic plaque in the brachiocephalic trunk of a 6-month-old apolipoprotein E-/- mouse fed normal chow. The plaque appears vulnerable morphologically, consisting of a lipid-rich core with cholesterol crystals covered by a thin fibrous cap. Orcein, staining elastic tissue black.

It has proved much easier to prevent and regress the early inflammatory/immune response than the subsequent fibroproliferative response,[58,59,72-76] and, consequently, much more is known about the molecular mechanisms controlling the former than the latter. All plaque cells, including smooth muscle cells, are capable of forming a large number of growth factors and cytokines, and T cell-derived IFN-γ and responses mediated by CD40 ligation could play important roles in lesion progression.[56,60-62] The smooth muscle cell is the principal connective-tissue cell responsible for healing and repair of the arterial wall. It can elaborate all of the proteins of the matrix, including several forms of collagen (e.g., types I, III, and IV), elastic fiber proteins, and proteoglycans, which together create a complex, heterogeneous extracellular matrix.[72] Cartilaginous metaplasia[77] and calcification are frequently seen in advanced lesions, and both intimal calcification[78] and medial[79] calcification have been studied in atherosclerosis-prone mice.

In normal arteries and in arteries with early atherosclerosis, vasa vasorum are confined to adventitia, but neovascularization of plaques may occur with disease progression. In apoE $^{-/-}$ mice, the incidence of neovascularization is generally low but appears to increase in more advanced and thicker lesions. Thus, thin-walled capillary-like vessels (i.e., neovascularization) have been identified in 15 (13 percent) of 114 advanced aortic lesions from cholesterol-fed apoE $^{-/-}$ mice aged 36 to 60 weeks.[80]

Fibrinogen is not required for, and does not appear to influence, the development and progression of advanced lesions in mice, documented in double gene knockout mice lacking both apoE and fibrinogen.[75] On the other hand, the loss of a key fibrinolytic factor - plasminogen - greatly accelerates lesion formation in apoE $^{-/-}$ mice.[81] Plasminogen deficiency may accelerate atherosclerosis by influencing processes in the vessel wall unrelated to fibrin(ogen) and impaired fibrinolysis.

PLATELET-VESSEL WALL INTERACTION

Before the creation of gene-manipulated atherosclerosis-prone mice, Paigen and colleagues evaluated the potential contribution of platelets to the development of atherosclerosis by

comparing the severity of atherosclerosis in susceptible C57BL/6 mice carrying either a normal or a variant phenotype for platelet function.[82] Five genetically distinct mutants with increased bleeding times and abnormal dense granules were studied, and three of these mutants (light ear, maroon, and ruby eye) developed less atherosclerosis than the controls on the atherogenic diet.[82] The result indicates that some particular component of platelet function affects atherosclerosis. Other defects than those in platelets are, however, present in these mice, which precludes any firm conclusion regarding the significance of the platelet-vessel wall interaction in atherogenesis in these mice.

Platelets may contribute to atherogenesis in at least two different ways: mural thrombi may form on denuded plaques and subsequently be incorporated into developing lesions, and/or they may serve as a source of platelet-derived growth factors and stimulate smooth muscle cell proliferation. Although the endothelium is intact, but activated, early during atherogenesis in both humans and atherosclerosis-prone mice, endothelial denudation or frank plaque rupture with subsequent thrombus formation contribute significantly to plaque development in humans. Spontaneous endothelial denudation with subsequent platelet adhesion (monolayer) or thrombus formation (aggregation) have not been described in mice.

Plaque Disruption and Thrombosis

Although we have learned a lot about atherogenesis by studying the initiation and development of lesions in atherosclerosis-prone mice, nothing has been learned about atherosclerosis-mediated thrombogenesis-the final pathogenetic chain of events precipitating life-threatening heart attacks in humans. Plaque rupture with superimposed thrombosis, which is a rather common feature of human atherosclerosis, is extremely rare in mice and all other animal models of atherosclerosis.[83] This shortcoming is probably the most significant distinction between human atherosclerosis and human-like atherosclerosis in mice.[75]

A variety of proteinases, mostly released by infiltrating mac rophages, have been implicated in plaque rupture in humans, but the actual enzymatic culprits have not yet been conclusively identified.[84] Of the many proteinases present in plaques, members of the matrix metalloproteinase (MMP) family, cysteine proteinases (e.g., elastolytic cathepsins S and K), and serine proteinases [mostly plasminogen and its activators: urokinase-type plasminogen activator (u-PA) and tissue-type plasminogen activator (t-PA)] have received much attention.[84] Atherosclerotic plaques in apoE $^{-/-}$ mice contain a lot of macrophages, both superficially in plaque and at their base, many of which express MMPs, including MMP-3, MMP-9, MMP-12, and MMP-13.[85,86] However, although macrophages at the base of plaques often infiltrate and destroy the internal elastic membrane, media, and adjacent adventitia, which may give rise to aneurysm formation, the plaque surface almost always remains intact without disruption and/or thrombosis. Not a single case of plaque disruption with superimposed thrombosis in mice has been reported. We have performed a meticulous search for ruptured and thrombosed plaques in middle-aged apoE $^{-/-}$ mice (age, >1 year), some of which had died spontaneously of natural causes. Although we have studied several hundred mice, each of which contained many rupture-prone plaques, only two ruptured plaques were identified, one with superimposed thrombosis (Fig. 35-3, Plate 79).

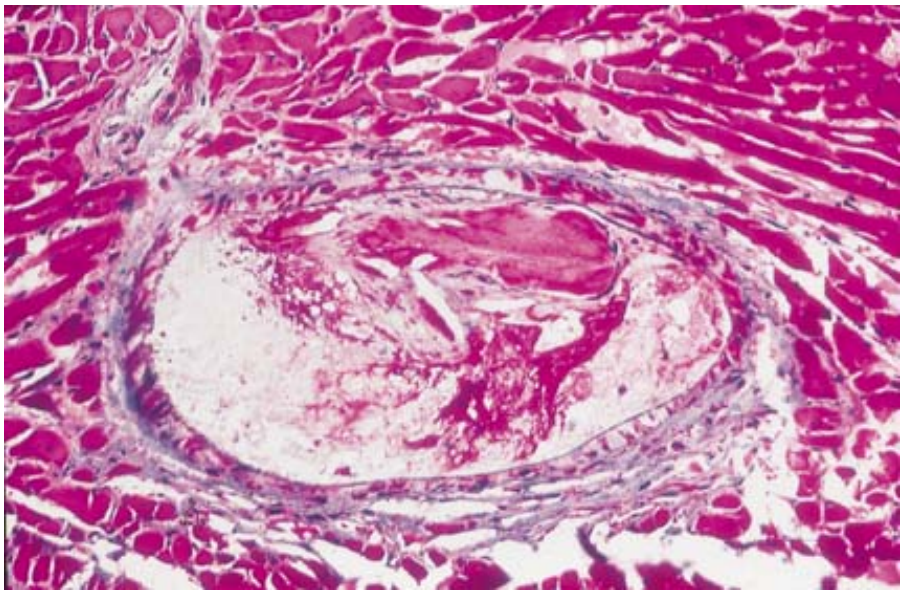

Figure 35-3: (Plate 79) Ruptured coronary plaque with occlusive thrombosis superimposed (natural death of a 21-month-old apolipoprotein E-/- mouse). Spontaneous plaque rupture and/or luminal thrombosis are extremely rare in animal models of atherosclerosis. Elastin trichrome stain.

Remodeling

Consistent with what is observed in human atherosclerosis, arteries in apoE $^{-/-}$ mice remodel in response to plaque growth with no correlation between lesion mass and lumen loss.[87] In the ascending aorta, a normal lumen is preserved due to compensatory vascular enlargement during plaque growth, in contrast to the external carotid arteries, where stenotic lesions tend to develop associated with adventitial inflammation and medial atrophy.[87] Vascular remodeling with preservation of the aortic lumen despite marked intimal thickening has also been described in apoE $^{-/-}$ × LDLR $^{-/-}$ mice.[88]

Vascular Protection

Preventing or retarding atherosclerosis is more than just controlling lipid and other major risk factors. Atherosclerosis is a lipid-driven disease, but not all mice or all arteries within the same mouse are equally susceptible to atherosclerosis;[83] that is, hypercholesterolemia does not necessarily lead to advanced atherosclerosis. The final result depends critically on the participation of many processes not directly related to lipid, and the inhibition of just one necessary step in the pathogenetic chain of events is enough to prevent or retard plaque development. To date, most interventions have targeted the initial step in atherogenesis-hypercholesterolemia-but it may prove to be as, or even more, effective to target subsequent but necessary steps for lesion development in the vessel wall.

TARGETING MONOCYTE/MACROPHAGE FUNCTIONS

Some monocyte/macrophage functions are crucial in the initiation and progression of lesions, documented by reduced lesion development in hypercholesterolemic atherosclerosis-prone mice lacking ICAM-1,[89] macrophage-colony stimulating factor,[90-92] MCP-1,[49,50] MCP-1 receptor CCR2 on monocytes,[53,93] macrophage-expressed 12/15-lipoxygenase,[54] or macrophage scavenger receptors,[94-96] or mice treated with an antibody against the M-CSF receptor c-fms.[73] In contrast, macrophage overexpression of MCP-1 accelerates atherosclerosis.[48]

TARGETING OTHER EVENTS NOT MEDIATED BY LOW-DENSITY LIPOPROTEIN

Interventions, in addition to the monocyte/macrophage-related just described, that have proved to *slow the development of lesions* in atherosclerosis-prone mice, and not mediated by LDL lowering, include apoA1 overexpression;[24,25,29,76,97] apoA1 Milano injection;[98] inactivation IFN-γ receptor;[56] immunization with oxLDL[99,100] or native LDL;[100] antioxidant treatment with high-dose vitamin E[101] (compared with lower dosing),[102] (co)antioxidants H212/43,[103] DPPD,[104] or licorice;[105] treatment with estrogen,[106] L-arginine,[107] the angiotensin-converting enzyme inhibitor captopril,[108] the angiotensin-II receptor antagonist losartan,[109] (cf. Makaritsis et al.[110]), or normal human polyspecific immunoglobulins;[111] inhibition or blocking of endothelin ET_A receptor[20] or interleukin-1 receptor;[112] CD40 ligation;[61,62] angiogenesis (advanced lesions only);[113] and cellular receptor for advanced glycation end products (in diabetic mice);[114] dietary soy protein;[115] and iron-deficient diet.[116]

Interventions that have proved to *accelerate the development of atherosclerosis* independently of LDL cholesterol include probucol (paradoxically and in contrast to other antioxidants such as vitamin E),[117-119] Cp infection,[68,69] cytomegalovirus infection,[120] interleukin 12 administration,[121] immunization with β_2-glycoprotein I,[122,123] absence of the tumor-suppressor protein p53,[124] plasminogen deficiency,[81] and angiotensin II injection.[125]

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Chapter 35: ATHEROGENESIS AND ITS DETERMINANTS

HUMAN ATHEROSCLEROSIS

The Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association, has defined the normal arterial intima and its atherosclerosis-prone regions,[126] asymptomatic early lesions,[127] and advanced and potentially symptomatic lesions.[128] Based on these definitions, a practical histologic classification of human atherosclerotic lesions was published in 1995 (Fig. 35-4),[129] which is summarized by M. J. Davies in Chap. 36. The following description is based on these excellent publications but differs to some extent from the 1995 AHA classification.

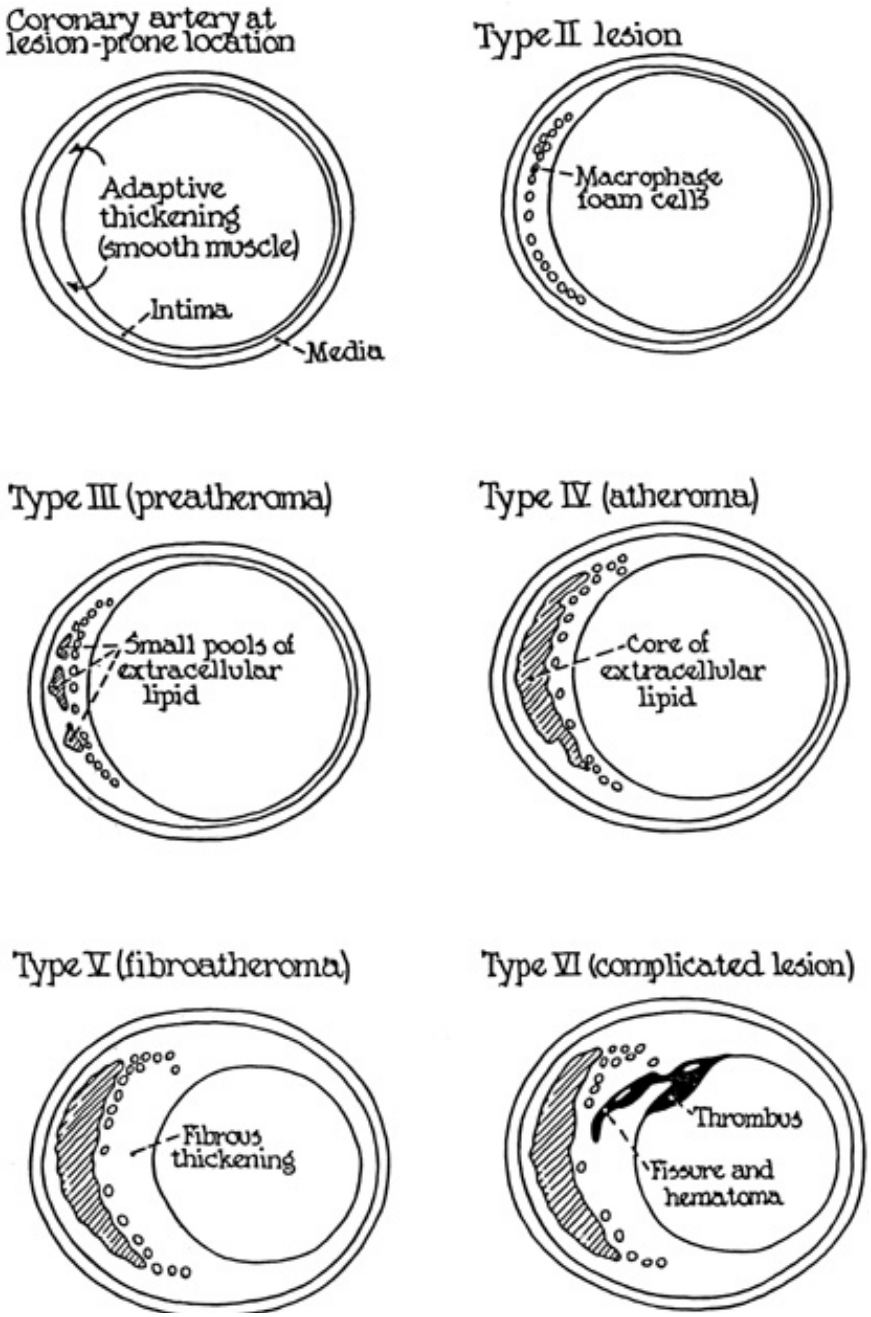

Figure 35-4: The 1995 American Heart Association classification of atherosclerotic lesions. The type I (initial) lesion, which consists of small, isolated groups of macrophages containing lipid droplets, is not shown in this figure. (Adapted from Stary et al.[128] Reproduced with permission from the publisher and authors.)

Endothelial Dysfunction

Atherogenic stimuli may give rise to nonadaptive changes in endothelial structure and function, such as enhanced permeability to plasma lipoproteins, hyperadhesiveness for blood leukocytes, and functional imbalances in local pro- and antithrombotic factors, growth stimulators and inhibitors, and vasoactive substances.[129] These manifestations, collectively termed *endothelial dysfunction*, play an important role in the initiation, progression, and clinical complications of atherosclerosis.[129] It is generally assumed, but not proved, that endothelial dysfunction as just defined equates with endothelial dysfunction as identified clinically as an impairment in endothelium-dependent vasodilation, largely mediated by the endogenous vasodilator nitric oxide and usually reversible. The mere presence of risk factors for ischemic heart disease, such as hypercholesterolemia, hypertension, cigarette smoking, diabetes mellitus, hyperhomocyst(e)inemia, and aging, is associated with endothelial dysfunction as defined clinically, even in the microcirculation and in arteries, such as the brachial artery, that are resistant to atherosclerosis.[130,131] Thus, clinically defined endothelial dysfunction is related to atherosclerosis but not necessarily causally.

Atherosclerosis-Prone Areas

The normal human intima is covered by endothelial cells and contains, in contrast to intima of many laboratory animals (including mice), smooth muscle cells, isolated macrophages, occasional mast cells, and extracellular matrix.[127] The latter constitutes up to 60 percent of the volume and contains proteoglycans (predominantly chondroitin and dermatan sulfates), collagens (predominantly types I and III), elastin, and other components such as fibronectin, laminin, and plasma proteins.[127] Apparently, all plasma proteins are present in lesion-free intima in concentrations related directly to the protein's plasma concentration and inversely to its molecular weight. In the normal artery, LDL is present in intima but is usually not detectable in media.[126]

Regardless of atherogenic stimuli, nonobstructive intimal thickenings are present at constant locations in everyone from birth, particularly at bifurcations, and progress with time. Such adaptive intimal thickenings develop in response to mechanical forces such as pressure, circumferential stretch or tension, and shear stress.[126] Low shear stress and, probably more importantly, oscillatory flow and flow reversal may promote both adaptive intimal thickening and subsequent influx and accumulation of atherogenic lipoproteins.[31] Reduced wall shear stress (dilatation) and increased wall tensile stress (hypertension) promote adaptive intimal thickening, which tends to normalize shear and tension.[126] Eccentric intimal thickening is frequently seen near bifurcations and branch points where shear and tensile stresses are not uniformly distributed, and diffuse thickening may develop in relatively straight arterial segments with evenly distributed stresses.[126] Evidence suggests that the shape of a vessel, rather than the flow patterns, may determine the degree of adaptive intimal thickening and ultimately constitute a risk factor for development of symptomatic lesions.[132]

In human arteries, there is no need for migration of smooth muscle cells into the intima from the media to initiate plaque formation, in contrast to many laboratory animals, where the intima does not normally contain smooth muscle cells. Under the influence of atherogenic stimuli, adaptive intimal thickenings appear to be good soil for the development of atherosclerosis.[133] The smooth

muscle cells present early in preexisting intimal thickenings and later show "clonality" in superimposed atherosclerotic lesions, suggesting clonal expansion during lesion development.[134] Although advanced lesions are not confined to regions with adaptive intimal thickenings, particularly not in hyperlipidemia-induced atherosclerosis in animals, lesions form earlier and more rapidly in these atherosclerosis-prone areas than elsewhere.[33] In humans, the topographic distribution of eccentric intimal thickening and of advanced atherosclerotic lesions is similar in the coronary arteries, the carotid bifurcation, the parasellar carotid artery, and the aorta.[126,132,135]

Fatty Streaks

The early lesions of atherosclerosis develop under an intact but activated and dysfunctioning endothelium, particularly in atherosclerosis-prone areas with preexisting intimal thickening. Inflammation and immune responses play an important role in atherogenesis from its very beginning.[67,136,137] Hypercholesterolemia is associated with increased endothelial permeability, increased transcytosis and intimal retention of lipoproteins, and endothelial activation with focal expression of VCAM-1 leading to monocyte and T-lymphocyte recruitment. Within intima, the monocyte-derived macrophages engulf the blood-derived LDLs, probably via their scavenger receptors after oxidative modification, and become lipid-filled foam cells. These inflammatory cells constitute by far the major part of the early fatty-streak lesion, with a ratio of approximately 1:10 to 1:50 between T cells and macrophages, and they probably play a significant role in the progression of fatty streaks to mature atherosclerotic plaques.[137] The presence of activated macrophages and T cells strongly suggests that an immunologic reaction has taken place in the atherosclerotic plaque. The antigens that elicit this response are not yet known, and both autoantigens (e.g., against oxidized LDL) and microorganisms (e.g., Cp) have been proposed to play a role.[137]

Although immunoglobulins are found in abundance in lesions, B cells are noticeably absent from human plaque. Similarly, although plasma cells have been noted in inflammatory infiltrates in the adventitia surrounding atherosclerotic arteries, few if any such cells have been seen in the plaque itself.[35]

Accumulations of lipid-filled foam cells within intima may be visible to the naked eye as yellow dots or streaks-fatty streaks. Microscopically, fatty streaks are highly cellular inflammatory lesions consisting of macrophage foam cells (intracellular lipid) and T lymphocytes (immune reaction). Extracellular lipid is hardly identifiable microscopically and B lymphocytes and polymorphonuclear neutrophil (PMN) are not seen. Fatty streaks do not protrude into the lumen, and they are therefore asymptomatic.

The fate of fatty streaks remains controversial. It has been known for decades that aortic fatty streaks are present in infants all over the world, irrespective of ethnicity or prevalence of ischemic heart disease in the population.[138] Recently, it was shown that fatty streaks are present already in arteries of human fetuses,[139,140] but, associated with the low blood cholesterol in late pregnancy and early childhood, fetal aortic fatty streaks may regress, just to progress again later during childhood.[3] In laboratory animals, fatty streaks are the most readily produced lesions and regress completely when serum cholesterol is reduced. It is generally assumed that fatty streaks can progress to more advanced lesions because they occur at the same anatomic sites and because transitional stages have been observed.[127] A smaller subgroup of fatty streaks, those superimposed on preexisting intimal thickenings, appear to be particularly prone to progress to advanced symptomatic lesions, but the mode of progression and the factors controlling it are not clear.[127] For example, aortic fatty streaks are universally present in all populations around the world early in life, even in populations at low risk for symptomatic atherosclerosis later in life, such as the South African Bantu.[138] Females have more aortic fatty streaks than males early in life even though males develop more advanced lesions than females later in life.[138,141] Blacks have

more aortic fatty streaks than whites early in life, but the latter have more advanced lesions than the former later in life.[138,141] The thoracic aorta has more fatty streaks than the abdominal aorta early in life, but the opposite applies for advanced lesions later in life.[138] These contrasting relations seen in the human aorta between asymptomatic fatty streaks in young persons and advanced and potentially symptomatic lesions in adults may put into question the relevance of results obtained in short-term animal experiments in which only the development of foam cell lesions (fatty streaks) in aorta are studied.

Advanced Plaques

Advanced lesions may cause luminal narrowing and produce symptoms. In contrast to mice and many other laboratory animals, smooth muscle cells are already present within the human intima early during atherogenesis, beneath developing fatty streaks.[127] When lipids begin to accumulate extracellulary, then atherogenesis has passed beyond the fatty-streak stage. Oxidatively modified LDL is present in atherosclerotic plaques but not in the normal intima.[35,67] Two different processes are responsible for the extracellular accumulation of lipids: blood-derived atherogenic lipoprotein particles may be trapped and retained directly within the proteoglycan-rich extracelluar matrix, and/or lipid may be released from macrophage foam cells following their death. Macrophages both proliferate and die within atherosclerotic plaques, and the balance probably depends on whether the lesion is progressing, quiescent, or regressing.

Progression beyond the fatty-streak stage is not only associated with lipid accumulation; also, connective tissue, produced by smooth muscle cells, accumulates, giving rise to very heterogeneous atherosclerotic lesions. Some plaques are lipid rich, whereas others are lipid poor, and morphologically dissimilar plaques may evolve next to each other.[6] The endothelium is intact early during atherogenesis, but denuded areas, often related to superficial foam cell infiltration (inflammation), with adherent platelets are later seen over mature plaques.[142,143] Then, growth factors released from adherent platelets and microthrombi may stimulate the smooth muscle cells within the plaques to produce more connective tissue matrix.[72] Because of a leaky endothelium, not only lipoproteins but also many other blood-derived components, including albumin and fibrinogen, are present in evolving lesions.[144]

Neovascularization, often expressing leukocyte adhesion molecules such as VCAM-1 and ICAM-1 and associated with inflammatory cell infiltration, is frequently present at the base of advanced plaques, and it has been suggested that these "new" vessels could play an active role in the recruitment of leukocytes into plaques and thus contribute to the progression of the disease.[145] Extravasated erythrocytes are also frequently seen in these neovascularized areas.

VULNERABLE PLAQUES

A subset of the advanced lesions is particularly dangerous-the vulnerable plaques-because they are at high risk of becoming complicated by luminal thrombosis (Fig. 35-5, Plate 80). Disruption of vulnerable plaques with superimposed thrombosis is the most frequent cause of the acute coronary syndromes of unstable angina, myocardial infarction, and sudden coronary death.[7,146,147]

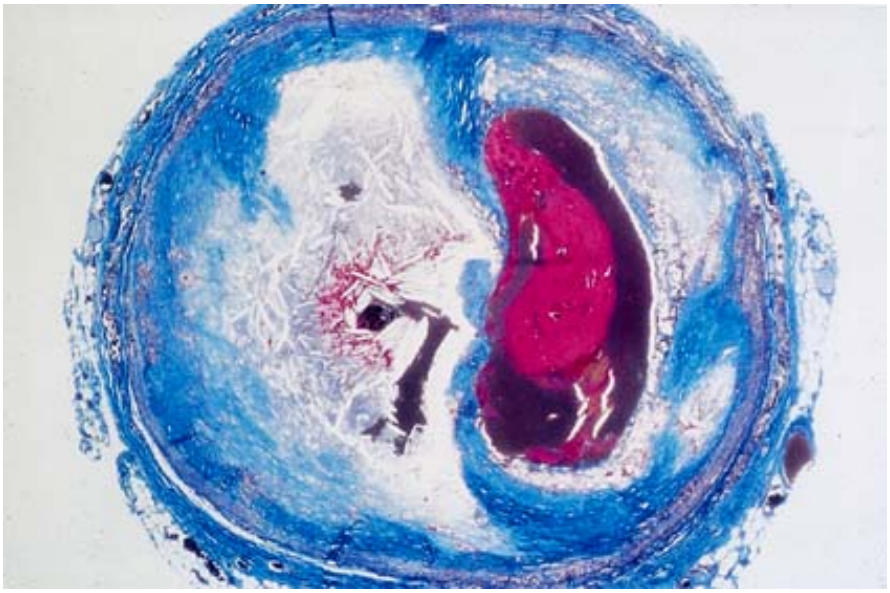

Figure 35-5: (Plate 80) Cross-sectioned coronary artery, containing a vulnerable plaque (large lipid-rich core covered by a thin fibrous cap) with ruptured surface and a nonocclusive luminal thrombosis superimposed. Trichrome stain.

The risk of plaque disruption depends more on plaque type than on plaque size: lipid-rich and soft plaques are more vulnerable and prone to rupture than are collagen-rich and hard plaques.[7] Furthermore, plaques are highly thrombogenic after disruption, because of a high content of tissue factor.[148] Pathoanatomic studies have identified three major determinants of a plaque's vulnerability to rupture (Fig. 35-6): (1) the size of the lipid-rich core, (2) inflammation with plaque degradation, and (3) lack of smooth muscle cells with impaired healing.

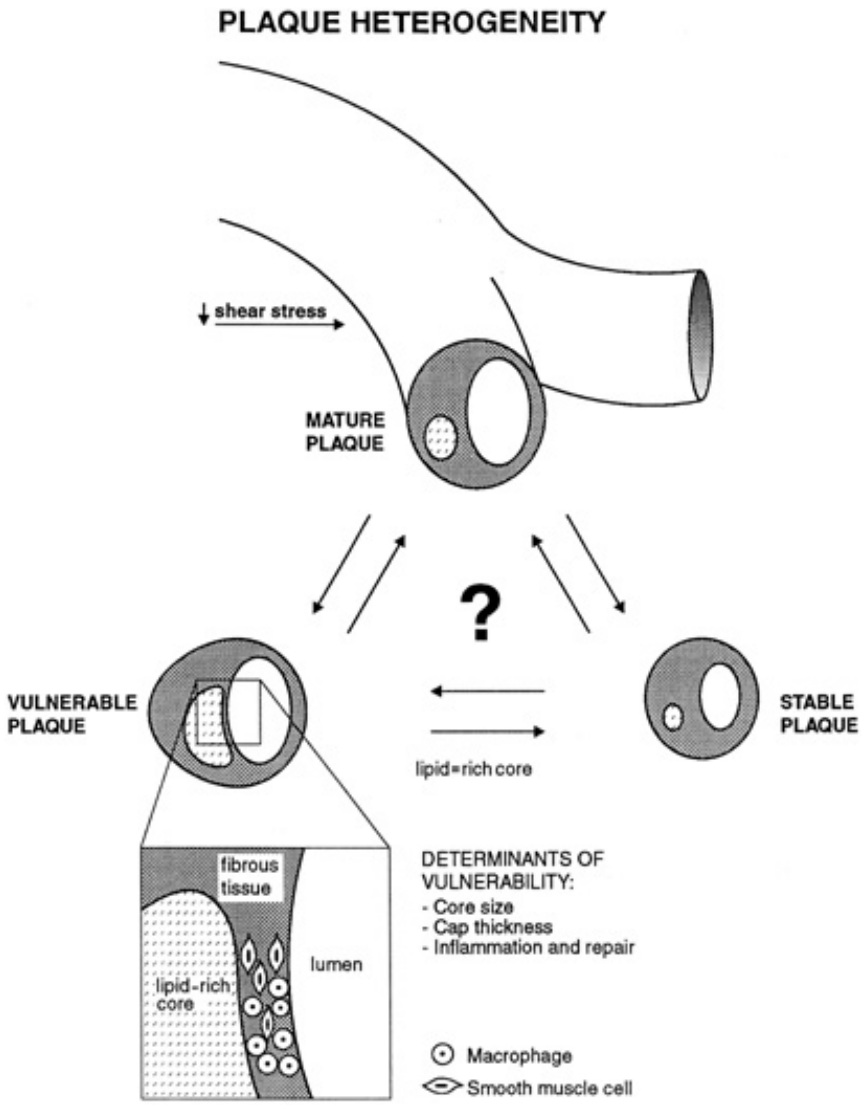

Figure 35-6: Advanced atherosclerotic plaques are extremely heterogeneous in composition. A subset of the advanced plaques are vulnerable (i.e., rupture-prone) with high risk of becoming complicated by luminal thrombosis. The relation between vulnerable and stable plaques is not well defined. (Adapted from Ravn and Falk.[412] Reproduced with permission from the publisher and authors.)

Lipid accumulation, macrophage infiltration, and lack of smooth muscle cells destabilize plaques, making them vulnerable to rupture. In contrast, smooth muscle cell-mediated healing and repair processes stabilize plaques, protecting them against disruption.[136] Plaque size or stenosis severity tell nothing about a plaque's vulnerability.[149] Many vulnerable plaques are invisible angiographically due to their small size and compensatory vascular remodeling.

Lipid Accumulation

The atheromatous core of a plaque is avascular, hypocellular, lipid rich, soft like gruel, and totally devoid of supporting collagen.[7] The size of such a soft core is, of course, critical for the stability of a plaque. At autopsy, Gertz and Roberts found much larger atheromatous cores in coronary plaques with disrupted (compared with intact) surface,[150] and Davies and coworkers found a strong relation between core size and plaque rupture in aorta.[151] Recent studies using immunohistochemical and tunnel staining techniques have identified macrophage-specific antigens and apoptotic nuclear fragments within the gruel, indicating that lipid and other cell constituents released from dead macrophage foam cells could contribute significantly to the

formation and growth of the atheromatous core, which is why it also has been referred to as the "graveyard of dead macrophages," emphasizing the inflammatory origin of this destabilizing core.[152-154]

Plaque Degradation

Disrupted fibrous caps are usually heavily infiltrated by macrophage foam cells,[7,155] and recent observations have revealed that such rupture-related macrophages are activated, indicating ongoing inflammation at the site of plaque disruption.[156] Van der Wal and colleagues identified superficial macrophage infiltration in plaques beneath all 20 coronary thrombi examined, whether or not the underlying plaque was disrupted or just eroded,[156] although a more recent study of coronary thrombi responsible for sudden coronary death could not confirm that observation.[157] Evaluated by immunohistochemical technique, van der Wal and coworkers found that macrophages and adjacent T lymphocytes (smooth muscle cells were usually lacking at rupture sites) were activated, indicating ongoing disease activity.[156] Further evidence of immune activation is the upregulated expression of CD40 receptor and its ligand by all cell types present in advanced atherosclerotic lesions.[60] Comparable results were obtained by the same group in a study of atherectomy specimens showing an inverse relation between the extent of inflammatory activity in plaque tissues of culprit lesions and the clinical stability of the ischemic syndrome.[158] There was considerable overlap between groups, however, indicating that not all patients with clinically stable angina have histologically stable plaques.[158] These observations confirmed the findings of a previous study of atherectomy specimens from culprit lesions responsible for stable angina, unstable rest angina, or non-Q-wave infarction.[159] Culprit lesions responsible for the acute coronary syndromes contained significantly more macrophages than did lesions responsible for stable angina pectoris (14 versus 3 percent of plaque tissue occupied by macrophages).[159]

Macrophages are capable of degrading extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as members of the MMP family (collagenases, gelatinases, and stromeolysins), cysteine proteinases (e.g., elastolytic cathepsins S and K), and serine proteinases (mostly plasminogen and its activators, u-PA and t-PA), which may weaken the fibrous cap, predisposing it to rupture.[83,160] All these proteinases have been identified in human plaques and have been implicated in plaque rupture, but the actual enzymatic culprits have not yet been conclusively identified.[83] The MMPs are secreted in a latent zymogen form requiring extracellular activation, after which they are capable of degrading virtually all components of the extracellular matrix. The MMPs and their cosecreted tissue inhibitors or metalloproteinases TIMP-1 and TIMP-2, are critical for cell migration, tumor invasion and metastasis, and vascular remodeling. Collagen confers stability to plaques, and human monocyte-derived macrophages grown in culture are indeed capable of degrading the old and mature collagen present in advanced aortic plaques.[161] Simultaneously, they express MMP-1 (interstitial collagenase) and induce MMP-2 (gelatinolytic) activity in the culture medium.[161] Besides macrophages, a wide variety of cells may produce MMPs. Activated mast cells may secrete powerful proteolytic enzymes such as tryptase and chymase that can activate pro-MMPs secreted by other cells (e.g., macrophages), and mast cells are actually present in shoulder regions of mature plaques and at sites of disruption, although at very low density.[162] Neutrophils are also capable of destroying tissue by secreting proteolytic enzymes but are rare in intact plaques.[137,156]

Several infectious agents have been suggested to play an active role in the development of cardiovascular diseases, particularly Cp but also herpesviruses (including cytomegalovirus) and *Helicobacter pylori*.[163-165] *Chlamydia* has been identified in atherosclerotic plaques;[166] it contains lipopolysaccharide and heat-shock protein 60, which are well-known strong inducers of many enzymes including MMPs.[167] Nonspecific but sensitive blood markers of inflammation (acute-phase reactants such as C-reactive protein and serum amyloid A) have been identified as

strong risk factors for future cardiovascular events in apparently healthy men[168] and women,[169] in patients with stable[170] and unstable angina,[171-173] and after myocardial infarction.[174]

Impaired Healing

Obviously, the thickness and collagen content of the fibrous cap is very important for its strength and stability: the thinner the cap is, the weaker it is and the more vulnerable is the plaque to rupture.[175] Ruptured aortic caps contain fewer smooth muscle cells and less collagen than intact caps,[151,176] and smooth muscle cells are usually missing at the actual site of disruption.[156,162]

Collagen is responsible for the mechanical strength of the fibrous cap and is synthesized by intimal smooth muscle cells. It is important to realize that smooth muscle cell proliferation and matrix synthesis may, in fact, be good in protecting plaques against disruption, whereas local loss of smooth muscle cells or impaired smooth muscle cell function may be bad, leading to gradual plaque destabilization due to impaired healing and repair.[136] It is unknown why smooth muscle cells are lacking at sites of disruption, but apoptotic cell death could play an important role.[153,154]

Complicated Plaques

We use the term *complicated plaques* when referring to advanced lesions complicated by luminal thrombosis and/or plaque hemorrhage. Such an acute plaque event causes rapid progression of the lesion[177] and is probably the most important mechanism responsible for the unpredictable, sudden, and rapid progression of coronary lesions observed by serial angiographic examination. As just described, plaque disruption with superimposed thrombosis is the most frequent cause of a life-threatening acute myocardial infarction.

PLAQUE DISRUPTION

Vulnerable plaques rupture frequently. Autopsy data indicate that 9 percent of healthy persons harbor disrupted plaques (without superimposed thrombosis) in their coronary arteries, increasing to 22 percent in persons with diabetes or hypertension.[178] In fatal coronary artery disease, more than one disrupted plaque, with or without superimposed thrombosis, is usually present in the coronary arteries.[155,179]

The plaque surface is disrupted most often where the cap is thinnest and most heavily infiltrated by macrophages and therefore weakest, namely, at the cap's shoulders.[7,180] The weak shoulder regions, however, are also points where biomechanical and hemodynamic forces acting on plaques appear to be concentrated.[180,181] Thus, plaque disruption is probably the result of a dynamic interaction between *intrinsic* plaque changes (vulnerability) and *extrinsic* forces imposed on the plaque (triggers); the former predispose a plaque to rupture, whereas the latter may precipitate it. As the presence of a vulnerable plaque is a prerequisite for plaque disruption, plaque vulnerability is probably more important than rupture triggers in determining the risk of a future heart attack. If no vulnerable plaques are present in the coronary arteries, there is no rupture-prone substrate for a potential trigger to function on. Furthermore, the fact that exercise stress testing in individuals with advanced coronary artery disease rarely triggers an acute coronary event suggests that plaque vulnerability ultimately plays a more important role in plaque rupture than does physiologic stress or other potential triggers.

LUMINAL THROMBOSIS

The most feared consequence of coronary plaque disruption is thrombotic occlusion of the artery. About 75 percent of thrombi responsible for acute coronary syndromes are precipitated by plaque disruption whereby the highly thrombogenic gruel is exposed to the flowing blood.[155,182,183] In

the remaining 25 percent, superficial plaque erosion without frank disruption (i.e., no deep injury) is usually present.[2] Most disrupted plaques are resealed by a small mural thrombus, and only sometimes does a major luminal thrombus evolve. There are three major determinants of the thrombotic response to plaque disruption/erosion: (1) the local thrombogenic substrate, (2) the local flow disturbances, and (3) the systemic thrombotic propensity.

Inflammatory cells might also play an important role in the thrombotic response to plaque disruption/erosion via tissue factor expressed locally in plaque macrophages and systemically in blood monocytes.[148,184-186] The thrombotic response to plaque disruption is dynamic; thrombosis and thrombolysis occur simultaneously in many patients with acute coronary syndromes, with or without concomitant vasospasm, causing intermittent flow obstruction. The initial flow obstruction is usually due to platelet aggregation, but fibrin is important for the subsequent stabilization of the early and fragile platelet thrombus. Therefore, both platelets and fibrin are involved in the evolution of a persisting coronary thrombus.[187]

Clinical Manifestations

Plaque disruption itself is asymptomatic, and the associated rapid plaque growth is usually clinically silent. However, rupture-related hemorrhage into the plaque, luminal thrombosis, and/or vasospasm may cause sudden flow obstruction, giving rise to an acute coronary syndrome. The culprit lesion is frequently *dynamic*, causing intermittent flow obstruction, and the clinical presentation and the outcome depend on the severity and duration of myocardial ischemia.[146,147,187] A nonocclusive or transiently occlusive thrombus most frequently underlies primary unstable angina with pain at rest and myocardial infarction without ST-segment elevation, whereas a more stable and occlusive thrombus is most frequently seen in infarction with ST-segment elevation-overall modified by vascular tone and collateral flow. The coronary lesion responsible for out-of-hospital cardiac arrest or sudden coronary death is often similar to that of unstable angina: a disrupted plaque with superimposed nonocclusive thrombosis.[179]

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Chapter 35: ATHEROGENESIS AND ITS DETERMINANTS

ATHEROSCLEROSIS-RELATED FEATURES

Patients with CHD generally have many atherosclerotic plaques in their coronary arteries, which vary considerably in their composition. Although coronary angiography may show only one or a few stenotic lesions, many more plaques are observed on intravascular ultrasound examination in living patients and at autopsy in deceased patients.[188,189] Only a minority of plaques protrude into and compromise the lumen because of compensatory abluminal vascular enlargement (remodeling) during plaque growth.[190] Thus, the lumen may remain normal despite buildup of large volumes of atherosclerotic plaque in the vessel wall. For all practical purposes, diagnostically as well as therapeutically, coronary atherosclerosis is a diffuse disease with superimposed focal luminal narrowing.

Arterial Remodeling and Luminal Narrowing

Vascular remodeling is the ability of the vessel wall to reorganize its cellular and extracellular components in response to a chronic stimulus.[191] In human atherosclerosis, there is ample evidence for active remodeling during the early stages of disease prior to significant lumenal stenosis. It was originally assumed that atherogenesis was always associated with more or less compensatory enlargement of coronary arteries during plaque growth,[190] but recent studies suggest that remodeling is bidirectional.[192] Plaques responsible for acute coronary syndromes are usually relatively large and associated with compensatory enlargement, which tends to preserve a normal lumen despite the presence of significant, and potentially dangerous, vessel wall disease. In contrast, plaques responsible for stable angina are usually smaller but, nevertheless, may cause more severe luminal narrowing because of concomitant local shrinkage of the artery.[193] The reason for these different modes of remodeling is unknown, but processes in adventitia could play a critical role.

Stenosis as Predictor

The vulnerability and thrombogenicity of atherosclerotic plaques rather than their obstructive capability (stenosis severity), together with the status of the collateral circulation, have emerged as the most important determinants for the occurrence, type, and outcome of acute coronary events.[7,146,147] Thus, coronary angiography is not a good method to identify high-risk thrombosis-prone lesions, partly because the size of a plaque and its vulnerability correlate poorly, if at all,[149] and partly because vascular remodeling tends to preserve the lumen better with the larger but vulnerable plaques (compensatory enlargement) than with the smaller and stable plaques (shrinkage).[193]

The great majority of heart attacks and ischemic strokes originate from atherosclerotic lesions that, prior to the acute events, only were mild-to-moderately stenotic; i.e., they were hemodynamically insignificant and probably asymptomatic (Fig. 35-7). Although the risk for occlusion, or myocardial infarction or stroke, increases with stenosis severity, the great majority of coronary occlusions (71 percent) in the Coronary Artery Surgery Study and myocardial infarctions (86 percent) in pooled studies originated from lesions that caused less than 70 to 80 percent angiographic stenosis prior to the acute events.[7] The reason is that stenotic lesions are markers of plaque burden, and lower-risk nonstenotic lesions will always by far outnumber the higher-risk stenotic ones and altogether increase the risk for an acute event much more than the

few stenotic lesions at higher individual risk. And the same holds for ischemic stroke. Asymptomatic plaques at the carotid bifurcation, contralateral to symptomatic lesions, were evaluated and followed in the European Carotid Surgery Trial (n = 2240).[194] Only 13 (19 percent) of 67 new strokes were judged to have originated from initially asymptomatic lesions that at baseline caused more than 70 percent angiographic stenosis (Fig. 35-7). The reason: lower-risk nonstenotic carotid plaques (n = 2113) outnumbered by far the stenotic ones (n = 127) at higher risk.

Coronary stenosis: progression to occlusion

Serial angiography in 298 patients*

Stenosis at baseline	Segments n	Occlusion, 5-year %	n	
< 5%	2161	.7	15	
5 - 49%	430	2	10	51
50 - 80%	258	10	26	
81 - 95%	89	24	21	
All	2938		72	

*Alderman EL et al. *J Am Coll Cardiol* 1993; 22:1141-54

Coronary stenosis: progression to MI

Serial angiography in 239 patients#

Stenosis prior to MI	Segments n	Culprit for MI %	n	
0%	2674	0.3	8	
25%	287	3.5	10	
50%	123	4.1	5	29
75%	76	7.9	6	
90 - 99%	115	8.7	10	
All	3275		39	

#Nobuyoshi M et al. *J Am Coll Cardiol* 1991; 18:904-10

Carotid stenosis: progression to stroke

Angiography in 2240 patients¶

Stenosis at baseline	n	Ipsilateral stroke %, 3 y	n, 4.5 y

at baseline	n	%, 3 y	n, 4.5 y	
0 - 29%	1270	1.8	28	54
30 - 69%	843	2.1	26	
70 - 99%	127	5.7	13	
All	2240		67	

¶European Carotid Surgery Trial. *Lancet* 1995; 345:209-12

Figure 35-7: Most coronary occlusions (*top*, 51/72 = 71 percent), myocardial infarctions (*middle*, 29/39 = 74 percent), and ischemic strokes of carotid origin (*bottom*, 54/67 = 81 percent) are caused by acute thrombosis superimposed on atherosclerotic lesions that, prior to the acute events, were asymptomatic and only mildly to moderately stenotic. Overall, nonstenotic atherosclerotic lesions by far outnumber the stenotic ones at higher individual risk, which is why most acute clinical events originate from nonstenotic lesions at relative low individual risk. MI = myocardial infarction.

Vasoconstriction

Plaque disruption and vasospasm often coexist, and the former most likely gives rise to the latter.[7] Abnormal coronary vasoreactivity is common in acute coronary syndromes but *spasm* is usually confined to the culprit lesion, suggesting that it is caused by locally released vasoactive substances.[195] The plaque, particularly macrophages in disrupted plaques responsible for unstable angina, may contain potent vasoconstrictors such as endothelin 1,[196,197] and superimposed thrombosis may also contain or generate vasoconstrictors such as thrombin and platelet-derived serotonin and thromboxane A_2.[147]

Coronary Calcification

Focal calcification in atherosclerotic plaques is very common and increases with age, both in men and women. Both lipid-rich and collagen-rich components may calcify, and the process may be active and controlled, resembling calcification in bone, rather than being passive and *dystrophic*.[198,199] Coronary calcification in adults is almost always atherosclerosis related and intimal.[200] Medical calcification (Mönckeberg's calcinosis) is rare in coronary arteries, even in diabetic persons where it frequently occurs in other arteries, particularly the muscular arteries of the legs.[201] Both autopsy and clinical data indicate that coronary calcification is a marker for, and correlates closely with, the overall atherosclerotic plaque burden,[202-204] but calcification of a plaque does not correlate with its flow-limiting capacity (degree of stenosis) [202,203] or its risk of sudden occlusion (vulnerability). If anything, heavily calcified plaques appear to be more stable than noncalcified plaques.[203,205-207] The vascular remodeling phenomenon is the likely explanation for the poor correlation of plaque calcification with lumen narrowing and/or stenosis severity.[202]

It is possible to detect and quantify coronary artery calcification noninvasively by electron-beam [or *ultrafast*] computed tomography (EBCT). Plaque calcification detected by EBCT is not necessarily an end-stage irreversible phenomenon; recent data suggest that it may regress with lipid-lowering therapy.[208] Taking age, sex, and clinical presentation into account, coronary calcification may noninvasively identify patients, rather than plaques, at increased risk, because the overall plaque burden, of which coronary calcification is a marker, rather than the severity of individual plaques/stenoses, predicts future coronary events in both symptomatic and asymptomatic adults. The more plaques there are, the greater is the likelihood of one of them

being vulnerable and prone to thrombose.

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Chapter 35: ATHEROGENESIS AND ITS DETERMINANTS

FACTORS INFLUENCING ATHEROGENESIS

Atherosclerosis is the result of multiple and complex gene-environment interactions. Genetic factors alone may cause symptomatic atherosclerosis (e.g., homozygous LDLR deficiency), but it is rare. Most frequently, the genetic background determines an individual's response to proatherogenic factors and the susceptibility of the vessel wall to atherogenic stimuli, but environmental factors may markedly influence the speed of disease progression (plaque development) and, thus, determine whether CHD develops. In high-risk societies, epidemiologic studies with autopsy follow-up have revealed a large individual variation in the extent of atherosclerosis (plaque burden) in apparently homogeneous subgroups.[209] The three factors that most consistently have been shown to correlate with the extent of atherosclerotic lesions per se at autopsy in men (high total cholesterol, low HDL cholesterol, and high blood pressure) explain together only about 25 percent of the individual variation.[209] Thus, a large part of the individual variation in the development of atherosclerosis remains unexplained. Only sparse and inconclusive data are available for women.

Several major and independent risk factors for the clinical manifestations of atherosclerosis have been identified, including elevated serum total (and LDL) cholesterol, low serum HDL cholesterol, cigarette smoking, elevated blood pressure, diabetes mellitus, and advancing age.[210] If left untreated, any of these major risk factors has the potential to produce clinical disease. Nevertheless, in principle, only a single absolutely necessary and truly independent etiologic agent for atherosclerosis exists, and it is a high level of serum LDL cholesterol (or its surrogate, serum total cholesterol).[210-212] A strongly positive relation exists between serum cholesterol levels and CHD worldwide, and atherosclerotic events are rare in populations with total cholesterol less than 4 mmol/L (150 mg/dL), even in the presence of other major risk factors.[212-214] At higher cholesterol levels, smoking, hypertension, low HDL cholesterol, and diabetes mellitus promote development of coronary atherosclerosis and predispose individuals to CHD, but these statistically independent risk factors can not by themselves cause atherosclerosis.[211] In affluent societies, however, many patients with CHD have serum cholesterol levels within or below the average range for these high-risk populations, and there is considerable overlap (about 80 percent) in the distribution of cholesterol values among men with and without CHD.[215] Known risk factors for CHD, of which serum cholesterol concentration is just one, explain only half of the variance in the occurrence of the disease.[216] Although it is said that as many as 50 percent of CHD patients lack major cardiovascular risk factors,[217] recently published data indicate that very few, less than 5 to 10 percent, of young adult and middle-aged men and women in the United States lack major risk factors, defined as serum cholesterol level less than 5.17 mmol/L (<200 mg/dL), blood pressure less than or equal to 120/80 mmHg, no smoking, and no diabetes. In this small low-risk subgroup, long-term mortality is much lower and longevity is much greater.[218] Both human and experimental studies strongly indicate that a certain serum cholesterol level (~4 mmol/L; 150 mg/dL) needs to be present to initiate and drive the disease in the vessel wall: atherosclerosis.[210,216] Below that level, CHD is rare, regardless of other risk factors.

Except for LDL cholesterol, very little is known about the specific relation of cardiovascular risk factors to atherosclerosis. The matter is complicated by the fact that symptomatic human plaques develop over decades and are extremely heterogeneous. Even plaques developed next to each other in the same coronary artery and thus exposed to the same systemic risk factors may look

very dissimilar. If a particular risk factor plays a pathogenetic role in arterial occlusive disease, it could, in principle, do so by (1) accelerating the atherosclerotic process itself (plaque burden), (2) destabilizing established plaques (vulnerability, erosin, and rupture), and/or (3) promoting thrombosis on plaques via local (plaque thrombogenicity) and/or systemic factors. With these different pathways in mind, the role of the major risk factors in atherogenesis will be discussed.

Lipoproteins

Elevated serum total (and LDL) cholesterol and low serum HDL cholesterol are major independent risk factors for CHD.[210] Epidemiologic observations, angiographic studies, and lipid-lowering trials, as well as experimental studies, confirm the importance of LDL as a cause of atherosclerosis in both men and women with or without symptoms of CHD.[211,214] An elevated LDL-cholesterol level appears to be the primary CHD risk factor, and the higher the total and LDL cholesterol levels are, the greater is the risk of an atherosclerotic event.[210,211] A strongly positive relation exists between serum cholesterol levels and CHD worldwide,[212-214] and no threshold has been identified below which a lower blood cholesterol is not associated with a lower risk of CHD; the lower the cholesterol, the lower the risk of CHD, even in Chinese populations who, by Western standards, have a low cholesterol concentration.[219] Normal laboratory animals with low cholesterol levels do not develop atherosclerosis.

A low level of HDL cholesterol is a potent individual predictor for CHD in populations in which average cholesterol levels are relatively high, but it may not hold as a predictor in populations in which mean levels of serum total (and LDL) cholesterol are low.[211] In this regard, low HDL cholesterol resembles the other independent major risk factors (smoking, hypertension, and diabetes): it appears to promote coronary atherosclerosis when a high LDL level is present, but not when it is absent.[211] Thus, low HDL cholesterol and nonlipid risk factors aggravate the effect of LDL cholesterol, especially when total and LDL cholesterol are only moderately elevated; 5 to 6.5 mmol/L (190 to 250 mg/dL) and 3 to 4.5 mmol/L (115 to 175 mg/dL), respectively.[214]

Atherosclerosis is due to influx, retention, and modification of atherogenic lipoproteins in the intima, including LDL, intermediate-density lipoproteins (IDLs), and small species of very low density lipoproteins (VLDLs). The degree to which lipoproteins cause atherosclerosis depends in part on their size, explaining why large VLDLs and chylomicrons, which are too large to enter the artery wall, are not atherogenic.[214] The smallest lipoproteins, HDLs, enter the artery wall quite easily but also leave the artery wall easily and do not cause atherosclerosis. In fact, HDL probably affords protection by facilitating the removal of cholesterol from the vessel wall (reverse cholesterol transport).[214] Cholesterol and triglycerides are lipid components of all these various lipoproteins, and measurements of cholesterol or triglycerides therefore do not accurately reflect the particular lipoproteins that cause atherosclerosis. ApoB is a protein common to LDLs, IDLs, VLDLs, and chylomicrons. Since the latter are not present in plasma in the fasting state, almost all apoB is in atherogenic lipoproteins, which is why a fasting plasma apoB level is a good marker of cardiovascular risk.[214]

The relationship of triglycerides to atherosclerosis has been a source of confusion, partly because not all triglyceride-rich lipoproteins are atherogenic (smaller VLDLs versus larger VLDLs and chylomicrons) and partly because VLDLs and HDLs are metabolically closely linked (HDL-cholesterol concentrations are usually low when triglyceride concentrations are high).[214] Severe hypertriglyceridemia due to chylomicrons and large forms of VLDL is not atherogenic (but may cause pancreatitis), in contrast to less severe hypertriglyceridemia due to small VLDLs and IDLs (VLDLs normally carry most of the plasma triglyceride). Recent data have more clearly identified hypertriglyceridemia as a risk factor for CHD.[214] The strong inverse association between plasma

HDL cholesterol and CHD is a consistent observation, but exactly how this relationship comes about is not entirely understood. HDL cholesterol may, as already described, be a reciprocal measure of atherogenic lipoproteins such as small VLDLs, it may protect the vessel wall by inhibiting LDL oxidation, and/or it may promote the removal of cholesterol from the vessel wall (reverse cholesterol transport).[214] Experimental studies suggest that HDL and its major protein component, apoA1, indeed have an innate atheroprotective effect.[76,220-222]

Prospective epidemiologic studies with autopsy follow-up have shown that serum total cholesterol measured during life correlates with the amount of atherosclerosis (plaque burden) in all arterial segments studied (aorta and coronary and cerebral arteries) in men (only one small study included females).[209] In the only study in which HDL cholesterol was measured, it correlated inversely with coronary atherosclerosis.[209] Recent data from the Bogalusa Heart Study, a long-term epidemiologic study of cardiovascular risk factors in children and young adults, revealed that antemortem risk factors relate strongly to atherosclerosis in autopsied children and young adults.[223,224] LDL cholesterol, triglycerides, body mass index, and elevated blood pressure correlated positively with both fatty streaks and more advanced lesions in coronary arteries; no significant correlation was found with HDL cholesterol.[223]

In the multicenter Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, HDL cholesterol and non-HDL cholesterol in blood obtained postmortem correlated negatively and positively, respectively, with the extent of atherosclerosis in autopsied persons (n = 715).[225] Neither apoA1 nor apoB measures were as strongly or consistently correlated with extent of lesions as the corresponding lipid measure (HDL cholesterol and non-HDL cholesterol, respectively).[225] Including all available risk factors (sex, age, race, smoking status, hypertension, and the lipid measures) in a predictive model, only up to 25 percent of the variation in raised lesions were explained, and HDL cholesterol and non-HDL cholesterol alone increased the explanatory capability by only 2.5 percent. Thus, the larger part of the individual variation in the development of atherosclerosis remains unexplained.

High plasma concentrations of lipoprotein-a- (Lp-a-) identifies persons at increased risk of ischemic heart disease (IHD), but whether Lp(a) is causally related to occlusive arterial disease is unknown. Lp(a) predominantly localizes in atherosclerotic plaques,[39,226] but neither Lp(a) concentration nor its size correlated strongly or consistently with the extent of atherosclerosis in autopsied persons in the PDAY study.[225] It was therefore concluded that Lp(a), which contains apo(a) (which bears significant homology to plasminogen), probably acts by interfering with the thrombotic complications to atherosclerosis rather than promoting atherosclerosis itself.

Regarding plaque composition, recent studies of sudden coronary deaths indicate that elevated total cholesterol and reduced HDL cholesterol, but particularly a high total-to-HDL ratio, predispose men and postmenopausal women to the development of vulnerable rupture-prone plaques with superimposed thrombosis.[227,228]

Smoking

Cigarette smoking is a major, and the single most modifiable, risk factor for atherosclerosis-related clinical events, both in high-risk[211,229] and low-risk[230-232] populations. As many as 30 percent of all CHD deaths in the United States each year are attributable to cigarette smoking, and smoking is the predominant cause of peripheral arterial disease and abdominal aortic aneurysm, it is a major risk factor for ischemic stroke, and it increases the risk of many other chronic diseases.[229] Evaluated statistically by multivariate analysis, smoking contributes to CHD risk independently of other risk factors, but this does not mean that smoking is an independent cause of CHD. Cigarette smoking is pathogenetically a cholesterol-dependent risk factor and acts

synergistically with other risk factors, substantially increasing the risk of CHD.[211,229] Smoking is only weakly, if at all, atherogenic, and smoking alone does not cause a high incidence of CHD, exemplified by low CHD rates in populations in which cigarette smoking is heavy but total cholesterol levels are uniformly low (<4 mmol/L; 150 mg/dL).[212] A dose-related and potentially reversible impairment of endothelium-dependent vasodilation was found in healthy young adults who smoked cigarettes,[233] and smoking also contributes to coronary artery spasm.[234]

Cigarette smoking is a strong predictor of myocardial infarction but not for uncomplicated angina pectoris.[211,235,236] This could mean that smoking does not cause coronary atherosclerosis per se but rather increases the risk for thrombotic events in those who already have reached a certain level of coronary atherosclerosis. Support for this view comes from prospective epidemiologic studies with autopsy follow-up: smokers do not have significantly more extensive coronary atherosclerosis, evaluated grossly as intimal surface covered by plaques, than nonsmokers.[209,237-241] This finding is supported by the more recent PDAY study, in which the extent of coronary atherosclerosis did not correlate significantly with serum thiocyanate (a marker of exposure to smoke, measured post mortem)[141] but, evaluated microscopically, established plaques appeared to be more rapidly progressing and thus reaching an advanced stage of the disease earlier.[242] A coronary thrombus is more freqently found in smokers than in nonsmokers dying suddenly of CHD,[227,228] and preliminary data suggest that smoking may increase the thrombogenicity of plaques by upregulating tissue factor expression.[243] In contrast to coronary atherosclerosis, aortic atherosclerosis and particularly abdominal aortic aneurysm are strongly related to smoking.[141,209,237,238,240,241]

A strong synergistic interaction exists between hypercholesterolemia and smoking in the genesis of myocardial infarction: the former promotes coronary atherosclerosis and the latter, in turn, precipitates myocardial infarction.[211] The specific mechanisms by which cigarette smoking precipitates myocardial infarction are not known but are most likely related to thrombosis on coronary plaques mediated by local factors (plaque thrombogenicity) and/or systemic smoking-dependent factors.[244,245] Some of the evidence for smoking being thrombogenic rather than atherogenic are[244,245] (1) smoking is a strong risk factor for thrombus-mediated events (myocardial infarction and sudden death), but not for symptoms caused by atherosclerosis alone (angina pectoris); (2) angiographically, smoking is associated with rapid coronary occlusion (thrombosis) rather than slow nonocclusive plaque progression (atherosclerosis); (3) after thrombolysis for myocardial infarction, less residual vessel wall disease persists (atherosclerosis) in smokers than in nonsmokers;[246-248] (4) smoking is associated with a systemic hyperthrombotic state (systemic thrombin generation, activated platelets, and high fibrinogen);[249,250] (5) pathoanatomically, smoking is strongly related to coronary thrombosis and only weakly to the underlying atherosclerosis; and (6) smoking cessation rapidly and markedly reduces risk for myocardial infarction, indicating that the responsible process is rapidly reversible.[244,251] Finally, also in experimental animals is smoking more thrombogenic than atherogenic; it promotes platelet-dependent cyclic flow variation after arterial injury,[252] but forced cigarette smoking does not induce coronary atherosclerosis in nonhuman primates.[253]

In the United States, about 43 percent of nonsmoking children and 37 percent of nonsmoking adults are exposed to environmental tobacco smoke, and passive smoking appears to be associated with a small increase in the risk of CHD.[254] Thus, the public health consequences of passive smoking with regard to CHD may be important.[254]

Hypertension

Systemic arterial hypertension is a major independent risk factor for CHD, although it pathogenetically appears to be a cholesterol-dependent accelerator of atherosclerosis.[212,213] When

hypertension is defined as a systolic blood pressure of 140 mmHg or greater, a diastolic blood pressure of 90 mmHg or greater, or both, it is associated with a relative risk of 1.5 (Seven Countries Study)[255] to 2.0 (Framingham Study)[256] for death from CHD, in both high-risk (United States and Northern Europe) and low-risk populations (Japan and Mediterranean Southern Europe).[255]

It is generally assumed that hypertension accelerates atherosclerosis directly by way of increased blood pressure, but it has been suggested that associated hormonal changes, including generation of angiotensin II by systemic and/or local renin-angiotensin systems, could also play a pathogenetic role.[67] However, the original observation of an association between the insertion (I)/deletion (D) polymorphism of the angiotensin-converting enzyme (ACE) gene, which explains as much as 30 to 40 percent of the total variation in serum ACE activity,[257] and myocardial infarction was not confirmed in the two largest studies to date,[258,259] and increased serum ACE activity has never been shown to be a risk factor for CHD.[257] The recently published Heart Outcomes Prevention Evaluation trial may shed new light on that question.[260]

Hypertension and hypercholesterolemia interact strongly in promotion of coronary atherosclerosis.[211] Hypertension does not induce atherosclerosis in normal laboratory animals with low cholesterol levels; it is not in itself atherogenic. In populations where total cholesterol is less than 4 mmol/L (150 mg/dL), atherosclerotic events are rare, even in people with hypertension.[212] That the blood pressure needs to be above a certain level to accelerate atherosclerosis is best illustrated by the following examples: (1) atherosclerosis does not develop in veins unless exposed to higher-than-normal pressure (e.g., veins used as coronary bypass grafts), (2) atherosclerosis does not develop to any significant degree in pulmonary arteries unless pulmonary hypertension is present, (3) more atherosclerosis is present in high-pressure arteries proximal to congenital aortic coarctation than in downstream low-pressure arteries, and (4) much less atherosclerosis develops in coronary arteries originating anomalously from the low-pressure pulmonary trunk than from the high-pressure aorta[261,262] (Fig. 35-8, Plate 81). Furthermore, in the International Atherosclerosis Project (n > 20,000), much more coronary and aortic atherosclerosis was found at autopsy in hypertensive compared with normotensive individuals-a relation already present from a young age.[263] But much more conclusive, prospective epidemiologic studies with autopsy follow-up revealed that blood pressure measured during life was a powerful and consistent predictor for the extent of raised atherosclerotic lesions per se: the higher the pressure during life, the more severe atherosclerosis post mortem in aorta and coronary and cerebral arteries[218,237-241]-an association that is present already in children and young adults.[223] Thus, hypertension and atherosclerosis are related, probably causally. Also, the PDAY study has provided evidence for the association between hypertension and the development of atherosclerotic lesions.[264,265]

The principal components of blood pressure consist of a steady component (mean arterial pressure) and a pulsatile component (pulse pressure). As large-artery stiffness increases in middle-aged and elderly subjects, systolic pressure rises and diastolic pressure falls (isolated systolic hypertension), with a resulting increase in pulse pressure.[266] Recent data from the Framingham Heart Study indicate that pulse pressure is superior to both systolic and diastolic blood pressures in predicting CHD risk, and age-related large-artery stiffening may thus constitute an important component of CHD risk in the elderly.[266]

Diabetes

Yet another pathogenetically cholesterol-dependent, but statistically independent, major cardiovascular risk factor is non-insulin-dependent diabetes mellitus (NIDDM).[211] NIDDM and hypercholesterolemia interact strongly in the genesis of CHD.[211] In populations where total

cholesterol is less than 4 mmol/L (150 mg/dL), atherosclerotic events are rare, even in diabetics.[212] Diabetes is, however, a powerful and gender-dependent risk factor in North America and Europe, increasing the risk of CHD three- to sevenfold in women compared with two- to threefold in men.[267] In fact, as recently expressed in a Scientific Statement from the American Heart Association, "diabetes *is* a cardiovascular disease."[268] Also, the precursor to type 2 diabetes, insulin resistance with impaired glucose tolerance, carries a strongly increased risk for cardiovascular disease, but the individual roles of insulin resistance itself, hyperinsulinemia, hyperglycemia (and advanced glycation end products),[113] hemostatic abnormalities (platelets, coagulation, and fibrinolysis), and conventional risk factors such as dyslipidemia (high triglycerides, low HDL, and small dense LDL particles) and hypertension are not clear. Not only hyperglycemia but also glucose levels in the nondiabetic range are associated with an increased risk of atherosclerosis-related diseases.[269-272] Thus, the mechanisms by which diabetes promotes atherosclerosis and/or its clinical manifestations are poorly understood.

Although diabetes increases the risk of CHD much more than what can be explained by a diabetes-related elevated level of conventional risk factors (e.g., dyslipidemia and hypertension), it is unclear whether the same applies for the underlying vessel wall disease: atherosclerosis. In the largest autopsy study of diabetes and atherosclerosis, the International Atherosclerosis Project, the amount of atherosclerosis (plaque burden) was greater in coronary arteries and abdominal aortas in diabetes (compared with nondiabetes), regardless of sex, age, race, and geographic location, but it was not possible to adjust for cholesterol and blood pressure levels.[263] In the Honolulu Heart Program, a prospective epidemiologic study among Japanese-American men with autopsy follow-up, more extensive coronary atherosclerosis was found in diabetics (n = 83) than in nondiabetics (n = 159), but the difference disappeared after adjustment for other cardiovascular risk factors such as age, smoking, cholesterol, systolic blood pressure, and body mass index. There was no association with duration of diabetes or type of treatment.[273] Thus, the more adverse risk factor profile among diabetics accounted for some, but probably not all, of the observed excess of coronary atherosclerosis. In the PDAY study, however, glycohemoglobin levels exceeding 8 percent (n = 10) were associated with substantially more extensive fatty streaks and raised lesions in the right coronary artery in persons 25 to 34 years of age (n = 648).[274] It has recently been reported that coronary plaques in diabetic patients appear morphologically similar to those in nondiabetic subjects, but there is some evidence, both pathologically and angiographically, that the coronary arteries are involved more diffusely and that disease may extend more distally in diabetes.[275]

If diabetes does not accelerate atherosclerosis, it could increase the risk of atherosclerosis-mediated events by promoting thrombotic complications. Diabetes is associated with increased platelet activity and elevated plasma fibrinogen and plasminogen activator inhibitor 1 (PAI-1) levels.[276] Endothelial dysfunction occurs commonly, and endothelial erosion, rather than plaque rupture, appears to be the dominant mechanism underlying coronary thrombosis in patients with diabetes.[182]

Diabetes predisposes individuals to medial artery calcification (MAC, Mönckeberg's calcinosis), especially of the muscular arteries of the legs, but is practically never seen in the coronary arteries of adults.[202] MAC is a nonobstructive condition (apparently independent of and unrelated to atherosclerosis) leading to reduced arterial compliance. MAC is a strong independent predictor of future cardiovascular events in patients with type 2 diabetes, supporting the hypothesis that reduced arterial elasticity (arterial stiffening) could play a role in arterial occlusion in diabetes.[277-279]

There are no well-controlled studies conclusively demonstrating that intensive blood-glucose control will reduce atherosclerotic events in patients with diabetes.[275] Only a relatively small and nonsignificant reduction was seen in the U.K. Prospective Diabetes Study (type 2 diabetes),

contrasting a substantial and highly significant reduction in microvascular complications.[280] On the other hand, lipid-lowering with a statin appears to benefit all people at risk, including diabetics and those with only *impaired fasting glucose*, defined as a fasting glucose level of 6.0 to 6.9 mmol/L.[281] Intensive insulin treatment in type 2 diabetes has been shown to have survival benefits after acute myocardial infarction.[282]

Inflammation/Infection

The Roman Cornelius Celsus, living in the first century, gave us the four "cardinal signs" of inflammation: redness and swelling, with heat and pain.[283] Although the term "hot" has been used to describe plaques at high risk of rapid progression to occlusion, only recently has it been shown clinically, using a catheter-based technique, that indeed the temperature of high-risk coronary plaques responsible for unstable angina and myocardial infarction are elevated 0.7°C and 1.5°C, respectively,[284] and hot spots on the surface of carotid plaques have been shown to correlate with macrophage infiltration, i.e., local inflammation.[285]

Inflammation, but not necessarily chronic infection, plays an important role in the initiation and progression of atherosclerosis,[67] and systemic blood markers of inflammation such as C-reactive protein, serum amyloid A, and fibrinogen (acute-phase reactants) have emerged as powerful predictors of coronary events[286,287] in asymptomatic men[168] and women,[169] in patients with stable[170] and unstable angina,[171-173] and after infarction.[174] These sensitive but nonspecific markers of low-grade systemic inflammation are produced in the liver in response to cytokine stimulation (e.g., interleukins 1 and 6),[288,289] but it is unclear whether the proinflammatory cytokines originate from the vessel wall itself (macrophages?), reflecting the quantity (burden) or quality (activity) of atherosclerosis, or from nonvascular sources, reflecting inflammatory states such as chronic infections. Other novel markers of vascular inflammation include the soluble forms of leukocyte adhesion molecules, such as sICAM-1,[290,291] which may reflect ongoing atherosclerosis. Proinflammatory cytokines, regardless of their sources, and the processes they mediate may accelerate atherogenesis and/or its manifestations, but it still remains unknown whether inflammation per se represents a modifiable risk factor.[292]

The hypothesis that infection is causally related to atherosclerosis is plausible but unproven. Most evidence, particularly seroepidemiologic, has been presented for Cp, *Helicobacter pylori* (Hp), and certain herpesviruses [particularly cytomegalovirus (CMV)].[163,164,293-295] Recent observational,[296-300] interventional,[301,302] and pathoanatomic[303-306] evidence have, however, weakened the case for a possible causal role of Cp in occlusive vascular disease, and the evidence for Hp is still questionable.[307,308] CMV may play a greater role in restenosis after angioplasty and transplant vascular disease than in atherosclerosis.[164,308] If infection plays a pathogenetic role, vaccination and/or antimicrobial agents might offer protection.

It has been extremely difficult, if not impossible, to culture infectious agents from atherosclerotic lesions, but this does not preclude their involvement in lesion formation.[164] CMV genomic DNA and antigens are commonly found in the human arterial tree, both in plaque and in plaque-free vessel walls (90 versus > 50 percent, i.e., considerable overlap),[164,309] in contrast to Cp DNA and antigens that appear to be confined to diseased vessel walls (up to 73 percent of coronary plaques were defined Cp positive by immunohistochemistry).[166,167] Hp has not been detected in vessel walls.

To date, more than 20 inflammation-associated cell adhesion molecules and almost 50 proinflammatory cytokines have been described,[45] and a significant number of these have already been shown to be present in human atherosclerotic plaques.[310-318] Acute-phase reactants are also frequently present in advanced lesions, including fibrinogen,[144,319] C-reactive protein,[320,321] and

serum amyloid A (expressed in lesions).[322] The relation, if any, of local inflammation in plaques to systemic markers of inflammation such as C-reactive protein has not yet been reported. No inflammatory markers of cardiovascular risk have been related with any histopathologic changes at the plaque level, and no published evidence suggests that atherosclerotic lesions containing infectious agent-related products differ histologically from those without signs of plaque infection.[323]

Hemostatic Factors

Several systemic hemostatic factors, including fibrinogen, factor VII, PAI-1, t-PA, and platelets, have been identified as determinants of future CHD events.[324-326] Thrombin generation and platelet activation play a causal role in atherosclerosis-mediated luminal thrombosis and, most likely, also in the slow progression of atherosclerotic lesions. Platelets can adhere to denuded areas and release their granules, which contain cytokines and growth factors that, together with thrombin, may contribute to activation, migration, and proliferation of cells and thus promote plaque development.[67] Local generation of plasmin may itself, but most likely via activation of latent MMPs, digest the extracellular matrix, which is essential for cell migration. If unopposed, matrix degradation may ultimately culminate in plaque disruption.[324]

The mere presence of a positive relation between abnormal hemostasis and CHD does not indicate whether the former is a cause of, related to, or a consequence of, the latter. The most powerful and most consistent predictor of CHD among the hemostatic factors-fibrinogen-is strongly related to smoking, diabetes, and C-reactive protein (an acute-phase reactant like fibrinogen), all of which are strong, consistent, and independent predictors of CHD.[326] To answer the question about causality and, if present, its strength, studying CHD risk in persons with congenital abnormalities in coagulation, fibrinolysis and platelet function provides important information. Although conflicting results have been published,[327,328] gene polymorphisms associated with different plasma levels of fibrinogen ($G_{-455}\rightarrow A$),[329,330] prothrombin (G20210A),[331] factor V (G1691A, Leiden),[331] factor VII (e.g., G10976A, R353Q),[331-333] factor VIII,[330] t-PA (I/D),[334] and PAI-1 (4G/5G)[330,335] appear not to be, or at best weakly, causally related to atherosclerosis or arterial thrombosis, even though many of these abnormalities are causally related to venous thrombosis.[330] On the other hand, polymorphisms of the platelet fibrinogen (PIA1/A2, glycoprotein IIIa)[331,336,337] and collagen (C3550T, glycoprotein Ib; 807T/873A, glycoprotein Ia/IIa)[338] receptor genes appear, at least under certain circumstances, to be causally related to coronary thrombosis and myocardial infarction, rather than to coronary atherosclerosis, emphasizing the primary role of platelets in arterial thrombosis. Prothrombotic genetic risk factors appear to be particularly important in precipitating myocardial infarction in young persons without severe atherosclerosis, and there is a strong adverse interaction with smoking.[331] It is possible to prevent arterial occlusion and, if it occurs, accelerate reperfusion and prevent reocclusion by targeting hemostatic factors (antiplatelet agents, anticoagulants, and fibrinolytic agents), but it has never been proven that such treatments also prevent or retard the slow progression of atherosclerosis not mediated by luminal thrombosis.

Homocyst(e)ine

Numerous retrospective case-control studies have identified mild-to-moderate homocyst(e)inemia as a strong and independent risk factor for CHD, stroke, and peripheral vascular disease,[339-342] and a clear association between plasma homocyst[e]ine (Hcy) and the anatomic extent of carotid, coronary, aortic, and peripheral vascular diseases has been demonstrated in several studies,[343,344] including at least one in a low-risk population.[345] Many prospective studies, but not all,[346-348] have, however, failed to demonstrate such an association, and it has been suggested that elevated Hcy could be a marker, or a consequence, rather than a cause of cardiovascular disease.[349-351] An

argument against Hcy being causally related to CHD is the fact that the homozygous form of the thermolabile methylene-tetrahydrofolate reductase (MTHFR) gene, although leading to elevated Hcy levels in those with low folate levels, has not consistently been associated with an increased CHD risk.[351] If Hcy is a causative factor, the mechanisms by which homocysteine causes occlusive vascular disease remain to be identified.[343]

Using high nonphysiologic concentrations in vitro, potential proatherogenic effects of Hcy have been identified, such as endothelial toxicity[352,353] and promotion of smooth muscle cell growth and collagen production.[354,355] In vivo, hyperhomocyst(e)inemia is associated with endothelial dysfunction,[356] but there is no experimental evidence from animal studies indicating that mildly to moderately elevated Hcy is a cause of atherosclerosis.[343,350,357] Also in humans is elevated Hcy associated with endothelial dysfunction,[358,359] probably mediated by increased oxidant stress because antioxidant vitamin C normalizes the impaired endothelium-dependent vasodilation seen with hyperhomocyst(e)inemia and the associated metabolic changes.[360]

Elevated Hcy appears to be more closely linked to thrombus-mediated coronary events (myocardial infarction) than to coronary atherosclerosis as seen on angiography,[361] and elevated Hcy is also linked to venous thrombosis.[351,362,363] Prothrombotic effects of Hcy have been described, such as downregulation of thrombomodulin on endothelial cells[364] and upregulation of tissue factor on both endothelial cells[365] and macrophages.[366] In homocystinuria, an inborn error of Hcy metabolism associated with extremely high plasma Hcy (usually >100 μmol/L), the few published autopsy reports confirm that both arterial and venous thrombosis are frequent and occur at an early age but apparently often without concomitant atherosclerosis.[367]

Alcohol

Generally, men and women who consume one to three drinks a day live longer than nondrinkers, due to reduced risk of CHD.[368] It also holds for low-risk Chinese people.[369] The inverse association between moderate alcohol intake and CHD is documented in over 40 prospective studies in diverse populations,[368] suggesting that mild to moderate alcohol intake is associated with a 10 to 40 percent lower risk of CHD than with no alcohol intake. The five largest cohort studies, with nearly 30,000 heart disease events, showed a consistent 20 percent reduction in CHD mortality among people who drank about 1 U of alcohol a day compared with nondrinkers.[370] This reduction is generally attributed to the beneficial effects of alcohol on lipids and hemostatic factors.[368] Moderate alcohol intake is strongly and consistently associated with higher concentrations of HDL cholesterol and apoA1 and lower concentrations of fibrinogen and is weakly associated with increased triglyceride concentration.[368] It was calculated that such changes, believed to be causally related to CHD, overall may reduce the CHD risk by 25 percent. Alcohol also inhibits platelet aggregation, which may substantially reduce the risk of CHD[371] and may promote fibrinolysis.[372,373] The effect of moderate alcohol intake on blood pressure is likely to be minor, but heavy intake (more than four drinks a day) is associated with hypertension[368] and increased risk of hemorrhagic stroke.[374-376] Several large cross-sectional studies have reported strong positive associations between alcohol and increased insulin sensitivity,[368] and moderate drinking seems to be associated with extraordinary benefit in patients with late-onset diabetes, possibly due to their greater baseline risk of CHD.[377]

With regard to wine, beer, and spirits, no consistent evidence has emerged that any one beverage confers a greater health benefit than another, indicating that a substantial portion of the benefit is mediated by ethanol.[377] Some studies suggest, however, that wine offers additional benefits.[378-381] A possible special effect associated with wine drinking could be due to specific nonalcoholic compounds in wine, particularly in red wine (e.g., antioxidant polyphenols).[382-384] Alternatively,

it could be due to confounding lifestyle factors associated with wine intake.[385] Moderate wine drinking seems to be associated with a healthier lifestyle in California (less smoking and more education)[386] and Britain (less smoking and obesity),[387] a healthier diet in Denmark (higher intake of fruit, vegetables, and fish),[385] and better subjective health in Finland.[388]

The health benefit associated with regular and moderate alcohol intake may not extend to populations with irregular drinking patterns and/or substantial higher consumptions. For example, in Central and Eastern Europe and the former Soviet Union, a growing body of epidemiologic research indicates a positive rather than negative association between alcohol consumption and cardiovascular deaths, especially sudden cardiac deaths.[389] In binge drinkers, atheroprotective changes in HDL are not seen, and irregular heavy drinking appears to be associated with an increased risk of rebound thrombosis, occurring after cessation of drinking, and sudden death due to ventricular fibrillation.[389-392]

In France, the CHD mortality rate is much lower that in Britain (1:4 in men and 1:6 in women, 1992 data) and other high-risk countries, despite similar average values of major CHD risk factors (except fewer female smokers in France). Low-dose alcohol consumption, in particular wine drinking, has been suggested as the most likely explanation for this lower-than-expected CHD mortality rate in France, called the *French paradox*.[371,393,394] However, a novel *time lag* hypothesis has recently been suggested to explain this paradox.[395] Animal fat consumption and serum cholesterol concentration were lower in France than in Britain up to 1970, and only in recent years have these major determinants of CHD been similar in the two countries. For a chronic disease like atherosclerosis that evolves over decades, it seems more appropriate to compare current mortality data with levels of risk factors in the past (30 year ago) rather than recent levels. If so done, the French paradox apparently disappears.[395] The same argument holds for cigarette smoking and lung cancer where the time lag between exposure and clinical disease is well recognized; current disease correlates better with smoking habits decades ago than with recent habits.[395] Many countries with high wine consumption are also those in which saturated fat consumption used to be low but increased in recent years (France, Italy, Spain, and Switzerland, for example). The low mortality from CHD reflects the earlier low levels of saturated fat consumption, for which wine may simply be an indirect marker.[395]

Sex

The major cardiovascular risk factors are similar for both sexes, but men develop CHD 10 to 15 years earlier than women.[396] By age 60 in the United States, only 1 in 17 women has had a coronary event, as compared with 1 in 5 men. After age 60, however, CHD becomes the leading cause of death among women as well as among men, and as many women as men eventually die of the disease.[396] Diabetes mellitus is a particularly strong risk factor among women, nearly eliminating the normal protection offered by female sex. The striking influence of sex on CHD risk is cholesterol dependent, because neither men nor women develop CHD unless total cholesterol is greater than 4 mmol/L (150 mg/dL), and the higher the level is, the greater is the chance of an event, and the earlier the event occurs irrespective of sex.[212]

Estrogen may be the most obvious factor responsible for the protection against CHD conferred by the premenopausal state. With menopause, LDL levels begin to increase, whereas HDL levels stop climbing or decrease slightly.[397] This leads to a worsening of the LDL-to-HDL ratio. Although estrogen replacement therapy overall restores the deteriorated lipid profile,[397] estrogen may have beneficial effects that go beyond changes in serum lipids. In particular, estrogen may have direct atheroprotective effects on the vessel wall (estrogen receptors are present in vascular cells), suggested by the improvement of endothelial function seen with estrogen administration.[398] In nonhuman primates[399,400] and rabbits,[401] estrogen reduced diet-induced atherosclerosis, probably

via an endothelium-dependent mechanism.[402]

Premature menopause (before age 45) due to oophorectomy or occurring naturally is known to lead to an increased CHD risk.[214] However, a simple hysterectomy with the ovaries and, consequently, estrogen production left intact also appears to increase the risk, and it has been suggested that this could be due to the loss of menstruation.[403] Iron is a powerful oxidant that mediates lipid peroxidation, which may explain the positive association between total body iron stores and cardiovascular risk found in epidemiologic studies. The *iron hypothesis*, suggesting that iron stores and CHD are causally related, has recently been revived by the finding of an increased CHD risk in heterozygous carriers of a common hemochromatosis gene mutation.[404,405]

In the International Atherosclerosis Project (IAP, 1960-1964), white men were unusually susceptible to atherosclerosis as compared with other sex-race subgroups, and sex differences in extent of aortic, coronary, and cerebral atherosclerosis were striking among whites but minimal among blacks.[209,406] In contrast, in the PDAY study initiated much later (1985) and involving young adults only (15 to 34 years of age), white men were no longer the most susceptible subgroup when evaluated by the same method as that used in the IAP (intimal surface grossly covered by plaques); there were no obvious sex differences, and blacks of both sexes appeared to be at least as susceptible to atherosclerosis as were white men.[407] When evaluated microscopically, however, coronary lesions appeared to progress faster in males than in females, evidenced by the presence of much more advanced plaque in 30- to 34-year-old men compared with age-matched women.[407] Regarding rapid thrombus-mediated plaque progression, the underlying mechanism appears to be in part sex dependent: plaque erosion (versus rupture) is more frequent in females than in males.[182,183,228]

Aging

Age is a powerful risk factor for CHD. The development of atherosclerosis increases markedly with age up to an age of about 65, regardless of sex and ethnic background.[141,223] Although atherosclerosis and the incidence of stable angina (caused by atherosclerosis alone) seem to increase less markedly beyond age 65,[408] most new-onset heart attacks (atherosclerosis plus thrombosis) occur after age 65, especially among women,[409] and the CHD mortality rate increases almost exponentially with age among elderly persons.[408] The reason for this paradox (more dangerous but not more extensive atherosclerosis with aging) is unknown but could be due to age-related changes superimposed on preexisting atherosclerosis and, of course, an increase in case fatality rates among the elderly. For example, increased pulse pressure and systolic blood pressure caused by age-related arterial stiffening are powerful predictors for myocardial infarction and coronary death, [266] and treatment of systolic hypertension even in very old patients reduces risk for both stroke and CHD.[410]

Although age is a strong and independent risk factor for CHD, the independent contribution of age to CHD risk is cholesterol dependent. In populations in which average serum total cholesterol levels are less than 4 mmol/L (150 mg/dL), atherosclerotic events are rare even among older persons.[213] Atherosclerotic events are also rare among North Americans and Europeans with that low cholesterol level, but only about 5 percent of persons older than 40 years of age have a total cholesterol level less than 4 mmol/L in these populations.[212] The mean serum total cholesterol of umbilical blood of newborns is approximately 1.9 mmol/L (75 mg/dL), but within 2 weeks of life that value rises to a mean of 4 mmol/L (150 mg/dL) and remains at that level until approximately age 20 years, when it gradually starts to rise. The average serum total cholesterol level in the United States in persons 20 to 74 years of age is 5.5 mmol/L (215 mg/dL).[411] Men have higher levels earlier in life, and women have higher levels in later life.[212]

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Chapter 35: ATHEROGENESIS AND ITS DETERMINANTS

CONCLUSION

Atherosclerosis is a complex and multifactorial disease, which means that many avenues for intervention can be applied. A certain blood-cholesterol level is necessary to initiate and drive the disease, but cholesterol alone is rarely enough for the development of symptomatic atherosclerotic lesions. Although many cardiovascular risk factors, such as smoking and hypertension, are not atherogenic on their own, they accelerate the development of occlusive arterial disease, and clinically it may be more rewarding to treat accelerators of the disease rather than its initiator, hypercholesterolemia. Maximum benefit, of course, is achieved by treating both. Experimental studies have clearly documented that the inhibition of just one necessary step in the atherogenetic chain of events in the vessel wall (e.g., macrophage recruitment) may markedly prevent or retard the development of mature plaques responsible for clinical disease.

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List of Figures

Figure 35-1: (Plate 77) An early atherosclerotic lesion (fatty streak) in the aortic root of a 3-month-old apolipoprotein E-/- mouse fed a high-fat Western-type diet for 6 weeks. The lesion consists of lipid-laden monocyte-derived macrophage foam cells and a few lymphocytes (T cells) beneath an intact endothelium. Elastin trichrome stain.

Figure 35-2: (Plate 78) An advanced atherosclerotic plaque in the brachiocephalic trunk of a 6-month-old apolipoprotein E-/- mouse fed normal chow. The plaque appears vulnerable morphologically, consisting of a lipid-rich core with cholesterol crystals covered by a thin fibrous cap. Orcein, staining elastic tissue black.

Figure 35-3: (Plate 79) Ruptured coronary plaque with occlusive thrombosis superimposed (natural death of a 21-month-old apolipoprotein E-/- mouse). Spontaneous plaque rupture and/or luminal thrombosis are extremely rare in animal models of atherosclerosis. Elastin trichrome stain.

Figure 35-4: The 1995 American Heart Association classification of atherosclerotic lesions. The type I (initial) lesion, which consists of small, isolated groups of macrophages containing lipid droplets, is not shown in this figure. (Adapted from Stary et al.[128] Reproduced with permission from the publisher and authors.)

Figure 35-5: (Plate 80) Cross-sectioned coronary artery, containing a vulnerable plaque (large lipid-rich core covered by a thin fibrous cap) with ruptured surface and a nonocclusive luminal thrombosis superimposed. Trichrome stain.

Figure 35-6: Advanced atherosclerotic plaques are extremely heterogeneous in composition. A subset of the advanced plaques are vulnerable (i.e., rupture-prone) with high risk of becoming complicated by luminal thrombosis. The relation between vulnerable and stable plaques is not well defined. (Adapted from Ravn and Falk.[412] Reproduced with permission from the publisher and authors.)

Figure 35-7: Most coronary occlusions (*top*, 51/72 = 71 percent), myocardial infarctions (*middle*, 29/39 = 74 percent), and ischemic strokes of carotid origin (*bottom*, 54/67 = 81 percent) are caused by acute thrombosis superimposed on atherosclerotic lesions that, prior to the acute events, were asymptomatic and only mildly to moderately stenotic. Overall, nonstenotic atherosclerotic lesions by far outnumber the stenotic ones at higher individual risk, which is why most acute clinical events originate from nonstenotic lesions at relative low individual risk. MI = myocardial infarction.

Figure 35-8: (Plate 81) Experiment of nature, illustrating the pathogenetic role of blood pressure in atherogenesis. The left anterior descending coronary artery (LAD) is departing normally and thus exposed to systemic blood pressure; the LAD is severely atherosclerotic, stiff, and calcified (*A*). In contrast, the right coronary artery (RC) is originating anomalously from the lower-pressure pulmonary trunk; the RC is elastic and compliant without atherosclerosis (*B*).

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Part 6: CORONARY HEART DISEASE
Chapter 36:

PATHOLOGY OF CORONARY ATHEROSCLEROSIS

Author: Michael J. Davies

THE PROCESS OF ATHEROSCLEROSIS

Atherosclerosis is an intimal disease of systemic arteries that range in size from the aorta to the epicardial coronary arteries. Atherosclerosis is characterized by discrete intimal plaques, although at an advanced stage the lesions may coalesce. Each plaque has variable combinations of extracellular lipid, lipid contained within cells that have foamy cytoplasm, and connective tissue matrix proteins, such as collagen, produced by smooth muscle cells. The majority of the foam cells are macrophages derived from monocytes, which enter the plaque from the arterial lumen.

Lipid is a fundamental component of the atherosclerotic plaque, which is essentially an inflammatory/repair response in the vessel wall invoked by lipid.[1] Lesions that consist entirely of proliferating smooth muscle cells, such as the response to endothelial denudation in animal models, are a repair response to mechanical injury and are not strictly atherosclerosis. Intimal thickening that consists solely of connective tissue and smooth muscle cells is also an adaptive response of the vessel wall to flow and occurs at branching points in human coronary arteries from a young age.[2,3] While this diffuse intimal thickening without a lipid component is not atherosclerosis as such, it does occur commonly in subjects who have atherosclerotic disease and plaques. Such intimal thickening can be measured by ultrasound in the carotid arteries in vivo and has been used as a surrogate marker for the detection of risk and in evaluating lipid-lowering therapy.[4]

Morphologic Forms of Atherosclerotic Plaques

The intimal surface of an opened human coronary artery reveals several types of plaque. Some are flat yellow dots or lines (fatty streaks), and others are raised above the surface as oval humps, which range in color from white to yellow (raised fibrolipid plaques).

Observations made on human necropsies allow a developmental sequence to be proposed for plaques based on cohorts of individuals dying at different ages from noncardiac disease.[2] In children from 5 to 10 years of age, fatty streaks often are present in the coronary arteries, suggesting that they are the initial point in a sequence of plaque development.[5] Raised plaques appear later in life and, by 20 years of age, are present in areas such as the proximal left anterior descending coronary artery, where fatty streaks are most prevalent in earlier life.[5] *By middle age, most subjects will have coronary plaques of all types, suggesting that plaque initiation continues throughout life.*

Plaque Evolution

The American Heart Association has recommended a nomenclature for the types of plaques and has suggested ways in which they may evolve.[6] The initial lesion (type I) develops when monocytes adhere to the endothelial surface and migrate from the lumen of an artery to accumulate in the intima. The type II lesion is the fatty streak that consists of a focal accumulation

of lipid-filled foam cells largely of monocyte origin immediately beneath the intact endothelium. The type III lesion contains in addition small pools of extracellular lipid. While type I to type III plaques are the precursors of more advanced lesions, they do not cause clinical symptoms.

Type IV is characterized by two additional features. Smooth muscle cells appear within the lesion beneath the endothelium, and the pools of extracellular lipid coalesce to form a lipid core. Type V shows significant connective tissue deposition and the formation of a fibrous capsule containing the lipid core. The portion of this capsule separating the core from the lumen is the plaque cap.

Plaques with a lipid core and a fibrous cap are designated as type Va (Figs. 36-1 and 36-2). *Type VI plaques are those complicated by thrombosis, which predominantly develops in type Va plaques.* Some plaques have heavy calcification (type Vb). Yet another form of advanced plaque (type Vc) is almost entirely composed of collagen and smooth muscle cells.

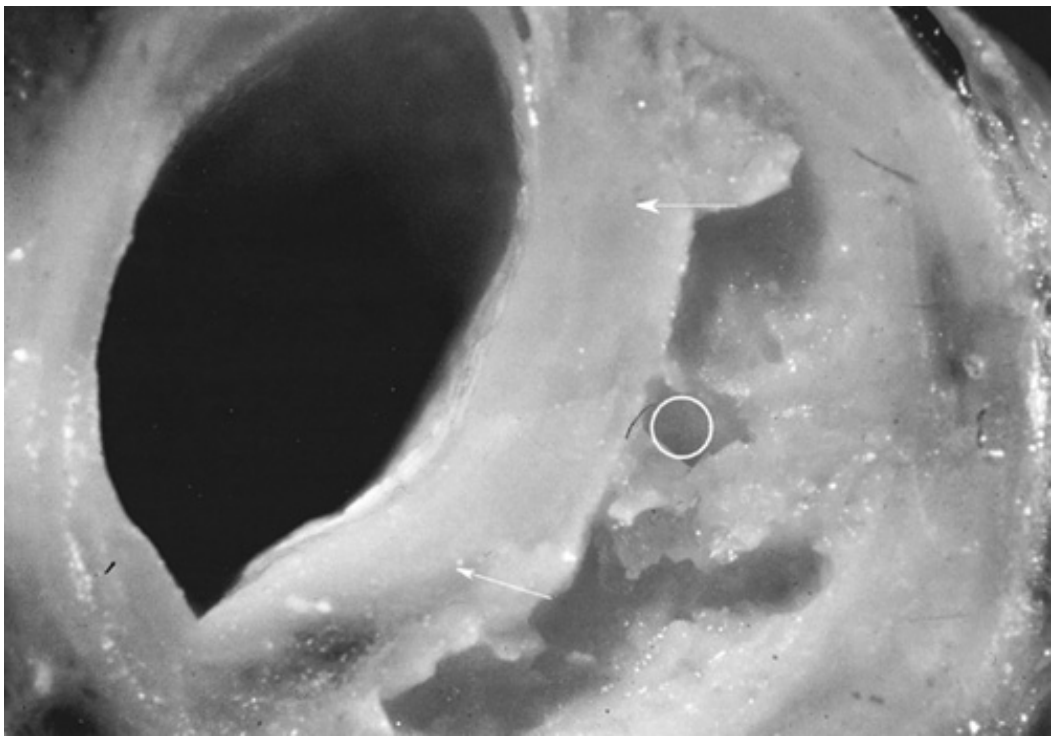

Figure 36-1: Human coronary artery in which there is a large lipid-rich plaque with a core (○) and a thick cap (*arrows*). This lesion would be designated as a type Va plaque.

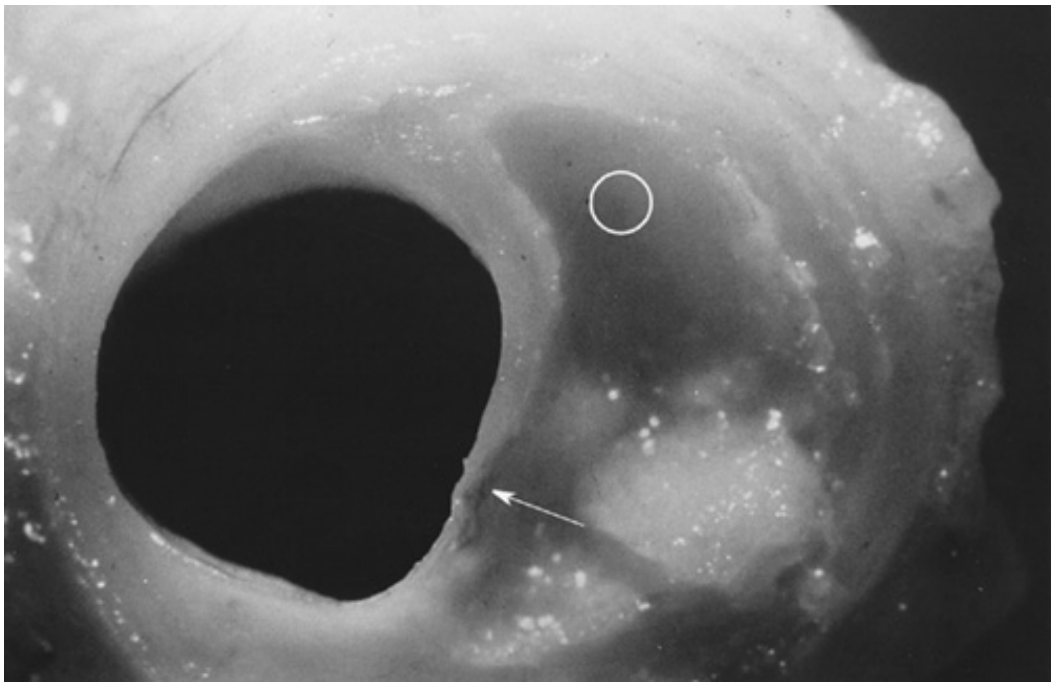

Figure 36-2: Human coronary artery in which there is a large lipid-rich plaque with a core (▫), but in contrast to Fig. 36-1, the cap (*arrow*) is thin. This lesion is also a type Va plaque.

In general, the plaques found in subjects with ischemic heart disease show the complete spectrum of possible morphologies. There are, however, individuals who show a more uniform pattern. Virtually all the plaques may contain very large amounts of extracellular lipid, or virtually all the plaques consist of connective tissue with a rich connective mucin content and a minimal lipid component. Such variations from individual to individual may depend on the profile of risk factors. Smoking and elevated homocysteine levels may produce lesions that have different characteristics than those associated with high plasma lipids.[7,8] The great majority of descriptive work on plaques is based on the hyperlipidemic white male, and there is evidence emerging that women may have a somewhat different plaque morphology. In familial hypercholesterolemia and diabetes, diffuse intimal involvement with many foam cells rather than the formation of discrete plaques occurs.

Basic Mechanisms in Plaque Formation

FOAM CELL FORMATION

In experimental models and human disease, the first morphologic phenomenon observed in plaque formation is adhesion of monocytes to an intact endothelial surface.[1,9] This adhesion is followed by monocyte migration into the intima. In the intima, monocytes are activated, converted to macrophages, and may divide. Lipid uptake by macrophages then leads to the formation of the foam cell. These observations have created a paradox in that although plasma low-density lipoprotein (LDL) freely enters the intima, it should not be taken up by macrophages, which lack the appropriate receptor. The apparent paradox can now be explained in the context of the chemical changes that LDL undergoes as it is modified by the cells in the arterial wall. The first minor modifications of the LDL molecule occur close to the endothelial surface.[10] This initial change produces a proinflammatory molecule called *minimally modified low-density lipoprotein* (MMLDL) that contributes to the endothelial expression of molecules mediating monocyte adhesion, such as *vascular cell adhesion molecule* (VCAM).[11] Other inflammatory mediators such as *intercellular adhesion molecule* (ICAM), *monocyte chemotactic protein* (MCP-1),[12] and *macrophage colony-stimulating factor* (MCSF)[13] are also induced (see also Chaps. 6 and 36). These factors act in concert to cause monocyte migration and to allow the incoming monocytes to

establish themselves and divide in the intima. Further changes in the LDL molecule lead to an oxidized form (oxidized LDL) that is recognized by the *macrophage scavenger receptor*. The scavenger receptor does not downregulate, as does the receptor for native LDL, and the cell becomes laden with lipid because of continued unregulated uptake. The macrophage foam cells that result produce a range of inflammatory cytokines including *tumor necrosis factor alpha* (TNF-α)[14] and metalloproteinases as well as the procoagulant *tissue factor*.[15] This sequence of lipid oxidation and lipid uptake by macrophages forms a credible explanation for the formation of foam cells, and oxidized LDL has been shown within macrophages in both human and rabbit atherosclerosis[16] (see also Chap. 35).

Transgenic models of atherosclerosis show the importance of these inflammatory mediators. Apoliprotein B knockout mice, for example, show a very marked susceptibility to form plaques when given lipid diets. Animals in whom in addition MCP-1 or its receptor or MCSF or VCAM or the scavenger receptors are knocked out show a profound attenuation of atherosclerotic lesions. MCP-1 is suggested by these models to be a major component of monocyte recruitment in plaques.[17,18]

LIPID CORE FORMATION

Lipid cores are potential spaces in the connective tissue matrix of the intima that are filled with cellular debris and cholesterol. Active plaques contain numerous macrophages clustered at the edge of the core, with the expression of a range of metalloproteinases that likely are engaged in the active destruction of the collagen matrix. Some extracellular lipid may be derived directly from LDL bound to proteoglycans within the intima,[19] but much of the cholesterol and esters in the lipid core is released from the cytoplasm of dying foam cells. Macrophages may be killed by lipid peroxides formed by LDL oxidation, but there is now evidence that cell death is by apoptosis.[20] Deprivation of growth factors such as MCSF-1 may induce apoptosis, particularly in association with the TNF-α present in large amounts in cellular plaques. Tissue factor (TF) expression by macrophages within the core makes this area of the plaque highly thrombogenic if it is exposed to the arterial lumen.[21]

SMOOTH MUSCLE PROLIFERATION AND CAP FORMATION

The caps of plaques with a lipid core consist of a lattice of collagen within which are lacunae containing smooth muscle cells that produce the connective tissue matrix. Intimal smooth muscle cells have the tendancy to die by apoptosis, and many caps of plaques become relatively acellular. Smooth muscle cell migration and proliferation, as well as collagen deposition, are driven by growth factors produced by virtually every cell type, including smooth muscle cells themselves.[22] Platelets, fibrin, and thrombin also can stimulate smooth muscle cell proliferation if deposited on the vessel wall, and there is increasing recognition that fibrinogen passes into the intima and can be converted to fibrin. Such fibrin is usually removed by plasminogen activation. Any residual fibrin-thrombin complexes are potent stimulators of smooth muscle cell proliferation. The plaque cap is now recognized as a dynamic structure in which there is deposition of collagen[23] balanced by degradation of the connective tissue matrix by a range of proteases. Numerous cytokines control this balance.

IMMUNE MECHANISMS IN PLAQUE FORMATION

Plaques contain T-lymphocytes,[24] the function of which may be, in part, to modify smooth muscle cell proliferation via the production of interferon-γ. CD40L-positive lymphocytes are present in plaques and react with CD40-positive macrophages to cause activation, cytokine expression, tissue factor expression, and metalloproteinase production. In experimental models, blockade of

CD40L attenuates plaque formation.[25] A significant proportion of lymphocytes within plaques are potentially cytotoxic producing perforins and granzymes and may contribute to death of smooth muscle cells and macrophages. B-lymphocytes are absent from the plaque itself but are present, often in large numbers, in the adjacent adventitia. Oxidized LDL is strongly antigenic, and the B-lymphocytes produce autoantibodies that can be measured in the plasma and may provide a marker of the activity or extent of the atherosclerotic process.[26]

A significant proportion of subjects with coronary atherosclerosis show colonization of the plaques by the intracellular bacterium *Chlamydia pneumoniae*. The frequency of such direct infection of the plaque is high, as shown by immunofluorescence studies when 40 to 50 percent of individuals with atherosclerosis have some positive plaques. Studies by polymerase chain reaction (PCR) for the detection of chlamydial DNA are less frequently positive. The current perception is that chlamydia reach the plaque by entering a monocyte in the lung or upper respiratory tract and then enter the bloodstream and migrate into the plaque. The higher frequency of immunohistochemical positivity than PCR positivity may suggest that the organism grows only for a limited time, but the capular antigens persist within macrophages. Chlamydia within macrophages in the plaque potentially would upregulate inflammatory activity and enhance plaque progression. Chlamydial heat-shock protein upregulates TNF-α production.[27,28] Antibiotic therapy may or may not turn out to be effective in slowing plaque progression.[29,30]

PLAQUE VASCULARIZATION

The normal media is avascular, but once intimal thickening occurs, new vessels grow in from the adventitia and reach the base of the plaque. Neovascularization may be visible on angiography in life.[31] The vessels that lie close to the base of the core are thin-walled, and extravasation of red cells is very common. When the core contains platelets, however, a direct continuity with the lumen is found via a cap tear (see below). Transmedial vessels strongly express adhesion molecules such as VCAM and may be another route by which monocytes enter the plaque.[32] Transgenic mouse models show that inhibition of new vessel formation will attenuate plaque formation.[33]

ENDOTHELIAL STATUS OVER PLAQUES

In early plaque formation (types I-III), the endothelial surface is intact, and there is no exposure of the subendothelial connective tissue matrix and therefore no adhesion of platelets to the vessel wall. The endothelium is structurally intact, although this does not mean that it is functionally normal. Once later plaque formation has occurred (types IV-V), however, small foci of endothelial loss do occur, and this denudation injury exposes connective tissue, allowing the formation of a monolayer of platelets adherent to the vessel wall. Associated with denudation injury is evidence of increased endothelial cell turnover. The thrombi that form are ultramicroscopic but do indicate endothelial instability in the atherosclerotic artery. Observational studies show that endothelial cell loss is associated with the proximity to macrophages.[34,35] Macrophages may induce endothelial cell apoptosis as well as producing a range of proteolytic enzymes that cut loose the endothelial cell from its attachment to the vessel wall.[36]

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Chapter 36: PATHOLOGY OF CORONARY ATHEROSCLEROSIS

CLINICAL SYMPTOMS AND PLAQUE TYPES

The presence of advanced plaques of types IV and Va allows clinical symptoms to develop. Atherosclerosis is a biphasic disease; in the first stage, advanced plaques are generated, but the patient is asymptomatic; in the second stage, symptoms develop. Plaques are ubiquitous in Western populations, but not everyone develops ischemic heart disease.

Large-scale epidemiologic studies-including the International Geographic Survey,[37] the Pathological Determinants of Atherosclerosis in Youth (PDAY) study,[4] and the Bogalusa Heart Study[38]-have produced consistent information: *In all geographic populations, the mean number of coronary plaques present in a large number of autopsied patients who die from all causes predicts the incidence of ischemic heart disease in that population.* The risk factors for large numbers of subjects developing ischemic heart disease depend on how many advanced plaques are present. Smokers will, on average, have more plaques than nonsmokers. Similar data exist for hyperlipidemia, hypertension, and diabetes (see Chap. 38). Thus risk factors operate in part by increasing the number of plaques that potentially can progress to cause symptoms. Such epidemiologic studies, however, do not mean that an individual cannot die of a single, strategically placed plaque.

The majority of types IV and Va advanced plaques are clinically silent and angiographically invisible because they do not encroach on the lumen of a coronary artery. Two mechanisms are responsible for this phenomenon. First, the media behind an atherosclerotic plaque undergoes thinning and atrophy, which allows the plaque to bulge outward rather than inward. Second, *the development of an intimal plaque causes remodeling of the arterial wall, increasing the external diameter and allowing the plaque to be accommodated without altering the lumen dimensions.*[39] Intravascular ultrasound confirms that coronary angiography is very insensitive for the detection of plaques[40] (see also Chap. 47).

Plaque Heterogeneity

Common to all type Va plaques is the presence of a fibromuscular cap, but even so, there is considerable heterogeneity (see Figs. 36-1 and 36-2). The cap may be relatively thick and uniform, or it may vary in thickness with interspersed thin areas. Thick caps have high numbers of smooth muscle cells, whereas relatively thin caps often have fewer smooth muscle cells and contain appreciable numbers of macrophages. The lipid core may occupy over 70 percent of the overall volume of the plaque or as little as 10 percent. Core margins may be surrounded by macrophages, or there may be no macrophages. *Plaque heterogeneity therefore involves both the micromorphology of the lesion (core size, cap thickness) and the degree of inflammatory activity.* A plaque in inflammatory terms can be "hot" or "burnt out." There is no readily discernible relation between plaque size and any of the variables that contribute to plaque heterogeneity.

Mechanisms of Induction of Symptoms

Three major mechanisms lead to clinical symptoms (see also Chap. 35). First, thrombosis leads to acute decreases in flow in a coronary artery. Second, a plaque grows without the clinically apparent involvement of thrombosis to the point that the lumen size is reduced to a degree that causes flow limitation during exercise.

Finally, in subjects with coronary atherosclerosis, coronary vasomotor tonal responses are abnormal. This disordered control of tone, which reflects in part endothelial dysfunction (see also Chaps. 6 and 36) may take the form of local spasm at the site of an eccentric plaque in which there is a residual segment of normal vessel wall, or vasospasm may be a more generalized phenomenon.

Acute Ischemic Syndromes

The major factor initiating acute ischemia in the crescendo form of unstable angina, acute myocardial infarction, and a high proportion of sudden ischemic deaths is a thrombus of sufficient size to protrude into the arterial lumen. This assertion does not imply that thrombosis is the only factor, but necropsy studies, angiography, and angioscopy, as well as the success of fibrinolytic therapy in restoring arterial patency in infarct-related arteries, all indicate a dominant role for thrombosis.

FACTORS INDUCING PLAQUE THROMBOSIS

Postmortem study of human coronary thrombi causing death has shown the involvement of two distinct processes.[41]

Endothelial Erosion

The endothelial surface over many plaques of types IV and Va has been shown to develop small foci of endothelial cell loss[34,35] that expose the subendothelial connective tissue and lead to local ultramicroscopic areas of platelet adhesion (Fig. 36-3). The extension of this process to cause large areas of endothelial denudation over a plaque leads to much larger thrombi capable of causing symptoms. The characteristics of these thrombi are that they are adherent to the luminal surface of the plaque, which is otherwise intact, and there is no intraplaque thrombosis (Fig. 36-4).

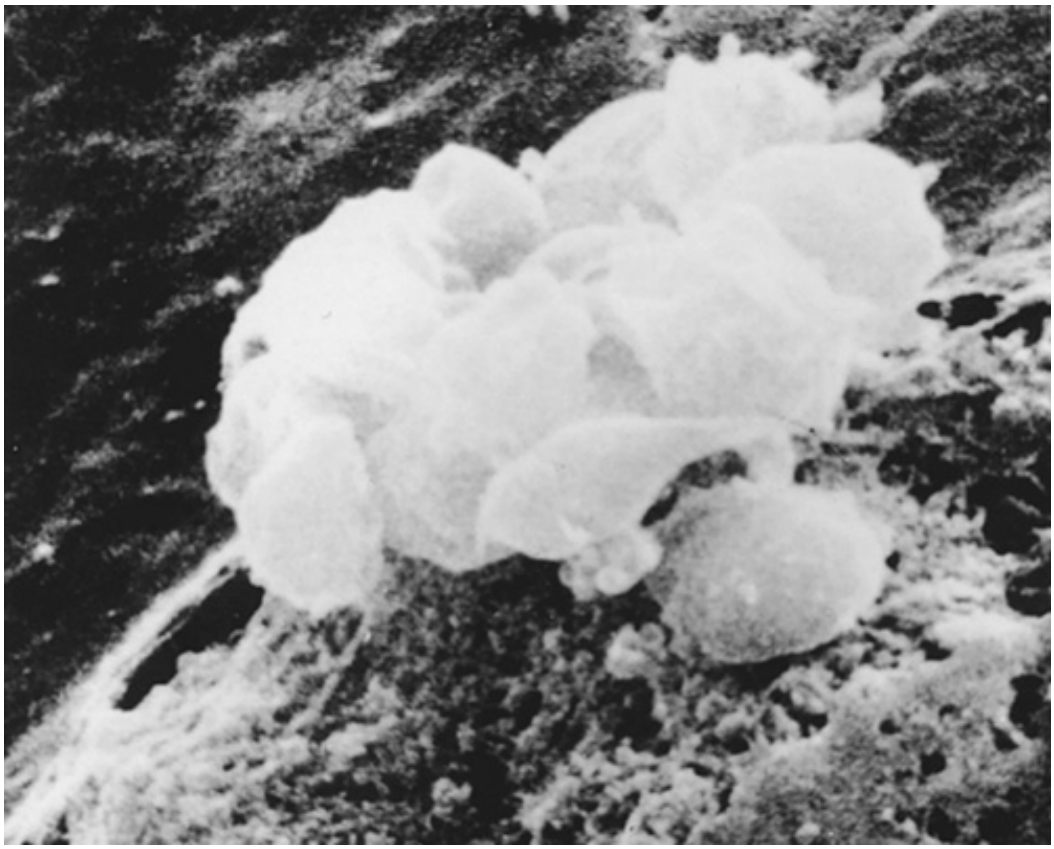

Figure 36-3: Scanning electron micrograph of human coronary artery. A single endothelial cell has undergone denudation. Over the exposed subendothelial tissue, a small clump of platelets has formed. No platelets adhere to adjacent intact endothelial cells.

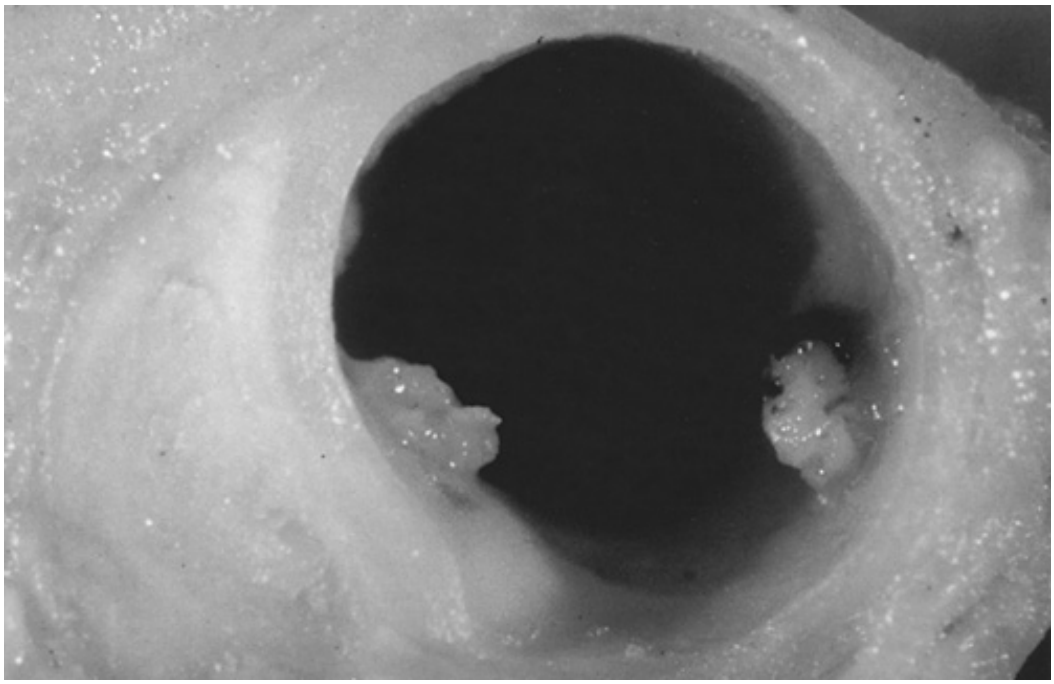

Figure 36-4: Two small thrombi due to endothelial erosion over a plaque. The thrombi are stuck onto the surface of the plaque-there is no intraplaque component of thrombus.

Plaque Disruption

Major coronary thrombi are also caused by plaque disruption (also known as *plaque cracking, fissuring, rupture,* or *ulceration*). In disruption, the cap of a plaque with a lipid-rich core will tear; blood from the lumen of the artery then enters the lipid core, where the presence of tissue factor and collagen induces platelet adhesion, aggregation, and activation.[41] Thrombus formation within the core itself expands and distorts the plaque, whereas the torn cap may project into the lumen (Fig. 36-5). Necropsy study of disrupted coronary and aortic plaques compared with intact plaques in the same individuals shows that plaques with a large lipid core occupying more than 50 percent of overall plaque volume and having a high macrophage density, a thin cap, and low smooth muscle cell density are the most vulnerable to rupture.[42] Of interest, core size and cap thickness, which are two major determinants of plaque vulnerability, are not statistically related, and neither is related to absolute plaque size or to the degree of stenosis.

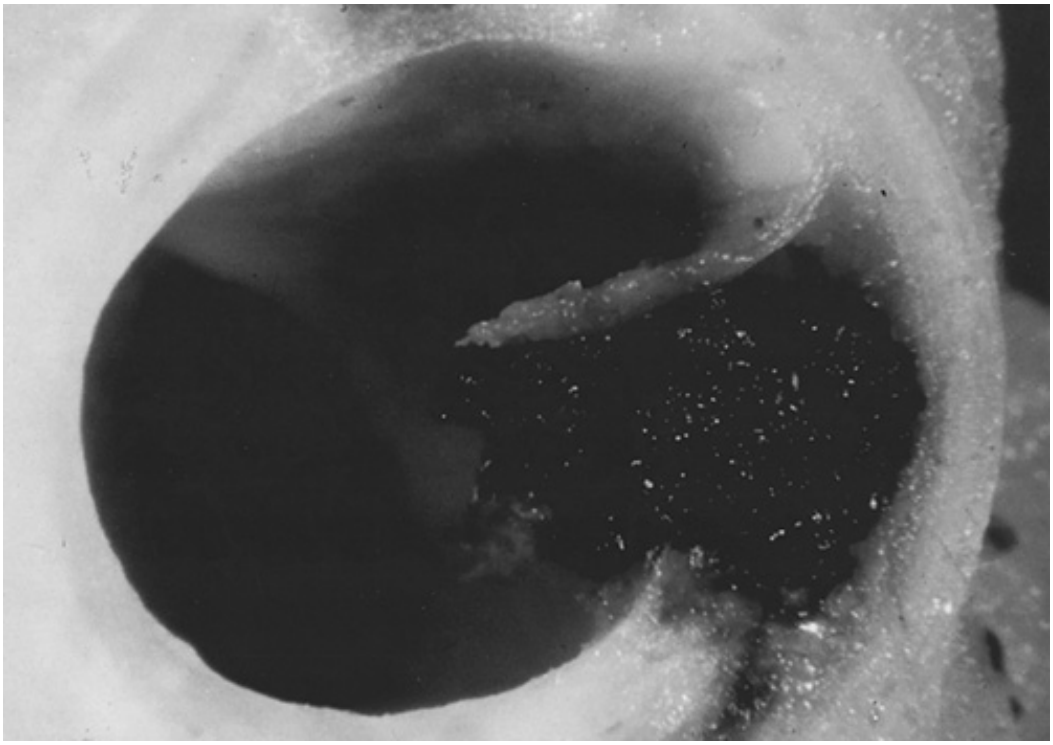

Figure 36-5: Plaque disruption in which the torn cap of a plaque projects into the lumen. The original site of the lipid core is filled with thrombus, which protrudes into but does not occlude the lumen.

Plaque disruption is responsible for at least 80 percent of major coronary thrombi causing sudden death or myocardial infarction in white males.[42] In contrast, the frequencies of disruption and erosion are almost equal in women with coronary thrombi.[43,44]

Postdisruption Events

The events that follow an episode of plaque cap disruption are dynamic and occur in stages (Fig. 36-6). Progression can be halted at any stage. The initial stage, in the past, often has been referred to as *plaque* or *intimal hemorrhage, intraplaque hematoma,* and *hemorrhagic dissection*. These names imply that the intraplaque component is predominantly composed of red blood cells. A large component of platelets and fibrin is also present, justifying the name *intraplaque thrombus.*[42] Within the area of the torn cap at the interface with the lumen, the thrombus composition is predominantly densely packed fibrin. From this transition zone, mural thrombus

may project out into the lumen without totally preventing antegrade flow. In the final stage, thrombus is predominantly made up of a loose network of fibrin-containing enmeshed red blood cells and totally occludes the arterial lumen.

Plaque disruption is a stimulus to the formation of thrombosis within the lumen. Many factors control whether or not thrombosis occurs. The magnitude of the tear varies. At one extreme it may be a narrow fissure running from the lumen to the core; at the other extreme the whole cap may be lost with extrusion of core material into the lumen. Another important factor is the local blood flow. Reduction of flow, either due to spasm or because of a large expansion of the plaque by thrombus within the core, increases the likelihood of major thrombosis within the lumen. The systemic balance of prothrombotic and natural fibrinolytic mechanisms is another factor influencing whether or not major intraluminal thrombi follow the stimulus of an episode of plaque disruption.

Plaque Healing

Plaque disruption is followed by a healing response. Natural fibrinolysis will remove a variable amount of the thrombus, which is followed by smooth muscle cell proliferation and deposition of new collagen. This healing process is analogous to that which follows angioplasty. The end stage of an episode of plaque disruption can range from a trivial increase in plaque size through more significant increases in size resulting in an increase in stenosis severity to chronic total occlusion (see Fig. 36-6).

Mechanism of Intimal Tears

Reconstruction of human atherosclerotic plaques that have undergone disruption shows that the majority have a large core of extracellular cholesterol occupying over 50 percent of the plaque by volume. Computer models of plaques using finite-element analysis have been used to show the distribution of circumferential wall stress in systole.[45,46] Normally, systolic circumferential stress is evenly distributed. Lipid cores are soft and cannot sustain stress, which has to be distributed elsewhere. The displaced stress is redistributed to the plaque cap. Focal points of maximal stress may be up to 10 times greater than that experienced by the rest of the arterial wall. Studies of coronary plaques show that the site of tearing coincides with the calculated point of maximal stress.[46] Concentration of stress on the plaque cap is also particularly enhanced in thin caps of plaques, causing minimal stenosis.[47] All these studies emphasize the concept that plaques with lipid cores and thin caps are mechanically inefficient, with stresses impinging excessively on the cap.

Another important aspect of plaque disruption is the innate mechanical strength of the cap tissue. Mechanical testing in vitro of cap tissue shows that a reduction in collagen and glycosoaminoglycans and an increase in the number of lipid-filled macrophages interact to reduce the amount of stress needed to fracture the tissue even after correction for the cross-sectional area of the test sample.[48] Collagen types and elastin content do not alter absolute tissue strength. These results lead to consideration of whether or not the cap is undergoing active destruction by proteases. Macrophages have the capacity when activated by the cytokines TNF-α and interleukin 1 (IL-1) to secrete inactive *metalloproteinases* (MMP). These connective tissue-degrading enzymes include interstitial collagenase (MMP1), gelatinase B (MMP9), stromelysins 1, 2, and 3 (MMP3, -10, and -11), and a membrane type (MTMPP). When activated by plasmin or by inactivation of intrinsic inhibitors in the tissue, these metalloproteinases can degrade the connective tissue matrix. Macrophages in plaques also produce cathepsins K and S, which will degrade elastin.[49] Both metalloproteinase mRNA and protein have been found in large amounts in the cap and core area,[30,50,51] but their activity may be neutralized by tissue inhibitors (TIMPS). Sections of plaques laid on a gelatin substrate in vitro, however, show that lysis occurs in focal areas, indicating that active degradation of collagen is occurring.[51] Evidence of enhanced collagen

destruction in lipid-rich plaques also has been shown by the presence of collagen breakdown products identified by specific immunohistochemistry.[52] *Plaque cap tears therefore can be seen as resulting from a destructive process initiated by macrophages that gains ascendancy over the repair process of collagen deposition by smooth muscle cells.*

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Chapter 36: PATHOLOGY OF CORONARY ATHEROSCLEROSIS

DETAILED PATHOLOGY OF CLINICAL SYNDROMES IN ISCHEMIC HEART DISEASE

Unstable Angina

Intermittent ischemia occurring at rest is the hallmark of unstable angina and is related to "dynamic" stenosis; i.e., the obstruction to flow varies rather than being fixed (see Chap. 41). Two main mechanisms, mural thrombosis at the site of a culprit plaque and varying vasomotor tone, have been proposed. Neither process is exclusive, and both may operate contemporaneously.

Angiographic studies in unstable angina of the crescendo form, in which there is a clear risk of subsequent acute infarction, emphasize the presence of eccentric stenoses with ragged outlines, designated as type II, and of intraluminal filling defects.[53] Necropsy studies (Fig. 36-7) confirm that these angiographic appearances are due to nonocclusive thrombi developing over a disrupted plaque. *A major cause of unstable angina therefore is a culprit plaque over which thrombus is arrested at an intermediate stage in which it is neither occlusive nor resolved sufficiently to allow the plaque to reseal and heal.*

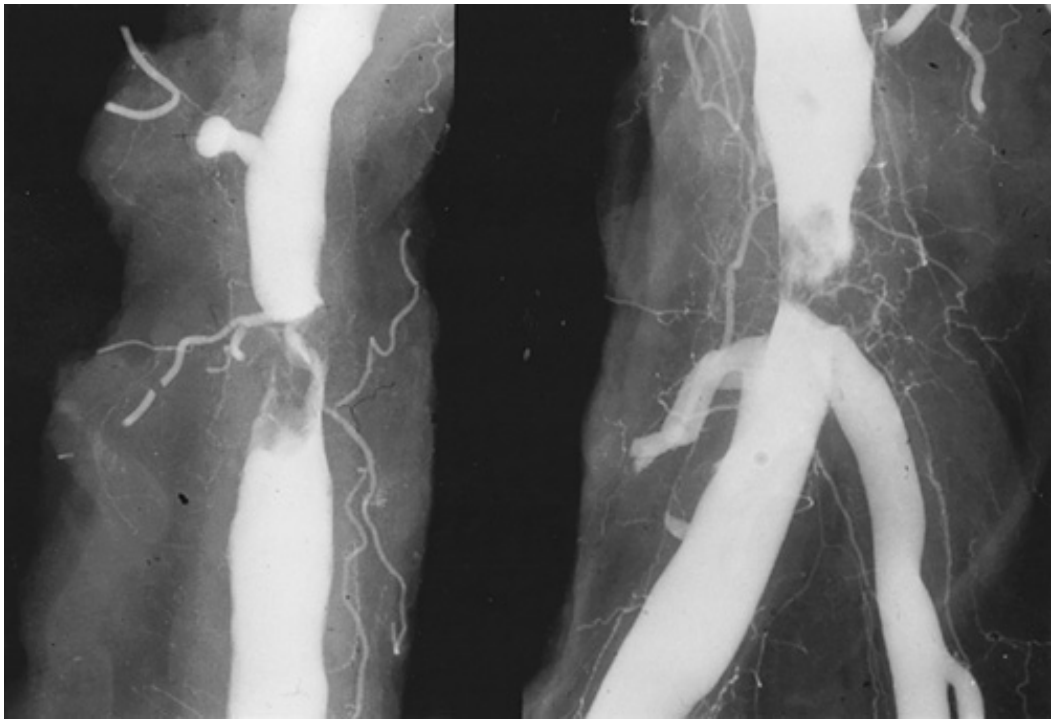

Figure 36-7: Postmortem angiograms of two patients who died suddenly after a prodrome of intermittent resting chest pain. Both had disrupted plaques. The angiograms show the typical eccentric stenoses with ragged edges. Both have related intraluminal thrombi-proximal in one (*left*) and distal in the other (*right*).

Necropsy studies of unstable angina are biased toward the worst-case scenario. To an extent, this limitation can be overcome by studies of plaque material retrieved by atherectomy of the culprit

lesion. Such studies confirm that macrophage infiltration is a feature of unstable plaques.[54] A number of atherectomy studies have shown that thrombotic material is recovered from a far higher proportion of plaques causing unstable as compared with stable angina but that this correlation is not 100 percent.[55,56] A far smaller proportion of apparently stable plaques also shows thrombotic material. Haft et al.,[57] for example, found thrombus in atherectomy material in 49 of 57 patients with unstable angina (86 percent) and in 7 of 24 patients with stable angina (29 percent). Atherectomy removes a random portion of the plaque, and this may explain the absence of thrombus in some patients with unstable angina. Timing is also important. Atherectomy samples that show accelerated growth with storiform smooth muscle cell proliferation[58] can be explained by the sample's having been taken after healing is initiated.[59] Angioscopy is probably more sensitive than angiography in identifying plaque thrombosis. A recent study[60] shows 70 of 95 (73.7 percent) patients with unstable angina had plaque thrombus. Four of 27 patients (14.8 percent) who had only exercise-related pain showed thrombus.

Pathologic studies show that platelet emboli into the distal myocardium lead to small foci of acute myocardial necrosis in subjects dying suddenly after unstable angina.[61,62] These small platelet emboli within the myocardium show intense expression of the type IIb/IIIa receptor (Fig. 36-8).

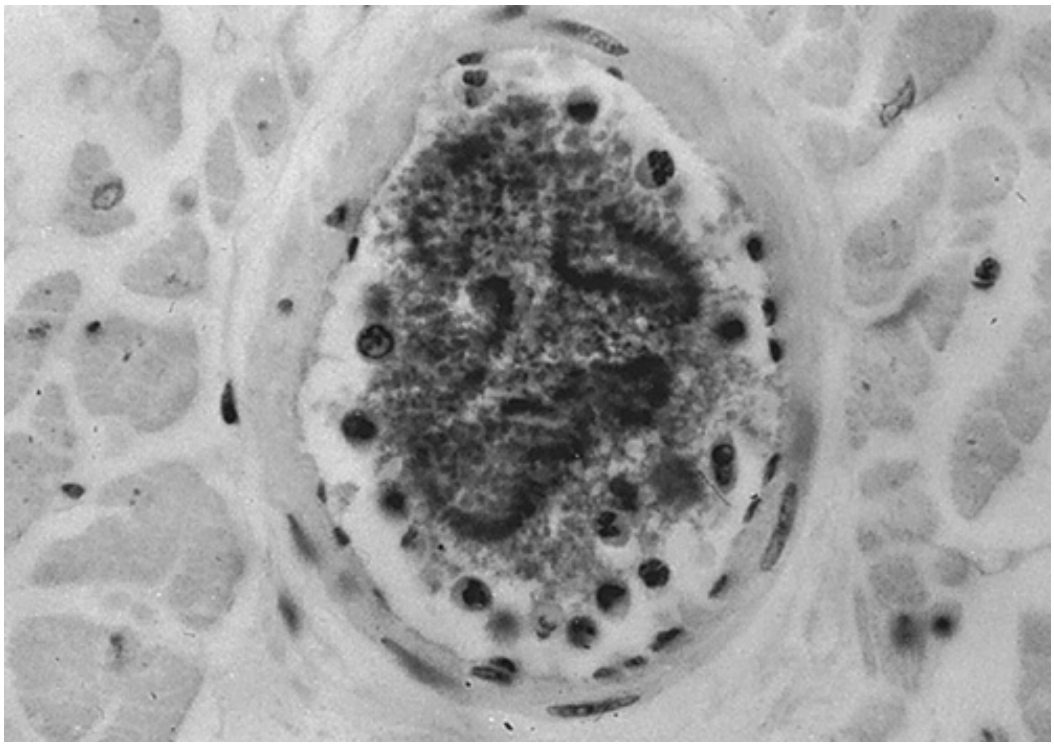

Figure 36-8: An intramyocardial artery distal to a disrupted plaque in a major epicardial artery is occluded by a mass of platelets and white blood cells. The platelets are expressing the type IIb/IIIa receptor (immunohistochemical staining with type IIb/IIIa antibody).

The arterial pathology of unstable angina differs from that of acute myocardial infarction only in that the artery remains open and some antegrade flow is retained, whereas in the latter antegrade flow ceases for at least a period of time, usually some hours. Unstable angina of the crescendo type, non-Q-wave or nontransmural infarction, and transmural infarction are different points in a continuous spectrum. It is therefore not surprising that sensitive methods of detecting myocardial necrosis, such as measuring plasma troponin-T levels, can be used to detect subjects with the clinical diagnosis of unstable angina who are at high risk of death or further infarction.[63]

The essence of the arterial pathology of unstable angina is that the process of thrombosis is arrested at the point of exposed mural thrombus. This arrest represents a balance between many active forces and does not imply that the thrombotic surface has become inert. The risk of thrombotic occlusion developing at the site remains increased for at least 6 to 12 weeks, and systemic hypercoagulative activity is also elevated for several months. Residual thrombotic material continues to be highly thrombogenic until it is completely replaced by smooth muscle cells and new connective tissue.[64]

Vasomotor Tonal Abnormalities in Unstable Angina

There is now abundant evidence in humans and in animals that atherosclerotic arteries have inappropriate vasoconstrictor responses. Vasoconstriction, which has been induced both by exercise and intracoronary infusion of acetylcholine, is caused by a failure of normal vasodilatory responses due, at least in part, to diminished nitric oxide release by the endothelium (see Chaps. 6 and 36).

Some cases of unstable angina have localized dynamic vasoconstriction, either at a site of eccentric stenosis or in a segment with minimal or no angiographic narrowing.[65,66] It is uncertain why one such lesion should acquire vasomotor excitability. Increased endothelin-1 production within plaques may be a contributing factor.[67] In one case, small amounts of thrombus, too small to be detected angiographically, were found on the endothelial surface at surgery.[68] The local release of vasoactive substances by platelets is one possible cause of spasm, and this possibility is supported by experimental models of coronary injury in pigs.[69] Another postulated cause is related to the heavy adventitial inflammation; mast cells may release pharmacologically active substances that act directly on adventitial nerve tissue.[70] The Prinzmetal variant form of angina frequently occurs in arteries that have some angiographic evidence of atherosclerosis but without an element of high-grade fixed stenosis[71] (see also Chap. 41). The greater frequency of unstable angina with either normal or mildly diseased arteries on angiography in women suggests they have a larger vasospastic component than males with acute ischemic events.[72]

Acute Myocardial Infarction

The blood supply of the mammalian myocardium is regional; each major branch of the coronary arteries supplies a specific segment of myocardium. There is considerable interspecies variation in the degree of innate cross-flow between adjacent epicardial arteries; humans and pigs share the property of having little natural collateral development.

In experimental animal models, the only way to produce regional infarction is to occlude the coronary artery supplying a given area. Clinical studies of regional myocardial infarction in humans confirm the importance of occlusion of the subtending ("infarct-related") artery. Angiography during the early hours of infarction shows the subtending artery to the region to be occluded.[73] The frequency with which occlusion is detected after a myocardial infarction diminishes with the passage of time; as antegrade flow returns (because of spontaneous lysis of thrombus), filling defects are seen within the lumen over a type II stenosis. Fibrinolytic therapy increases the speed with which the subtending artery reopens. These data suggest that a dynamic thrombotic process is occurring. Necropsy studies show a higher frequency of total thrombotic occlusion than equivalent angiographic studies of survivors of acute infarction. These findings suggest that persistent occlusion has an adverse influence on survival, probably by being linked to larger infarct size.[74]

Reconstruction of the microanatomy of occlusive coronary thrombi shows the majority to be due to plaque rupture in which there is both an intraplaque and an intraluminal component (Fig. 36-9). The thrombus found at autopsy varies in suggesting that it is formed by an intermittent process

taking place over some days. The intraplaque component of the thrombus consists predominantly of platelets; the thrombus within the fissure site is formed of densely packed fibrin. Much of the intraluminal thrombus, particularly that distal to the fissured plaque, is "venous" in type, suggesting that it has formed in a static column of blood. At least part of the intraluminal thrombus thus may be a late phenomenon. In vivo radiolabeling studies in subjects who subsequently died of acute infarction show that both fibrinogen and platelets given after the onset of the infarction can be incorporated into the coronary thrombus. Detailed studies, however, showed that the thrombus within the fissured plaque is not labeled, i.e., predates infarction, whereas a proportion of thrombus in the lumen is labeled, i.e., postdates infarction.[75]

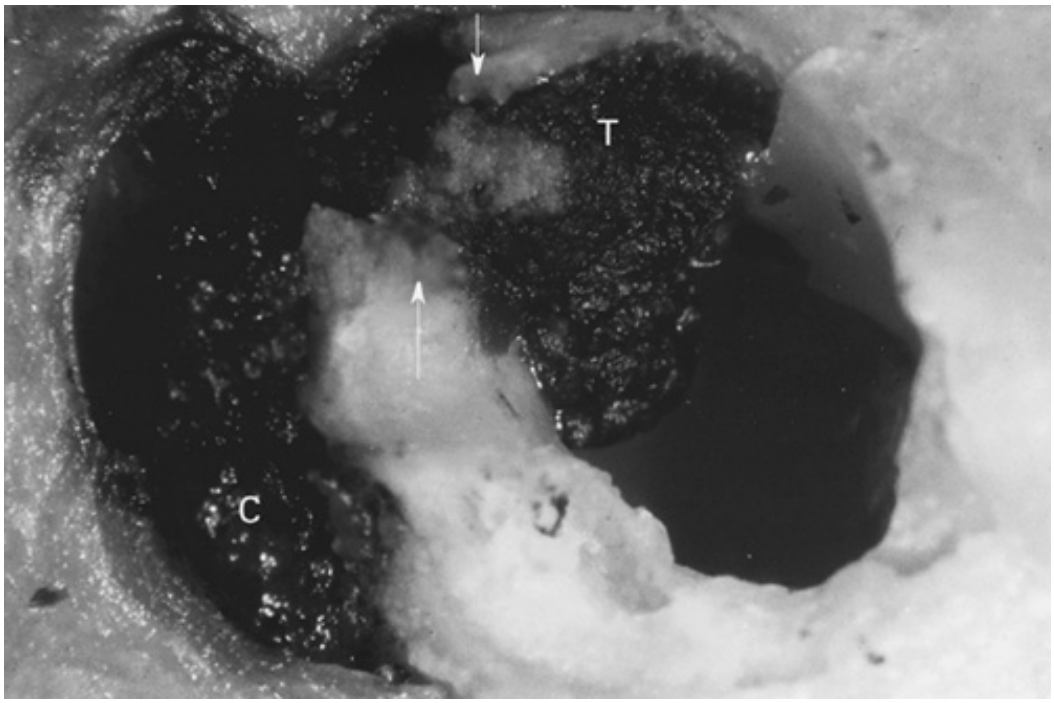

Figure 36-9: Plaque disruption related to an acute regional infarct. There is a mass of thrombus within the lipid core (*C*), which is continuous with thrombus (*T*) in the lumen via a discrete fissure (*arrows*) in the cap. The thrombus is not occlusive, presumably due to natural lysis.

INTERRELATION OF INFARCT MORPHOLOGY AND ARTERIAL THROMBI

Human regional infarcts may be formed of transmural necrosis of uniform age. Such infarcts are closely analogous to experimental infarction in the dog and represent the consequences of thrombus occurring suddenly and progressing to occlusion over a very short time in a vessel in which there was minimal or no preexisting stenosis. There may be preexisting high-grade stenosis, however, that has invoked collateral formation. In such arteries, thrombosis may occur without causing any infarction. Thrombosis may be mural and associated with distal embolization of platelet masses or intermittently occlusive prior to the final occlusive episode. Antegrade flow may or may not be restored spontaneously within a period of hours. These more complex developmental patterns of thrombosis are associated with regional infarcts that are built up by the coalescence of small, often microscopic areas of necrosis of different ages. Retention of areas of viable myocardium mixed with necrotic areas is common. Infarcts that are regional but confined to the subendocardial zone (nontransmural) are almost always of this type. In humans, nontransmural infarction, as compared with transmural infarction, has a higher frequency of previously established collateral flow and/or restoration of antegrade flow over the culprit plaque.[76,77] The sinister complications of infarct expansion, infarct rupture, and cardiogenic shock are virtually confined to transmural infarcts and are associated with persistent total occlusion of

long segments of coronary artery.

Coronary Syndromes and Markers of Inflammation

Atherosclerosis is an inflammatory response to modified lipids[78] within focal areas of the intima. All plaques at some point in their evolution have such an inflammatory response,[79] but this may burn out or progress to cause plaque disruption or endothelial erosion with resulting thrombosis and the potential to cause acute coronary syndromes.

A wide range of markers of inflammatory activity including C-reactive protein,[80] fibrinogen, neoptenin, and soluble intercellular adhesion molecule (ICAM) on a population basis give an indication of the risk of acute ischemic events in the future. These markers are not elevated to a degree that is strikingly outside the normal range, but, for example, if a population is divided into quartiles of the level of C-reactive protein, the upper quartile has a risk of myocardial infarction around three times the lowest quartile.[81] Such data can be interpreted in two ways, neither being exclusive of the other. The level of systemic inflammatory activity may be a measure of the total active plaque burden in the aorta and carotid and coronary arteries. In general, subjects with severe aortic disease have the most extensive coronary plaque formation. Alternatively, a non-lipid-dependent mechanism may be elevating overall inflammatory activity feeding back on the plaques. Such factors potentially would include *Helicobacter* and chlamydial infection, chronic peritonitis, rheumatoid arthritis, etc. Experimental evidence exists that elevation of systemic mediators will secondarily upregulate plaque inflammation.[82]

Coronary Artery Pathology in Stable Exertional Angina

Angiographic and necropsy studies[83] show that the basis of stable angina is segments of coronary artery in which the lumen is reduced in diameter by at least 50 percent (75 percent cross-sectional area) compared with the adjacent normal artery. Such stenoses are potentially flow-limiting on exertion. The number of arteries involved and the number of stenotic segments vary widely from case to case, with autopsy studies inevitably showing the more severe end of the spectrum. The morphology of lesions causing chronic high-grade stenosis can best be appreciated in coronary arteries that have been fixed after autopsy by perfusion with formalin at systolic pressures. In such preparations, the lumen is nearly circular in outline, indicating that the slitlike lumen shape shown in many pathology studies is an artifact. Segments of high-grade stenosis may be eccentric; i.e., there is an arc of vessel wall that has retained its normal media opposite the plaque[84] (see Fig. 36-2). Alterations in vascular tone in this residual segment of normal media may alter the cross-sectional area of the lumen. Stenoses may be concentric, however, surrounding the lumen and limiting variation in lumen size.

Many patients with stable angina but without a clinical history of infarction are found at autopsy to have a healed regional infarct. Arteries that supply such regions may be totally occluded by fibrous tissue, have high-grade stenosis due to complex type Vb plaques, or have many new, small vascular channels contained within the original lumen. This last appearance is pathognomonic of recanalization by organization of previous occlusive thrombus. In subjects with stable angina, such recanalized segments also may be present and unrelated to old scars, illustrating the fact that thrombotic occlusion is not inevitably followed by infarction. In one autopsy study of 54 men with stable angina who died within 6 h of the onset of symptoms, 38 patients had microscopic evidence of previous healed myocardial infarction; of these, 33 (87 percent) had one or more arterial segments in which the lumen was multichanneled. In the 16 patients who did not have microscopic evidence of an old infarction, 10 (62.5 percent) had one or more arterial segments that were multichanneled.[83]

CORONARY ANASTOMOSES (COLLATERALS)

Anastomotic flow is impossible to demonstrate in life or at necropsy without angiography. Anastomoses occur at several different levels. Local adventitial vessels open and provide very localized anastomoses at sites of short segments of high-grade or total chronic occlusion. While such periarterial vessels may show up strikingly in angiograms, the caliber of individual vessels is small, and useful flow may not be achieved. Similar-sized vessels develop within the arterial lumen, passing through an old organized thrombus. Larger anastomoses develop between adjacent arteries on the epicardial surface. These may be as much as 1000 μm in diameter and are probably preexisting smaller arteries altered by flow-induced pressure differentials between different coronary beds. These anastomoses at the epicardial surface are probably the most important functionally and develop a characteristic corkscrew configuration in angiograms. In areas of nontransmural scarring within the myocardium, a plexus of large subendocardial vessels appears that has a structure resembling that of venous sinusoids. In very diffusely scarred ventricles, these channels fill throughout the ventricle from injection into one coronary artery.

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MECHANISMS OF PROGRESSION AND REGRESSION

Any morphologic explanation of disease progression must take into account a number of clinical observations.[85-89] Sequential clinical angiographic studies show that progression is phasic and unpredictable in any particular arterial segment. High-grade lesions do not necessarily appear at sites where lower-grade lesions were present previously. New lesions causing luminal stenosis over 50 percent in diameter can appear between two angiographic examinations in apparently normal segments of artery. The sites of future acute occlusions causing infarction cannot be predicted. The progression of separate lesions in an individual is unrelated, and the progression of lesions in "normal" segments is often greater than in areas recognized to have an irregular outline. Thus individual plaques can enter an accelerated growth phase that is unrelated to their degree of stenosis. Despite this unpredictable behavior, high-grade stenoses (>70 percent by diameter) do tend to progress, particularly if the segment is long. Chronic total occlusions follow such high-grade lesions three times more frequently than in the case of less severe lesions[89] but frequently do not invoke infarction because of collateral development. Sequential coronary angiograms show that increases in the overall extent of disease also predict the risk of acute ischemic events in the future.[90,91]

Episodes of plaque disruption were regarded initially as events that inevitably caused thrombosis within the arterial lumen and therefore usually were manifest as episodes of acute myocardial ischemia. Several pathology studies have altered this concept. In a significant proportion of patients who had coronary atherosclerosis but who died of noncardiac causes such as accidents, small, recent plaque disruptions were found at autopsy. Up to 16 percent of such individuals who have diabetes and/or hypertension have these lesions.[92] In three studies of patients who died of acute myocardial ischemia, many were found at necropsy to have had two or three separate areas of disruption, although one was usually larger and regarded as the culprit lesion causing death.[93-95] Such data suggest that *episodes of plaque disruption are a characteristic feature of the progression of atherosclerosis and that many are clinically silent.*

An episode of plaque disruption heals by smooth muscle proliferation, replacing residual thrombus. The repair process is identical to that which follows plaque disruption produced by angioplasty. The final outcome of an episode of plaque disruption can range from chronic total occlusion at one extreme to a mild increase in stenosis at the other extreme (see Fig. 36-6).

Generation of Chronic High-Grade Coronary Stenosis

The simplest model of the generation of significant coronary stenosis is that the plaque simply grows by the process of atherosclerosis (lipid accumulation-collagen formation) in a linear fashion until the lumen is narrowed to a degree that limits flow. Sequential angiography, however, often shows that high-grade stenotic lesions appear within a year at sites that were normal previously by angiography.

As plaques grow slowly, the artery wall remodels to accommodate the lesion, compromising lumen size. The external cross-sectional area of a coronary artery may increase by up to 80 percent of its normal size. Such compensatory dilatation is often sufficient to allow relatively large plaques not to encroach on the lumen and be angiographically invisible. At points of high-grade coronary stenosis, the degree of remodeling is often minimal (inadequate remodeling) or

even shows a reduction in the artery size (negative remodeling). Thus stenosis arises both from an increase in plaque size and from the degree of remodeling.[96,97] Failure of remodeling may reflect the rate of plaque growth. Reconstruction of segments of high-grade stenosis in pathology studies show at least 70 percent of lesions to have healed disruption that would have triggered accelerated smooth muscle proliferation and a sudden increase in the rate of plaque growth.[59]

Lipid Lowering and Atherosclerosis

Lipid-lowering trials have shown consistently that disease progression can be slowed but that the degree of reduction in narrowing of established stenoses is minimal. Trials designed to study the risk of acute events after lipid lowering by drugs, however, have demonstrated a 30 percent drop in acute ischemic events and a fall in all-cause mortality. The effect becomes apparent after 18 months of therapy (see also Chap. 38).

Acute coronary syndromes largely are due to thrombosis developing on plaques that are vulnerable, i.e., have an increased risk of causing thrombus compared with other plaques in that individual that remain inert for years. The determinants of vulnerability are a large lipid core, a thin cap, endothelial loss, and reduced smooth muscle cell content. All these characteristics reflect a high density and activity of macrophages, i.e., active inflammation. The degree of risk for any individual of developing an acute event depends on the absolute numbers of vulnerable, highly active inflammatory plaques.

Lipid lowering in experimental models of atherosclerosis shows a very consistent message in that plaque morphology is significantly altered, although the reduction in size is small.[99] The number of macrophages falls, cytokine activity falls, metalloproteinase activity falls, smooth muscle density rises, and the plaque becomes more solid due to collagen deposition.[100] [101] Such changes would reduce plaque vulnerability to thrombosis. In human subjects, while lipid lowering has systemic effects and improves endothelial function, the time course of benefit is consistent with the induction of quantitative changes in plaques reducing vulnerability. The equal benefit observed in males and females would suggest that both erosion and disruption risks are reduced.

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Part 6: CORONARY HEART DISEASE
Chapter 37:

CORONARY BLOOD FLOW AND MYOCARDIAL ISCHEMIA

Authors: Attilio Maseri, Gaetano Antonio Lanza, Tommaso Sanna, Stefano Rigattieri

REGULATION OF CORONARY BLOOD FLOW

The task of the coronary circulation is to supply the myocardium with oxygen and substrates and remove metabolic waste products. Contractile cardiac function relies on aerobic metabolism and, as basal oxygen extraction is about 60 percent,[1] an adequate increase of coronary blood flow is required to meet increased myocardial oxygen consumption (M_{VO_2}).

During strenuous exercise coronary blood flow can increase about five times.[2] The maximal increase in coronary flow above resting levels is defined *coronary flow reserve* and is expressed as the ratio between the flow during maximal vasodilatation and basal flow.[3] Low M_{VO_2} at rest requires a low coronary flow; therefore it is associated with a larger coronary flow reserve than a high resting M_{VO_2}.

Vascular resistance in the coronary circulation is distributed into several functional compartments arranged in series. It is mainly determined by M_{VO_2} and modulated by neural stimuli, local vasoactive autacoids, and circulating vasoactive substances. The transmural distribution of resistance across the ventricular wall is largely determined by extravascular tissue compressive forces.

A brief description of determinants of M_{VO_2}, of the functional anatomy of the coronary circulation, and of the distribution of coronary vascular resistance is useful for a better understanding of the regulation of myocardial blood flow (see also Chap. 40).

Determinants of Myocardial Oxygen Consumption

Mechanical work performed by the myocardium is the most important determinant of M_{VO_2}, as the latter decreases to only 15 to 20 percent in the nonbeating heart. Heart rate, myocardial wall tension, and myocardial inotropic state are the major determinants of metabolic activity and therefore of M_{VO_2}.[4]

Heart rate is by far the major determinant of M_{VO_2}: when the heart rate doubles, myocardial oxygen uptake also approximately doubles. Myocardial tension developed during systole is directly proportional to aortic pressure (afterload), myocardial fiber length and ventricular volume (preload).* Myocardial oxygen uptake approximately doubles as mean aortic pressure is increased from 75 to 175 mmHg at constant heart rate and stroke volume. Finally, myocardial inotropic state determines ventricular performance independent of both preload and afterload. M_{VO_2} increases by about 30 percent when dp/dt† is doubled by extrasystolic potentiation or by norepinephrine at constant heart rate, aortic pressure, and cardiac output.

Direct measurement of M_{VO_2} requires determination of coronary blood flow and arteriovenous difference of blood oxygen content. Therefore, a number of noninvasive, indirect indices were proposed. Of these, the rate-pressure product (heart rate × systolic blood pressure) is the simplest one and is well correlated with direct measures of M_{VO_2} in a variety of physiologic and experimental conditions.

Functional Compartments of the Coronary Circulation

About 75 percent of total vascular resistance occurs in the arterial system, which can be divided into three functional compartments arranged in series: conductive vessels, prearteriolar vessels, and arteriolar vessels (Fig. 37-1).

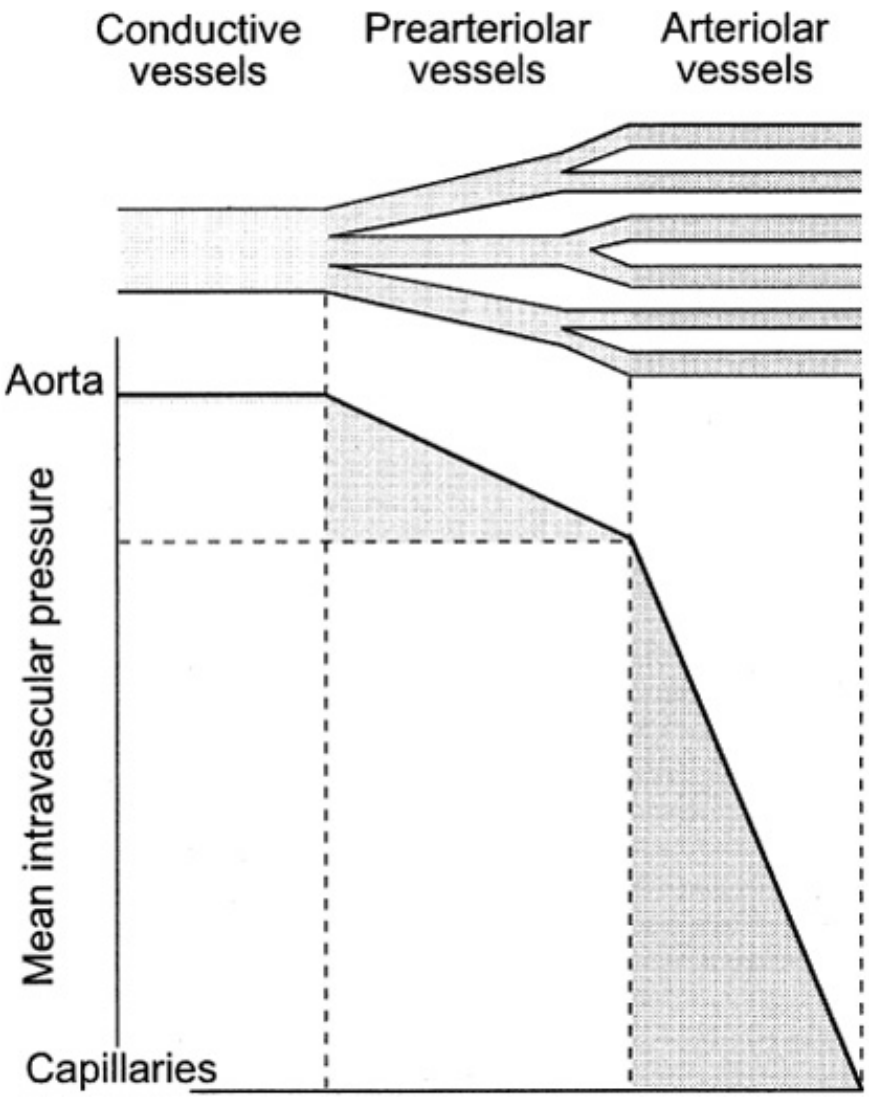

Figure 37-1: Schematic illustration of the subdivision of coronary arterial system into conductive, prearteriolar, and arteriolar vessels. Resistance to flow is negligible in conductive vessels (epicardial arteries) and maximal in arterioles, which are under the control of myocardial metabolic activity. Prearteriolar vessels offer an appreciable resistance to flow, but, unlike arterioles, are not under direct metabolic vasodilator control. Their specific function is to maintain pressure at the origin of arterioles within a narrow range when aortic pressure and coronary flow vary. The arterioles are the major site of metabolic regulation of flow. (From Maseri[46] by permission.)

1. The proximal compartment is represented by the large epicardial coronary arteries; these vessels have conductive function and do not contribute significantly to vascular resistance, as the pressure drop along their length is negligible. During systole, their blood content increases by about 25 percent as a result of anterograde flow from the aorta and retrograde flow from squeezed intramyocardial vessels. The elastic energy accumulated in the vessel wall during systole is transformed into blood kinetic energy at the beginning of diastole. About 60 percent of the wall thickness of conductive vessels is represented by the muscular media, which is responsible for myogenic autoregulation of the vascular lumen in response to changes in aortic pressure and for modulation of coronary tone in response to flow-mediated endothelium-dependent vasodilators, circulating vasoactive substances, and neural stimuli. Conversely, the caliber of large conduit arteries is totally unaffected by myocardial metabolites because of their extramural position.
2. The intermediate compartment is represented by prearterioles, which are resistive vessels connecting epicardial conduit arteries to the arterioles. The proximal and distal ends of prearterioles cannot be defined anatomically, but their diameter is in the range of 100 to 500 μm. They contribute to about 30 percent of total coronary flow resistance, but their vasomotor control mechanisms are much more like those of epicardial arteries than those of arterioles because they are largely unaffected by myocardial metabolic vasodilators. The main function of prearterioles is to maintain the driving pressure at the origin of arterioles within an optimal range. This regulatory function is mediated by myogenic autoregulation and flow-dependent vasodilatation in response to shear stress. Prearteriolar resistance is also modulated by neural stimuli and by local autacoids.
3. The distal arterial compartment is represented by the arterioles, which are the main site of metabolic regulation of coronary blood flow. They are smaller than 100 μm in diameter and are responsible for about 40 percent of coronary flow resistance. Also, their tone can be modulated by neural stimuli and local autacoids. At the arteriolar site, the effects of constrictor stimuli strong enough to induce ischemia are directly opposed by locally released myocardial vasodilator metabolites.

In an integrated response model,[5] an increase in metabolic demand of the myocardium initially causes arteriolar vasodilatation (metabolic domain) which is followed by a transient decrease in pressure at their origin, with consequent myogenic regulation (myogenic domain) as well as by an increase in flow, leading to flow-mediated, endothelium-dependent vasodilatation in proximal vessels (flow-sensitive domain). Arterioles branch into metaarteriolar and capillary vessels, which provide a regional microdistribution of flow that, under physiologic conditions, exhibits spatial and temporal heterogeneity. Such physiologic heterogeneity may have pathophysiologic consequences, as coronary hypoperfusion severe enough to cause ischemia was shown to produce a nonuniform maximal dilation of microvessels and a variable response to adenosine in adjacent myocardial regions.[6]

Diffusion of oxygen and substrates to myocardial cells takes place at the capillary level. On average, there is one capillary for each myocardial fiber, but their density is about 20 percent higher in the subendocardial layers.

The venous side of the coronary circulation has so far received little attention, although it contributes a detectable fraction of total coronary flow resistance and can influence capillary recruitment and blood volume content in the ventricular wall, increasing diastolic fiber length and therefore myocardial oxygen consumption ("garden hose" effect).

Physiologic Control Of Myocardial Perfusion

The in-series distribution of resistance as well as total vascular resistance are largely determined by changes of coronary vasomotor tone, while the transmural distribution of perfusion across the left ventricular wall is largely determined by extravascular compressive forces.

EXTRAVASCULAR MECHANICAL FORCES

At variance with all other organs, the heart generates its own perfusion pressure, and extravascular forces squeeze the vessels closed when extravascular pressure is higher than intravascular distending pressure.[7]

During systole, intramyocardial left ventricular pressure is sufficiently high to prevent systolic flow across the whole wall (perhaps with the exception of the outermost layers) and to squeeze intramyocardial blood forward out of the capillaries, venules, and veins toward the coronary sinus and backward from subendocardial and midwall layers toward epicardial arteries.[8] The extravascular compressive forces are highest in the subendocardium and decrease linearly toward the subepicardium. As intramyocardial tissue pressure is higher in subendocardial layers,[9] subendocardial vessels are squeezed more than subepicardial ones, so they take a longer time to refill and resume their caliber during diastole,[10] particularly when perfusion pressure is low (e.g., distal to flow-limiting coronary stenosis or in the presence of aortic stenosis) (Fig. 37-2). When poststenotic pressure is reduced, subendocardial perfusion is further impaired by tachycardia, which shortens the duration of diastole,[11] and by increased left ventricular diastolic pressure, which increases extravascular compressive forces in subendocardial layers. The higher extravascular resistance, together with a higher basal M_{VO_2}, determines a greater susceptibility to ischemia in subendocardial layers.

REGULATION OF CORONARY VASOMOTOR TONE

The mechanisms of contraction and relaxation of vascular smooth muscle cells are influenced by several factors and are not the same in the different compartments of the coronary circulation. Vasomotor tone is mainly determined by M_{VO_2} in arteriolar vessels (metabolic vasodilatation) and by perfusion pressure and flow-mediated vasodilatation in prearterioles and in large arteries (myogenic and endothelial control); it is also influenced by neurogenic stimuli, local autacoids, and circulating vasoactive substances in all vascular compartments.

Metabolic Regulation

Arteriolar vasomotor tone is under metabolic control, as arterioles are directly exposed to the effects of the myocardial metabolites, which diffuse into the interstitial space. When M_{VO_2} increases, vasodilator metabolites released from myocardial cells diffuse into the arteriolar wall, causing smooth muscle cell relaxation. The resulting arteriolar vasodilatation causes flow to increase, so that vasodilator metabolites are washed out and flow is reset at a higher level.

Adenosine is a major component of myocardial metabolic regulation of flow.[12] According to a "microhypoxia" model, adenosine production reflects adenosine triphosphate (ATP) degradation resulting from a local myocardial imbalance between oxygen supply and demand. ATP dephosphorylation first results in the formation of adenosine monophosphate (AMP), and then, by 5′-nucleotidase action, in adenosine production. Adenosine, diffusing into the interstitial space and arteriolar wall, can stimulate $alpha_2$-receptors of smooth muscle cells, inducing adenylate-cyclase activation, cyclic-AMP synthesis, and consequent smooth muscle cell relaxation.

However, adenosine is unlikely to be the only component of metabolic vasodilatation[13] and of reactive hyperemia following release of coronary occlusion.[14] Oxygen tension, pH, potassium, osmotic pressure[15] and ATP-sensitive potassium channels[16] also contribute to metabolic regulation of flow.

Myogenic Regulation

When metabolic requirements do not vary, the heart, like other organs, exhibits an intrinsic tendency to maintain blood flow constant despite changes in arterial perfusion pressure. Pressure-flow curves in experimental models show that flow remains nearly constant over a range of perfusion pressure from 60 to 120 mmHg, partly resulting from myogenic control. Myogenic control of vasomotor tone tends to keep the vessel wall tension constant in response to changes in vascular distending pressure: myogenic tone increases when pressure increases and decreases when pressure decreases.

The role of myogenic control of vasomotor tone cannot be easily separated from the effects of stretch-induced release of endothelium-derived relaxing factor (EDRF, see below) and of metabolic regulation. However, myogenic activity has been demonstrated in coronary vessels 40 to 200 μm in diameter[17] and the responses of vascular tone to changes in transmural pressure is not affected by endothelial denudation, confirming that myogenic activity is an intrinsic property of vascular smooth muscle cells.

Neural Regulation

Coronary vessels are innervated both by sympathetic and parasympathetic efferents of the autonomic nervous system.[18] Nerve endings are mainly located at the adventitial-medial border of vessels and their density is greater in prearterioles and arterioles than in epicardial coronary arteries. Besides acetylcholine and norepinephrine, several "nonadrenergic noncholinergic" neurotransmitters identified in axonal varicosities may play a modulatory role on adrenergic and cholinergic output.[19] These substances include purines (ATP), amines (serotonin and dopamine), and peptides [neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), substance P, and vasoactive intestinal peptide (VIP)].

Sympathetic Control

Both $alpha_1$ and $alpha_2$ and both $beta_1$ and $beta_2$ adrenergic receptors have been identified in coronary arteries. Electrical stimulation of sympathetic nerves and intracoronary infusion of norepinephrine cause an increase in coronary flow resistance mediated by alpha-receptors, whereas pharmacologic stimulation of beta-receptors results in a modest reduction (20 to 30 percent) of coronary flow resistance.[20] In humans, abolition of alpha-adrenergic tone causes an approximate 10 percent increase in resting coronary blood flow and a proportionate increase in coronary sinus oxygen saturation, indicating the presence of a tonic basal, alpha-mediated coronary vasoconstriction. Subepicardial alpha-adrenergic-mediated coronary vasoconstriction may counterbalance the greater extravascular compressive forces in subendocardial layers.[21]

Parasympathetic Control

The role of the parasympathetic nervous system in coronary blood flow regulation is still unclear. Muscarinic receptors are present on smooth muscle cells, where they trigger contraction; on sympathetic nerve varicosities, where acetylcholine inhibits norepinephrine release; and on the endothelium, where their activation induces EDRF release.[22] However, the extent to which acetylcholine released at the site of vagal nerve endings in the adventitia reaches endothelial receptors is unknown. The variable effect of cholinergic stimulation may depend on the balance among its different sites of action. VIP co-released with acetylcholine exerts a significant vasodilator effect.[23]

Purinergic Control

Two types of purinergic receptors have been identified: P_1, which is most sensitive to adenosine and mediates smooth muscle cell relaxation both directly and by endothelial release of EDRF, and P_2, which is most sensitive to ATP and mediates endothelial release of EDRF but also direct vasoconstriction. ATP was found to be released from nerve terminals together with norepinephrine. However, the role of purine release by nerve endings in the regulation of coronary blood flow and coronary vasomotion is not well defined.

Peptides

NPY is released with norepinephrine during sympathetic nerve stimulation[24] and its infusion was shown to cause severe myocardial ischemia by microvascular constriction in patients with normal coronary arteries (see below). Both CGRP and substance P are also found in cardiac nerves; their intracoronary infusion causes EDRF release and dose-dependent dilation of epicardial coronary arteries with a maximum effect similar to that produced by nitrates.

Reflex Control

Coronary vasomotor tone is also under the influence of cardiac reflexes; afferent stimuli arising outside the heart (from chemoreceptors in the carotid bodies and from mechanoreceptors in the carotid sinus, aortic arch and lungs) may produce efferent stimuli that influence coronary flow resistance. Hypotension at the level of carotid sinus baroceptors would tend to increase coronary flow resistance by alpha-adrenergic stimulation, but this effect in vivo is obscured by metabolic vasodilatation in response to the increase in heart rate and contractility consequent to enhanced cardiac sympathetic drive.

Endothelial-Mediated Regulation

Among the multiple roles of the endothelium, the production of vasoactive autacoids contributes to the regulation of coronary blood flow. (The nonvasomotor endothelial functions are presented in the following section.) Endothelial cells release several vasodilator autacoids that contribute to the physiologic regulation of coronary vasomotor tone, such as EDRF, prostacyclin (PGI_2) and endotheliumderived hyperpolarizing factor (EDHF), as well as vasoconstrictor autacoids that may have a pathologic role, such as endothelin-1 (ET-1), angiotensin II, and endothelium-derived contracting factors (EDCFs) (Fig. 37-3).

Physiologic Vasodilator Function

The maintenance of a tonic basal vasodilatation and the flow-mediated regulation of vascular tone are largely dependent on the release of EDRF, identified as nitric oxide (NO) or a NO carrier compound, e.g., L-nitrosocysteine.[25] NO exerts its vasodilator action on vascular smooth muscle cells by activating the enzyme guanylate cyclase, which leads to cyclic-GMP production. EDRF is released in response to a large number of agonists acting on endothelial receptors, including neurotransmitters (acetylcholine and norepinephrine), substances released by platelets (serotonin, adenosine diphosphate) or formed during coagulation of the blood (thrombin), and autacoids formed in the vessel wall, such as histamine, bradykinin, and endothelin. Moreover, EDRF is released also in response to pulsatile stretch and flow shear stress.

EDRF has a 5-s half-life and is continuously released, tonically reducing basal vasomotor tone as the infusion of its inhibitor NG-monomethyl-L-arginine (LNMMA) reduces forearm blood flow and coronary diameter in humans[26,27] and causes blood pressure increase in animals.

Flow-mediated vasodilatation in large arteries and in prearteriolar vessels reduces wall shear stress

when flow increases. Fluid shear stress and viscous drag, through endothelial mechanotransduction, cause EDRF release as well as transcriptional changes, with protein synthesis and vascular remodeling.[28]

Coronary vascular resistance is also modulated by PGI_2 and by EDHF. PGI_2 is synthesized from arachidonic acid, has a 10-s half-life, and is released in response to pulsatile pressure, bradykinin, thrombin, serotonin, and platelet-derived growth factor (PDGF). It contributes to resting conduit and resistance vessel tone and to flow-mediated vasodilatation.[29] EDHF is most likely a short-lived metabolite of arachidonic acid,[30] thought to open ligand-gated potassium channels, and is released in response to several stimuli, including shear stress, pulsatile flow, acetylcholine, substance P, bradykinin, and CGRP.

Pathologic Vasoconstrictor Function

Vasoconstrictor autacoids are released by endothelial cells in several pathologic conditions (hypertension, diabetes, atherosclerosis, and acute inflammation), but their physiologic role is uncertain.

ET-1, a 21-amino acid peptide released abluminally by endothelial cells, is the most powerful vasoconstrictor known.[31] Despite its short plasmatic half-life (about 5 min), it exerts a prolonged action, interacting with two major types of receptors (ET_A and ET_B) and activating the membrane phospholipase C. Its release is reduced by NO and stimulated by thrombin, angiotensin II, catecholamines, interleukin-1β, transforming growth factor beta, and by hypoxia and ischemia.[32] ET-1 was shown to exert a potent vasoconstrictor effect on small coronary vessels; in dogs, intracoronary infusion of ET-1 causes severe reduction in coronary flow without constriction of angiographically detectable arteries (see below). Under physiologic conditions, there seems to be no significant role for ET-1-mediated regulation of coronary blood flow, as myocardial perfusion is not affected by ET-1 antagonists.

Other endothelial constrictor substances include angiotensin II (produced through a local angiotensin-converting enzyme) and EDCFs, including prostaglandin H_2 and oxygen-derived free radicals.[33]

Blood/Vessel Wall Interface

In addition to its vasomotor function, the endothelium plays a major role in the homeostasis of the vessel wall and in the control of the blood/vessel wall interface. The latter is of fundamental importance, as coronary thrombosis is a major pathogenetic mechanism of acute coronary syndromes.

HOMEOSTASIS OF THE VESSEL WALL

Endothelial cells produce several constituents of the basement membrane and of the intercellular intimal matrix. They also synthesize growth factors for smooth muscle cells as well as heparan sulfates and NO, which inhibit cellular growth and migration.[34,35] The integrity of the endothelium is essential for preventing the diffusion of atherogenic components into the arterial wall. The response of smooth muscle cells to trophic stimuli produced by the endothelium depends on their phenotype:[36] cells in the proliferative phenotype respond with increased protein synthesis and proliferation to growth factors and to constrictor stimuli, whereas cells in the mature contractile phenotype respond with contraction.

CONTROL OF BLOOD/VESSEL WALL INTERFACE

The endothelium plays a key role in preserving blood fluidity and in preventing thrombosis (Fig. 37-4*A*). This overall function is performed by different mechanisms. The glycocalyx of endothelial cells, represented by proteoglycans such as heparan sulfate, forms an electronegative barrier, which prevents adhesion of platelets and circulating cells. NO production also prevents platelet adhesion, and PGI_2 opposes platelet aggregation.[37] Moreover, endothelial cells produce and bind anticoagulants such as heparan sulfate, which catalyzes the inactivation of thrombin by plasma antithrombin III, and thrombomodulin, which binds thrombin and protein C, leading, ultimately, to factor V and VIII inactivation. Finally, endothelial cells are involved in fibrinolysis by the secretion of two plasminogen activators, a urokinase type (u-PA) and a tissue type (t-PA).

ALTERATIONS OF ENDOTHELIAL FUNCTION

Chronic Endothelial Dysfunction

Patients with coronary atherosclerosis and also individuals with cardiovascular risk factors (such as hypertension, diabetes, hypercholesterolemia, hyperomocysteinemia, and smoking) show a reduced or abolished vasodilator response to acetylcholine.[33] However, acetylcholine is also a direct powerful constrictor of vascular smooth muscle cells; therefore it is impossible to establish whether an abnormal vasomotor response to acetylcholine is due to defective endothelial EDRF production or to enhanced smooth muscle vasoconstrictor response. The latter possibility is suggested by the preserved dilator effect to substance P in atherosclerotic vessels.[38] It is also unknown to what extent an abnormal response to acetylcholine implies alterations of the endothelial antithrombotic properties. As many patients with extensive coronary atherosclerosis may remain totally free from ischemic events for months and years, it would seem reasonable to consider the possibility that, in some patients and under some circumstances, coronary atherosclerosis may be associated with the development of compensatory, protective factors.

Acute Inflammatory Activation

Increasing evidence suggests that inflammatory activation of the endothelium may play a role in the pathogenesis of some acute ischemic syndromes, determining a rapid switch of its functional properties from vasodilator to vasoconstrictor and from anticoagulant to procoagulant.[39,40] Also, in the absence of detectable histologic changes such as erosion or fissure, endothelial activation by inflammatory cytokines abolishes EDRF and PGI_2 release and stimulates ET-1 release, induces the expression of tissue factor and of adhesive receptors for platelets and leukocytes on the luminal surface, causes the production of plasminogen activator inhibitors (PAI-1), and inhibits that of plasminogen activators (u-PA, t-PA) and of heparan sulfate (Fig. 37-4*B*). In addition, cytokines may also activate metalloproteases, with consequent endothelial erosions and lysis of the plaque caps.[41,42] The causes of such inflammatory processes may be multiple, acute, and chronic, infectious or noninfectious,[43] and be variably modulated by the individual inflammatory and immune responses.[44,45]

Therefore, acute activation of the endothelium and of the vascular wall is one of the possible mechanisms that set the stage for local thrombosis and vasoconstriction in presence of a very variable severity of the chronic atherosclerotic background.

* According to Laplace's law, wall tension = (pressure × radius)/2 × wall thickness.

† *dp*/*dt* indicates the rate of pressure development in the left ventricle.

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Chapter 37: CORONARY BLOOD FLOW AND MYOCARDIAL ISCHEMIA

MECHANISMS OF MYOCARDIAL ISCHEMIA

Myocardial ischemia develops when coronary blood flow becomes inadequate to meet myocardial oxygen and metabolic substrate requirements for maintaining adequate cardiac function. Myocardial ischemia can result from (1) an increase of myocardial workload, and hence oxygen demand, in the presence of a flow-limiting coronary artery stenosis or (2) a reduction of coronary blood flow caused by epicardial or microvascular coronary artery constriction or by acute thrombosis. These mechanisms may act in combination in some patient as well as in different ischemic episodes in a same patient (Fig. 37-5).[46]

In clinical practice, coronary stenoses are often considered the only or main cause of myocardial ischemia, because they are the most obvious and readily plausible culprits. Indeed, acute thrombosis can be recognized until thrombi are lysed or become incorporated into the atherosclerotic plaques. The detection of coronary spasm and of dynamic stenosis is even more elusive, because they are very transient and usually require repetition of angiography following nitrates or provocative tests. Finally, microvascular constriction may only be indirectly inferred by slow distal flow dye progression at angiography or by special diagnostic studies (see also Chap. 40).

The clinical presentation of anginal syndromes can provide useful clues about the role of these distinct pathogenetic mechanisms in precipitating myocardial ischemia.

Flow-Limiting Stenosis

EFFECTS OF FLOW-LIMITING STENOSIS ON BLOOD FLOW

The presence of epicardial coronary artery stenosis, caused by atherosclerotic plaques, is by far the most frequent angiographic finding in any cardiac ischemic syndrome. However, a stenosis becomes flow-limiting only when it determines a measurable transstenotic pressure gradient at rest. The transstenotic pressure gradient increases with increase in flow, more than doubling when blood flow doubles.

A basal gradient at rest may not cause myocardial ischemia, as flow is maintained by compensatory distal arteriolar dilatation. In turn, compensatory arteriolar dilatation implies a local reduction of coronary flow reserve. The greater the basal trans-stenotic pressure gradient, the greater the reduction of coronary flow reserve and the lower the level of cardiac work at which myocardial ischemia appears during effort (*ischemic threshold*).

Experimental studies in dogs showed that the acute reduction of coronary diameter by more than 50 percent causes a measurable basal transstenotic pressure gradient.[47] Further decreases in diameter cause an exponential increase of trans-stenotic pressure gradient and reduction of maximal coronary blood flow (Fig. 37-6). A sudden 85 to 90 percent reduction of an epicardial coronary artery diameter is required to exhaust compensatory arteriolar dilatation and cause myocardial ischemia at rest. The decrease of poststenotic pressure may be reduced by the gradual development of collateral blood flow (see ahead).

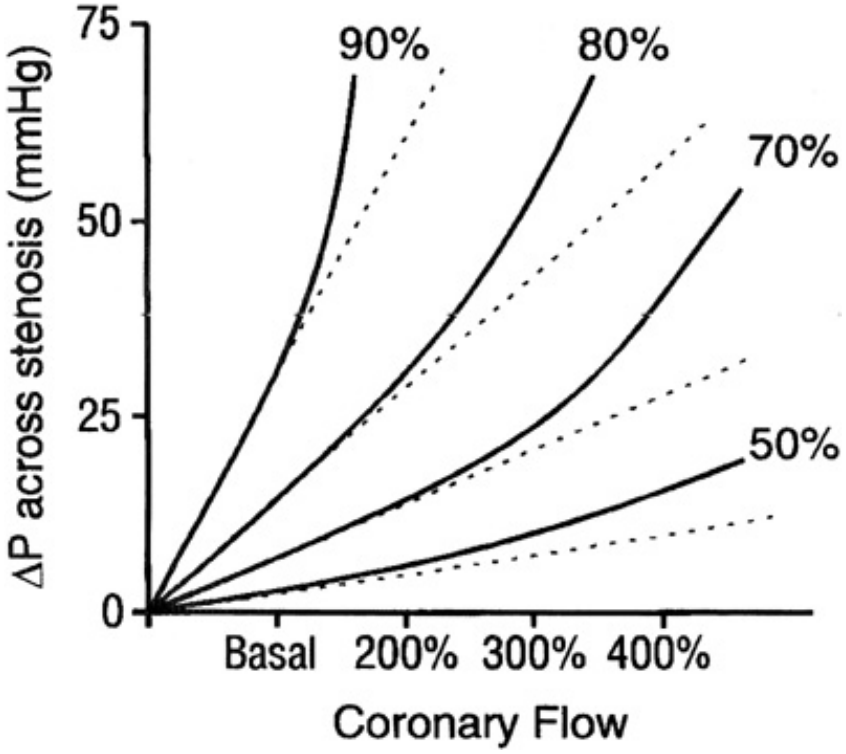

Figure 37-6: Schematic illustration of the relationship between coronary blood flow and transstenotic pressure gradient. This relationship becomes curvilinear because of energy losses caused by blood flow turbulence across the stenosis (*solid lines*). Poststenotic pressure decreases progressively with the increase of stenosis severity and, for a given stenosis, it decreases markedly with increasing flow. In the absence of collateral flow, an 80 percent diameter stenosis causes a drop in poststenotic pressure of about 12 mmHg, which would increase to about 30 mmHg when flow doubles. (From Maseri,[46] modified from Klocke,[47] by permission.)

In presence of a decreased poststenotic pressure, ischemia initially occurs in subendocardial layers, because the subendocardium is more vulnerable to ischemia than the subepicardium (see above).

The general relationship between severity of coronary stenosis as assessed on coronary angiography and impairment of coronary flow reserve has been confirmed in patients.[48,49] However, the angiographic judgment of the hemodynamic consequences of coronary stenoses is difficult because (1) quantitative angiography does not allow an accurate three-dimensional measurement of severe stenoses; (2) the lumen reduction is estimated with reference to the coronary segment proximal to the stenosis, which may be restricted by atheroma or, conversely, enlarged because of vascular remodeling; (3) the stenosis resistance is linearly related to the length of the stenosis and to the flow turbulence caused by the stenosis irregularities.

Several invasive and noninvasive methods have been proposed to assess the hemodynamic effects of coronary stenoses,[50] but the "gold standard" remains the direct measurement of basal transstenotic pressure gradient. Such measurement should be performed after intracoronary nitrates to eliminate the possible vasomotor component of the stenosis. In the absence of a measurable basal gradient, the development of ischemia, at rest or even during effort, cannot be attributed to the hemodynamic effect of the stenosis.

DYNAMIC MODULATION OF CORONARY STENOSES

Coronary flow-limiting stenoses are caused by concentric or eccentric atherosclerotic plaques,

with or without potential for local vasomotor changes. Fixed flow-limiting stenoses present smooth muscle cell atrophy and/or plaque rigidity and are associated with a predictable ischemic threshold and a stable pattern of effort-related myocardial ischemia. Dynamic stenoses are usually eccentric, with compliant segments of the wall and preserved muscular media, and are associated with a variable ischemic threshold. The vasomotor potential of coronary stenoses can also be assessed directly at angiography by intracoronary infusion of vasodilator and/or vasoconstrictor substances.[51,52]

Vasoconstriction at the site of stenoses may result from (1) neural vasoconstrictor stimuli, (2) impairment of vasodilator mechanisms, (3) increased response of dysfunctional vascular smooth muscle cells to vasoconstrictor stimuli, or (4) variable combination of these mechanisms. For example, exercise and cold pressor test cause vasodilatation in normal vessels but vasoconstriction at the site of stenoses.[53,54] Vasoconstrictor autacoids, produced locally by the endothelium (endothelin)[55,56] in the adventitia (histamine, leukotrienes) or released by activated platelets (thromboxane A_2, serotonin), are also powerful potential constrictor stimuli. Defective production and/or release of vasodilator substances (in particular, EDRF) may increase basal coronary tone and prevent flow-mediated arterial vasodilatation during increased M_{VO_2}.[57-59] In animal models, and possibly in unstable patients, the severity of stenosis may also be modulated by transient deposition of platelet aggregates.

CORONARY COLLATERAL CIRCULATION

The drop in poststenotic pressure caused by flow-limiting stenoses stimulates the development of collateral circulation from other coronary artery beds. The supply of collateral blood flow increases poststenotic pressure, thus improving coronary flow reserve and increasing ischemic threshold.

Collateral vessels develop from the progressive enlargement of preexisting intercoronary arterial anastomoses. These vary greatly in number among mammalian species, being more numerous in guinea pigs and dogs, less in pigs and rats, and practically absent in rabbits and sheep. Blood flow through these anastomoses begins as a consequence of the flow-limiting stenosis, when a pressure gradient develops between their origin and termination. In unanesthetized dogs, a pressure gradient of about 10 mmHg, caused by a lumen reduction of 70 to 80 percent, has been shown to elicit the development of collateral flow.[46]

Preexisting anastomoses progressively transform into mature collaterals over a period of 3 to 6 months by initial widening and remodeling, subsequent proliferation of endothelial and smooth muscle cells, and development of a smooth muscle coat, leading to vessels with a final diameter of 20 to 200 μm. Collateral blood flow may also develop by vessel neoformation, but in dog this mechanism contributes only by less than 5 percent of total collateral flow.[46]

Blood flow through collaterals is determined by the driving pressure and by their resistance, which is influenced by neural and humoral stimuli and by local vasoactive autacoids.[60-63]

In patients with flow-limiting stenoses, the number and size of collateral vessels is quite variable. At one extreme, some patients with an occluded coronary artery do not have signs of ischemia because collateral circulation provides adequate blood supply to the territory of the occluded coronary branch. At the other extreme, some patients with severe flow-limiting coronary stenosis do not show detectable improvement of their ischemic threshold over time and, when the vessel occludes, develop myocardial infarction. The causes of these individual differences in coronary collateral circulation are likely to be related to genetic factors.[64]

In experimental animals, no intervention was convincingly shown to improve the development of

collateral vessels. In patients, heparin[65] and fibroblastic growth factor 1 (FGF-1)[66,67] have been suggested to promote collateral growth, but the data are still uncertain.

CORONARY STEAL DISTAL TO FLOW-LIMITING STENOSIS

In the presence of flow-limiting stenoses, myocardial ischemia may develop as a result of a diversion of blood flow from a myocardial region with a very severe impairment of coronary flow reserve, determining an almost maximal arteriolar dilatation in basal conditions, toward a myocardial region with sufficiently preserved coronary flow reserve.

Such a coronary diversion may occur (1) from the subendocardium, as a result of vasodilatation of subepicardial vessels, which increases subepicardial flow but causes a further critical drop of poststenotic pressure (*transmural coronary steal*)[46,68] or (2) from collateralized territories when the parent coronary artery supplying the collaterals presents a flow-limiting stenosis proximal to their origin. In this case, arteriolar dilatation in the territory of the stenosed parent artery increases flow thus causing a further drop of perfusion pressure at the origin of collaterals, which reduces collateral flow (*lateral coronary steal*).[69] In both instances the vasodilatation responsible for the blood flow steal can be induced by vasodilator drugs or an increase in M_{VO_2}.

Coronary Artery Spasm

Epicardial coronary artery spasm is the pathogenetic mechanism of variant angina, but it can play a role in some patients who present with acute coronary syndromes (see also Chap. 40).

CORONARY SPASM IN VARIANT ANGINA

In patients who present with a variant form of angina (see below), myocardial ischemia is caused by an occlusive epicardial coronary spasm.[46] Usually, spasm develops at the site of subcritical or critical stenoses, but it may also occur in angiographically normal coronary arteries, the so-called variant of the variant form of angina. Occlusive spasm causes transmural ischemia with ST-segment elevation, but when spasm is subocclusive, it may cause subendocardial ischemia and ST-segment depression.[70]

In patients with variant angina, spasm tends to recur in the same arterial segment and can be precipitated by sympathetic and parasympathetic stimuli and by a variety of triggers, such as ergonovine, histamine, dopamine, acetylcholine, and serotonin, acting on different receptors, as well as by an increase in arterial pH to 7.65 to 7.70.[71-76] Collectively, these findings suggest a local smooth muscle hyperreactivity to a wide variety of constrictor stimuli. Such hyperreactivity may be caused by a variety of postreceptoral intracellular abnormalities.[46,60] The postmortem findings at the site of coronary spasm are not specific, but fibromuscular hyperplasia was observed in some cases. The animal model of coronary spasm developed in minipigs[77] is unlikely to adequately reflect the mechanisms of vasospastic angina occurring in patients.

CORONARY SPASM IN ACUTE CORONARY SYNDROMES

Although occlusive spasm is typically observed in patients with variant angina, it may also represent a pathogenetic component of other, more common acute coronary syndromes, including unstable angina,[78] unheralded myocardial infarction,[79,80] resuscitated sudden cardiac death,[81] and postcoronary bypass graft angina.[82] In fact, there appears to be a higher prevalence of coronary spasm in patients with acute coronary syndromes (20 to 38 percent) than in patients with stable angina (<6 percent).[46] Coronary spasm has been found to occur more frequently in Asian patients than in Caucasian patients with a recent acute myocardial infarction[80] (Fig. 37-7).

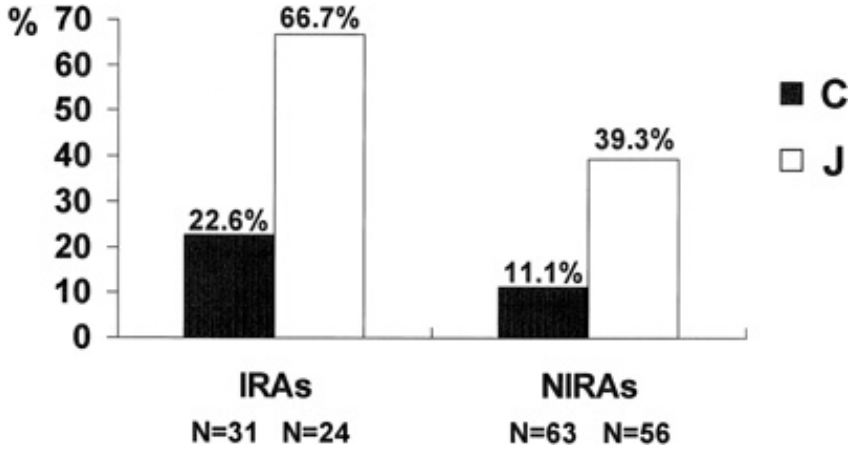

Figure 37-7: Induction of coronary spasm by intracoronary acetylcholine injection in infarct-related arteries (IRAs) and non-infarct-related arteries (NIRAs) of Japanese (J) and Italian (C) patients with a recent acute myocardial infarction. Japanese patients had about a threefold higher prevalence of spastic response in both IRAs and NIRAs. The spastic response was more frequent in IRAs than in NIRAs in Japanese, but not in Italian Caucasian, patients. (Modified from Pristipino et al.[80] by permission.)

The differences in clinical presentation between variant angina and other ischemic syndromes suggest possible different underlying pathogenetic mechanisms. In unstable plaques, the degree of constriction produced by thromboxane A_2, serotonin, and thrombin could be greatly amplified geometrically at the site of fresh mural thrombi and, in some patients, a local smooth muscle coronary hyperreactivity may contribute to the transition from a nonocclusive platelet-fibrin mural thrombus to an occlusive red thrombus.[46]

Dysfunction of Small Coronary Vessels

The possibility that an impairment of coronary blood flow could occur at the level of distal rather than proximal coronary vessels, has received little consideration until recently, as epicardial coronary artery stenoses, spasm, and thrombosis provide readily available, plausible mechanisms for ischemia. However, several animal and clinical studies indicated that ischemia can be also caused by small coronary vessel constriction.[83,84]

PHARMACOLOGIC STUDIES IN HUMANS

In patients with angiographically normal coronary arteries, the intracoronary infusion of neuropeptide Y and that of high doses of acetylcholine was found to induce myocardial ischemia without changes of large epicardial vessels but with extremely slow dye progression or diffuse constriction of distal branches, respectively, indicating microvascular constriction.[46,85] In patients with coronary stenoses, the intracoronary infusion of serotonin caused myocardial ischemia with only small changes in stenosis lumen but with diffuse constriction of distal branches and reduced filling of collateral vessels. In dogs, endothelin infusion caused marked ischemia without detectable changes of epicardial vessels, suggesting powerful microvascular constriction.[46,85]

CLINICAL CLUES TO MICROVASCULAR DYSFUNCTION

In some patients in whom myocardial ischemic episodes cannot be blamed on fixed or dynamic epicardial coronary stenoses, constriction of small coronary vessels could account for the development of myocardial ischemia (see also Chap. 40).

Patients with occlusion of a single epicardial coronary artery and no other stenoses may present very wide variations in the ischemic threshold during daily life and exercise testing, which cannot be attributed to dynamic modulation of stenoses or spasm and are most likely caused by vasomotor changes in small distal coronary vessels.[86]

Patients with single-vessel disease following successful percutaneous coronary angioplasty (*PTCA*) may continue to present with angina, ST-segment depression on exercise testing, and perfusion defects on stress myocardial scintigraphy;[87] in such patients, a dysfunction of small coronary vessels has been confirmed by intracoronary Doppler blood flow measurements and myocardial positron emission tomography (PET) following administration of vasodilator stimuli.[88,89] Microvascular dysfunction is most likely responsible for the reduced coronary dilator response of nonstenosed coronary arteries in patients with coronary disease[90,91] and also in patients with risk factors but no flow-limiting coronary stenoses.[92,93]

Patients with syndrome X who present with angina pectoris, positive exercise testing but angiographically normal coronary arteries and no evidence of epicardial spasm[94] may suffer from some form of microvascular dysfunction. Such a possibility is suggested by stress-induced myocardial perfusion defects on radionuclide studies,[95,96] transient ischemic ST-segment changes during effort test, and reproduction of typical anginal pain with or without ST-segment ischemic changes, by dipyridamole.

However, an ischemic origin of this syndrome is widely questioned because, in the vast majority of studies, no myocardial lactate production or left ventricular dysfunction can be detected during angina and transient ischemic ST-segment changes.[97,98] This apparent paradox could be explained by a patchily distributed coronary microvascular dysfunction, causing dispersed small foci of ischemia. A patchily distributed small vessel constriction may not cause detectable contractile abnormalities or lactate production but rather electrocardiographic (ECG) changes and myocardial perfusion defects when sufficiently confluent.[46,85] This possibility is suggested by observations in animal models, in which ischemia was caused by impaired coronary microcirculation by microspheres[46] or endothelin-1 infusion.[99]

Recent data showing intracardiac production of lipid peroxidation products, which are sensitive markers of ischemia-reperfusion injury,[100] during angina and ischemic ST changes following atrial pacing in syndrome-X patients strongly support the microvascular ischemic origin of the syndrome.[101,102] The occurrence of myocardial ischemia sufficiently confluent and extensive to be detected by phosphorus nuclear magnetic resonance has been reported in 20 percent of syndrome-X patients during the hand-grip stress test.[103]

SITE OF MICROVASCULAR DYSFUNCTION

Theoretically, myocardial ischemia caused by microvascular dysfunction may result from abnormal constriction or failure of adequate dilatation of arteriolar or prearteriolar vessels. Arteriolar constriction as a cause of myocardial ischemia would require constrictor stimuli sufficiently strong to overcome the dilator effect of ischemic metabolites on the arterioles themselves.[46,85] The prearteriolar vessels appear to be a more likely site of microvascular alterations responsible for myocardial ischemia. An increased, patchily distributed prearteriolar vasoconstriction was proposed as a causal mechanism of syndrome X[46,85] (Fig. 37-8).

MECHANISMS OF MICROVASCULAR DYSFUNCTION

In patients with coronary stenoses, the causes of small coronary vessel dysfunction are commonly attributed to atherosclerosis, although such dysfunction may also be related to neurohumoral

stimuli[104] or to vascular abnormalities (e.g., perivascular fibrosis, medial hypertrophy) associated with systemic diseases, such as hypertension or diabetes.[105,106] Small vessel dysfunction in these patients is also frequently attributed to EDRF deficiency on the basis of an abnormal vasomotor response to acetylcholine, but a reduced vasodilator response or a vasoconstrictor response to acetylcholine[107,108] could also be caused by an increased constrictor effect of the drug on smooth muscle cells.

In patients with syndrome X, the mechanisms responsible for microvascular dysfunction can be multiple and not necessarily the same in all patients. They may include (1) structural abnormalities, such as fibrosis and medial hypertrophy;[46] (2) impaired endothelial and nonendothelial vasodilator function;[109] (3) enhanced constrictor response of smooth muscle cells, possibly related to an increased membrane Na^+-H^+ exchanger activity;[110,111] (4) increased release of local vasoconstrictor autacoids-e.g., endothelin 1[112,113] or angiotensin;[46] and (5) abnormal neural stimuli. Evidence of abnormal cardiac sympathetic function was documented by ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, which showed total absence of cardiac MIBG uptake in 42 percent of patients and regional defects, matching thallium perfusion defects, in another 33 percent of cases[114] (Fig. 37-9).

Each of these putative mechanisms of microvascular dysfunction may involve a very variable number of prearteriolar vessels. Therefore there may be a spectrum of vascular involvement ranging from very sparse foci of microvascular dysfunction to confluent alteration of all small coronary vessels in large vascular territories.

Acute Thrombosis

Intraluminal thrombi are the most common finding in patients with acute coronary syndromes. Most thrombi are composed of platelets and fibrin in variable proportions and often develop at the site of non-flow-limiting coronary stenoses. Thrombosis may reduce or interrupt blood flow by itself or in combination with local or distal vasoconstriction (triggered by thromboxane, serotonin, and thrombin)[115] (Fig. 37-10). Fresh thrombi may have a different fate. They may (1) grow to occlude the artery; (2) lyse completely; or (3) become organized and contribute to plaque growth.

MECHANISMS OF ACUTE THROMBOSIS

Thrombus formation is the first physiologic self-limiting step of vascular injury repair-but, under some circumstances, it may become a major mechanism of acute disease. Intracoronary thrombosis may result from strong or weak thrombogenic stimuli.[115]

Strong thrombogenic stimuli cause rapid thrombus growth with massive inclusion of red cells in the fibrin mesh (*red thrombi*), leading to persistent vessel occlusion within a few minutes, like in the copper-coil animal model. Strong thrombogenic stimuli may be represented by the mechanical rupture of a lipid-rich atherosclerotic plaque.

Weak thrombogenic stimuli cause slow, progressive deposition of platelets and formation of platelet-fibrin thrombi (*white thrombi*, as in the electrical wire animal model). Weak thrombogenic stimuli may result from the fissure of plaques with low thrombogenic potential or from a local inflammatory activation of the vascular wall caused by infectious or noninfectious stimuli.[40,116-118] Thrombus growth is mainly determined by the intensity, duration, and recurrence of the weak inflammatory stimuli.

Occlusive thrombosis may develop in the presence of strong or weak but persistent thrombogenic stimuli in spite of the continuous dilution of local prothrombotic factors and of the continuous

supply of anticoagulant and fibrinolytic factors by blood flow, as well as in spite of antiplatelet and anticoagulant drug therapy.

Occlusive thrombosis may also be caused by weak, nonpersistent thrombogenic stimuli, but only when associated with prothrombotic or deficient fibrinolytic states and when combined with blood flow stasis resulting from local spasm or from massive distal small vessel constriction.

The hypothesis that thrombosis may occur at the site of identifiable "vulnerable" coronary plaques is attractive and currently stimulates the development of new research tools for their clinical detection. However, plaques may be vulnerable for two different reasons: they may be potential sites of thrombosis because they are prone to mechanical rupture (as they have a large central lipid pool and a thin cap)[119] or because they are the site of inflammatory processes.[45] Plaque vulnerability may last days, weeks, or months.

The different mechanisms responsible for coronary thrombosis or contributing to it and acute coronary occlusion may not have the same prevalence in different geographic, ethnic, age, and sex groups; yet they may influence the individual response to antiplatelet, antithrombotic, and acute reperfusion strategies.

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Chapter 37: CORONARY BLOOD FLOW AND MYOCARDIAL ISCHEMIA

CONSEQUENCES OF MYOCARDIAL ISCHEMIA

Myocardial ischemia causes myocardial cells to switch from aerobic to anaerobic metabolism with a progressive depletion of high-energy phosphate stores and impairment of mechanical and electrical function. When prolonged or repetitive, ischemia also modifies cell gene expression, which may contribute to postischemic cell dysfunction.

The most obvious clinical manifestation of myocardial ischemia is anginal pain, but most ischemic episodes are clinically silent. The consequences of myocardial ischemia vary according to its severity, extension, duration, mode of onset, and recurrence and may result in global impairment of contractile function and life-threatening arrhythmias as well as in preconditioning, stunning, hibernation, or myocardial infarction, which occurs when severe ischemia persists for longer than 30 min.

Metabolic Consequences

During ischemia, several metabolic changes occur. ATP is degraded to adenosine, which, diffusing out of cardiomyocytes, causes arteriolar dilation and anginal pain. Free fatty acids and acyl-carnitine accumulate and protein synthesis and turnover are impaired in myocardial cells. Furthermore, myocardial ischemia-reperfusion produces free radicals, which contribute to postischemic myocardial cell dysfunction by reacting with proteins, lipids, and nucleic acids. Impaired Ca^{2+} release from sarcolemma and sarcoplasmic reticulum, cross-bridge cycling inhibition,[120] and competition of H^+ accumulating during ischemia for Ca^{2+} binding sites on contractile proteins thus also contribute to systolic dysfunction. Reduced ATP availability and a decreasing Ca^{2+} reuptake rate into sarcoplasmatic reticulum also prolong the interaction of Ca^{2+} with myofilaments, causing diastolic dysfunction.

Impairment of ion pumps causes loss of intracellular K^+ and accumulation of intracellular Na^+, Ca^{2+}, and H_2O. Alterations of transsarcolemmal ion gradients may cause increased automaticity, triggered activity, and abnormalities of impulse conduction, which favor the development of reentry circuits.[121]

The consequences of ischemia and ischemia-reperfusion injury may not be limited to the myocytes but extend to endothelial cells with inflammatory changes,[122-124] resulting in vasoconstriction and a local thrombogenic tendency.

Effects on Cardiac Function

The effects of myocardial ischemia have been studied in experimental animals by producing a sudden coronary occlusion, by gradually reducing coronary flow at rest, and by increasing M_{VO_2} in the presence of a flow-limiting coronary stenosis. Such experimental models mimic, at least in part, the consequences of myocardial ischemia observed in variant angina, unstable angina, and effort angina, respectively (see ahead).

EFFECTS OF SUDDEN CORONARY OCCLUSION

Occlusion of a major coronary artery is followed within a few seconds by a typical sequence of events that includes a reduction in the velocity of ventricular relaxation and contraction, ST-segment elevation, increased end-diastolic pressure with dyssynchrony (delayed onset of contraction in ischemic myocardial segments), hypokinesis (reduced contractility), akinesis (cessation of contraction), and dyskinesis (paradoxical expansion of affected segment during systole). The sequence of hemodynamic and electrocardiographic events observed in experimental animals is similar to that observed in patients during episodes of occlusive epicardial coronary artery spasm (Fig. 37-11) or during coronary angioplasty

balloon occlusion in patients.[46] It is typically characterized by the following sequence of events: a decrease in peak relaxation -*dp*/*dt*, a decrease of peak contraction *dp*/*dt*, an increase in diastolic pressures, and a fall in systolic and in pulse pressure. In patients with variant angina and coronary occlusive spasm, pain, when present, usually appears only several seconds or minutes later.

EFFECTS OF GRADED REDUCTION OF CORONARY FLOW AT REST

In anesthetized dogs, a 25 percent reduction of basal coronary blood flow through a major coronary branch is associated with increased myocardial extraction of oxygen and with decreased oxygen consumption.[46] Further reductions of flow are followed by a decrease in the rate of left ventricular relaxation and contraction, then by ST-segment depression, elevation of end-diastolic pressure, decreased stroke volume, and, finally, by elevation of the ST segment, which develops when flow is reduced to about 70 percent and myocardial ischemia becomes transmural. Local contractile function in subendocardial layers begins to fall slightly when regional subendocardial flow is reduced by 10 to 20 percent and becomes marked as flow decreases by 50 to 80 percent. Segments with a flow reduction greater than 80 percent show paradoxical movement, with bulging of the left ventricular wall[46] (Fig. 37-12).

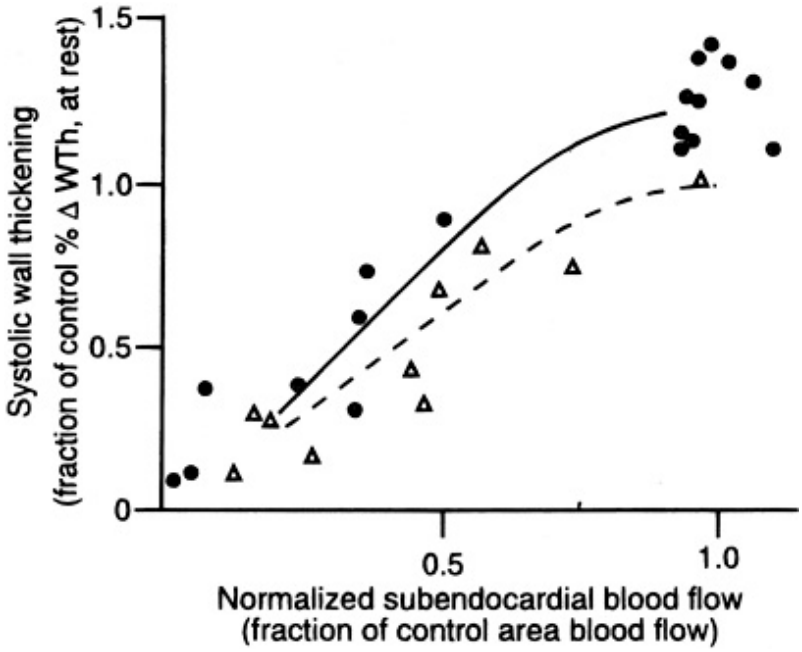

Figure 37-12: Effect of decrease of subendocardial blood flow on systolic segment shortening. In conscious dogs the percentage decrease of subendocardial segment shortening is small until blood flow is reduced by 20 percent. Systolic bulging (segment lengthening) develops only when flow is reduced by more than 80 percent. (From Maseri,[46] modified from Gallagher et al.,148 by permission.)

EFFECT OF INCREASED WORKLOAD IN THE PRESENCE OF A FLOW-LIMITING STENOSIS

When exercise reduces mean transmural blood flow by 30 percent in chronically instrumented dogs with coronary artery stenosis, a mild reduction of systolic thickening is observed, whereas in the normally perfused wall, thickening increases by 20 percent.[46] During exercise, severe regional dysfunction develops when mean flow is about 80 percent lower than in nonischemic myocardial segments. Thus a severe reduction of coronary blood flow is necessary to produce detectable effects on global ventricular contractile function.[46]

At variance with the late occurrence of pain following sudden coronary occlusion by spasm, anginal pain may precede electrocardiographic changes in about one-third of the cases during effort-induced ischemia.[46]

PRECONDITIONING

The term *preconditioning* was originally used with reference to the ability of short periods of ischemia to limit infarct size after subsequent prolonged coronary occlusion in animals. However, it is now used also to include a protective effect of transient ischemia on myocardial suffering induced by subsequent ischemic episodes. An early ischemic preconditioning after an ischemic episode was reported during the initial 2 h (early preconditioning), but a later protection was also reported beginning 24 h after the preconditioning stimulus and extending to 48 h (delayed preconditioning).[125] Findings compatible with early ischemic preconditioning were reported following balloon occlusion during coronary angioplasty, in preinfarction angina, in coronary artery bypass surgery, and in exercise-induced ischemia (warmup phenomenon).[46] In experimental settings, ischemic preconditioning was also shown to reduce ventricular tachyarrhythmias appearing in the ischemic or reperfusion phase of ischemic episodes, and a reduction of ischemia-related ventricular arrhythmias following episodes of transmural myocardial ischemia was reported in patients with vasospastic angina.[126] Preconditioning could partly explain the more favorable prognosis of patients in whom acute myocardial infarction is preceded by unstable angina.[127,128]

The bases of preconditioning are not completely understood. Extrapolation of experimental results to patients should be cautious. Early preconditioning is thought to derive from phosphorylation of a sarcolemmal protein, possibly the ATP-sensitive K^+ channel, resulting from G protein-coupled receptor activation of protein kinase C. Late preconditioning may be mediated by activation of genes encoding for protective proteins such as heat-shock proteins and growth factors (see also Table 37-1).

Table 37-1: Features of Ischemia, Stunning, and Hibernation[a]

	Coronary Blood Flow	Lactate Production	Contractile Function
Ischemia	Markedly reduced	Yes	Impaired
			Recovers after relief of ischemia
Stunning	Preserved	No	Impaired
			Transiently restored by inotropic stimulation
			Recovers spontaneously over time
Hibernation	Reduced in the presence of typical histologic changes	No	ImpairedRecovers only after revascularization

[a]Ischemia is characterized by inadequate perfusion, resulting in lactate production and impaired contractile function. Stunning develops after an ischemia-reperfusion sequence and is characterized by preserved regional blood flow and transient impairment of contractile function, which recovers spontaneously over time. Hibernation may develop after repeated episodes of ischemia-reperfusion, and is characterized by myocardial histologic changes, absence of contraction, reduced M_{VO_2}MVO2, reduced regional blood flow but no lactate production. Contractile function recovers following revascularization over a period of weeks and months.

STUNNING

The term *stunning* defines a prolonged but reversible contractile dysfunction observed after an episode of transient myocardial ischemia. It has been observed in animals following sudden coronary occlusion lasting 10 to 15 minutes or after repeated shorter periods of occlusion as well as in patients after positive exercise tests, in ischemic peri-infarction regions, and following extracorporeal circulation. The spontaneous recovery of cardiac contractile function may take hours or days, depending on the severity and duration of ischemia, but contraction can be transiently restored by inotropic stimuli such as after extrasystolic potentiation or beta-adrenergic drugs. In stunned myocardium, the delayed recovery of contractile function

is associated with a normal average myocardial perfusion in the presence of reduced myocardial oxygen consumption. It is not clear to what extent stunning represents a gradual physiologic recovery from the ischemic insult or a consequence of a reperfusion-induced injury, which could delay or reduce the benefits of reperfusion.

Several components may contribute to stunning.[129] A decreased Ca^{2+} sensitivity of myofilaments, troponin I degradation by Ca^{2+}-activated proteases, Ca^{2+} overload and the generation of free radicals,[130] slow resynthesis of adenosine nucleotides, microvascular damage with leukocyte activation, myocyte electromechanical uncoupling,[131] and extracellular matrix alterations were observed in experimental models (see also Table 37-1).

HIBERNATION

Myocardial *hibernation* was originally defined as a condition of persistent impairment of contractile function at rest, in the presence of reduced M_{VO_2} and coronary blood flow and in absence of ischemia, that partially or totally recovers when myocardial blood flow is restored. The time to functional recovery of hibernated myocardium after revascularization varies from 10 days to 6 months and is related to the severity of structural changes of cardiomyocytes and interstitium.

Hibernation is characterized[132] by progressive loss of sarcomeres, sarcoplasmatic reticulum, and T tubules in cardiomyocytes with glycogen replacement. Mitochondria appear small and scattered and nuclei distorted, with uniformly dispersed heterochromatin. Hibernated myocardial cells have normal ATP, total adenine nucleotides, and phosphocreatine content and exhibit normal glucose uptake and no lactate production. Several of these characteristics suggest that hibernation may be the result of a dedifferentiation process related to changes in gene expression, as hibernated cardiomyocytes show many features of neonatal cardiomyocytes.[132]

Hibernation is caused by a severe reduction of coronary flow reserve, as a result of which any increase in M_{VO_2} and any further reduction in coronary blood flow (e.g., by vasoconstriction or platelet aggregation) results in repeated episodes of myocardial ischemia-reperfusion (see also Table 37-1).

CLINICAL MANIFESTATIONS OF MYOCARDIAL ISCHEMIA

Chest Pain

The most obvious clinical manifestation of myocardial ischemia, irrespective of its multiple causal mechanisms, is angina pectoris. However, myocardial ischemia may occur without angina and angina may occur without detectable signs of myocardial ischemia. Typically anginal pain is retrosternal in location, with a crushing, squeezing, or burning character. It may radiate to the throat, neck, ulnar side of the left and/or right arm, interscapular region, epigastrium, and the jaw and teeth. The intensity of the discomfort can vary greatly, from a mild feeling of retrosternal fullness or tingling in only one dermatome to a diffuse, unbearable pain. These features are totally unrelated to the actual cause of ischemia and are not completely specific for ischemia, as they may also be caused by cardiac nonischemic causes and by extracardiac causes.

Myocardial ischemia, with or without angina, may occasionally present with other symptoms, including dyspnea (when ischemia is extensive with transient impairment of left ventricular function or ischemia of papillary muscles with mitral regurgitation), palpitations, syncope, or cardiac arrest (when ischemia is associated with arrhythmias).

Anginal pain originates from the stimulation of polymodal receptors (more abundant around small coronary vessels) by chemical mediators produced during ischemia.[46] The best studied of such mediators is adenosine. The algogenic effects of adenosine were studied by its intracoronary infusion and are mediated by $alpha_1$ receptors, while its vasodilator effects are mediated by $alpha_2$ receptors.[133]

Comparison of pain location during selective intracoronary infusion of adenosine in the right and left

coronary arteries has shown that, in nearly 70 percent of patients, afferent stimuli from different myocardial regions cannot be discriminated, thus suggesting that they converge on the same neurons of the dorsal roots of spinal cord.[134] In contrast, in the remaining 30 percent of patients, anginal pain during infusion of adenosine in the separate coronary beds caused a different location of pain. The possibility that a different location of pain in the same person reflects a different location of myocardial ischemia has been confirmed in patients undergoing PTCA and with a second myocardial infarction.[135,136] Moreover, convergence of afferent painful stimuli from different visceral organs and somatic dermatomes on the same ascending neurons can cause noncardiac pain to have features indistinguishable from angina. The central transmission of painful stimuli is strongly modulated at the spinal cord level by a "gating" system regulated by descending and afferent stimuli. After modulation at the spinal cord level, afferent stimuli reach thalamic centers and are finally projected to the cortex, where their processing and decoding occur.

Painless Ischemia

The total lack of pain represents one extreme of the spectrum of the possible clinical presentations of myocardial ischemia. Painless ischemia can only be diagnosed by techniques capable of detecting ischemia and depends entirely on their sensitivity and specificity. Continuous ECG recording reveals that about 70 percent of episodes of transient myocardial ischemia do not cause chest pain or any other symptom.[46] The percentage of episodes of silent ischemia is similar in chronic stable angina, unstable angina, variant angina, and microvascular angina. Thus, the presence or absence of pain is totally unrelated to the actual cause of transient ischemia. Furthermore, myocardial infarction (MI) may be totally silent in about 20 percent of the cases.

The reasons why myocardial ischemia does not elicit pain in the majority of cases are multiple.[134] Although angina is less likely to accompany myocardial ischemia when it is brief, there is no strict relationship between duration and extension of ischemia and development of chest pain also in the same patient.

The gating system at the spinal cord and possibly at the thalamic level, together with the cortical decoding of afferent stimuli, probably play a major role in determining the perception of pain. Moreover, personality, emotional status, and previous experience of pain may modulate such perception.

Arrhythmias

Arrhythmias are major potential consequences of acute ischemia, as they are responsible for most of the deaths observed during the early phases of acute MI as well as in variant angina, and thus for sudden death in the community.

During ischemia, increased automaticity, triggered activity, conduction delay and reentry may cause the development of ventricular tachycardia and ventricular fibrillation. Moreover, altered impulse formation and conduction defects may cause asystole and atrioventricular block.

The arrhythmic response to ischemic insult of individual patients is unpredictable but is influenced by the cardiac anatomic background (left ventricular hypertrophy, previous infarction), sympathetic activity (as suggested also by experimental studies on cardiac sympathetic denervation) and nervous autonomic imbalance.

Fatal ventricular arrhythmias are exceptional during mild transient ischemic episodes, but they may develop after the onset or soon after the termination of episodes of severe subendocardial ischemia and in transmural ischemia caused by occlusive spasm or by occlusive thrombosis. Reperfusion arrhythmias, although particularly common in anesthetized animals, are less frequently observed both in patients with variant angina and during myocardial reperfusion in acute MI.[46]

Effects of Persistent Myocardial Ischemia: Myocardial Infarction

In dogs, focal cell necrosis begins about 20 min following coronary flow interruption. Such foci become confluent in subendocardial layers by 40 min, reaching subepicardial layers with a progressive wavefront at about 3 to 4 h. By this time, necrosis has developed, on average, to about 90 percent of its final extension,

which is reached after 6 h.

In patients, the extension of myocardial necrosis depends not only on the area perfused by the occluded vessel, the level of myocardial oxygen consumption, and the presence of collaterals but also on the intermittence of coronary occlusion. Actually, MI is a dynamic process with intermittence of occlusion occurring in about two-thirds of the cases during the initial 6 h.[46] Therefore it is reasonable to undertake reperfusion strategies in all patients irrespective of actual delay from the onset of symptoms as long as ECG shows persistent massive ischemia without completed necrosis. The impairment of global myocardial function depends on the extension of myocardial necrosis. When infarction involves more than 15 percent of the left ventricle, ejection fraction decreases and left ventricular end-systolic volume and pressure increase. When it involves more than 25 percent of the left ventricle, signs of heart failure develop; when it involves more than 40 percent, cardiogenic shock occurs. The development of primary ventricular fibrillation is independent of infarct size but strongly influenced by high adrenergic tone.

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RELATIONSHIP BETWEEN MECHANISMS OF ISCHEMIA AND CLINICAL SYNDROMES

The mechanisms responsible for the development of ischemia do not influence the location and radiation of anginal pain but may determine specific clinical patterns of anginal episodes that, at least in typical cases, provide useful clues for personalized patient management. Therefore a carefully collected clinical history is the fundamental first step in the assessment of the pathogenetic mechanisms of MI and for the selection of the appropriate sequence of diagnostic tests.

Chronic Stable Angina

Some patients presenting with chronic stable angina report that anginal pain develops predictably only and every time they exceed a rather fixed level of exertion that they learn to recognize and avoid. The pain disappears within 1 to 2 min after the interruption of the effort or after sublingual nitrates. In these patients, the fixed anginal threshold suggests that myocardial ischemia is caused exclusively by an excessive increase in oxygen demand in the presence of a fixed coronary stenosis (*fixed-threshold effort angina*) (see Chap. 40).

On careful questioning, however, the majority of patients with chronic stable angina report that they have "good and bad days" and a variable threshold for angina, which sometimes develops unpredictably for efforts usually well tolerated and occasionally also at rest (*mixed angina*). A variable ischemic threshold, with "good days" during which patients have a good effort tolerance, is suggestive of a strong modulation of residual flow reserve by changes in vasomotor tone at the level of a potential flow-limiting stenosis or in distal vessels; therefore it represents an indication for vasodilator therapy. This indication is supported by a significant increase of effort tolerance on exercise testing following sublingual nitrates. Conversely, a low effort tolerance, persisting after sublingual nitrates, represents a mandatory indication for drugs that reduce M_{VO_2} and for coronary angiography with a view to revascularization procedures.

Syndrome X

Patients with a chronic stable pattern of mixed angina, "ischemic" ST-segment depression, and/or myocardial perfusion defects during stress test, but angiographically normal coronary arteries are classified as having syndrome X.[94] In these patients, angina also predominantly occurs on exertion, typically with a variable ischemic threshold and occasionally at rest, but very seldom at night. Although the location and radiation of pain are often indistinguishable from those of patients with flow-limiting stenosis, some distinct features raise the suspicion of syndrome X: (1) patients usually report persistence of angina for several minutes after the interruption of exertion, and many report attacks lasting over 30 min; (2) they have a poor response to sublingual nitrates, which were also shown to worsen exercise tolerance, in sharp contrast with their established beneficial effect in patients with flow-limiting stenosis (Fig. 37-13); (3) they show a variable individual response to prophylactic long-acting nitrates, calcium antagonists, and beta blockers,[137] possibly because of differences in the underlying causes of microvascular dysfunction; (4) they develop their typical pain (often with transient ischemic ECG changes) during dipyridamole test but without development of left ventricular contractile abnormalities; (5) they often have an enhanced response to painful stimuli,[138] which contributes to explain the paradox of severe angina in the absence of detectable myocardial contractile dysfunction (

Fig. 37-14); and (6) Holter monitoring demonstrates that some episodes of chest pain and ST-segment depression are not associated with tachycardia, and it may show episodes of transient ST-segment depression in patients with a negative exercise test, suggestive of possible episodic occurrence of microvascular constriction.[139]

The diagnosis of syndrome X is confirmed by (1) the evidence of a cardiac origin of pain because of its consistent association with transient ischemic ECG changes and/or myocardial perfusion defects during exercise test or by diagnostic ECG changes on Holter monitoring;[140] (2) normal coronary angiogram; and (3) the exclusion of epicardial coronary spasm on the basis of distinct clinical history, absence of transient episodes of ST-segment elevation, and failure to induce coronary spasm by provocative tests (see also Chap. 40).

Unstable Angina

The characteristic clinical feature of unstable angina is the sudden appearance and/or worsening of angina, with more frequent and prolonged attacks occurring at rest or on efforts that were previously well tolerated. In patients with a de novo angina and those with known ischemic heart disease (in the absence of anemia, fever, hyperthyroidism and tachyarrhythmias), this pattern of presentation suggests a transient, recurring impairment of myocardial perfusion by thrombosis and vasoconstriction. The crescendo, waxing, waning, and persistence of anginal attacks over a period of days and weeks suggests stimuli causing thrombosis and vasoconstriction. A sudden reduction of the ischemic threshold on exertion suggests a rapid development or increased severity of a flow-limiting stenosis by organized thrombus. Many patients continue to present recurrent instability and/or to develop MI in the initial weeks and months following hospital discharge. Unstable patients are also at an increased risk of restenosis following PTCA. The waxing and persistance of instability and restenosis following PTCA are correlated with elevated blood levels of systemic markers of inflammation-for example C-reactive protein[140] and interleukin 6[141]-consistent with the hypothesis that inflammatory cytokines may be an important component of instability.

In the first few days after onset, the presentation of unstable angina may be clinically indistinguishable from that of an acute onset of variant angina, unless repeated short episodes of transient ST-segment elevation are detected on the ECG. The absence of detectable systemic inflammatory markers is a distinctive feature of variant angina as opposed to unstable angina[142] (see also Chap. 41).

Variant Angina

The clinical diagnosis of variant angina can only be suspected when sufficient time has elapsed from the onset of symptoms to allow the emergence of a distinctive pattern of angina. The following features suggest the clinical diagnosis of variant angina: (1) a report of pain occurring predominantly at rest, without apparent cause, more often at night, in the early morning hours or at the same time of the day, usually with preserved effort tolerance (many patients with variant angina report with amazement that they have anginal attacks without apparent cause and yet can perform considerable efforts without symptoms); (2) anginal episodes are usually of short duration (2 to 5 min) and respond to sublingual nitrates within 1 to 2 min (at variance with syndrome X); (3) anginal episodes may occur in clusters of two to three in the early morning hours and then be absent throughout the day; (4) anginal episodes may be associated with syncope caused by ventricular tachycardia/ventricular fibrillation[81] or by complete atrioventricular block; (5) the exercise stress test is usually negative but in some patients it may cause ST-segment elevation during or after the test; the exercise test becomes negative after sublingual nitrate administration.

The clinical suspicion elicited by these features is supported by the demonstration of ST-segment elevation, usually a typical "lesion wave," during angina. The demonstration of ST-segment

elevation can be obtained by chance with a standard 12-lead ECG, by Holter monitoring, or soon after or during the exercise stress test. The diagnosis is confirmed by the angiographic demonstration of spasm occurring spontaneously or following provocative tests. Among these, ergonovine and hyperventilation have a 100 percent specificity but a low sensitivity, whereas acetylcholine seems to have a greater sensitivity but a lower specificity.

The occlusive spasm typically occurs at the site of coronary stenosis, but it may also occur in angiographically normal coronaries, in particular in Asian patients.[143] The diagnosis of variant angina is a mandatory indication for calcium antagonists and nitrates, as beta blockers are totally ineffective.

Myocardial Infarction

In some patients MI develops totally unheralded with the single first episode of uninterrupted anginal pain that brings them to hospital. In others, the final persistent episode of pain is preceded by a typical history of unstable angina. In an intermediate group, the final episode of persistent pain is preceded by one or two isolated anginal attacks, compatible with a hyperacute presentation of preinfarction unstable angina. During the initial 6 h from the onset of symptoms in unselected patients with acute MI, the infarct-related artery recanalizes spontaneously in 40 percent of the cases and exhibits occasional, transient reperfusion in about 70 percent. Spontaneous and early reperfusion seems to be more frequent in patients in whom MI is preceded by unstable angina[144] (see also Chap. 42).

Thus in some patients, coronary occlusion appears to develop like lightning out of a blue sky and to be persistent and uninterrupted, compatible with the fissure of a strongly thrombogenic plaque, with a persistent coronary inflammatory stimulus or with persistent spasm or distal coronary vessel constriction. In some patients with a history of preinfarction unstable angina, the coronary occlusion is transient and very occasional before the final episode; in others, the final coronary occlusion exhibits spontaneous, transient, or persistent recanalization, consistent with waxing, waning, and recurrence of weak inflammatory thrombogenic stimuli.

The presence of systemically detectable inflammatory markers in about 70 percent of patients with Braunwald class IIIB unstable angina and the much higher recurrence of instability among the 50 percent of patients in whom the elevation persists at discharge and at 3 months[145] may represent an objective marker of inflammatory thrombogenic triggers. This possibility is supported by the elevation of such markers at the time of hospital admission in nearly all patients in whom MI was preceded by unstable angina but in less than 50 percent of those in whom MI was totally unheralded.[146] The absence of inflammatory markers also allows an objective distinction of variant angina,[142] which sometimes has a clinical presentation indistinguishable from that of the more common form of unstable angina.

Different pathogenetic components of coronary occlusion are also suggested by the earlier recanalization in response to t-PA observed in patients with preinfarction angina as compared to those with a totally unheralded MI.[127]

The prodromal symptoms of MI also provide clues about its pathogenetic mechanisms. In some patients, MI occurs without any apparent cause; in others, a history of severe psychological distress[147] or of flu-like symptoms can be elicited on careful questioning. These prodromal symptoms may be associated with a different mode of presentation of acute MI and might provide clues of distinct pathogenetic mechanisms, which may not have the same prevalence in different age, sex, geographic, and ethnic groups.

Understanding the precise mechanisms of acute coronary occlusion would allow more effective

coronary reperfusion strategies to be reserved to those patients who are unlikely to respond to simpler ones. The alternative is to treat indiscriminately all patients with the newest, most efficacious, but possibly also more complex and expensive coronary reperfusion strategies. The subgroups of patients that benefit from antiplatelet drugs, anticoagulants, beta blockers, statins, and ACE inhibitors should be identified. Again, the alternative is to prescribe indiscriminately all these treatments to each patient, with the consequent burden of polytherapy, risk of low compliance, and high cost.

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Figure 37-13: Acute effects of nitrates on exercise testing in syndrome X. The administration of isosorbide dinitrate (ISDN, 5 mg sublingual) significantly improved exercise test variables in patients with chronic stable angina and documented coronary artery disease (*right panel*). In contrast, ISDN caused a worsening of exercise variables in a significant number of patients with syndrome X (*left panel*). ST, ST segment; RPP, rate pressure product. (Modified from Lanza GA, Manzoli A, Bia E, et al. Acute effects of nitrates on exercise testing in patients with syndrome X: Clinical and pathophysiological implications. *Circulation* 1994; 90:2695, by permission.)

Figure 37-14: Main pathogenetic mechanisms of syndrome X. Syndrome X likely results from a variable combination of two components: a coronary microvascular dysfunction and an increased pain sensitivity, both of which may have a bell-shaped prevalence in the population. (From Maseri[46] by permission.)

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Part 6: CORONARY HEART DISEASE
Chapter 38:

DYSLIPIDEMIA, OTHER RISK FACTORS, AND THE PREVENTION OF CORONARY HEART DISEASE

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Identification and management of risk factors are essential for preventing coronary heart disease (CHD) in asymptomatic individuals (*primary prevention*) and for preventing recurrent events in patients with established disease (*secondary prevention*). *Risk factor management should be conceived as prevention or treatment of the atherosclerotic disease process itself and, as such, should be included as an integral part of any management plan for the many acute or chronic manifestations of this disease.* The intensity of risk factor intervention should correspond to the patient's level of risk.[1] The presence of unmodifiable risk factors may necessitate more intense management of modifiable risk factors. The 27th Bethesda Conference proposed a classification scheme according to the strength of evidence that risk factor intervention favorably affects outcome.[1] This chapter is organized to reflect that classification scheme (Table 38-1) and reviews risk assessment for primary prevention, reviews CHD risk factors, discusses the efficacy and cost-effectiveness of managing risk factors, and provides practical recommendations for preventive cardiology practice.

RISK ASSESSMENT IN PRIMARY PREVENTION

As detailed in this chapter, the efficacy of secondary prevention of CHD using a variety of therapies has been well established. Therefore, an individual with established CHD or other atherosclerotic disease should be considered at highest risk for a CHD event and deserves the most aggressive evidence-based risk-reduction therapy. The therapeutic success achieved in secondary prevention of CHD has generated enthusiasm for extending this success to primary prevention in clinical practice. The essential issues for primary prevention are the selection of patients and selection of appropriate interventions. The first step in patient selection is to estimate a patient's risk. The key parameter for risk assessment for medical intervention is the *absolute risk*, i.e., the probability of developing CHD over a finite period.

Categories of Absolute Risk

For the sake of simplicity, absolute risk can be divided into three categories: high, intermediate, and low.[2] Patients at high risk deserve aggressive risk-reduction therapy. Those at intermediate risk also deserve medical intervention to the extent that therapy is effective, safe, and cost-effective. Finally, low-risk patients can be encouraged by their physicians to follow public health recommendations for primary prevention of CHD.

Each category of absolute risk can be examined in quantitative terms (Table 38-2). Patients at high risk are those whose absolute risk for CHD equals that of patients who already manifest clinical CHD.[2,3] Evidence from clinical trials of cholesterol-lowering therapy indicates that patients with a prior history of myocardial infarction (MI) have a 10-year risk for recurrent nonfatal or fatal MI of about 26 percent.[3-5] Patients with stable angina pectoris have a 10-year risk for acute MI of about 20 percent.[6,7] Thus, it is reasonable to say that *patients without manifest CHD who have a 10-year*

risk for MI of greater than 20 percent are at high risk. These patients also can be said to have a *CHD risk equivalent.*[3] In accord, *intermediate-risk patients have a 10-year risk for MI of 10 to 20 percent.* Assignment of risk category is first made by measurements of standard risk factors.[2] In some patients, however, estimates of absolute risk may require adjustment on the basis of other kinds of risk factors or the presence of subclinical coronary artery disease.[2] *Low-risk patients are those whose 10-year risk for MI is less than 10 percent.*

Table 38-2: Risk Categories

Risk Category	10-Year Absolute Risk for Myocardial Infarction (%) (Nonfatal + Fatal)
High	>20
Intermediate	10-20
Low	<10

Identification of High-Risk Patients (Coronary Heart Disease Risk Equivalents)

NONCORONARY FORMS OF CLINICAL ATHEROSCLEROTIC DISEASE

Patients in this group include those with peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease. The absolute risk for MI in patients with noncoronary forms of atherosclerotic disease equals that for recurrent MI in patients with established CHD.[8]

TYPE 2 DIABETES

Patients with type 2 diabetes who do not manifest CHD still appear to carry a risk for major coronary events equivalent to that of nondiabetic patients with established CHD.[9] Moreover, many patients with type 2 diabetes have had a silent MI, and many other asymptomatic patients have silent ischemia. This has led the American Diabetes Association to designate type 2 diabetes as a CHD risk equivalent.[10]

HIGH-RISK PATIENTS WITH MULTIPLERISK FACTORS

The category of CHD risk equivalents has been extended to include asymptomatic patients who have multiple risk factors (other than diabetes).[11] A modified version of the Framingham score sheet is presented in Table 38-3. Framingham scores are used to estimate the absolute risk for the development of CHD over the next decade.[12] Table 38-4 shows absolute risk for *hard CHD* (nonfatal and fatal MI) and excludes *soft CHD* (stable and unstable angina). *Hard* CHD seems a better end point for defining CHD risk equivalency because risk-reduction therapy is aimed primarily at reducing risk for MI. When absolute 10-year risk for hard CHD exceeds 20 percent, a CHD risk equivalent is identified.

Table 38-3: Scoring for Global Risk Assessment (Adjusted Framingham Scoring Points for Risk Factors)

Risk Factor	Risk Points	
	Men	Women
Age		
<34	−1	−9
35–39	0	−4
40–44	1	0
45–49	2	3
50–54	3	6
55–59	4	7
60–64	5	8
65–69	6	9
70–74	7	10
Total cholesterol (mg/dL)		
<160	−3	−2
169–199	0	0
200–239	1	1
240–279	2	2
≥280	3	3
Blood pressure (mmHg)		
<120	0	−3
120–129	0	0
130–139	1	1
140–159	2	2
>160	3	3
Smoker		
No	0	0
Yes	2	2
HDL cholesterol (mg/dL)		
<35	2	5
35–44	1	2
45–49	0	1
50–59	−1	0
≥60	−2	−3
Plasma glucose (mg/dL)		
<110	0	0
110–126	1	2
>126	2	4
Adding up the Points		
Age_____ Cholesterol_____		
Diabetes_____ HDL cholesterol_____		
Smoker_____ Blood pressure_____		
Total_____		

Adjusting Framingham Age Points for Coronary Calcium Scores

Percentile of Calcium Score[a]	Point Adjustment[b]
0–24th	−2
25–49th	−1
50–74th	+1
75–89th	+2
>90th	+3

[a]For percentile of calcium score, see Table 38-5.
[b]The adjustment shown should be substituted for the age score of a given patient, whether men or women.

HIGH-RISK PATIENTS IDENTIFIED BY MAJOR RISK FACTORS PLUS SUBCLINICAL ATHEROSCLEROSIS

Many patients will be found to be at intermediate risk by Framingham scoring (Tables 38-3 and 38-4), i.e., absolute 10-year risk will be 10 to 20 percent.[13] Some of these patients

undoubtedly will be at higher risk because of advanced subclinical coronary atherosclerosis. If the latter could be identified by noninvasive methods, risk could be raised to a level of CHD risk equivalent. The potential utility of noninvasive testing for this purpose has recently been reviewed in the American Heart Association's Prevention V Conference.[2] In the past, noninvasive testing in asymptomatic patients has been contentious. Many investigators are concerned that asymptomatic patients with advanced subclinical atherosclerosis will be labeled as having CHD; if so, patients receiving this label might be referred inappropriately for invasive procedures. *Only if noninvasive techniques are used for risk assessment (prognosis) and not for diagnosis can noninvasive testing be justified for asymptomatic patients.* The goal of such testing thus is to identify persons who will benefit from aggressive medical therapy for risk reduction, not for case finding for invasive intervention. Some authorities question whether the scientific evidence supporting this testing is sufficient to justify its recommendation.[14] Still others doubt that it is cost-effective. Various techniques for noninvasive testing and their utility in risk assessment are reviewed briefly below.

Exercise Treadmill Testing

Exercise treadmill testing identifies patients whose coronary atherosclerosis has advanced sufficiently to produce myocardial ischemia with exercise (see also Chap. 14). A considerable body of data exists on risk prognostication on men of ages 45 to 70 years.[15] Exercise testing has reduced predictive value when the pretest probability for CHD is low. In middle-aged men, the combination of standard risk factors and an abnormal exercise ECG denotes a high risk for developing clinical CHD. Risk for angina pectoris is 12-fold elevated above that of men with a normal test result.[15] Risk for MI is elevated fourfold. These extremely high risk ratios are sufficient to elevate an intermediate-risk category to the level of CHD risk equivalent.

Electron-Beam Computerized Tomography

Electron-beam computerized tomography (EBCT) can be used to identify coronary calcification, which is a close correlate of coronary atherosclerosis.[16-19] As shown by EBCT, coronary calcium increases progressively with advancing age in parallel with coronary atherosclerosis (Table 38-5).[20] The finding of a certain degree of coronary calcium by EBCT (Table 38-5) may provide a means to improve on the risk estimate denoted by age in the Framingham algorithm (Tables 38-3 and 38-4). Patients at apparently intermediate risk with a high calcium score may be reclassified as having a CHD risk equivalent (see also Chap. 17).

Carotid B-mode Ultrasonography

Carotid B-mode ultrasonography, which measures the intimal-medial thickness (IMT) of carotid arteries, provides an independent approximation of coronary atherosclerosis.[2] The extent of carotid atherosclerosis correlates with coronary atherosclerosis.[21-23] Recent reports indicate that carotid IMT carries independent predictive power for development of CHD.[24,25] Like coronary calcium scores, IMT scores could be used to replace age as a risk factor in the Framingham algorithm.[3,26] A high IMT score thus could elevate some apparently intermediate-risk patients to the level of CHD risk equivalent.

INFLAMMATORY MARKERS

Inflammatory markers also may improve risk prognostication in apparently intermediate-risk patients. For example, high-sensitivity C-reactive protein has been reported to carry independent predictive power.[27,28] An elevated concentration of circulating inflammatory markers might point to the presence of unstable coronary lesions. If this is confirmed, abnormalities in inflammatory markers could be used to raise a finding of intermediate risk by conventional risk factors to a

CHD risk equivalent.

UNDERLYING AND PROVISIONAL RISK FACTORS

Finally, should *underlying risk factors*-e.g., obesity, physical inactivity, diet, genetic factors, and socioeconomic status-and *provisionally atherogenic risk factors*-e.g., elevated concentrations of triglycerides, lipoprotein(a), [Lp(a)], small dense low-density lipoprotein (LDL) particles, homocysteine, and coagulation factors-be used to adjust the risk of patients found to be at intermediate risk by Framingham scoring? The best approach may be to attempt to modify these factors directly through appropriate therapy, but not to use them in risk assessment. Nevertheless, this question is contentious and its answer unresolved.

RISK ASSESSMENT IN ELDERLY PATIENTS

The predictive power of conventional risk factors declines in older patients, and age becomes the predominant risk factor. Thus, the reliability of the Framingham algorithm is suspect in people over age 65. For this reason, measures of myocardial ischemia, coronary plaque burden, or markers of inflammation could be especially useful in differentiating between high-risk and intermediate-risk elderly patients. The demonstration that aggressive medical therapy significantly reduces risk for CHD in the older population increases the need to define absolute risk in this population more accurately.

Intermediate-Risk and Low-Risk Patients

For patients found to be at intermediate risk by Framingham scoring, additional noninvasive evaluation for subclinical atherosclerotic disease may be considered to define their risk status further (see above). Patients at intermediate risk by the Framingham algorithm deserve medical intervention. Primary prevention is for the long run. Even though these patients are not at high absolute risk for the short term, their risk mounts over time. In view of the proven effectiveness of risk-reduction therapies, there is a growing debate over whom among intermediate-risk patients should receive drug therapy for risk reduction. The issue revolves around efficacy, safety, and cost-effectiveness of drug therapies. Advances in pharmacologic therapy promise to improve safety and to reduce costs; therefore, in the future, it should be possible to extend the benefits of risk-reducing drugs to more patients. In addition, advances in nondrug therapies may also make these options more attractive to many patients.

An important question is how to manage patients with a single categorical risk factor but who are otherwise at low risk. A fundamental principle of primary prevention is that *all categorical risk factors must be treated, regardless of absolute risk.*[29] For example, cigarette smoking can cause cancer and cardiovascular disease even in the absence of other risk factors. Hypertension alone can cause stroke, heart failure, and kidney failure. Therefore, patients with categorical risk factors must not be ignored even if they are found to have a low absolute risk by Framingham scoring (Tables 38-3 and 38-4).

NEXT

Chapter 38: DYSLIPIDEMIA, OTHER RISK FACTORS, AND THE PREVENTION OF CORONARY HEART DISEASE

RISK FACTORS FOR WHICH INTERVENTIONS HAVE PROVED TO LOWER RISK OF CORONARY HEART DISEASE

Dyslipidemia

LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Evidence of several types supports the concept that LDL is the primary atherogenic factor, and controlled clinical trials show that lowering LDL reduces the risk for CHD. Accordingly, the National Cholesterol Education Program (NCEP)[8] has identified LDL cholesterol as the primary target of lipid-lowering therapy. Five decades of research on the role of LDL in the pathogenesis of CHD represents one of the major advances in modern medicine and public health.[30] This evidence is summarized briefly.

Low-Density Lipoprotein as the Primary Atherogenic Agent

Many studies in laboratory animals indicate that raising serum levels of LDL and related lipoproteins will initiate and sustain atherogenesis.[31] Moreover, humans with genetic forms of severely elevated LDL exhibit premature atherosclerotic disease.[32] Both of these examples demonstrate that elevated LDL alone, without the need for other CHD risk factors, is independently atherogenic. For many years, it was believed that the major action of LDL was merely to deposit its cholesterol within the arterial wall. More recently, LDL has been found to be a proinflammatory agent:[33] it sets into motion the chronic inflammatory response that is the hallmark of the atherosclerotic lesion. Elevated LDL appears to be involved with all stages of atherogenesis: endothelial dysfunction, plaque formation and growth, plaque instability and disruption, and thrombosis. Elevated LDL-cholesterol levels in the plasma lead to increased retention of LDL particles in the arterial wall, their oxidation, and the secretion of various inflammatory mediators and chemoattractants[35] (see Chap. 35). One sequela of this is the disruption of endothelial cell function by oxidized LDL,[35] with subsequent loss of production of nitric oxide. Treatment of elevated LDL-cholesterol levels has been shown to reestablish normal coronary vasodilatory response to acetylcholine.[36,37] LDL is also a potent mitogen for smooth muscle cells.

The primacy of LDL as a pathogenic agent is supported by epidemiologic data of several types. In different populations, the risk for CHD is positively correlated with the serum total cholesterol level;[38] the total cholesterol level in turn is highly correlated with LDL-cholesterol levels.[8] The association between serum cholesterol levels and CHD risk is curvilinear (or long-linear).[38] Risk rises exponentially at higher cholesterol levels. In populations that have very low total (and LDL) cholesterol, risk for CHD likewise is low, even when other CHD risk factors (cigarette smoking, hypertension, and diabetes) are common.[32] This latter observation strongly suggests that an elevated LDL cholesterol is the *primary* risk factor.

Primary and Secondary Prevention

There is a long history of clinical trials of cholesterol-lowering therapy that have included dietary and drug trials.[30] One trial also induced cholesterol lowering by intestinal surgery.[39] Some trials have included patients with established CHD (secondary prevention), and others recruited patients without CHD (primary prevention). The aggregate results of early trials, both primary and secondary prevention, demonstrated that cholesterol-lowering therapy (or lipoprotein modification) reduces risk for CHD.[40] However, earlier trials failed to show that cholesterol reduction decreased total mortality.[40,41] This latter deficiency left many clinicians skeptical of the benefits of cholesterol-lowering therapy.

The introduction of HMG-CoA reductase inhibitors (statins), which are powerful LDL-lowering drugs, made possible a more effective test of the cholesterol hypothesis.[42,43] Since 1993, five major trials with statins have been published: three secondary prevention[4,5,44] and two primary prevention trials.[45,46] The results of these studies are summarized in Table 38-6. All trials showed a marked reduction in major coronary events. Three found a reduction in total mortality.[5,44,45] No increases in noncardiovascular mortality occurred in any of the trials. These trials documented convincingly that cholesterol-lowering therapy is both safe and effective for reducing CHD risk.

In this same time period, a series of angiographic trials was performed to determine whether reducing LDL-cholesterol levels would decrease progression or promote regression of coronary atherosclerotic lesions. These trials typically employed aggressive cholesterol-lowering therapy, often with combined drug regimens. Indeed, most studies revealed that marked reductions of LDL levels will slow progression, and in some cases promote regression, of coronary lesions.[47,48] Although measurable angiographic changes in lesion size were small, the incidence of major coronary events was reduced strikingly. This observation engendered the concept that LDL reduction *stabilizes* coronary lesions rather than causing them to shrink markedly. Seemingly, LDL lowering modifies lesion structure and composition more than it changes lesion size. Consequently, short-term cholesterol-lowering therapy appears to reduce the likelihood of coronary plaque rupture and thrombosis.

Practice Recommendations for Low-Density Lipoprotein Lowering

LDL lowering can be accomplished with nondrug and drug therapies. *The importance of nondrug therapies must not be minimized.* Chief among them are reducing intake of cholesterol-raising fatty acids (saturated and *trans* fatty acids) and dietary cholesterol.[8] The major sources of dietary saturated fatty acids are dairy fats (e.g., milk, butter, cream, cheese, and ice cream) and animal fats [e.g., fatty cuts of meat (especially hamburger), fatty processed meats, lard and tallow]. *Trans* fatty acids are present in shortening, hard margarine, and processed foods containing these forms of fat. Rich sources of dietary cholesterol are eggs, dairy fats, and other animal products. Current intake of cholesterol-raising fatty acids in the United States is in the range of 15 percent of total calories. For patients on cholesterol-lowering therapy, this should be reduced to less than 7 percent. Dietary cholesterol should be lowered to less than 200 mg/day. Achieving a desirable body weight will reduce LDL-cholesterol levels in most overweight patients and will decrease risk for CHD in several other ways.[49]

There is growing interest in obtaining further risk reduction by use of dietary adjuncts. A daily intake of 3 g/day of plant stanols will reduce LDL-cholesterol concentrations 10 to 15 percent beyond that which can be achieved by reducing cholesterol-raising fatty acids and cholesterol in the diet.[50] Highintakes of dietary fiber will produce another 3 to 5 percent decrease in LDL levels.[51] Unsaturated fatty acids (monounsaturated, *n*-6 polyunsaturated, and *n*-3 polyunsaturated fatty acids) will lower LDL and may reduce global risk for CHD via several other mechanisms.[52]

Statins head the list of cholesterol-lowering drugs. Table 38-7 compares the efficacy of the currently available statins in patients without hypertriglyceridemia. Most patients tolerate statins with few side effects. Occasional patients will have a mild rise in liver transaminases, but this change is currently not believed to be an indication of hepatotoxicity. Rare patients will exhibit signs and symptoms of myopathy. This side effect is more likely to occur in patients who have chronic renal failure or liver disease or who are on drugs that utilize or inhibit the cytochrome P450 3A4 pathway. For every doubling of the dose of a statin, the LDL-cholesterol level will fall by about 6 percent; a more efficacious way to enhance LDL lowering is to combine statins with bile acid sequestrants. For patients with borderline elevated triglycerides (200 to 400 mg/dL) and high LDL, niacin or a statin is an acceptable first-line drug. When triglycerides exceed 400 mg/dL, a fibrate or niacin is usually the most appropriate first-line agent.

Table 38-7: Comparative Efficacy of the Six Currently Available Statins on Lipids and Lipoproteins in PatientsWithout Hypertriglyceridemia

Statin Drug (mg)						Change in Lipid and Lipoprotein Levels (%)			
Atorvastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	Cerivastatin	Total	LDL	HDL	Triglycerides
-	10	20	20	40	0.2	-22	-27	+4-8	-10-15
10	20	40	40	80	0.4	-27	-34	+4-8	-10-20
20	40	80	-	-	-	-32	-41	+4-8	-15-25
40	80	-	-	-	-	-37	-48	+4-8	-20-30
80	-	-	-	-	-	-42	-55	+4-8	-25-35

Note: For the purpose of illustration, the lipid and lipoprotein responses are based on short-term clinical trials and are approximations of what might be observed in clinical practice.
Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Source: From Maron et al.,[298] with permission.

Goals of Therapy Lowering Low-Density Lipoprotein

For patients with established CHD, the NCEP recommends an LDL-cholesterol goal of ≤100 mg/dL.[8] This recommendation is based on the combined data from epidemiologic studies, angiographic trials, and end-point trials. New clinical trials have been initiated to define the optimal LDL-cholesterol goal for secondary prevention. However, the NCEP contends that multiple lines of evidence already converge to support an LDL-cholesterol target of ≤100 mg/dL.[53] The American Heart Association recommends starting cholesterol-lowering drugs immediately in all CHD patients when the LDL-cholesterol level is >130 mg/dL.[54] Whether to initiate cholesterol-lowering drugs in patients whose baseline LDL-cholesterol is in the range of 100 to 129 mg/dL is unsettled. Without question, these patients should receive maximal nondrug therapy, possibly including dietary adjuncts (see above). Such therapy alone will often achieve the LDL-cholesterol goal of ≤100 mg/dL.

For patients with noncoronary forms of atherosclerotic disease, the NCEP also recommends an LDL-cholesterol goal of ≤100 mg/dL.[8] This is because other atherosclerotic disease constitutes a CHD risk equivalent. Patients with CHD risk equivalents should have the same goal for LDL cholesterol as patients with known CHD, i.e., ≤100 mg/dL.

For patients at intermediate risk (Table 38-2), a reasonable LDL-cholesterol goal is <130 mg/dL. The last NCEP report essentially made such a recommendation, although the method for establishing CHD risk was not with the Framingham algorithm (Tables 38-3 and 38-4). Rather it recommended counting categorical risk factors (Table 38-8), which is less precise for estimating absolute risk. Most men over age 65 who are not found to be at high risk can be considered to be at intermediate risk; their LDL-cholesterol goal should be <130 mg/dL. Women under age 55 generally are at lower risk than men of equivalent age and should be evaluated by Framingham scoring for risk stratification. The strategy for achieving an LDL-cholesterol level <130 mg/dL should be initiated with nondrug therapy, but some patients undoubtedly will require LDL-lowering drugs.

Table 38-8: National Cholesterol Education Program Risk Categories for Primary Prevention

Intermediate-to-high risk
Two or more major risk factors in the presence of LDL cholesterol ≥160 mg/dL[a]
▪ Cigarette smoking ▪ Hypertension (blood pressure >140/90 mmHg) or on treatment for hypertension ▪ Low HDL cholesterol (<35 mg/dL) ▪ Age (men >45 years; women >55 years or postmenopausal) ▪ Family history of premature coronary heart disease ▪ Diabetes mellitus
Low risk
Zero to one risk factor in the presence of LDL cholesterol ≥160 mg/dL

[a]Subtract one risk factor if HDL cholesterol >60 mg/dL.

ABBREVIATIONS: HDL = high-density lipoprotein; LDL = low-density lipoprotein.
SOURCE: From National Cholesterol Education Program,[8] with permission.

Finally, for patients who are at low risk (Table 38-2), the LDL-cholesterol goal is <160 mg/dL. This target can be considered to be a minimal goal, but it must be recognized that the desirable LDL in primary prevention is <130 mg/dL.[8] Most low-risk patients, however, are not candidates for cholesterol-lowering drugs unless their LDL-cholesterol levels are very high, e.g., >190 mg/dL. In low-risk patients whose baseline LDL-cholesterol concentration is in the range of 160 to 189 mg/dL, clinical judgment is required whether to start cholesterol-lowering drugs.[8] Most patients whose LDL is in this range should achieve an LDL-cholesterol level of < 160 mg/dL with maximal nondrug therapy including dietary adjuncts.

Cost-Effectiveness of Drug Therapy for Lowering Low-Density Lipoprotein

Cost-effectiveness analysis is used to consider both the effectiveness of an intervention and its cost and is commonly expressed as a ratio of cost in dollars per quality-adjusted years of life gained[1] (see also Chap. 94). The validity of the assumptions used to determine direct and indirect cost is critical to computing an accurate ratio. By convention, less than $20,000 per year of life saved is considered highly cost-effective, $20,000 to $40,000 is relatively cost-effective, and greater than $60,000 is considered expensive. Studies of the cost-effectiveness of cholesterol lowering have demonstrated the importance of effective therapies in patients at highest risk. Studies of LDL-cholesterol reduction with statins have demonstrated cost-effectiveness in CHD patients. Estimates of cost per year of life range from $22,900 in asymptomatic 55- to 64-year-old men with total cholesterol <250 mg/dL to actual cost savings in hypercholesterolemic, male CHD patients 45 to 54 years old.[55] In a direct cost analysis of the Scandinavian Simvastatin Survival Study, cost of simvastatin therapy ranged from $3800 for 70-year-old men with a cholesterol level of 309 mg/dL to $27,400 for 35-year-old women with a cholesterol level of 213 mg/dL.[56] When indirect costs were considered, the results ranged from a savings in the youngest patient to a cost of $13,300 per year of life gained in older patients. In contrast, the use of less effective agents, such as bile acid-binding resins, in low-risk, asymptomatic patients does not appear to be cost-effective.[57]

ATHEROGENIC DYSLIPIDEMIA: HYPERTRIGLYCERIDEMIA, LOW HIGH-DENSITY LIPOPROTEIN, AND SMALL DENSE LOW-DENSITY LIPOPROTEIN

Although high LDL is the primary lipid risk factor, other lipid parameters increase the risk of CHD in persons with or without an elevated LDL cholesterol. Specifically, the combination of *elevated concentrations of triglycerides, small dense LDL and low levels of high-density lipoprotein (HDL) is referred to as atherogenic dyslipidemia.*[58] This is a complex dyslipidemia that usually results from a

generalized metabolic derangement. Although an elevated LDL cholesterol deserves primary emphasis for management, atherogenic dyslipidemia is assuming increasing importance as a contributor to CHD because of the growing prevalence of obesity in the United States and worldwide.[58] Most patients with atherogenic dyslipidemia have a generalized metabolic disorder called *insulin resistance*. This syndrome is described later in this chapter.

Relation of Atherogenic Dyslipidemia to Coronary Heart Disease

A long-standing debate is whether the individual components of atherogenic dyslipidemia are independent risk factors. This question has been difficult to resolve because each of the three lipid components is highly correlated with the other two. Nevertheless, there is growing evidence for independent atherogenicity of each component. For triglycerides, *recent meta-analyses of multiple prospective studies strongly suggest that elevated serum triglycerides are an independent risk factor for CHD*.[59,60] *Other prospective studies show that a low HDL-cholesterol level is an independent risk factor*.[61,62] Two important mechanisms by which HDL is thought to play a protective role against atherosclerosis are reverse cholesterol transport and inhibition of LDL oxidation. *A lesser body of data also suggests that small, dense LDL particles are more atherogenic than normal-sized LDL*.[63] Atherogenic dyslipidemia is commonly accompanied by the other atherogenic risk factors of the metabolic syndrome[58] (see the section "Insulin Resistance Syndrome" below).

Primary and Secondary Prevention Among Subjects with Atherogenic Dyslipidemia

No controlled clinical trials have been conducted to address specifically whether modifying atherogenic dyslipidemia will reduce risk for CHD. Indirect evidence comes from post hoc analyses of large clinical trials and from trials using drugs that modify atherogenic dyslipidemia. The latter drugs include nicotinic acid and the fibric acids. These drugs have only small effects on LDL levels, and most changes occur in the components of atherogenic dyslipidemia. The results of clinical trials[64-69] in which nicotinic acid or a fibric acid was used are shown in Table 38-9. None of these trials except for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[69] specifically targeted patients with atherogenic dyslipidemia. Nevertheless, most of the trials either showed a significant reduction in coronary events by drug therapy or a trend toward a reduction. In the Helsinki Heart Study,[65] the Stockholm Ischemic Heart Disease Study,[67] and the Bezafibrate Infarction Prevention Study,[68] the most favorable results were observed in patients with elevated triglycerides, an indicator of atherogenic dyslipidemia. These trials generally did not reveal a reduction in total mortality, nor were they statistically powered to do so. Nonetheless, taken as a whole, these trials are strongly suggestive that modification of atherogenic dyslipidemia by drug therapy will reduce the risk for CHD. This likelihood is enhanced by the findings of angiographic trials that fibrates slow progression of coronary atherosclerosis.[65,70]

It must be noted that statins also modify atherogenic dyslipidemia by reducing remnants of triglyceride-rich lipoproteins, reducing concentrations of small dense LDL, and by raising HDL-cholesterol levels modestly. Thus, some of the risk reduction from the statin trials could be related to favorable modification of the component of atherogenic dyslipidemia as well as to lowering of LDL-cholesterol levels.

Practice Recommendations for Atherogenic Dyslipidemia

First-line treatment of atherogenic dyslipidemia is weight control and physical activity. Most patients with atherogenic dyslipidemia are either overweight [body mass index (BMI), 25 to 29 kg/m^2] or obese (BMI ≥30 kg/m^2).[49] Weight reduction in these patients often will improve the lipoprotein abnormalities associated with this form of dyslipidemia.[49] Introduction of regular physical activity will further correct the lipoprotein pattern. Not only will weight control and regular exercise improve atherogenic dyslipidemia, it also will mitigate the other components of the metabolic syndrome.[71] The increasing prevalence of obesity and physical inactivity in the United States has caused a corresponding increase in the metabolic syndrome among Americans. This unfortunate trend threatens to reverse the advances made in reducing morbidity and mortality from cardiovascular disease over the past two decades. It also poses a challenge to physicians to modify their practice to place more emphasis on lifestyle changes.

Both fibric acids and nicotinic acid will improve the lipoprotein pattern in patients with atherogenic

dyslipidemia. Fibric acids have been shown to activate nuclear receptors (PPAR alpha) that favorably modify regulators of lipoprotein metabolism in the liver.[72] The mechanism of action of nicotinic acid is not known, but its effects are similar to those of fibric acids, except that nicotinic acid is more effective for raising HDL-cholesterol levels.[73] Unfortunately, nicotinic acid has several side effects that prevent its use in high doses in many patients. Nonetheless, the drug is usually well tolerated in moderate doses (1.0 to 1.5 g/day).

The primary goal of lipid therapy in patients with atherogenic dyslipidemia is to reduce LDL-cholesterol concentration to the targets recommended for primary and secondary prevention. In many patients, statin therapy will be required to achieve the LDL target. If abnormalities persist after reaching the LDL goal, renewed efforts at weight control and increased physical activity may be indicated. If these measures are not successful, a second lipid-lowering drug may be added to modify these other lipoproteins. Either a fibric acid or nicotinic acid can be employed as the second agent to achieve the secondary NCEP goals of HDL > 35 mg/dL and triglycerides < 200 mg/dL. The combination of fibrates with a high dose of a statin should be avoided because of the increased risk of myopathy.

Some investigators believe that an appropriate target of therapy in patients with atherogenic dyslipidemia is non-HDL cholesterol.[74,75] This fraction includes cholesterol in LDL and in remnants of triglyceride-rich lipoproteins. If non-HDL cholesterol is taken as a target of therapy, the goals of therapy are 30 mg/dL higher than the LDL-cholesterol goals for secondary and primary prevention. An alternate target is the serum triglyceride level. Although clinical trials are suggestive of benefit, there is no universal agreement among authorities that additional risk reduction is achieved by targeting atherogenic dyslipidemia beyond LDL cholesterol.

LIPOPROTEIN(a)

Lp(a) consists of an LDL particle linked via a disulfide bond to an apolipoprotein(a) [apo(a)] polypeptide chain. Because of homology between apo(a) and plasminogen, Lp(a) has been hypothesized to serve as a competitive inhibitor for plasminogen binding and thus may inhibit endogenous fibrinolysis.[76] Lp(a) is largely genetically determined, and distributions differ between men and women, as well as between races.

Several retrospective case-control studies support the view that Lp(a) is an independent risk factor for thromboembolic disease. However, results of the major prospective studies evaluating baseline Lp(a) concentration and future risks of MI and stroke have been inconsistent.[77-83] One possibility to explain these divergent results may relate to the fact that Lp(a) appears to be a greater marker of risk among patients with hypercholesterolemia[78,84] or among younger individuals only.[85] Another possibility is that electrophoretically detected Lp(a) may be a better marker than actual plasma level.[86,87]

Primary and Secondary Prevention

Although nicotinic acid and estrogen appear to reduce Lp(a) levels in some patients, no clinical trials have been conducted to test whether reducing plasma levels results in reduced risk.

Practice Recommendations

It is not yet clear whether Lp(a) provides information independent of the conventional lipid profile, and no recommendation for screening can be made. If elevated levels prove clearly to increase risk among hypercholesterolemic individuals, it may be prudent to lower LDL-cholesterol levels even more aggressively in such individuals than current guidelines dictate. Knowledge of Lp(a) levels may also be useful in the selection of LDL-lowering drugs (e.g., niacin) and may identify a possible treatable cause in the occasional patient with CHD and none of the major risk factors. Unfortunately, many commercial assays for plasma Lp(a) are poorly standardized.[88]

Atherogenic Diet

An atherogenic diet and a lack of physical activity are considered leading preventable causes of death,

second only to tobacco use.[89] Considerable epidemiologic data indicate that populations with diets high in cholesterol and animal fats have high rates of CHD.[90,91] Conversely, those populations consuming large amounts of calories as vegetables, cereals, and fish have lower rates of CHD.[90] Countries that increased their animal fat consumption during the 1970s and 1980s increased their CHD mortality rates, while those that decreased their annual fat consumption showed CHD mortality reductions.[92] Similarly, populations consuming larger amounts of sodium in their diet have higher average blood pressures.[93] Caloric imbalance, in part due to excess calorie consumption, is related to a rising prevalence of obesity. On an individual basis, recent clinical trials of modified diets have demonstrated reductions in angiographic progression[94] and in recurrence of clinical disease.[95]

It has been assumed that the harmful effects of the *Western* diet have been mediated by saturated fats, dietary cholesterol, and sodium, via their effects on traditional risk factors such as LDL cholesterol, body weight, diabetes, and blood pressure. A portion of the effect of a Western diet appears to be attributable to these factors. However, there is evidence for mechanisms other than the traditional risk factors. The Western Electric Study adjusted for these factors and continued to find an independent risk associated with dietary cholesterol.[96] The Lyon Diet Heart Study compared a Mediterranean-type diet high in alpha-linolenic acid with a Western diet and showed a 65 percent reduction in recurrent coronary events despite no demonstrable change in any of the traditional risk factors.[95] Mechanisms suggested as explanatory of these benefits include antioxidant, anti-inflammatory, and antiplatelet effects. This apparent independent benefit of a diet low in saturated fat, cholesterol, and sodium, and high in monounsaturated fats, fruits, vegetables, and fish provides the rationale for inclusion of *atherogenic diet* as a separate, modifiable risk factor.

PRIMARY PREVENTION

Reduction in the dietary consumption of animal fat, cholesterol, and sodium should be the mainstay of population-wide coronary disease prevention. Population-wide cholesterol reductions observed in the United States from 1979 to 1991 are attributed solely to changes in dietary consumption patterns.[97] Two older clinical trials of long-term inpatients demonstrated reductions in coronary endpoints of 34 to 50 percent among patients on low saturated fat and cholesterol diets.[98,99] Therefore, *dietary interventions should be the initial step in the treatment of dyslipidemia, hypertension, diabetes, and obesity.*

SECONDARY PREVENTION

Studies of low-fat diets, such as the STARS Trial[100] and the Lifestyle Heart Study[94] have used angiographic end points and shown a marked reduction in LDL cholesterol and a reduction in new or progressive coronary stenoses. However, these studies are too small to test for clinical end-point reduction. The Oslo Diet-Heart Study demonstrated a significant reduction in reinfarction rates with a low saturated fat diet as well as a smoking cessation program.[101] As noted, the Lyon Diet Heart Study, with a Mediterranean-type diet enriched in alpha-linolenic acid, demonstrated a 65 percent reduction in recurrent cardiac events and death over a 4-year period of follow-up.[95] *The magnitude of benefit was similar to or greater than those shown in numerous trials of lipid-lowering drugs.*

COST-EFFECTIVENESS

Dietary interventions might be targeted at the general population or at high-risk groups such as coronary disease patients. Population-wide interventions to alter eating behaviors intend to make relatively small changes in dietary habits in a large number of people. Studies from Finland[102] and the United States[103] suggest that population-wide education programs can reduce LDL-cholesterol levels 3 to 4 percent at a cost of $4 to $10 per person per year. Using a model to project benefits of such programs, Goldman et al. predicted that the Finnish program would cost $10,000 per year of life saved, whereas the U.S. program would actually be cost saving.[104] The cost-effectiveness of such a population-wide intervention was compared with a more individualized dietary intervention in a study of Norwegian men.[105] The population-wide approach cost approximately $20 per year of life saved versus $20,000 per year of life saved for the program of individual counseling. *Both approaches are considered highly cost-effective and favorable to drug treatment in that study.*

PRACTICE RECOMMENDATIONS

The current dietary recommendations emphasize a wellbalanced diet low in saturated fat, cholesterol, and sodium, while rich in fruits and vegetables.[102] Very low fat diets are poorly complied with and have little long-term safety and efficacy data to support them.[106] A diet with less than 30 percent of calories from fat is generally recommended, but with caloric content compatible with maintenance of ideal body weight. For patients with vascular disease or hyperlipidemia, less than 7 percent of calories from saturated fat and less than 200 mg of dietary cholesterol per day are suggested. Monounsaturated fats and omega-3 fatty acids from fish may be a beneficial source of calories, as compared with carbohydrates.[107] Consultation with a registered dietitian or other nutrition specialist can be recommended as part of a risk-modification program in high-risk patients.

Cigarette Smoking

Strong dose-responsive relationships between cigarette smoking and CHD have been observed in both sexes, in the young and in the elderly, and in all racial groups.[108] Cigarette smoking increases risk two- to threefold and interacts with other risk factors to multiply risk. There is no evidence that filters or other modifications of the cigarette reduce risk.[109] Pipe smoking and cigar smoking, when not inhaled, as well as oral tobacco use, whether chewing tobacco or snuff, carry rather small risks but are related to later resumption of cigarette smoking. Clearly, cigarette smoking remains a leading preventable cause of mortality, much of it due to cardiovascular disease.

Whereas active cigarette smoking has long been established as a cardiovascular risk factor, exposure to environmental tobacco smoke, or passive smoking, has increasingly been recognized as a modifiable risk factor.[110,111] In a recent meta-analysis of 18 epidemiologic studies, exposure to tobacco smoke by nonsmokers was consistently associated with a 20 to 30 percent increase in risk.[112] This is in addition to an increased risk for respiratory tract cancers and other smoking-related diseases.

Pathophysiologic studies have identified a panoply of mechanisms through which cigarette smoking may cause CHD. Smokers have increased levels of oxidation products, including oxidized LDL.[113] Cigarette smoking also lowers the cardioprotective levels of HDL. These effects, along with direct effects of carbon monoxide and nicotine, produce endothelial damage. Possibly through these mechanisms, smokers have increased vascular reactivity.[113,114] The reduced capacity of the blood to carry oxygen also lowers the threshold for myocardial ischemia and increases the risk of coronary spasm. Cigarette smoking is also related to increased levels of fibrinogen and increased platelet aggregability.[115]

PRIMARY PREVENTION

Cessation of smoking is associated with a precipitous fall in CHD events. *In a previous smoker, the relative risk declines nearly to that of a nonsmoker in a year or less.*[116] It is estimated that a 35-year-old who quits smoking extends survival by 3 to 5 years,[117] with much of the improved life expectancy caused by a reduction in CHD deaths.

SECONDARY PREVENTION

The risk of a recurrent event in a patient surviving an MI is strikingly reduced by smoking cessation. Compared with a patient who continues to smoke, the risk of recurrence can be reduced by 50 percent.[118,119] *The benefits of achieving complete abstinence from smoking for a patient with CHD compare favorably with the health benefits of any intervention in modern cardiology.*

COST-EFFECTIVENESS

Interventions to achieve smoking cessation are among the most cost-effective in either primary or secondary prevention, with or without the use of nicotine replacement therapy.[120,121] Physician counseling of middle-aged patients without vascular disease is estimated to cost only $1000 to $1400 per year in men and $1700 to $3000 per year in women.[122] The use of nicotine gum by these patients increased the cost to up to $9000 per

year in men and $13,500 per year in women.[123] In contrast, counseling to achieve smoking cessation in MI patients is exceptionally cost-effective, costing only $250 per year of life saved.[124]

PRACTICE RECOMMENDATIONS

Nothing less than complete cessation of smoking and other tobacco use should be acceptable in patients with cardiovascular disease. Moreover, the home and work environments to which patients return should be smoke free, both to encourage cessation and to reduce the risk from passive smoking. Cardiovascular specialists often have unique and time-limited opportunities to influence the behaviors of patients. After an acute event, the patient and their family members may be especially receptive to a smoking cessation intervention.

Smoking Cessation Clinical Practice Guidelines were first published by the Agency for Health Care Policy and Research in 1996 and form the basis for a successful smoking cessation program.[125] Those guidelines emphasize that tobacco use status be documented in every patient and that every smoker should be offered one or more of three effective treatment interventions. Even a brief intervention may be effective and should, at a minimum, be provided to every patient who uses tobacco (Table 38-10). Three elements of a treatment program found to be effective include social support, skills training/problem solving, and nicotine replacement. More intense efforts by the care provider to achieve complete cessation will generally result in a greater success rate. The huge reduction in risk resulting from smoking cessation in the cardiovascular disease patient provides a strong rationale for sustained and intense efforts to be expended.

Table 38-10: Strategies for Successful Cessation of Cigarette Smoking: The Four A's

Ask	Systematically identify all tobacco users at every visit (e.g., include tobacco as a vital sign).
	Determine exposure to environmental tobacco smoke at home or at work.
	Identify patients with nicotine addiction.
Advise	Provide a clear, strong, and personalized message, urging every tobacco user to quit.
	Review benefits of quitting and risk of continuing.
	Assess patient's willingness to quit.
Assist	Have the patient develop a quit plan, including setting a quit date, identifying sources of support for cessation for family and friends, removing tobacco and other cues from the home and work environment.
	Provide counseling, information materials and other behavioral interventions.
	Recommend use of pharmacotherapy including bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray or nicotine patch.
Arrange	Provide a reminder on the quit date.
	See the patient shortly after the quit date to assess success.
	If unsuccessful, identify barriers and solutions to their removal

SOURCE: From Fiore M et al.[125] and Pearson TA.[299]

Addiction to tobacco is a major barrier to cessation, and a number of pharmacologic agents can be recommended as an adjunct to a concurrent behavioral intervention on the basis of clinical trials demonstrating significantly increased rates of smoking cessation.[126] Bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch are all first-line drugs to prevent nicotine withdrawal; clonidine is reserved for second-line therapy. Safety of the use of these agents in coronary disease patients

was initially a concern, but several studies have now established the lack of association between the use of nicotine replacement agents and further cardiac events.[127-129]

Hypertension

(See also Chap. 51.) Several major prospective epidemiologic studies have found that both systolic and diastolic hypertension have a strong, positive, continuous, and graded relationship to CHD without evidence of a threshold risk level of blood pressure.[130-132] Among populations in different countries, the relative risk for CHD imposed by a given increase in blood pressure is similar, but the absolute risk at a given blood pressure value varies substantially.[133] This may be due to widely varying baseline risk among populations. Hypertension clusters with insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, left ventricular hypertrophy, and obesity, and occurs in isolation in less than 20 percent of individuals.[134] The potential mechanisms by which hypertension may cause coronary events include impaired endothelial function, increased endothelial permeability to lipoproteins, increased adherence of leukocytes, increased oxidative stress, hemodynamic stress that may trigger acute plaque rupture, and increased myocardial wall stress and oxygen demand. A widened pulse pressure, an indicator of arterial stiffness, is gaining an evidence base as another blood pressure measurement that predicts CHD.[135]

PRIMARY PREVENTION

A meta-analysis of 17 randomized trials of antihypertensive drugs in over 47,000 men and women with mild to moderate hypertension found that stroke was reduced by 38 percent and CHD was reduced by 16 percent.[131] The mean difference in diastolic blood pressure over 5 years between treatment and control groups was 5 to 6 mmHg. An important subset in whom events were reduced was elderly subjects with isolated systolic hypertension (systolic blood pressure ≥160 mmHg; diastolic blood pressure ≤90 mmHg).

For a prolonged 5- to 6-mmHg difference, observational studies predict a reduction of 35 to 40 percent in stroke risk and 20 to 25 percent in CHD risk. Although clinical trials indicate that antihypertensive therapy achieves the reduction in stroke expected from observational studies, the reduction in CHD is not as great as expected. Potential explanations for this are (1) the shortfall was due to chance, (2) the duration of observation was too short and the full benefit was not seen, (3) the treatment benefits were partially offset by metabolic side effects of medications, (4) excessive reduction in diastolic blood pressure led to excess CHD events, or (5) metabolic disturbances associated with hypertension that potentiate CHD were not corrected by the antihypertensive therapy used in the studies (see the section "Insulin Resistance Syndrome," below). Most of these trials were based on high-dose diuretic therapy, with or without beta blockers, leading some experts to propose that adverse metabolic consequences of high-dose diuretics were responsible for the less than expected benefits of antihypertensive treatment. Nevertheless, diuretics and beta blockers are the only classes of antihypertensives extensively tested to date that have been shown to reduce CHD morbidity and mortality in primary prevention. The efficacy of newer antihypertensives in reducing initial coronary events is currently being tested.[136] Blood pressure can be lowered by weight loss, exercise, salt restriction, and avoidance of alcohol,[132] but the long-term utility of these measures to prevent CHD in hypertensives has not been tested in randomized controlled studies.

SECONDARY PREVENTION

Clinical trials to test the effect of blood pressure lowering per se in CHD patients have not been performed.

COST-EFFECTIVENESS

Treatment of hypertension for primary prevention is highly cost-effective, with an estimated cost per year of life saved of about $23,000 (in 1993 dollars) for moderate to severe hypertension and twice as much for mild hypertension.[1] Estimates (in 1993 dollars) vary depending on the choice of medication, ranging from $14,000 per year of life saved for propranolol, to $20,000 for hydrochlorothiazide, and up to $90,000 for newer medications. The cost-effectiveness of blood pressure lowering for secondary prevention is unknown.

PRACTICE RECOMMENDATIONS

The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends a treatment goal of <140/90 mmHg.[132] A goal of <130/85 is appropriate for patients with diabetes, renal insufficiency, or CHF.[132,137] Please refer to Chap. 51 for a complete discussion of the treatment of hypertension.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH), defined either by electrocardiography or echocardiography, is a potent independent risk factor for CHD, roughly doubling the risk of cardiovascular death in both men and women.[138] LVH is the adaptive response of the heart to chronic pressure or volume overload (see Chap. 67). In addition to hypertension, LVH is associated with obesity, salt intake, advanced age, and heredity.[139] Progressive LVH may lead to decreased left ventricular compliance, decreased coronary reserve, ventricular ectopy, and impaired systolic function. The Framingham Heart Study observed that ECG evidence of LVH regression was associated with a reduction in cardiovascular disease morbidity and mortality.[140] Another observational, prospective evaluation of LVH using echocardiography indicated an improved prognosis among patients with a reduction of left ventricular mass on antihypertensive therapy.[141] Most antihypertensive drugs can reduce LVH (except direct vasodilators, e.g., hydralazine and minoxidil),[132] although not all drugs are equally effective in this regard despite their equipotent blood pressure-lowering capabilities. An analysis of several comparative studies and some meta-analyses, including only double-blind, randomized, controlled clinical studies with parallel group design, indicates that angiotensin-converting enzyme (ACE) inhibitors reduced left ventricular mass by 12 percent, calcium channel blockers by 11 percent, beta blockers by 5 percent, and diuretics by 8 percent.[142] A study of the effect of monotherapy with six antihypertensive agents on reduction of left ventricular mass revealed that captopril, hydrochlorothiazide, and atenolol reduced left ventricular mass and that diltiazem, clonidine, and prazosin did not.[143] The impact of new antihypertensive agents such as angiotensin II-receptor antagonists is still uncertain. Randomized clinical trials have not yet tested whether regression of LVH lowers CHD risk, but the observational data merit its classification as a risk factor that should be modified.[132]

Thrombogenic Factors

See the section "Antiplatelet and Anticoagulant Therapy," below.

PREVIOUS | NEXT

Chapter 38: DYSLIPIDEMIA, OTHER RISK FACTORS, AND THE PREVENTION OF CORONARY HEART DISEASE

RISK FACTORS FOR WHICH INTERVENTIONS ARE LIKELY TO LOWER RISK OF CORONARY HEART DISEASE

Insulin Resistance Syndrome: The Basis of Multiple Risk Factors

Reaven[144,145] has hypothesized that *resistance to insulin-stimulated glucose uptake and compensatory hyperinsulinemia are the common metabolic bases for a cluster of coronary risk factors, particularly hypertension, diabetes, hypertriglyceridemia, low HDL, predominance of small dense LDL, and a prothrombotic state* with elevated levels of plasma fibrinogen, plasminogen activator inhibitor 1 (PAI-1), and factor VII.[146] This clustering has been called the *insulin resistance syndrome* or the *metabolic syndrome.* Interestingly, hypertensive individuals, both treated and untreated, obese and nonobese, are hyperinsulinemic compared with a matched group of normotensive individuals. Also, patients with atherogenic dyslipidemia have an increased frequency of hypertension. Hypertriglyceridemia or low HDL, major components of the syndrome, can be considered as *markers* for the presence of the metabolic syndrome. Obesity, particularly when located abdominally, exacerbates insulin resistance, and weight loss improves insulin sensitivity. Insulin sensitivity is associated with endothelial nitric oxide production in healthy persons, providing a clue as to how insulin resistance may promote CHD directly.[147] Furthermore, hyperinsulinemia has been found in a prospective study to be an independent risk factor for CHD in nondiabetic men after adjusting for body weight, blood pressure, and dyslipidemia.[148]

Some experts believe the primary mechanism for insulin resistance is lipid overload in skeletal muscle, liver, and pancreatic beta cells. This overload of tissues with lipid may derive both from an excess of adipose tissue (obesity) and physical inactivity. In skeletal muscle, lipid overload impairs glucose uptake and promotes hyperglycemia.[149] In the liver, lipid overload contributes to atherogenic dyslipidemia. And in pancreatic beta cells, excess lipid overstimulates the secretion of insulin, producing hyperinsulinemia.[150] In a significant portion of the population, the adverse consequences of an overload of tissues with lipid are accentuated by an underlying genetic susceptibility to insulin resistance.[146]

A comprehensive lifestyle approach is required to address the cluster of risk factors related to insulin resistance. Weight loss and physical activity are clear goals because they counteract insulin resistance. Although a low-fat diet is clearly beneficial for hypercholesterolemia, it might be detrimental in insulin-resistant, hypertriglyceridemic patients.[145]

Diabetes Mellitus

(See Chap. 78 for a complete discussion about diabetes and CHD.) Diabetes mellitus is an independent risk factor for CHD, increasing risk by two to four times for men and women, respectively.[9,71] CHD is the leading cause of death among diabetics, and approximately 25 percent of MI survivors have diabetes.[8,71] *Diabetic patients without a history of MI have as high a risk of coronary mortality as nondiabetic patients with a history of MI.*[9] Once patients with type 2 diabetes suffer a myocardial infarction, their prognosis for survival is much worse than that for

CHD patients without diabetes.[151,152]

Diabetes abolishes the usual protection from CHD afforded a premenopausal woman.[71] *Diabetic women have twice the risk of recurrent MI compared with diabetic men.*[153] The greater risk of CHD in diabetic women compared to diabetic men may be explained in part by the greater adverse effect of diabetes on lipoproteins in women.[154] Potential mechanisms by which diabetes may cause atherosclerosis include low HDL, high triglycerides/increased lipoprotein remnant particles, increased small dense LDL, elevated Lp(a) concentration, enhanced lipoprotein oxidation, glycation of LDL, increased fibrinogen, increased platelet aggregability, increased PAI-1, impaired fibrinolysis, increased von Willebrand factor, hyperinsulinemia, and impaired endothelial function. Most patients with type 2 diabetes have multiple risk factors. High-risk populations in the United States include whites, blacks, Hispanics, and South Asians.

PRIMARY AND SECONDARY PREVENTION

Despite overwhelming observational data that diabetes increases the risk of CHD, few data are available to determine whether glycemic control reduces risk. The University Group Diabetes Program was the first large-scale randomized clinical trial to study cardiovascular end points in patients with type 2 diabetes, and treatment with sulfonylurea therapy was associated with *increased* cardiovascular mortality.[155] The Diabetes Control and Complications Trial studied the effect of intensive insulin therapy in patients with type 1 diabetes.[156] Intensive therapy reduced microvascular end points, but the study was not of sufficient size to examine CHD end points. The United Kingdom Prospective Diabetes Study (UKPDS) examined the impact of intensive glycemic control with sulfonylureas or insulin compared with conventional therapy on the risk of complications in patients with type 2 diabetes.[157] The treatment goal in the intensive therapy group was a fasting glucose of <108 mg/dL. In the conventional treatment group, drugs were added to diet only if there were hyperglycemic symptoms or if the fasting glucose was >270 mg/dL. After a 10-year follow-up, there was a significant reduction in microvascular end points but not in macrovascular end points. There was no evidence that intensive treatment with sulfonylureas or insulin had an adverse effect on macrovascular disease.

COST-EFFECTIVENESS

The cost-effectiveness of treating diabetes for primary and secondary prevention of CHD has not been established.

PRACTICE RECOMMENDATIONS

Weight loss and exercise are key therapeutic interventions because they improve the constellation of metabolic abnormalities that accompany diabetes. Although the optimal proportion of dietary fat and carbohydrate is controversial, calorie restriction for obesity and avoidance of sugar and saturated fat are definitely recommended. *Beta blockers should not be withheld from diabetic patients following MI unless strong contraindications exist, because diabetic MI survivors have fewer deaths if treated with a beta blocker.*[158] Although there is no consistent evidence to support intensive glycemic control as a strategy to reduce macrovascular end points, aggressive lipid management in patients with diabetes lowers CHD risk. The NCEP and American Diabetes Association guidelines recommend a more aggressive LDL goal (<100 mg/dL) in primary prevention of CHD in diabetics.[8,71] The American Heart Association (AHA) recommends near-normal fasting glucose and hemoglobin A_{1c} (HgA_{1c}) ≤1 percent above normal as treatment goals for patients with diabetes.[71]

Physical Inactivity

Physical inactivity is an independent risk factor for CHD[159] *and roughly doubles the risk.* There is a dose-response relation between the amount of exercise performed weekly, from 700 to 2000 kcal of energy, and death from cardiovascular disease and all causes.[159] Data linking sedentary lifestyle with CHD derive from numerous lines of evidence, including animal studies, observational studies, and clinical trials. Moderate-intensity exercise reduces coronary atherosclerosis and widens coronary arteries in monkeys fed an atherogenic diet compared with monkeys fed the same diet but forced to be sedentary. Physical activity slows progression of angiographically defined coronary atherosclerosis in humans.[160] Over 50 observational studies, primarily of men, have established that physical fitness, on-the-job physical activity, and leisure-time physical activity reduce the risk of CHD.[161] These studies of physical activity are subject to important potential biases, including self-selection and unmeasured confounding variables. The risk of MI and sudden cardiac death is greatest during exercise, but the overall risk of MI and sudden cardiac death is reduced among those who exercise regularly.[162] The greatest potential for reduced mortality is in sedentary individuals who become moderately active.[159] Moderate-intensity activity, as opposed to high-intensity activity, produces most of the beneficial effects of physical activity on cardiovascular mortality. A recent prospective study of more than 72,000 apparently healthy female nurses indicated that brisk walking and vigorous exercise are associated with substantial and similar reductions in coronary events.[163] In addition to decreasing myocardial oxygen demand and increasing myocardial efficiency and electrical stability, other potential mechanisms of benefit include increasing HDL, lowering triglycerides, reducing blood pressure, reducing obesity, improving insulin sensitivity, decreasing platelet aggregation, and increasing fibrinolysis.[161]

PRIMARY PREVENTION

A randomized, controlled trial of physical activity for primary prevention of CHD is not likely to be conducted because of cost and compliance issues.

SECONDARY PREVENTION

(See Chap. 50 on cardiac rehabilitation.) Meta-analyses of randomized trials of cardiac rehabilitation with exercise in over 4000 MI survivors demonstrated a 20 to 25 percent reduction in cardiovascular mortality, although there were no significant differences in nonfatal reinfarction.[164,165] Most of the studies combined exercise training with other risk factor modification. The small number of trials with exercise as the only intervention does not permit definitive conclusions. The benefit of physical activity in female CHD patients is uncertain.

COST-EFFECTIVENESS

The cost-effectiveness of physical activity for primary prevention is not established. Given the low monetary cost of physical activity and its numerous favorable effects on other risk factors, exercise for primary prevention is likely to be highly cost-effective. The cost-effectiveness of cardiac rehabilitation has been estimated (in 1993 dollars) at less than $8000 per quality-adjusted year of life gained.[8]

PRACTICE RECOMMENDATIONS

The American College of Sports Medicine and the Centers for Disease Control and Prevention recommend that every adult should accumulate 30 min or more of moderate-intensity physical activity on most, preferably all, days.[166] Only about 20 percent of U.S. adults meet this goal. The AHA recommends a minimal goal of 30 min of moderate-intensity activity three to four times a

week for individuals with and without CHD.[167,168] Large-scale studies indicate that high-intensity physical activity is *not* required to achieve a mortality benefit, and that 200 calories expended daily in moderate-intensity physical activity will confer the majority of CHD risk reduction that exercise can provide. To accomplish this requires about 30 min of brisk walking; however, intermittent activity also provides substantial benefit.[167] Therefore, the minimal goal of 30 min can be accumulated in short bouts of typical daily activities like walking, climbing stairs, housework, and gardening. Exercise testing should be recommended to apparently healthy men over 40 and women over 50 who are sedentary, as well as to younger adults with coronary risk factors, before starting a *vigorous* physical activity program (intensity > 60 percent individual maximum oxygen consumption).[169] For secondary prevention, exercise testing is recommended to guide exercise prescription, and high-risk patients should exercise in a medically supervised setting.[167] Structured exercise programs, whether on site or at home, help compliance with an exercise prescription[170] (see also Chap. 50).

Obesity

Obesity is defined by the AHA as a major risk factor for CHD.[171] Obesity promotes insulin resistance, hyperinsulinemia, type 2 diabetes, hypertension, hypertriglyceridemia, low HDL cholesterol, small dense LDL, prothrombotic factors, and LVH.[132] It is associated with an increase in cardiovascular and all-cause mortality.[132,172]

Body mass index (BMI) has been adopted widely as a measure of adiposity. BMI is calculated as weight (kg)/height squared (m^2) and estimated as [weight (pounds)/height (inches)^2] × 704.5 *Overweight* is defined as a BMI of 25 to 29.9, and *obesity* is defined as BMI ≥ 30. The number of overweight and obese adults in the United States has increased since 1960. Nearly one-third of adults in the United States are overweight, and an additional one-fifth meet the definition of obese.[172] BMI correlates with total body fat content. Abdominal obesity adds to the health risks of obesity, and waist circumference correlates positively with abdominal fat content. In adults with a BMI between 25 and 35, increased relative risk is indicated in men with a waist circumference of >102 cm (>40 inches) and in women of >88 cm (>35 inches).[132]

In univariate analysis, many observational studies have found obesity strongly and positively correlated with the risk of CHD. In multivariate analysis, when controlling statistically for risk factors such as hypertension, diabetes, and dyslipidemia, obesity is usually not found to be an independent risk factor. This reflects that many of the adverse consequences of obesity are mediated through resultant metabolic risk factors acting as pathogenetic links in the causal pathway. Nevertheless, some large prospective observational studies of long duration indicate that obesity is independently related to coronary and cardiovascular mortality in men and women.[173-175] In general, the greater the degree of overweight, the higher is the risk of coronary mortality. Weight loss improves insulin sensitivity and glucose disposal, reduces HbA_{1c} in patients with type 2 diabetes, reduces blood pressure and triglycerides, produces a modest reduction in LDL, and increases HDL cholesterol.[132]

PRIMARY AND SECONDARY PREVENTION

Although weight loss leads to a number of favorable short-term changes in metabolism, it is unknown whether long-term weight loss results in reduced CHD events. No primary or secondary prevention trials of weight loss have been conducted.

COST-EFFECTIVENESS

The cost-effectiveness of weight loss is unknown. Given the favorable effect of weight loss on other risk factors, it may prove to be highly cost-effective.

PRACTICE RECOMMENDATIONS

BMI should be listed as a vital sign, used to assess overweight and obesity, and used to monitor changes in body weight. Tracking body weight alone can be used to determine the efficacy of weight-loss therapy. National Institutes of Health guidelines recommend that waist circumference be measured in patients with a BMI between 25 and 35 because of its incremental predictive power.[132] Treatment of overweight (BMI, 25 to 29.9) is recommended only when patients have two or more risk factors, increased waist circumference, or CHD or a CHD risk equivalent. Treatment should focus on diet and exercise to prevent weight gain and to produce moderate weight loss over years. The initial goal of weight-loss therapy is to reduce body weight by approximately 10 percent from baseline in 6 months. For patients with BMI in the range of 27 to 35, a decrease of 300 to 500 kcal/day will result in this degree of weight loss. Lost weight is usually regained unless a program consisting of dietary therapy, physical activity, and behavior therapy is continued indefinitely.

Smoking cessation is associated with weight gain, on average 4.5 to 7 lb. The health hazards of smoking exceed the risks of moderate obesity; therefore, cigarette smokers should be given the clear message that smoking cessation is of the highest priority even if it results in weight gain. Weight-loss drugs approved by the Food and Drug Administration for long-term use may be useful as an adjunct to diet and physical activity for patients with a BMI $\geq$ 30 and for patients with a BMI $\geq$ 27 with CHD or obesity-related risk factors. CHD end-point trials with weight-loss drugs, however, have not been conducted. Fenfluramine and dexfenfluramine have been withdrawn from the market because of associated valvular heart disease.

Postmenopausal Status

CHD is relatively uncommon in premenopausal women. There is a dramatic rise in CHD incidence in women after age 55, coinciding with increasing age and a decline in endogenous estrogen levels. Early menopause (natural or surgical) is associated with increased CHD risk.[176] These observations are consistent with the notion that estrogen deficiency permits or promotes CHD and that estrogen reduces risk. Numerous observational studies show that postmenopausal users of estrogen replacement therapy (ERT) have a 50 percent lower risk of initial CHD events compared with nonusers.[176] Because of their observational design, these studies have been subject to selection bias and uncontrolled or unknown confounding variables. In most of these studies, ERT has been unopposed by concomitant progestin therapy. Proposed mechanisms by which estrogen may confer benefit include raising HDL; lowering LDL, small dense LDL, Lp(a), and fibrinogen levels; inhibiting LDL oxidation; and enhancing endothelium-dependent and endothelium-independent coronary vasodilation.

Unopposed ERT increases the risk of endometrial carcinoma, but the addition of a progestin erases that risk.[176] Estrogen with or without progestin may increase slightly the risk of breast cancer, particularly among older women who have taken hormones for 5 or more years.[176,177] For women aged 65 to 74 years, the absolute risk of dying of CHD over the next 10 years is 15 times that of dying of endometrial cancer and 6 times that of dying of breast cancer.[178] The Postmenopausal Estrogen/Progestin Interventions Trial assessed differences between placebo, unopposed estrogen, and three estrogen/progestin combinations over 3 years on selected CHD risk factors in healthy postmenopausal women.[179] Compared with placebo, estrogen alone or in combination with a progestin raised HDL cholesterol and lowered fibrinogen levels. The best regimen for raising HDL cholesterol was unopposed estrogen, but in women with an intact uterus

this caused a high rate of atypical or adenomatous endometrial hyperplasia.

PRIMARY AND SECONDARY PREVENTION

The Heart and Estrogen/Progestin Replacement Study (HERS) investigated the impact of estrogen plus progestin on the risk of CHD in 2763 postmenopausal women with established coronary disease and an intact uterus.[180] Subjects were randomly assigned 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone daily or a placebo with a mean follow-up of 4 years. There was no difference in the primary end point of nonfatal MI or CHD death. The lack of an overall effect occurred despite a net 11 percent lower LDL level and 10 percent higher HDL level in the hormone treatment group. Although there was no difference overall between groups, there was a statistically significant time trend, with more CHD events in the hormone group in year 1 and fewer events in years 4 and 5. More women in the hormone group suffered venous thromboembolic events and gallbladder disease. Other large randomized trials of hormone replacement therapy for primary and secondary prevention are currently in progress.

COST-EFFECTIVENESS

The cost-effectiveness of ERT for prevention of CHD is undefined.

PRACTICE RECOMMENDATIONS

On the basis of HERS, we recommend that postmenopausal women with CHD who have not been on ERT should not be started routinely on hormone therapy for the purpose of preventing CHD events. Those with CHD who have been on ERT for at least 2 years without a CHD event should not have hormone therapy discontinued. For postmenopausal women without known CHD, clinical trial evidence is still lacking and the decision whether to treat must be individualized according to other health risks. Oral estrogen therapy is contraindicated in women with hypertriglyceridemia (e.g., serum triglycerides >400 mg/dL).

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RISK FACTORS FOR WHICH INTERVENTIONS MIGHT LOWER RISK OF CORONARY HEART DISEASE

Psychosocial Factors

The role of personality, environment, social support, social contact, stress and lack of control at work, and depression have all been associated with increased risk for CHD. See Chap. 80 for a discussion of these topics.

Acute emotional reactions have been implicated as triggers of acute coronary syndromes. In the absence of atherosclerosis, mental stress causes vasodilation or no change in the diameter of epicardial coronary arteries. In the presence of atherosclerosis, mental stress induces silent myocardial ischemia[181] and coronary vasoconstriction.[182] An episode of anger is capable of triggering acute MI.[183] There was a fivefold increase in the number of sudden cardiac deaths related to atherosclerosis on the day of one of the strongest earthquakes ever recorded in North America.[184] Most of these deaths did not occur in association with heavy physical exertion and were presumably related to major emotional stress. In most cases, the length of time between the earthquake and sudden death was less than 1 h. A mechanism by which acute emotional stress could trigger coronary events is release of catecholamines, leading to an increase in heart rate, blood pressure, myocardial oxygen demand, vasoconstriction, platelet aggregability, and coagulation with an inhibition of fibrinolysis. These factors could contribute to the rupture of a vulnerable plaque, with subsequent thrombosis, or to the precipitation of ventricular arrhythmias.

PRACTICE RECOMMENDATIONS

Optimal comprehensive secondary prevention should include attempts to identify and treat depression and anxiety in patients with CHD. Group support and stress management can be provided in formal cardiac rehabilitation programs.

Total Plasma Homocysteine Level

Total plasma homocysteine level reflects the sum of homocysteine and homocysteinyl moieties of oxidized disulfides, homocystine, and cysteine-homocysteine. Together, these amino acid derivatives appear to have direct toxic effects on the vascular endothelium and can result in the oxidation of LDL, both important steps in atherogenesis. Although there are genetic determinants of total homocysteine level (see Chap. 62), the most important factor affecting plasma concentration is dietary intake of folate and vitamins B_6 and B_{12}.[185] Of note, folate fortification exists in the United States, and less than 1 percent of the population has low levels of folic acid.[186]

A series of cross-sectional and case-control studies strongly supports an independent association between total plasma homocysteine level and atherosclerotic risk.[187] In addition, prospective studies have found increased risk of MI[188-193] and stroke[194] among patients with moderate hyperhomocysteinemia. However, not all large-scale studies are positive.[195-197] When pooled, these data suggest that as much as 10 percent of the population risk of CHD may be attributable to

homocysteine level.[187]

PRIMARY AND SECONDARY PREVENTION

Although folate and vitamins B_6 and B_{12} reduce homocysteine concentration,[198] no randomized trial data are yet available to indicate that reducing plasma levels reduces risk.

PRACTICE RECOMMENDATIONS

Measurement of homocysteine may be useful in patients with CHD in the absence of major risk factors or with a history of recurrent arterial thromboses.

Oxidative Stress

Oxidative modification of LDL has been hypothesized to play a major role in the initiation and progression of atherosclerosis.[34] Because naturally occurring antioxidants such as vitamins E, C, and beta-carotene may slow this process, there has been substantial interest in these compounds as agents for both primary and secondary prevention. A series of observational epidemiologic studies supports the hypothesis that increased dietary intake of antioxidants is associated with reduced cardiovascular risk, with the strongest evidence for vitamin E.[199-202] Unfortunately, it is impossible to conclude from observational studies that a given vitamin supplement is responsible for observed vascular risk reduction, since individuals who take vitamins are also likely to employ other preventive lifestyle and dietary measures. This issue can only be resolved through large-scale, randomized clinical trials.

PRIMARY PREVENTION

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, which enrolled 29,133 male smokers,[203] there was no evidence that vitamin E (given as 50 mg of alpha-tocopherol daily) reduced the subsequent risk of CHD or stroke, and a small increase in rates of cerebral hemorrhage was reported. In the same trial, beta-carotene was associated with a small increase in lung cancer and deaths due to CHD. In the Carotene and Retinol Efficacy Trial conducted among 18,314 smokers, former smokers, and asbestos-exposed workers,[204] the combined use of 30 mg/day of beta-carotene plus 25,000 IU of retinol was associated with a small but statistically significant increase in lung cancer and all-cause mortality, as well as a nonsignificant increase in cardiovascular mortality. In constrast, among 22,071 men participating in the Physicians' Health Study who were randomly allocated to 50 mg of beta-carotene on alternate days for a period of 12 years, supplementation resulted in no evidence of benefit or harm in terms of the incidence of cardiovascular disease or cancer.[205]

SECONDARY PREVENTION

In the Cambridge Heart Antioxidant Study,[206] higher doses of vitamin E were found to reduce rates of nonfatal MI substantially among a group of patients with known CHD. Specifically, in this high-risk secondary prevention trial, the use of 400 to 800 IU of alpha-tocopherol daily over an average period of only 17 months was associated with a statistically significant 47 percent risk reduction in cardiovascular death and nonfatal infarction. By contrast, in the large-scale Heart Outcomes Prevention Evaluation (HOPE) trial, these effects were not confirmed, as no overall benefit was observed among those randomly allocated to vitamin E.[207]

PRACTICE RECOMMENDATIONS

Based on these randomized trial data, it is impossible to make recommendations for or against supplementation with vitamin C to prevent CHD, although beta-carotene and vitamin E appear to carry no benefit. Given observational evidence suggesting benefit for diets rich in fruits and vegetables, however, it is prudent to continue such diets that contain several hundred micronutrients that may have chemopreventive properties.

No Alcohol Consumption

Heavy alcohol intake is associated with increased risks of death from several causes and is a major public health concern. However, cross-sectional, case-control, and prospective cohort studies indicate that mild to moderate alcohol consumption is associated with reduced rates of CHD compared with abstainers.[208-210] These studies suggest a J-shaped relationship between level of alcohol consumption and total mortality such that a protective effect is apparent at low levels of consumption (one to two beverages daily), whereas there is substantial hazard among heavy consumers.[211] In large part, this dose-dependent balance reflects summation of three effects: (1) a positive association between alcohol use and cancer; (2) a U-shaped relationship between alcohol use and total cardiovascular disease due to increased risks of cardiomyopathy, sudden death, and hemorrhagic stroke among heavy drinkers; and (3) a well-established L-shaped protective effect for coronary disease.[211,212]

Several mechanisms are important in the cardioprotective effect of moderate alcohol use. Alcohol intake increases total HDL-cholesterol levels as well as HDL2 and HDL3 subfractions.[213-216] Alcohol consumption also has potentially beneficial effects on fibrinolytic function[217,218] and on platelet aggregation.[219,220]

PRIMARY AND SECONDARY PREVENTION

There have been no randomized trials of alcohol use for primary or secondary prevention.

PRACTICE RECOMMENDATIONS

How best to advise patients concerning the potential use of alcohol for cardiovascular protection is a complex process, because of this agent's potential for abuse.[221] Abstinence is advised for patients who are pregnant or who have hepatic disorders, pancreatic disease, congestive heart failure, idiopathic cardiomyopathy, or degenerative neurologic conditions. On the other hand, the recommendation to drink moderately (one drink per day for women and two drinks for men) may be safe when made on a case-by-case basis in the absence of a history of abuse or medical contraindication.[221] Whether specific beverage type matters in terms of cardiovascular protection is uncertain. Evidence indicating benefits for white wine, red wine, beer, and liquor suggest that alcohol content rather than type is the more important predictor of cardiovascular risk reduction.[209,210]

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UNMODIFIABLE RISK FACTORS

Age and Sex as Risk Factors for Atherosclerotic Disease

The incidence and prevalence of CHD increase sharply with age, so that age might be considered one of the most potent cardiovascular risk factors. Atherosclerotic involvement of the coronary arteries is well established in men by young adulthood, as shown in Korean War and Vietnam War casualties.[222,223] CHD incidence rates in men are similar to those in women 10 years older.[224] Approximately 52 percent of women and 46 percent of men will eventually die of atherosclerotic disease.[225] The increased risk for men and older persons should trigger more intense management of modifiable risk factors. Persons at very advanced age (e.g., 75+ years) should have the risks and benefits of preventive cardiology interventions weighed on an individual basis.

Socioeconomic Status: An Unmodifiable Coronary Risk Factor?

At any one point in time, markedly different CHD rates may be observed between socioeconomic subgroups of the population, as defined by occupation, education, income, or other measures. As a group becomes affluent, its members use their new wealth to purchase high-fat and high-salt foods, tobacco products, and automobiles. Less affluent groups lag behind this development, achieving access to these deleterious behaviors later. Affluent groups then learn about and adopt healthful lifestyles, reducing deleterious behaviors. Again, less affluent and less educated groups lag behind, eventually exceeding the rates of CHD in those educated groups whose CHD rates have begun to fall.

Currently, persons with low socioeconomic status are at high risk for CHD. A number of mechanisms may explain this.[226] First, risk factors for atherosclerosis, such as smoking, hypertension, obesity, and sedentary lifestyle, are higher in persons with low socioeconomic status. Second, some of these risk factors, as well as psychosocial responses to stressors, may increase exposure to CHD triggers in these groups. Finally, these groups may have less access to care.

Family History of Early-Onset CHD

Over 35 case-control and prospective studies have consistently identified an association between CHD and a history of first-degree relatives with early-onset CHD.[227] This risk generally persists even after adjustment for other risk factors. The family history most predictive of coronary disease is that of a first-degree relative developing CHD at an early age. Although CHD in a male relative with onset at age 55 or less or a female relative with onset at age 65 or less is defined as a positive family history, the larger the number of relatives with early-onset CHD or the younger the age of CHD onset in the relative, the stronger is the predictive value.[228,229]

Although considered a nonmodifiable risk factor, a positive family history should result in the careful screening of individual risk factors known to aggregate in families. Such familial aggregations may represent monogenic factors with known phenotypic expressions and

inheritance patterns, polygenic factors with less clear modes of expression and inheritance, or shared environments. In early-CHD families, Williams et al.[229] estimate that only 10 percent of families will not have a concordant risk factor, most of which are amenable to intervention. Thus, family members of patients with CHD at a young age represent fruitful targets for risk factor assessment. *However, risk factor screening often does not extend beyond the coronary patient. A strong recommendation that siblings and children of early-CHD patients be screened for CHD risk factors should be delivered to each patient and their family members.*

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OTHER PHARMACOLOGIC THERAPY

Antiplatelet and Anticoagulant Therapy

See also Chap. 44.

PRIMARY PREVENTION

Several prevention trials of aspirin have been completed in healthy men. The largest of these, the Physicians' Health Study, enrolled 22,071 apparently healthy male physicians aged 40 to 84 years of age and randomized them to 325 mg aspirin on alternate days or to placebo.[230] Among those given active aspirin, a highly statistically significant 44 percent reduction in nonfatal MI was observed. In this study, aspirin had little effect on the clinical characteristics of MI[231] or on the rate of development of angina pectoris.[232] When the Physicians' Health Study data are combined with those of a similar trial among British men,[233] an overall 32 percent reduction in risk of first nonfatal MI appears to be associated with chronic aspirin prophylaxis.[234] These trials have also demonstrated the efficacy of low-dose aspirin in the prevention of MI among patients with stable angina pectoris.[235] In the Thrombosis Prevention Trial, low-dose aspirin (75 mg daily) and low-dose warfarin (target INR = 1.5) were both effective, although combination therapy as compared with monotherapy remains controversial.[236]

SECONDARY PREVENTION

At least 25 trials have been completed in the study of antiplatelet therapy for secondary prevention.[237] Overall, among patients with known clinical manifestations of atherosclerotic disease, antiplatelet therapy is associated with a 32 percent reduction in subsequent MI, 27 percent reduction in subsequent nonfatal stroke, and 15 percent reduction in vascular mortality.[238] Although thienopyridines such as clopidogrel also appear effective, evidence that these agents are superior to aspirin alone is marginal.[239]

Few studies of anticoagulant therapy in the secondary prevention of coronary disease are available. In the Dutch Sixty Plus Study,[240] patients over 60 years of age who had been taking anticoagulants following infarction were randomly assigned to continue or discontinue warfarin. Patients continuing anticoagulant therapy had a 26 percent lower mortality rate and a 51 percent lower reinfarction rate.

The utility of warfarin initiated soon after infarction has also been demonstrated.[241] In a trial of 1214 patients with acute or subacute MI, the randomized use of warfarin with a target INR between 2.8 and 4.8 was associated with a 24 percent reduction in mortality, a 34 percent reduction in nonfatal reinfarction, and a 55 percent reduction in stroke over a mean period of 37 months. These reductions were achieved with acceptably low bleeding rates for those assigned to warfarin.

COST-EFFECTIVENESS

For primary prevention, aspirin is likely to be extremely cost-effective because of its low cost and high efficacy for preventing MI. Following MI, both aspirin and anticoagulant therapy have been shown to be cost saving.[21]

PRACTICE RECOMMENDATIONS

The United States Preventive Services Task Force has recommended that low-dose aspirin be considered in men age 40 and over who are at high risk for MI and lack contraindications.[242] Although observational data generally support the use of aspirin in women,[243] the risk-to-benefit ratio in women may differ from that of men, since the average age at first infarction is higher. For secondary prevention, 80 to 325 mg of aspirin daily is recommended, with treatment continued indefinitely. If aspirin is contraindicated, clopidogrel and then warfarin are recommended for secondary prevention, with an INR goal of 2 to 3.5.[137,167]

Fibrinogen

Plasma fibrinogen level has been shown in several studies to predict the future risk of MI and stroke.[244-248] When pooled, these studies indicate that individuals with fibrinogen concentrations in the upper third of the control distribution have a relative risk of future cardiovascular disease 2.0 to 2.5 times that of individuals with lower levels.[249] High fibrinogen levels result in increased whole blood viscosity and may play a direct role in atherogenesis and platelet aggregation. While fibrinogen levels increase with smoking, age, oral contraceptive use, and diabetes, fibrinogen is poorly correlated with dyslipidemia and therefore may provide additional risk information beyond lipid and lipoprotein measurement.

HIGH-SENSITIVITY C-REACTIVE PROTEIN

C-reactive protein (CRP) is a hepatically derived marker of low-grade systemic inflammation that largely reflects circulating cytokine function. When measured with high-sensitivity assays, CRP can be detected within the normal range and used for cardiovascular risk prediction. To date, several large-scale prospective studies have shown the inflammatory marker high-sensitivity CRP (hs-CRP) to be a potent predictor of future myocardial infarction, stroke, and peripheral vascular occlusion among apparently healthy men and women,[27,250-252] as well as among high-risk smokers[253] and the elderly[254] (see Fig. 38-1). Levels of hs-CRP are also elevated among those with acute coronary syndromes at high risk for recurrent events[255,256] and among post-MI patients at high risk for recurrent instability.[257] These effects are independent of other risk factors and appear to add to the predictive value of lipid screening in terms of risk prediction.[28] Thus, as a clinical marker reflecting the presence of an enhanced systemic inflammatory response, hs-CRP appears to have utility in the detection of high-risk patients for plaque instability.

PRIMARY AND SECONDARY PREVENTION

Exercise frequency and body mass both correlate with hs-CRP levels,[258,259] and randomized trial data indicate that lipid reduction with pravastatin lowers hs-CRP in an LDL-independent manner.[260] Further, the effectiveness of low-dose aspirin in reducing risk of first MI appears related to hs-CRP level.[250] However, no data are yet available which indicate that reducing plasma levels of hs-CRP reduces vascular risk.

PRACTICE RECOMMENDATIONS

Practice guidelines for hs-CRP screening are in development. As hs-CRP levels appear to add to

the predictive value of lipid screening[28] and pedict risk even among those with low levels of LDL cholesterol, knowledge of hs-CRP may be of use as an adjunct to lipid profiling on a population basis. A standardized commercial assay for hs-CRP has recently been approved by the Food and Drug Administration for use in cardiovascular risk assessment.[261]

Endogenous Fibrinolysis: Tissue Plasminogen Activator, PAI-1, and *D*-Dimer

The activity of the endogenous fibrinolytic system reflects a balance between plasma concentration of tissue-type plasminogen activator (tPA) and its primary inhibitor, PAI-1. Prospective studies of initially healthy individuals[262,263] as well as patients with known CHD[264] indicate that elevated antigen levels of both enzymes are associated with increased risk of future MI. Further, prospective data also indicate that tPA antigen level is a potent marker of risk for stroke.[265]

Because both tPA and PAI-1 contribute to the net fibrinolytic balance, it has been hypothesized that individuals at risk for future vascular occlusive events suffer from a net inhibition of fibrinolytic function, a finding supported in at least one prospective study.[266] Other data, however, indicate that elevations of *D*-dimer are also associated with increased risk of future MI[267] and peripheral vascular disease.[268,269] Since plasma *D*-dimer levels increase with fibrinogen turnover, these data raise the possibility that the endogenous fibrinolytic system is activated among individuals at risk.

Evidence is not available to support fibrinogen reduction as a measure to prevent CHD, although smoking cessation, physical activity, and hormone replacement therapy[179,270] all favorably affect fibrinogen levels. Other fibrinogen-reducing agents, such as bezafibrate, are also under investigation in ongoing clinical trials.[271] Many factors affect endogenous fibrinolytic activity, including obesity, estrogen status, and exercise. In addition, pharmacologic interventions may soon be available that can favorably shift fibrinolytic function in an attempt to reduce vascular risk. To date, aspirin therapy, alcohol use, and ACE inhibitors have all shown promise in this regard.[272]

Beta-Adrenergic Blocking Agents

Beta-adrenergic blocking agents reduce heart rate, systemic blood pressure, and ventricular contractility, all factors that decrease myocardial oxygen consumption (see Chap. 3). Beta blockers further have antiarrhythmic properties and appear to increase thresholds for ventricular fibrillation.[273]

PRIMARY PREVENTION

Little clinical trial data are available that directly test beta-blocking agents in the primary prevention of MI. The use of this class of agents in the treatment of hypertension, however, has been shown to be efficacious for CHD prevention,[274] and beta blockers have few long-term side effects.

SECONDARY PREVENTION

The utility of beta-blocking agents in the acute, subacute, and chronic phases following MI has been demonstrated in many clinical trials. Overview analyses indicate that therapy with beta blockers reduces mortality approximately 20 percent compared with placebo.[275,276] The mortality effect of long-term beta blockade results primarily from prevention of sudden death (pooled

relative risk = 0.68), presumably due to a reduction in the incidence and complexity of ventricular arrhythmias. Beta blockers have also proven effective in reducing rates of nonfatal reinfarction (pooled relative risk = 0.74), an effect more likely to result from chronic reductions in heart rate, contractility, and vascular stress.

COST-EFFECTIVENESS

Estimates of the cost of beta blockers after MI range from $3600 per year of life saved when used in high-risk patients to $23,400 per year of life saved when used in low-risk patients.[277] This is cost-effective as compared with other accepted CHD interventions.

PRACTICE RECOMMENDATIONS

For primary prevention, beta blockers are recommended as first-line therapy for hypertension.[132] For secondary prevention, beta blockers are recommended in post-MI patients with arrhythmias, left ventricular dysfunction, and inducible ischemia.[167] Although specific studies of beta-blocker cessation are not available, it is commonly recommended that beta-blocker therapy be continued indefinitely as long as side effects are not present.[273]

Angiotensin-Converting Enzyme Inhibitors

PRIMARY PREVENTION

Although ACE inhibitors are used widely as first-line therapy for hypertension, no data on primary prevention with this class of drugs are available. A large-scale trial is in progress.[136]

SECONDARY PREVENTION

ACE inhibitors reduce mortality in patients with congestive heart failure and reduced left ventricular ejection fraction.[278-280] More recently, this class of agents has been recognized as important adjunctive therapy following acute MI.[281] The primary rationale for using these agents in this setting is based on the experimental observation that ACE inhibition slows the process of ventricular remodeling.[282,283] This effect appears time dependent in that the use of ACE inhibition after MI requires a sufficient length of therapy to result in detectable changes in ventricular volumes and size. The observation in several trials that rates of recurrent MI may also be reduced with ACE inhibition[281,284,285] raises the possibility that these agents also result in enhanced endogenous fibrinolysis.[286] The ability of ACE inhibition with ramipril to reduce risk of MI and cardiovascular mortality among high-risk patients without heart failure further demonstrates the efficacy of these agents (HOPE trial).[207]

COST-EFFECTIVENESS

The cost-effectiveness of ACE inhibitor therapy after MI in patients with left ventricular ejection fraction < 0.40 compares favorably with other commonly accepted therapies for patients with CHD. Depending on the age of the patient and the assumptions used, estimates for the cost-effectiveness of captopril range from $3600 to $60,800 per quality-adjusted life-year.[287]

PRACTICE RECOMMENDATIONS

No data are available to recommend ACE inhibitors for primary prevention. For secondary prevention, ACE inhibitors should be prescribed to patients with congestive heart failure and

reduced left ventricular function unless contraindicated. The results of the recent HOPE trial suggest it is reasonable to prescribe ramipril for patients with CHD or CHD risk equivalent and normal left ventricular function.[207] We await the results of ongoing trials to learn whether other ACE inhibitors will confer a similar benefit for patients with normal left ventricular function.

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THE PRACTICE OF PREVENTIVE CARDIOLOGY

The evidence for a causal role of risk factors in the etiology of CHD and the feasibility and efficacy of risk factor modification in lowering CHD risk is some of the most convincing in all of medicine. Despite this, there are both qualitative and quantitative gaps in our treatment of coronary risk factors, even in patients at highest risk. Qualitative gaps entail the lack of any risk factor detection and management in many patients. Among patients with established coronary disease, only 40 to 60 percent receive beta blockers, only 60 percent of patients with reduced left ventricular ejection fractions receive ACE inhibitors, and only 70 to 90 percent take aspirin.[288,289] Likewise, many of those patients receiving treatment are not being treated to the goals as set by various guidelines or as documented as efficacious in randomized clinical trials. For example, in a recent study of 4888 patients receiving treatment for lipid disorders, only 17 percent of CHD patients reached their LDL-cholesterol goal of ≤100 mg/dL, and only 37 percent of high-risk (2+ risk factors), non-CHD patients reached their goal of <130 mg/dL.[290] Thus, preventive cardiology strategies backed by strong evidence for efficacy and cost-effectiveness are simply not being applied sufficiently widely, constituting a missed opportunity to reduce costs and improve prognosis.

Barriers to Implementation of PreventiveCardiology Services

A number of barriers to the implementation of preventive services can be identified at the patient, physician, health care setting, and community/society levels (Table 38-11).[291,292] The improved implementation of proven interventions therefore requires a variety of strategies targeted at patients, healthcare providers, inpatient care settings, ambulatory care settings, and health systems.

Table 38-11: Barriers to Implementation of Preventive Services

Patient

- Lack of knowledge and motivation
- Lack of access to care
- Cultural factors
- Social factors
- Physician
- Problem-based focus
- Feedback on prevention is negative or neutral
- Time constraints
- Lack of incentives, including reimbursement
- Lack of training
- Poor knowledge of benefits
- Perceived ineffectiveness
- Lack of skills
- Lack of specialist-generalist communication
- Lack of perceived legitimacy
- Health care settings (hospitals, practices, etc.)
- Acute care priority
- Lack of resources and facilities
- Lack of systems for preventive services
- Time and economic constraints
- Poor communication between specialty and primary care providers
- Lack of policies and standards
- Community/society
- Lack of policies and standards
- Lack of reimbursement

SOURCE: From Pearson TA et al.,[292] with permission.

Strategies to Improve Preventive Cardiology Services

IMPROVING PATIENT COMPLIANCE

While there is a pervasive tendency to blame the patient, health care providers can take a number of actions to improve their patients' compliance with the treatment regimen.[293,294] These include (1) encouragement to engage in prevention and treatment behaviors essential to adherence with a regimen, such as acceptance and understanding of the need to control risk factors, (2) establishment of specific behavioral or physiological goals, (3) skills training of patients for adopting and maintaining the recommended behaviors, (4) recommending self-monitoring of progress toward the goals, and (5) helping patients anticipate and resolve problems that keep the goals from being realized. This will require regular communication between providers and patients about the goals and actions agreed upon.[293]

IMPROVING PERFORMANCE BY HEALTHCARE PROVIDERS

Providers must foster effective communication with both their patients and other health professionals on the preventive cardiology team.[293] Strategies to improve this communication include verbal and written instructions, negotiation of goals and a plan with the patient, and anticipation of barriers to successful attainment of goals. There also must be documentation and monitoring of progress toward goals, with assessment of patient compliance at each visit and reminder systems (e.g., listing smoking status as a vital sign) to assure that risk factors are identified and attended to. One barrier to physician action in this area is a perceived lack of legitimacy by cardiovascular specialists for involvement in risk factor management. *Professional societies counter this problem by strongly recommending that risk factor management be part of the optimal care of patients at high risk for cardiovascular disease and therefore be the responsibility of all health care providers.*[1]

IMPROVING THE INPATIENT CARE SETTING

The admission to an inpatient unit provides an enormous opportunity for risk behavior change that should not be missed, for several reasons. First, the opportunity to reduce short-term risk in patients following infarction or revascularization has not been extensively studied, but several interventions such as antiplatelet therapy, ACE inhibitors, beta blockers, and even lipid management appear to provide benefit within days or weeks. Second, the patient and family are aroused to the risk of disability and death, and their receptivity to behavior-change messages is likely highest at this time. Finally, the message communicated to the patient and their primary care provider is that behavior change is an important, integral part of their postcoronary care, along with revascularization and pharmacotherapy.

The inpatient setting can be reorganized to provide efficient risk factor assessment and management. The joint AHA/American College of Cardiology (ACC) guidelines for comprehensive risk reduction for patients with coronary and other vascular disease provide a convenient list of risk factor goals and modification strategies (Table 38-12).[167] These can be transcribed onto a simple checklist or more elaborate care protocols. The cardiovascular specialist should confirm the diagnosis of prevalent risk factors, set goals for treatment, and integrate a treatment plan into the overall regimen of care. However, the physician is often not the best person to carry out the plan, due in part to time constraints, acute care focus, and short hospital length of stay. A better model is the multidisciplinary

team approach, with nurses, nutritionists, and exercise physiologists assigned specific tasks for the patient's care. A strategy with proven effectiveness is the nurse case-manager approach, with a nurse initiating care in the hospital and following the patient to the ambulatory care setting. In one randomized trial of this approach, smoking cessation, LDL-cholesterol levels, and aerobic capacity all improved in patients assigned to a system of nurse case management, as compared with usual care.[295]

Table 38-12: American Heart Association Guide to Comprehensive Risk Reduction for Patients with Coronary and Other Vascular Disease

Risk Intervention	Recommendations
Smoking Goal complete cessation	Strongly encourage patient and family to stop smoking. Provide counseling, nicotine replacement, and formal cessation programs as appropriate.
BP control Goal <140/90 mmHg or <130/85 mmHg if heart failure, renal insufficiency or diabetes.	Initiate lifestyle modification—weight control, physical activity, alcohol moderation, and moderate sodium restriction—in all patients with blood pressure ≥130 mmHg systolic or 85 mmHg diastolic. Add blood pressure medication, individualized to other patient requirements and characteristics (i.e., age, race, need for drugs with specific benefits) if blood pressure is not less than 140 mmHg systolic or 90 mmHg diastolic or if blood pressure is not <130 mmHg systolic or 85 mmHg diastolic for individuals with heart failure, renal insufficiency, or diabetes.
Lipid management Primary goal LDL <100 mg/dL Secondary goals HDL >35 mg/dL; TG <200 mg/dL	Start AHA Step II Diet in all patients: ≤30% fat, <7% saturated fat, <200 mg/ day cholesterol and promote physical activity. Assess fasting lipid profile. In post-MI patients, lipid profile may take 4 to 6 weeks to stabilize. Add drug therapy according to the following guide:

LDL <100 mg/dL	LDL 100 to 130 mg/dL	LDL > 130 mg/dL	HDL <35 mg/dL
No drug therapy	Consider adding drug therapy to diet, as follows:	Add drug therapy to diet, as follows:	Emphasize weight management and physical activity. Advise smoking cessation. If needed to achieve LDL goals, consider niacin, statin, fibrates.

Suggested drug therapy		
TG <200 mg/dL	TG 200 to 400 mg/dL	TG >400 mg/dL
Statin Resin Niacin	Statin Niacin	Consider combined drug therapy (niacin, fibrates, statin)

	If LDL goal not achieved, consider combination drug therapy.
Physical activity Minimum goal 30 min 3 to 4 times per week	Assess risk, preferably with exercise test, to guide prescription. Encourage minimum of 30 to 60 min of activity 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work). Maximum benefit 5 to 6 h a week. Advise medically supervised programs for moderate- to high-risk patients.
Weight management Goal BMI 21–25 kg/m^2	Measure patient's weight and height, BMI, and waist-to-hip ratio at each visit as part of routine evaluation. Start weight management and physical activity as appropriate. Desirable BMI range: 21–25 kg/m^2. Desirable waist circumference <40 inches in men and <36 inches in women.
Diabetes	Appropriate hypoglycemic therapy to achieve near normal fasting plasma glucose as indicated by HbA_{1c}.

management	Treatment of other risks (e.g., physical activity, weight management, blood pressure) and for cholesterol manage-
Near normal fasting plasma glucose and near normal HbA_{1c}(<7)	ment see recommendations above.
Antiplatelet agents/ anticoagulants	Start aspirin 80 to 325 mg/day if not contraindicated. Consider clopidogrel as an alternative if aspirin contraindicated.
	Manage warfarin to international normalized ratio = 2 to 3.5 post-MI patients not able to take aspirin.
ACE inhibitors post-MI	Start early post-MI in stable high-risk patients [anterior MI, previous MI, Killip class II (S_3 gallop, rales, radiographic CHF)].
	Continue indefinitely for all with LV dysfunction (ejection fraction ≤40%) or symptoms of failure.
	Use as needed to manage blood pressure or symptoms in all other patients.
Beta blockers	Start in high-risk post-MI patients (arrhythmia, LV dysfunction, inducible ischemia) at 5 to 28 days. Continue 6 months minimum. Observe usual contraindications.
	Use as needed to manage angina, rhythm, or blood pressure in all other patients.
Estrogens	Estrogen replacement: individualize consistent with other health risks.

ABBREVIATIONS: ACE = angiotensin-converting enzyme; AHA = American Heart Association; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; MI = myocardial infarction; TG = triglycerides; CHF = congestive heart failure.
SOURCE: Adapted from Gibbons et al.,[137] and Smith et al.,[56] with permission.

IMPROVING THE AMBULATORY CARE SETTING

The AHA guidelines for primary prevention of cardiovascular diseases (Table 38-13) and for comprehensive risk reduction for patients with coronary and other vascular disease (Table 38-12) provide clear risk factor goals and risk-reduction strategies.[168] The office or clinic should strive to develop an environment supportive of risk factor management, including staff trained in behavior-modification skills, follow-up protocols, and tracking systems and reminders. A clear assignment of tasks and responsibilities is important, with defined roles for the physician, nurse, nutritionist, and even receptionist.

Table 38-13: American Heart Association Guide to Primary Prevention of Cardiovascular Diseases

Risk Intervention	Recommendations
Smoking Goal complete cessation	Ask about smoking status as part of routine evaluation. Reinforce nonsmoking status. Strongly encourage patient and family to stop smoking. Provide counseling, nicotine replacement, and formal cessation programs as appropriate.
Blood pressure control Goal <140/90 mmHg or <130/85 mmHg if heart failure, renal insufficiency or diabetes	Measure blood pressure in all adults at least every 2 years. Promote lifestyle modification: weight control, physical activity, moderation in alcohol intake, and moderate sodium restriction. If blood pressure ≥140/90 mmHg after 6 months of lifestyle modification or if initial blood pressure >160/100 mmHg or >130/85 mmHg with heart failure, renal insufficiency or diabetes, add blood pressure medication. Individualize therapy to patient's age, race, need for drugs with specific benefits, etc.
Cholesterol management Primary goal LDL <160 mg/dL if 0–1 risk factors or LDL <130 mg/dL if ≥2 risk factors Secondary goals HDL >35 mg/dL; TG <200 mg/dL	Ask about dietary habits as part of routine evaluation. Measure total and HDL cholesterol in all adults ≥20 years and assess positive and negative risk factors at least every 5 years. For all persons: promote AHA Step I diet (≤30% fat, <10% saturated fat, <300 mg/day cholesterol), weight control, and physical activity. Measure LDL if total cholesteral ≥240 mg/dL or ≥200 mg/dL with ≥2 risk factors or if HDL <35 mg/dL. Risk factors: age (men ≥45 years, women ≥55 years or postmenopausal), hypertension, diabetes, smoking, HDL <35 mg/dL, family history of CHD in first-degree relatives (in male relatives <55 years, female relatives <65 years). HDL ≥60 mg/dL, subtract 1 risk factor from the number of positive risk factors. If LDL ≥160 mg/dL with 0–1 risk factors; or ≥130 mg/dL on 2 occasions with ≥2 risk factors; then Start Step II diet (≤30% fat, <7% saturated fat, <200 mg/dL cholesterol) and weight control. Rule out secondary causes of high LDL (LFTs, TFTs, UA). If LDL ≥160 mg/dL plus 2 risk factors; or ≥190 mg/dL; or ≥220 mg/dL in men <35 y; or in pre-menopausal women; then consider adding drug therapy to diet therapy for LDL levels > those listed above that persist despite Step II diet. Suggested drug therapy for high LDL levels (≥160 mg/dL) (drug selection priority modified according to TG level) TG <200 mg/dL: Statin, Resin, Niacin TG 200–400 mg/dL: Statin, Niacin TG >400 mg/dL: Consider combined drug therapy (niacin, fibrates, statin) HDL <35 mg/dL: Emphasize weight management and physical activity, avoidance of cigarette smoking. Niacin raises HDL. Consider niacin if patient has ≥2 risk factors and high LDL (except patients with diabetes). If LDL goal not achieved, consider combination drug therapy.
Physical activity Goal Exercise regularly 3–4 times per week for 30–60 min	Ask about physical activity status and exercise habits as part of routine evaluation. Encourage 30 min of vigorous-intensity dynamic exercise 3 to 4 times per week as well as increased physical activity in daily life style activities (e.g., walking breaks at work, gardening, household work). Advise medically supervised programs for those with low functional capacity and/or comorbidities.
Weight management Goal BMI 21–25 kg/m^2	Measure patient's weight and height, BMI, and waist-to-hip ratio at each visit as part of routine evaluation. Start weight management and physical activity as appropriate. Desirable BMI range: 21–25 kg/m^2. Desirable waist circumference <40 inches in men and <36 inches in women.
Diabetes management:	Appropriate hypoglycemic therapy to achieve near normal fasting plasma glucose as indicated by HbA_{1c}. Treatment of other risks (e.g., physical activity, weight management, blood pressure and for cholesterol manage-

Near normal fasting plasma glucose and near normal HbA_{1c} (<7)	ment see recommendations for patients with coronary disease on other side.)
Estrogens	Consider estrogen replacement in all postmenopausal women, especially those with multiple CHD risk factors. Individualize recommendation consistent with other health risks.

ABBREVIATIONS: BMI = body mass index (704.5); CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LFT = liver function test; TFT = thyroid function test; TG = triglycerides; UA = uric acid.
SOURCE: Adapted from Grundy et al.,[166] with permission.

A number of specialty units might be convenient platforms for risk factor management. Cardiac rehabilitation has been documented, in meta-analyses of randomized clinical trials, to reduce coronary disease recurrence and death significantly, especially when the service includes risk factor modification.[164] The patients' extended exposure (after 12 weeks or longer) to a supportive environment provides the opportunity for behavior change, monitoring, and reinforcement. Likewise, a nurse case-manager program with extension to the ambulatory care setting provides long-term continuity and support for meaningful behavior change.[295]

IMPROVING THE HEALTH SYSTEM

Supportive of this are a large number of guidelines from professional societies, expert bodies, and governmental agencies that support preventive cardiology practices. The joint AHA/ACC guidelines in risk reduction[167] are coordinated with more extensive guidelines for individual risk factors, including hyperlipidemia,[8] hypertension,[132] smoking,[296] cardiac rehabilitation,[297] and obesity.[49] These provide clear recommendations for health care providers as to the goals and scenarios required for optimal risk reduction. Increasingly, these guidelines are being used in quality assurance programs that use provision of preventive services and attainment of risk factor goals as quality-of-care indicators. The use of preventive cardiology services as such quality indicators has motivated health care systems to implement the reorganization and reallocation of resources that have been shown to be effective in improving preventive cardiology care.

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Chapter 38: DYSLIPIDEMIA, OTHER RISK FACTORS, AND THE PREVENTION OF CORONARY HEART DISEASE

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Part 6: CORONARY HEART DISEASE
Chapter 39:

NONATHEROSCLEROTIC CORONARY HEART DISEASE

Author: Bruce F. Waller

Although atherosclerotic disease of the coronary arteries is the most common cause of luminal narrowing and coronary heart disease, there are multiple nonatherosclerotic (congenital and acquired) causes of severe luminal narrowing and subsequent clinical coronary events (angina pectoris, acute myocardial infarction, and sudden death) (Table 39-1).

Table 39-1: Nonatherosclerotic Causes of Coronary Artery Disease (Coronary Heart Disease)

Congenital anomalies	Metabolic disorders
Anomalous origin from the aorta	Mucopolysaccharidoses (Hurler, Hunter)
Right-from-left sinus of Valsalva	Homocystinuria
Left-from-right sinus of Valsalva	Fabry's disease
Single coronary artery	Amyloid
Atresia of coronary ostium	Intimal proliferation
High-takeoff coronary ostium	Irradiation therapy
Ostial ridges	Cardiac transplantation
Anomalous origin from the pulmonary trunk	Fibromuscular hyperplasia (methysergide therapy)
Fistula	Ostial cannulation
Myocardial bridges (tunneled epicardial artery)	Transluminal balloon angioplasty
Embolus Natural	Idiopathic infantile arterial calcification (juvenile internal sclerosis)
Thrombus	Cocaine
Tumor	External compression
Calcium	Aortic aneurysm
Vegetation (infective, noninfective)	Tumor metastases
Iatrogenic	Muscle bridges
Cardiac surgery	Thrombosis without underlying atherosclerotic plaque
Cardiac catheterization	Polycythemia

Coronary angioplasty	Thrombocytosis
Prosthetic valves	Hypercoagulability
Paradoxical	Substance abuse
Dissection	Cocaine
Coronary artery	Amphetamines
Aortic	Myocardial oxygen demand-supply disproportion
Spasm	Aortic stenosis
Trauma	Systemic hypotension
Nonpenetrating	Carbon monoxide poisoning
Penetrating	Increased myocardial function (thyrotoxicosis)
Surgery	Intramural coronary artery disease (small vessel disease)
Catheterization	Hypertrophic cardiomyopathy
Arteritis	Amyloid
Takayasu's disease	Cardiac transplantation
Polyarteritis nodosa	Neuromuscular
Systemic lupus erythematosus	Diabetes mellitus
Kawasaki's syndrome (mucocutaneous lymph node syndrome)	Normal coronary arteries
Syphilis	
Other infections (infective endocarditis, *Salmonella*, parasites)	
Buerger's disease	
Giant-cell arteritis	

SOURCES: Adapted from Waller,[1] Alpert and Braunwald,[2] Cheitlin et al.,[4] and Baim and Harrison.[5]

Various nonatherosclerotic coronary artery diseases can reduce or interrupt coronary arterial blood flow by various mechanisms: (1) fixed luminal obstructions (internal narrowing), (2) encroachment of the lumen by disease of the arterial wall or adjacent tissues (external narrowing), or (3) both.[1] Reduction in coronary arterial blood flow also may result from dynamic changes in the walls of an otherwise normal artery (spasm) or from a disproportion of myocardial oxygen supply and demand. In view of current trends toward rapid coronary artery reperfusion to salvage jeopardized myocardium during evolving acute myocardial infarction, the various nonatherosclerotic etiologies of coronary artery disease must be kept in mind.

FREQUENCY OF NONATHEROSCLEROTIC CORONARY NARROWING PRODUCING FATAL MYOCARDIAL INFARCTION

Approximately 4 to 7 percent of all patients with acute myocardial infarction and nearly 4 times this percentage for patients under age 35 do not have atherosclerotic coronary artery disease (CAD) as

demonstrated by coronary arteriography, at necropsy, or both.[1-5] In view of the fact that coronary angiography simply represents an image of one lumen, the specificity for etiology of the coronary luminal narrowing is extremely low. Review of necropsy studies[1,3,4] suggests that approximately 95 percent of patients with fatal acute myocardial infarction have at least one major epicardial coronary artery with severe luminal narrowing or total occlusion (Fig. 39-1). The remaining 5 percent of patients apparently have normal major epicardial coronary arteries. Of the 95 percent of patients with severe coronary artery luminal narrowing, 95 percent have typical atherosclerotic plaque, with a superimposed thrombus in 85 percent of these.

The remaining 5 percent of the patients with severe coronary artery luminal narrowing have a host of etiologies (see Table 39-1), including coronary arteritis, trauma, systemic metabolic disorders, intimal fibrous proliferation, and coronary emboli. Medical centers with large populations of cardiac transplant patients will exceed the 5 percent nonatherosclerotic approximation owing to the high frequency of intimal fibrous proliferation in the coronary arteries late after transplantation. Of the 5 percent of patients seen at necropsy after fatal acute myocardial infarction with normal or nearly normal epicardial coronary arteries, perhaps 50 to 60 percent represent clinical coronary spasm, but the remaining 40 to 50 percent represent a combination of congenital coronary artery anomalies, spontaneous recanalization, and mismatches of coronary supply and myocardial demand (see also Chap. 35).

NEXT

Chapter 39: NONATHEROSCLEROTIC CORONARY HEART DISEASE

CONGENITAL CORONARY ARTERY ANOMALIES

Variation in the origin, course, or distribution of the epicardial coronary arteries is found in 1 to 2 percent of the population[1,6-14] (Table 39-2 and Fig. 39-2). Certain types of these anomalies-including ostial lesions, passage of a major artery between the walls of the pulmonary trunk, a major coronary artery originating from the pulmonary trunk, or perhaps myocardial bridges-may produce ischemia with subsequent myocardial infarction[8] (see also Chaps. 15 and 63).

Table 39-2: Certain Coronary Arterial Anomalies Associated with Clinical Coronary Events or Coronary Artery Narrowing

Anomalous origin of one or more coronary arteries from the aorta	High-takeoff coronary ostia	Ostial narrowing
Origin of both right (R) and left (L) from same sinus of Valsalva R + LM (left main) from right sinus	Syphilis	Takayasu's disease (pulseless disease)
R + LM (left main) from left sinus	Single coronary artery	Fibromuscular hyperplasia (drug-induced)
Arising from right sinus Arising from left sinus Arising from posterior sinus	Aortic valve surgery	Fibrous ridges Protruding masses
Anomalous origin of one or more coronary arteries from pulmonary trunk (PT)	Calcific nodules	Supravalvular aortic stenosis
Origin of R from PT Origin of LM from PT Origin of left anterior descending from PT	Aortic dissection wall	Adhesion of aortic cusp to sinus Embolism
Origin of left circumflex from PT	Fibroelastosis	
Coronary artery atresia Atresia of R Atresia of LM	Coronary artery fistula	Myocardial bridges

Origin of Both Right and Left Coronary Arteries from the Same Sinus of Valsalva

When either the right or left coronary artery arises from the left or right sinus of Valsalva, respectively, the anomalous vessel transverses the base of the heart in a course anterior to the pulmonary trunk, posterior to the aorta, or between the aorta and the pulmonary trunk (Figs. 39-3 and 39-4). At least 43 cases have been reported with necropsy where the origin of the left main coronary artery is from the right sinus with passage between the aorta and pulmonary trunk.[7] In 79 percent of these patients,[3,4] death was related to the anomaly with sudden death or an

acute myocardial infarction. At necropsy, 5 of 26 patients younger than 20 years old had myocardial infarcts.[7] When the right coronary artery originates from the left sinus of Valsalva and passes between the aorta and the pulmonary trunk, symptoms of myocardial ischemia, infarction, or sudden death may occur.[7] Of 12 patients with this anomaly,[9] 3 died suddenly, and 2 had angina or syncope. At necropsy, transmural ventricular scars (healed infarction) were seen in 2.

The mechanism of ischemia, infarction, and/or sudden death in this coronary anomaly appears related to the shape of the coronary ostium of the anomalous vessel (Fig. 39-4). Normally, the coronary ostia are round to oval in shape, but in this anomaly, the coronary artery has an acute angle of takeoff that makes the ostium slitlike in shape. With increased cardiac output, the aorta dilates with stretching of the aortic wall so that this slitlike ostium may become severely narrowed (see Figs. 39-3 and 39-4). Similar mechanisms of coronary ischemia with exercise and aortic dilatation occur in case of the presence of a very acute angle of takeoff of the left main coronary artery (see Fig. 39-5) or of valvelike ridges at the ostia (see Fig. 39-6). It is unlikely that there is "compression" of the anomalous coronary artery by the aorta and pulmonary trunk in view of the marked differences in diastolic pressures. At best, there would be an anterior shift of the anomalous vessel rather than a viselike compression.

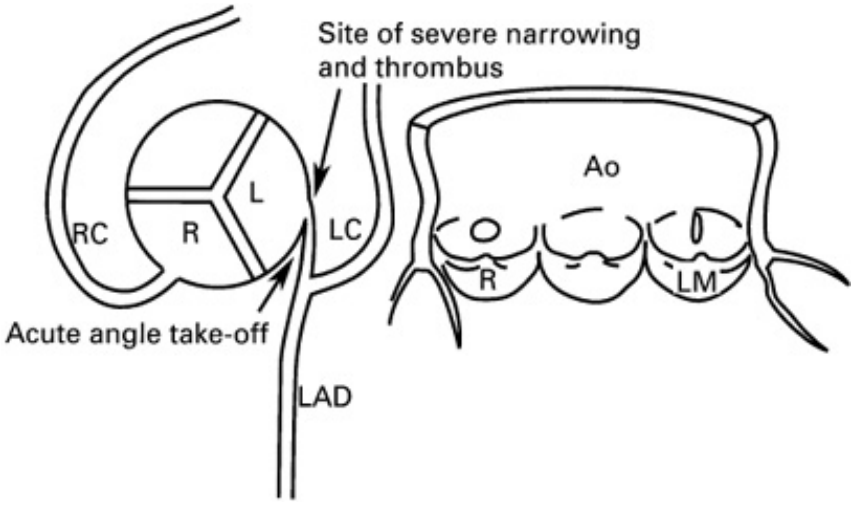

Figure 39-5: Diagram showing acute-angle takeoff of the left main coronary artery with ostial ridge and slitlike orifice. The proximal left main coronary artery is occluded by atherosclerotic plaque and thrombus, but the remaining vessels are normal. Accelerated coronary atherosclerosis may result from the acute-angle takeoff malformation. Ao, aorta; L, left cusp; LM, left main; LC, left circumflex; LAD, left anterior descending; R, right cusp; RC, right coronary. (From Menke et al.[11] Reproduced with permission from the publisher and author.)

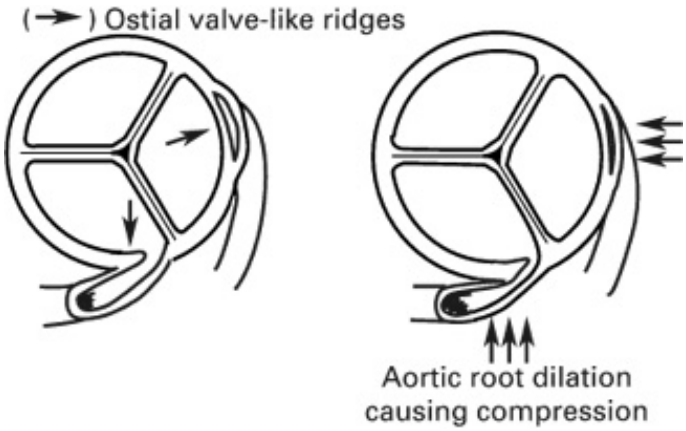

Figure 39-6: Diagram illustrating ostial valvelike ridges and the proposed mechanism of ostial compression with aortic root dilatation. (From Virmani et al.[12] Reproduced with permission from the publisher and author.)

Single Coronary Artery

Origin of the entire coronary circulation from a single aortic ostium has been termed *single coronary artery*. This anomaly is rare in the absence of other associated anomalies of the heart. One or more branches of the single artery may cross the base of the heart in a fashion described above and thus may be exposed to the risks of ischemia owing to acute angulation.[5] Angina pectoris and myocardial lactate production have been demonstrated in patients with single coronary arteries in whom coronary atherosclerosis or an anomalous coronary artery passage was absent[13] (see also Chap. 63).

Coronary Artery Atresia

Atresia of one of the two main coronary ostia may be associated with myocardial ischemia and infarction in infancy or childhood.[5] The involved vessel becomes dependent on collateral coronary blood flow from the contralateral coronary artery.

High-Takeoff Coronary Ostia

Normally, the coronary ostia are located within the sinuses of Valsalva, which optimizes coronary arterial blood flow in diastole. Location of the ostia in the tubular portion of the aorta (i.e., high-takeoff position) may be associated with decreased coronary perfusion (Figs. 39-7 and 39-8). Morphologic evidence of chronic ischemia has been reported in a patient with a high-takeoff right coronary artery who had right ventricular (RV) and left ventricular (LV) wall scarring.[14,15] High-takeoff position of the coronary ostium also has been postulated as a cause of sudden coronary death.[16] In a series of 54 major and minor coronary artery anomalies,[17] both coronary artery ostia arose above the sinotubular junction in 2, the right coronary artery ostium arose high in 5, and the left coronary artery ostium was in a high-takeoff position in 3. In 2 cases of high origin of the right coronary artery ostium, ischemia and death were attributed to the ostial lesion in 1.[18]

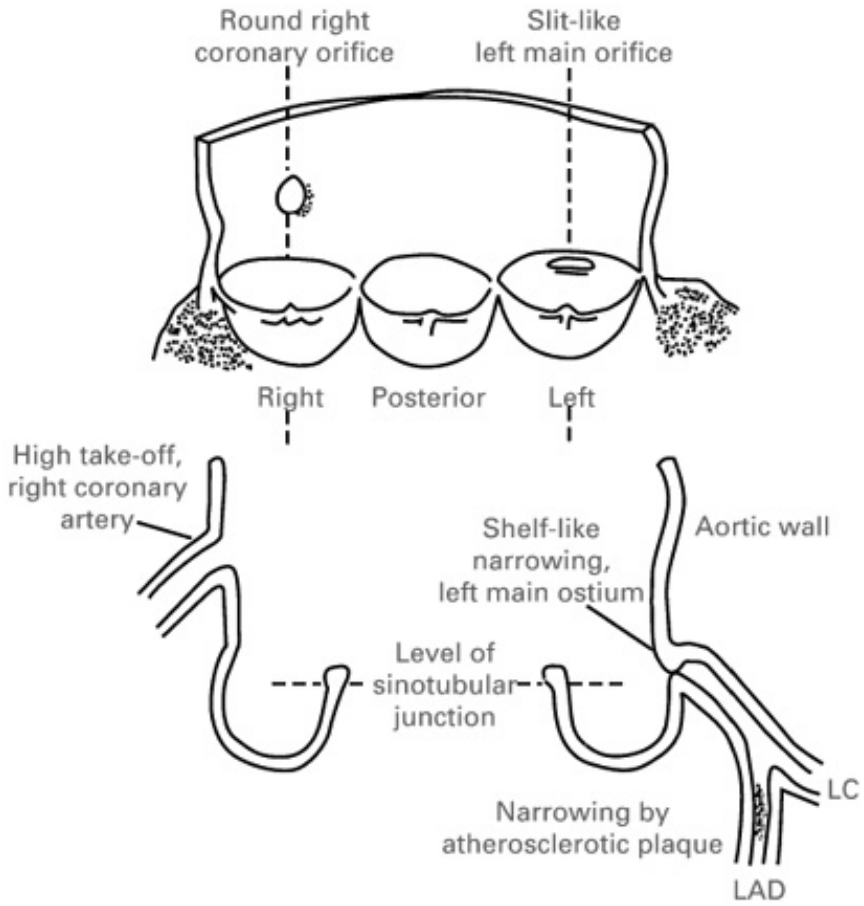

Figure 39-7: Diagram showing high-takeoff position of the right coronary artery and the nonatherosclerotic fibrous ridge occluding the left main coronary ostium. LAD, left anterior descending; LC, left circumflex. (From Foster et al.[14] Reproduced with permission from the publisher and author.)

Ostial Fibrous Ridges

Nonatherosclerotic causes of coronary ostial narrowing include syphilis,[19] Takayasu's disease (pulseless disease),[20] fibromuscular hyperplasia associated with methysergide therapy,[2122] aortic valve surgery with or without coronary artery cannulation,[14,23] and ostial valvelike ridges (see Fig. 39-7). A nonatherosclerotic fibrous shelflike ridge can project from the wall of aorta into the left main ostium.[14,15] It may have been responsible for chronic ischemia and myocardial necrosis. Other rare diseases that may narrow or occlude the coronary ostia have been summarized by Baroldi[24]: (1) a nonatheromatous, calcific protrusion from the sinotubular junction into the right or left ostium, (2) saccular aneurysm of the aorta, (3) aortic dissection extending into the coronary ostium-the right ostium involved more commonly than the left, (4) supravalvular aortic stenosis with severe intimal thickening, (5) obliteration of the ostium due to adhesion of the free edge of an aortic cusp to the aortic wall above the coronary ostium, (6) occlusion by embolus (see below), and (7) occlusive fibroelastosis.

Anomalous Origin of One or Two Coronary Arteries from the Pulmonary Trunk

Anomalous origin of a coronary artery from the pulmonary trunk (Figs. 39-9 and 39-10) may be responsible for myocardial ischemia and infarction in infants and children. In more than90 percent of cases,[5,7] the left main artery is the anomalous one; thus the anteroseptal and anterolateral LV myocardium may be at jeopardy for injury. Asymptomatic older patients with this coronary artery anomaly are usually found when they present with an abnormal

electrocardiogram (ECG), a systolic murmur, or sudden death.[7] The murmur and abnormal ECG are the result of papillary muscle and/or anteroseptal myocardial wall damage (see Chap. 42).

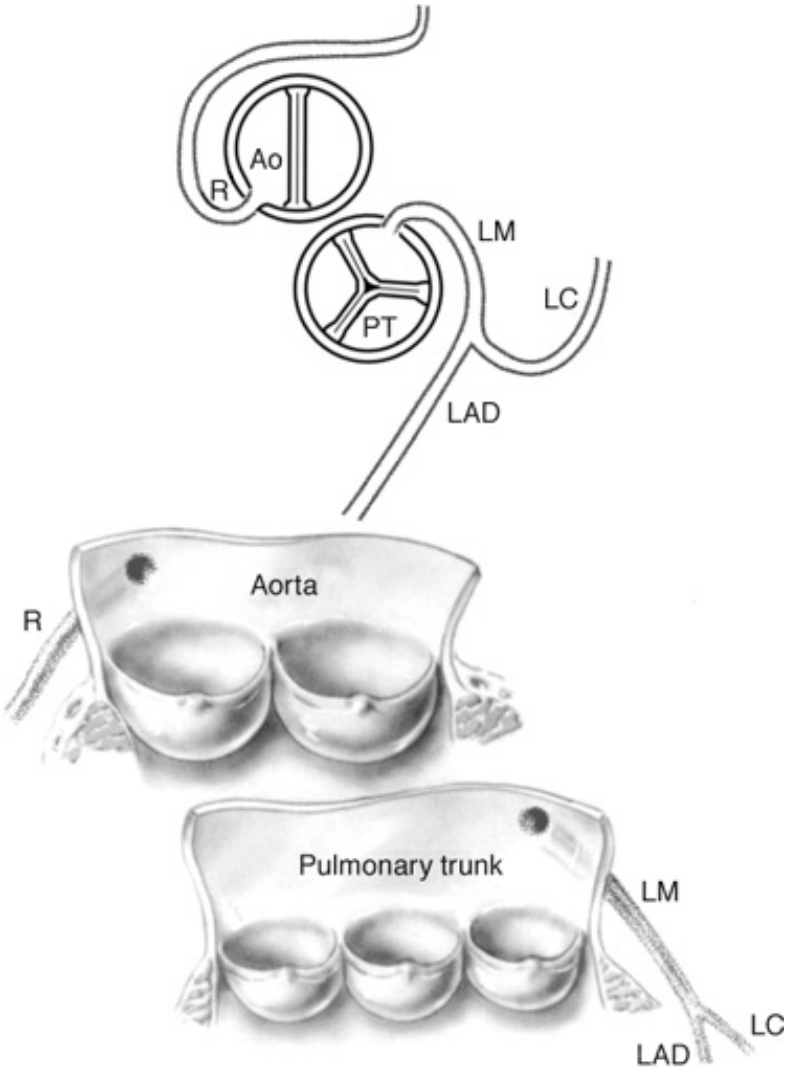

Figure 39-10: Anomalous origin of the main (LM) coronary artery from the pulmonary trunk causing acute myocardial infarction in an infant. Of interest is that both the anomalous LM and normal right coronary arteries arise in high-takeoff positions from the pulmonary trunk and aorta (Ao), respectively. LAD, left anterior descending; LC, left circumflex.

Myocardial Bridges (Tunneled Epicardial Coronary Artery)

The coronary arteries may dip into the myocardium for varying lengths and then reappear on the heart's surface (Figs. 39-11, 39-12, 39-13, 39-14, 39-15, 39-16, 39-17 and 39-18). The muscle overlying the intramyocardial segment of the epicardial coronary artery is termed a *myocardial bridge*, and the artery coursing within the myocardium is called a *tunneled artery*[25-63] (see Figs. 39-11, 39-12 and 39-13). Tunneled coronary arteries have long been recognized anatomically,[25] but suggested associations between myocardial ischemia and myocardial bridges have heightened their clinical relevance.[26,27]

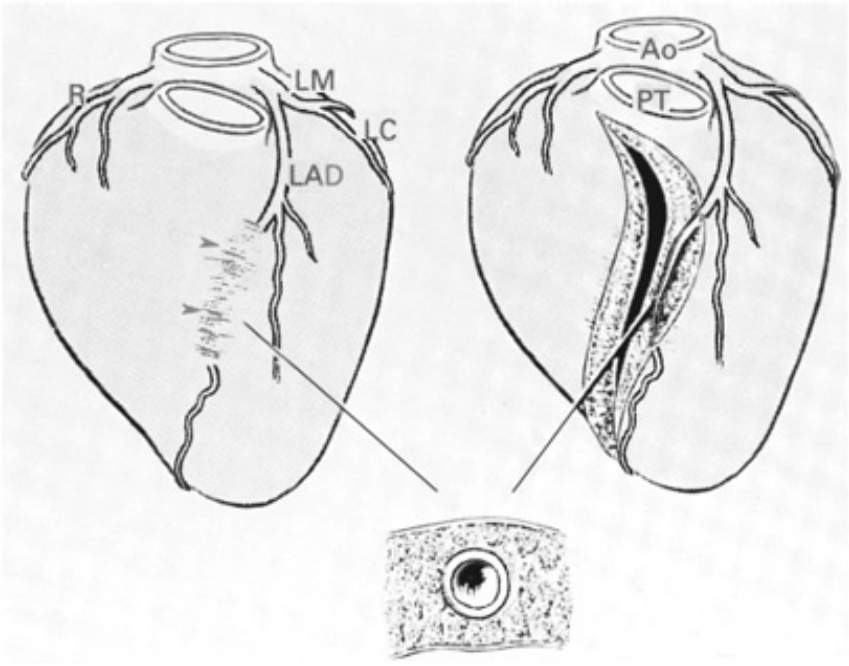

Figure 39-11: (*Left*) Diagram showing tunneled left anterior descending coronary artery (LAD) (*arrowheads*). (*Right*) Opened left ventricle showing intramyocardial segment. (*Below*) Transverse section of LV wall showing tunneled coronary artery surrounded by myocardium. (From Waller.[1] Reproduced with permission from the publisher, editor, and author.)

Tunneled coronary arteries have been presumed congenital in origin.[28] At least three factors have been postulated to account for differences between the high frequency of tunneled major coronary arteries observed at necropsy (5-86 percent[29,30,57]) and the lower frequency of tunneled coronary arteries observed angiographically (0.5-12 percent[26,31,32,58-60]) or associated with symptoms of myocardial ischemia (18 percent[32]): (1) length of the tunneled coronary segment, (2) degree of systolic compression, and (3) heart rate. Longer tunneled segments of coronary arteries,[27] more severe systolic diameter narrowing of the tunneled segment,[27] and tachycardia[33] may contribute to the production of myocardial ischemia with myocardial bridging (see Figs. 39-17 and 39-18). The length of coronary tunneling may not always be an important factor in causing myocardial ischemia, since three patients with left main intramyocardial tunneling of greater than 40 mm have been described without evidence of myocardial ischemia[34,35] (Fig. 39-19).

Treatment of symptomatic, clinically recognized myocardial bridges has involved beta and calcium-channel blockers (control of tachycardia and antispasmodic effects) and surgery. Several patients have now been reported[61-63] in which "supraarterial myotomy" (release of the myocardial bridge, excision of the myocardial bridge) has resulted in relief of symptoms and improvement in previously abnormal nuclear imaging tests. High-frequency intraoperative echocardiography has been used to image the intramyocardial coronary artery before and after surgical release.[61]

Coronary Artery Fistula

A *coronary artery fistula* is an abnormal communication between an epicardial coronary artery and a cardiac chamber, major vessel (vena cava, pulmonary veins, pulmonary artery), or other vascular structure (mediastinal vessels, coronary sinus)[5,64-113] (Fig. 39-20). This infrequent abnormality can affect persons of any age and is the most important hemodynamically significant coronary artery anomaly.[5,64-113] Many are small and found incidentally during coronary arteriography, whereas others are identified as the cause of a continuous murmur, myocardial ischemia and angina, acute myocardial infarction, sudden death, coronary steal, congestive heart

failure, endocarditis, stroke, arrhythmias, coronary aneurysm formation (rupture, emboli), or superior vena cava syndrome.[64-76] Of over 33,000 patients undergoing coronary arteriography,[34] coronary artery fistula occurred in 0.1 percent,[76] whether due to congenital[77-85] or acquired causes[76-113] (Table 39-3). Fistulas from the right coronary artery are more common than from the left,[64-113] and over 90 percent of the fistulas drain into the venous circulation.[64-113] Most fistulas are single communications, but multiple fistulas have been identified.[106] The natural history of coronary artery fistulas is variable, with long periods of stability in some and sudden onset or gradual progression of symptoms in others. Spontaneous closure is uncommon.[106-108] Surgical repair of the fistula is recommended for symptomatic patients and for those asymptomatic patients at risk for future complications (coronary steals, aneurysms, large shunts).[109-112] Transcatheter embolization of fistulas has been reported.[113] Direct connection between a major epicardial coronary artery and a cardiac chamber or major vessel (vena cava, coronary sinus, pulmonary artery) is the most common hemodynamically significant coronary artery anomaly[5] (see Fig. 39-19). Myocardial ischemia has been documented in some patients with coronary artery fistulas who have no evidence of coronary atherosclerosis.[5]

Table 39-3: Causes and Associations of Coronary Artery Fistula

I. Congenital[77-85]

1. Embryonic
2. Multiple; systemic hemangioma

II. Acquired

1. Closed-chest ablation of accessory pathway[86]
2. Percutaneous coronary balloon angioplasty[87-89]
3. Hypertrophic cardiomyopathy[90]
4. Right/left ventricular septal myectomy[101]
5. Penetrating and nonpenetrating trauma[102-104]
6. Acute myocardial infarction[91,93]
7. Dilated cardiomyopathy[94]
8. Mitral valve surgery[95]
9. 'Sign' of mural thrombus[96]
10. Tumor[100]
11. Permanent pacemaker placement[99]
12. Cardiac transplant[92]
13. Endomyocardial biopsy[97,98]
14. Coronary artery bypass grafting[105]

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Chapter 39: NONATHEROSCLEROTIC CORONARY HEART DISEASE

CORONARY ANEURYSMS

Aneurysm formation of the coronary arteries may result from congenital or acquired conditions. Congenital coronary artery aneurysms are found most commonly in the right coronary artery.[114] Abnormal flow patterns within the aneurysm may lead to thrombus formation with subsequent vessel occlusion, distal thromboembolization, and myocardial infarction.[115] In general, angina pectoris or acute myocardial infarction present in patients younger than 20 years of age should prompt suspicion of a congenital coronary artery anomaly or a congenital coronary artery aneurysm.[114] Coronary artery aneurysms are found in about 1.5 percent of patients studied at necropsy or by coronary arteriography.[37] Coronary artery aneurysms, which may be multiple, can be congenital or the result of atherosclerosis, trauma, angioplasty, atherectomy, laser procedures, arteritis (including syphilis), mycotic emboli, mucocutaneous lymph node syndrome (Kawasaki's disease), systemic lupus erythematosus,[116] or dissection (spontaneous or secondary) (Table 39-4). Atherosclerosis-induced aneurysms are thought to result from primary thinning and/or destruction of the media and may represent up to 50 percent of the causes (see Table 39-4). Angioplasty, atherectomy, vasculitis, and arteritis also may damage the arterial wall (media) and lead to coronary aneurysms.

Table 39-4: Causes of Coronary Arterial Aneurysms

Atherosclerosis (destruction of coronary media)
Trauma
Angioplasty
Atherectomy
Laser
Arteritis (including syphilis, lupus erythematosus)
Mycotic emboli
Mucocutaneous lymph node syndrome (Kawasaki's disease)
Congenital
Dissection
Neoplasm
Connective tissue disorders (Ehlers-Danlos, Marfan's)

Chapter 39: NONATHEROSCLEROTIC CORONARY HEART DISEASE

CORONARY ARTERY EMBOLI

Coronary arterial emboli (Figs. 39-21 to 39-25) are clinically suspected in patients who develop severe chest pain with acute myocardial infarction in the presence of a prosthetic left-sided valve, active infective endocarditis, native left-sided valve stenosis, atrial fibrillation, LV aneurysm, dilated cardiomyopathy (see Fig. 39-22), known cardiac tumor, or during cardiac catheterization or cardiac surgery. Coronary emboli can be due to natural, iatrogenic, or "paradoxical" causes (Table 39-5; see also Figs. 39-21 to 39-25).[117-138] Coronary embolism most often involves the left anterior descending coronary artery.[36]

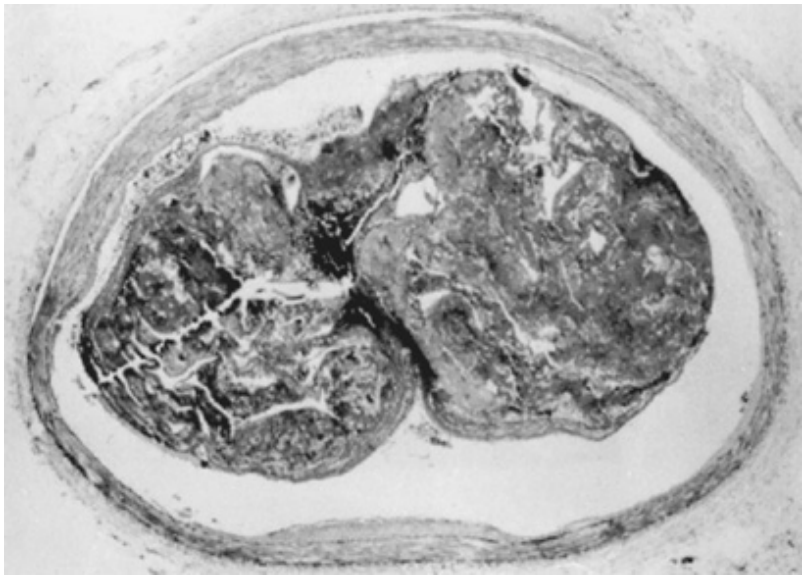


Figure 39-21: Coronary artery embolus. Fibrin-platelet thrombus occluding the left anterior descending coronary artery. The source of the embolus was not established, but the patient recently underwent cardiac surgery. (From Waller.[1] Reproduced with permission from the publisher, editor, and author.)

Table 39-5: Etiology of Coronary Artery Emboli

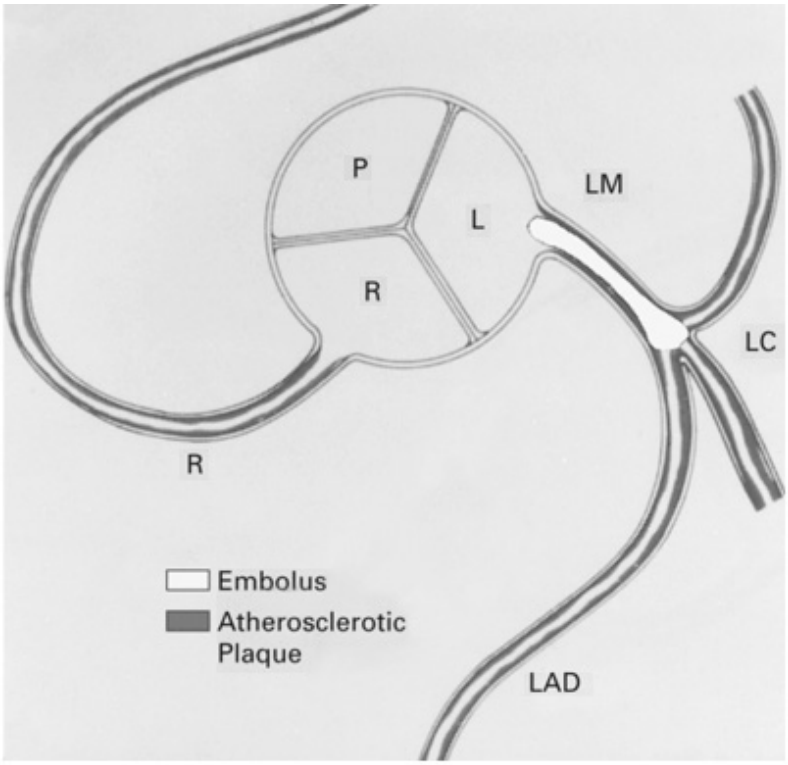
Natural	Iatrogenic
Vegetation Active infective endocarditis (native valve)	Cardiac surgery (ostial cannulization, prosthetic valve, patch repair)
Active infective endocarditis (prosthetic valve) Mural endocarditis	Cardiac catheterization and angiography (catheter thrombus, catheter fragments)
Noninfective (marantic) endocarditis Calcific deposit	Coronary angioplasty, other interventions, catheter balloon valvuloplasty and thrombolysis
Aortic valve stenosis Mitral valve stenosis	Prosthetic valves (thrombus, vegetation, occluders, leaflets, cloth covering, struts)

Intracardiac thrombus Left ventricle (myocardial infarction, cardiomyopathy, fibroelastosis with mural thrombus, ventricular aneurysm)	Cardioversion (left atrial thrombus, left ventricular thrombus) Cardiac resuscitation (thrombus)
Left atrium-appendage (low-cardiac-output states) Left atrium-body (mitral stenosis, native or prosthetic)	Trauma-blunt penetrating, nonpenetrating, foreign body (bullet)
Pulmonary veins (mitral stenosis)	'Paradoxical'
Intracardiac tumor Primary (myxoma)	Congenital heart disease (atrial septal defect, ventricular septal defect)
Secondary (extension from pulmonary veins, lymphatic extension, direct extension)	Probe patent foramen ovale defect (thrombophlebitis, right atrial catheters)
Coronary artery	Pulmonary hypertension (acquired atrial septal defect)
Plaque rupture (cholesterol)	Interatrial flap valve (fossa ovale aneurysm)
Thrombus dislodgment	

SOURCE: Waller.[1] Reproduced with permission from the author, editor, and publisher.

Coronary embolism is suspected as the cause of acute myocardial infarction when, at necropsy, the zone of necrosis is large but discrete (since there was little time to develop effective collaterals). Embolic coronary artery lesions can resolve completely and spontaneously and provide an explanation for angiographically normal coronary arteries several months following an acute myocardial infarction.[36]

The consequences of coronary embolism depend on two major factors (see Fig. 39-25): the size of the embolus and the size of the lumen of the artery in which it becomes impacted.[139,140] The smaller the embolus, the greater is the chance that it will travel distally to a small coronary arterial segment and the less is the likelihood of myocardial infarction or fatal arrhythmia.[139] An embolus so small that it travels distally and impacts in a single intramural vessel is probably clinically silent and observed only at necropsy.[139,140] The status of the coronary lumen before the embolus appears also determines the subsequent myocardial consequences. An embolus to a previously normal coronary artery is likely to migrate distally and result in localized myocardial infarction because of absence of collaterals. An embolus traveling to a previously diseased coronary artery is more likely to impact proximally. Emboli to the left main coronary arteries are rare but usually fatal[140] (see Fig. 39-24).



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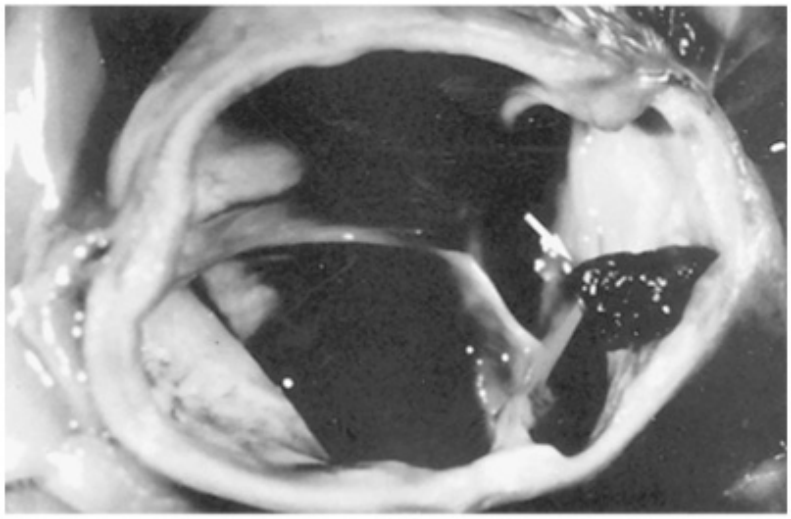

B

Figure 39-24: Coronary artery embolism. *A*. Diagram showing location and extent of occlusion of the left main (LM) coronary artery by an embolus. *B*. Photograph of aortic root showing embolus protruding from the LM coronary ostium (*arrow*). LAD, left anterior descending; LC, left circumflex; R, right. (From Waller et al.[140] Reproduced with permission from the publisher, editor, and author.)

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Chapter 39: NONATHEROSCLEROTIC CORONARY HEART DISEASE

CORONARY ARTERY DISSECTION

Separation of the media by hemorrhage with or without an associated intimal tear is termed *coronary artery dissection*. The medial separation forces the intimal-medial layer (wall of the true channel) toward the true coronary lumen and produces distal myocardial ischemia/infarction (Figs. 39-26 and 39-27). Coronary artery dissections may be primary or secondary[141-168] (Table 39-6). Secondary coronary artery dissections are more frequent, especially those associated as an extension from aortic root dissection (8 percent).[5] Primary coronary artery dissections may occur spontaneously or as a consequence of coronary angioplasty or angiography, cardiac surgery, or chest trauma (0.3 percent).[158] Most spontaneous coronary artery dissections occur in women who are most commonly postpartum; they may be associated with coronary artery wall eosinophils.[141-165] The left anterior descending artery is the one most frequently involved. Systemic hypertension does not appear to provide a significant factor of risk.[114]

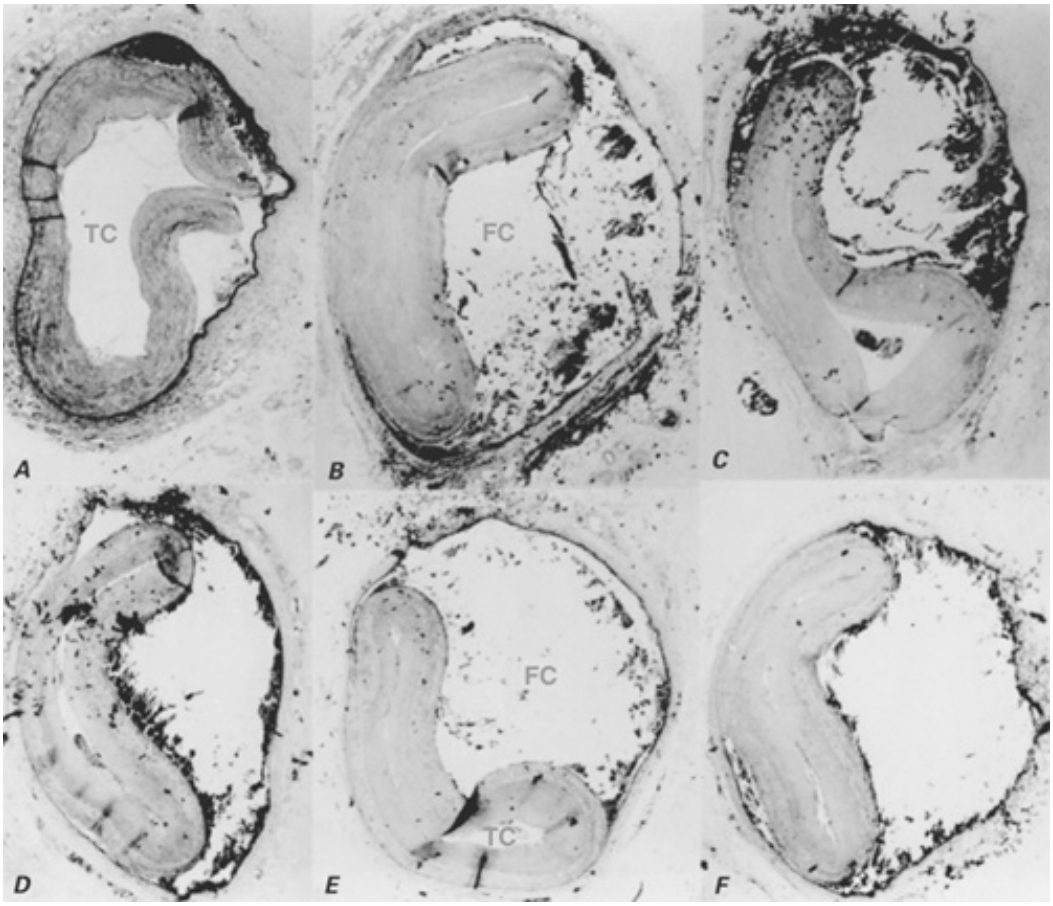

Figure 39-26: Coronary artery dissection. Serial cross section (*A-F*) showing dissection of the left anterior descending coronary artery. The true channel (TC) is severely compromised by external compression from the false channel (FC) ("dissection channel"). (From Waller.[1] Reproduced with permission from the publisher, editor, and author.)

Table 39-6: Causes of Coronary Artery Dissections[141-168]

I. Spontaneous
   A. Post- or peripartum[142,146,148,156,160,161,163,164,166,167]
   B. With or without eosinophilia[142,156,161,163]
   C. Idiopathic[145,150-152,154,158,159,162,163,165]
   D. Systemic hypertension[155]
   E. Coronary spasm
   F. Aortic root dissection[163] (hyperten-sion, medial degeneration)
   G. Arteritis[162]
   H. Fibromuscular hyperplasia

II. Trauma
   A. Post- or peripartum[146,148,160,164,167]
   B. Blunt chest[157] (penetrating, nonpene-trating)
   C. Coronary angiography[153]
   D. Coronary interventions[147,168] (angi-oplasty, atherectomy, laser, stenting,rotablade)
   E. Cardiac surgery (coronary bypass, cor-onary ostial cannulation, endarter-ectomy)
   F. Aortic root dissection[149] (surgery, non-penetrating, penetrating)

Spontaneous coronary artery dissection may result in sudden death or acute myocardial infarction and subsequent death. Parenthetically, localized and limited coronary artery dissection (i.e., intimal-medial tear) appears necessary for a clinically successful coronary artery balloon angioplasty procedure[143,144] (see also Chap. 45).

Coronary angioplasty dissections viewed in short- or long-axis tomographic images help distinguish dissections that are *therapeutic* (mechanism) from those which are *complications of angioplasty* (complications).[168] In the short-axis image, dissection involving more than 50 percent of the coronary medial circumference has been considered a complication. Similarly, in the long-axis image, dissections (antegrade, retrograde, or both) longer than 1 cm in length also have been defined as a complication of angioplasty (Fig. 39-28). A combination of dissection greater than 50 percent of the short-axis circumference and greater than 1 cm antegrade or retrograde of long-axis length may result in "intussusception" of intimal-medial tissue. Spiral dissections ("the ugly") are among the most serious dissection injuries after balloon angioplasty (Fig. 39-29). The spiral dissection as reviewed angiographically appears to alternate from side to side, extending antegrade and retrograde (see Fig. 39-29*A*), or it has an unaltered dissection course but appears alternating from limited angiographic views (see Fig. 39-29*B*).

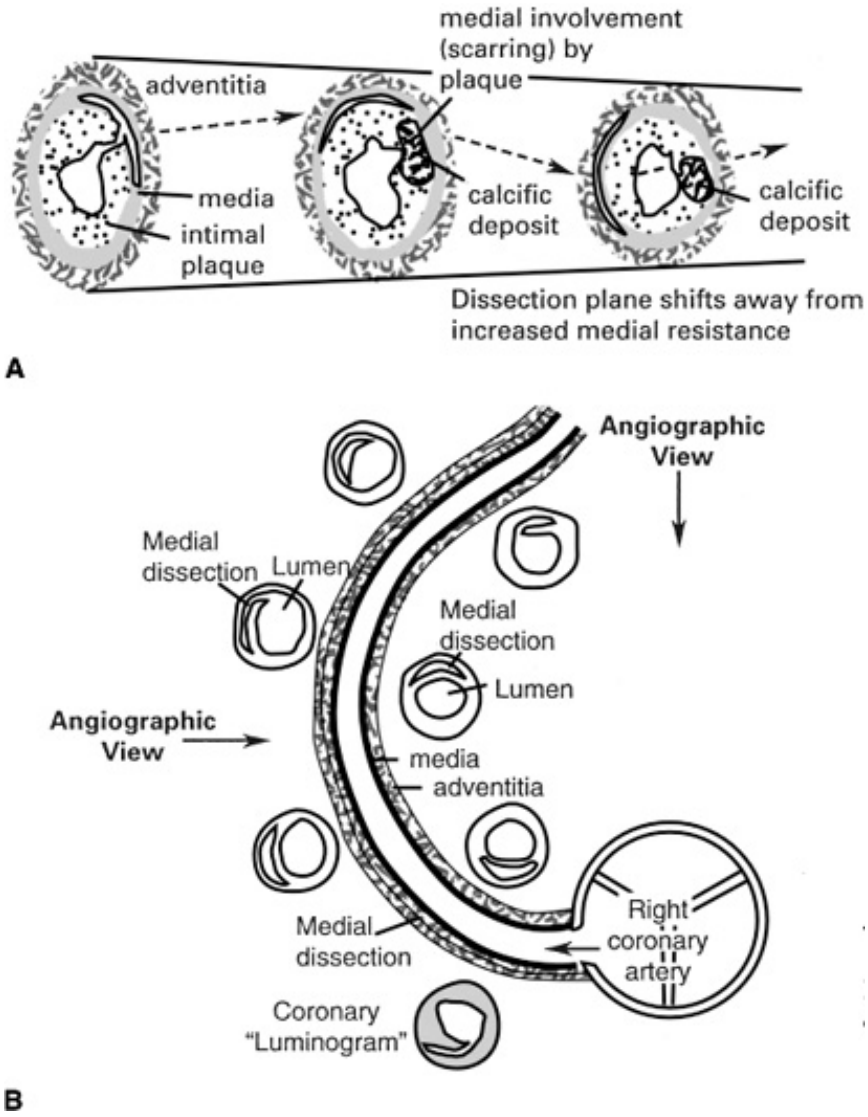

Figure 39-29: Diagram showing pathologic change accounting for angiographic appearance of coronary artery "spiral" dissection. *A.* Alteration in course of dissection. *B.* Angiographic appearance of unaltered course of dissection. (From Waller et al.[168] Reproduced with permission from the author, editor, and publisher.)

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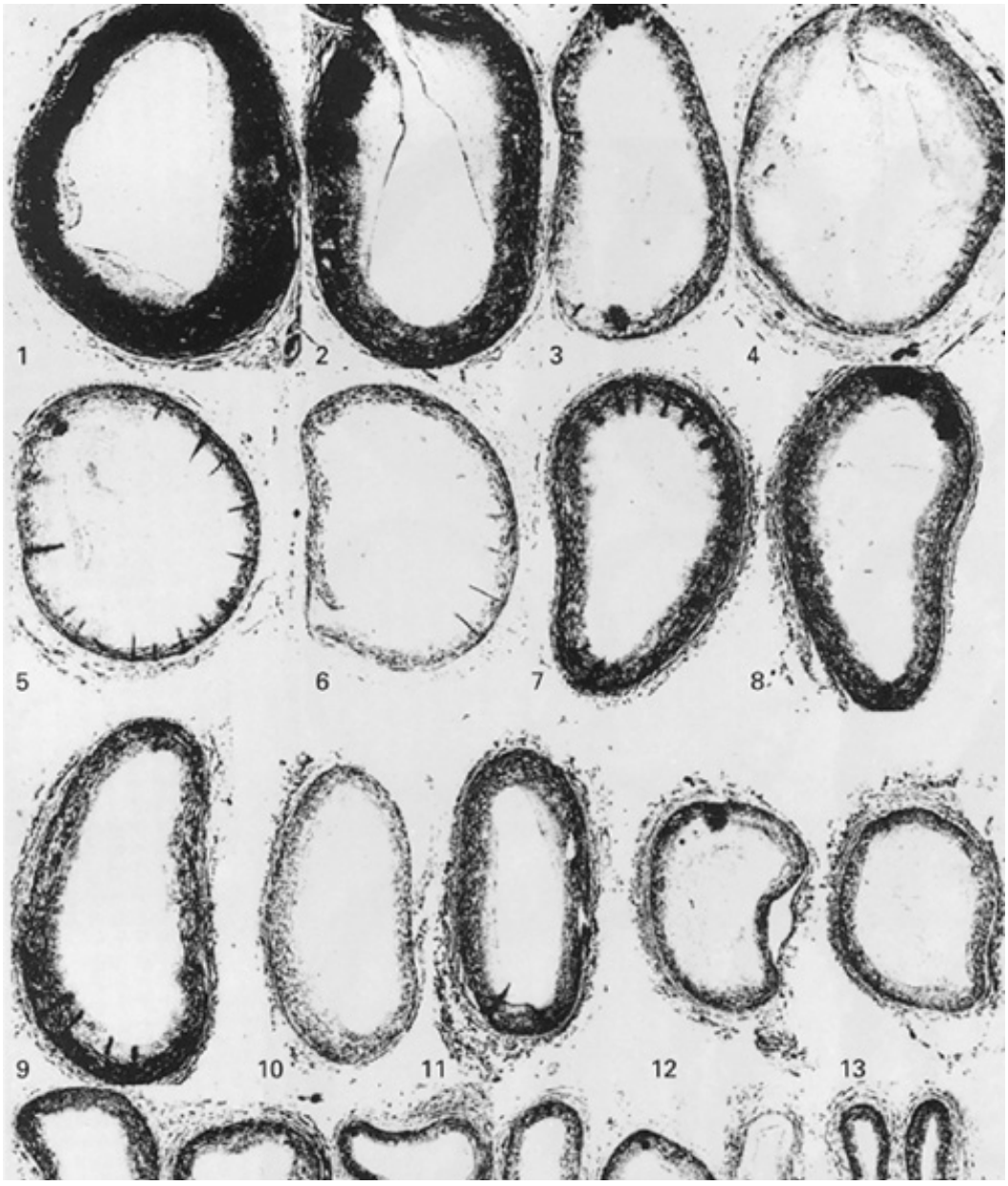
Chapter 39: NONATHEROSCLEROTIC CORONARY HEART DISEASE

CORONARY ARTERY SPASM

Coronary artery luminal narrowing produced by spasm has been associated with angina pectoris, acute myocardial infarction, and sudden death[141,169-195] (see also Chap. 41). Despite the extensive clinical information about coronary artery spasm, relatively few necropsy data are available.[169-181] Smooth muscle cells in the coronary artery wall may contract in response to various neurologic and pharmacologic stimuli and temporarily reduce the vessel lumen. Specific pathogenesis of this disorder is unknown.[180] Enhanced α-adrenergic tone[191] and various vasoactive substances-such as histamine, catecholamines, prostaglandins, and thromboxane[189-192]-are presently thought to be relevant factors. Necropsy findings have been reviewed in 13 previously reported patients and in 3 new patients[141,180,195] (Figs. 39-30 and 39-31).



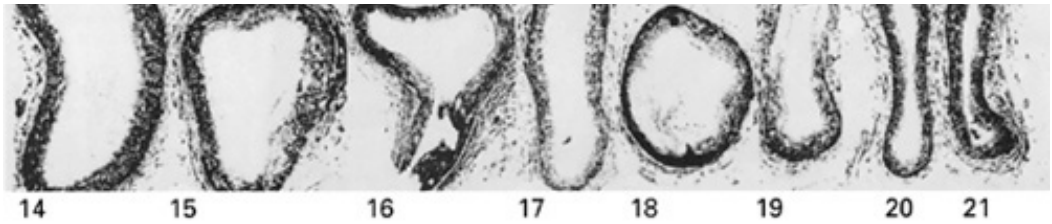


Figure 39-30: Coronary artery spasm. Composite of coronary artery cross sections of a patient with coronary spasm during life. Clinical spasm involved segments 3 to 7. Severe atherosclerotic plaque is seen in 8 of the 21 segments. (From Roberts et al.[180] Reproduced with permission from the author, editor, and publisher.)

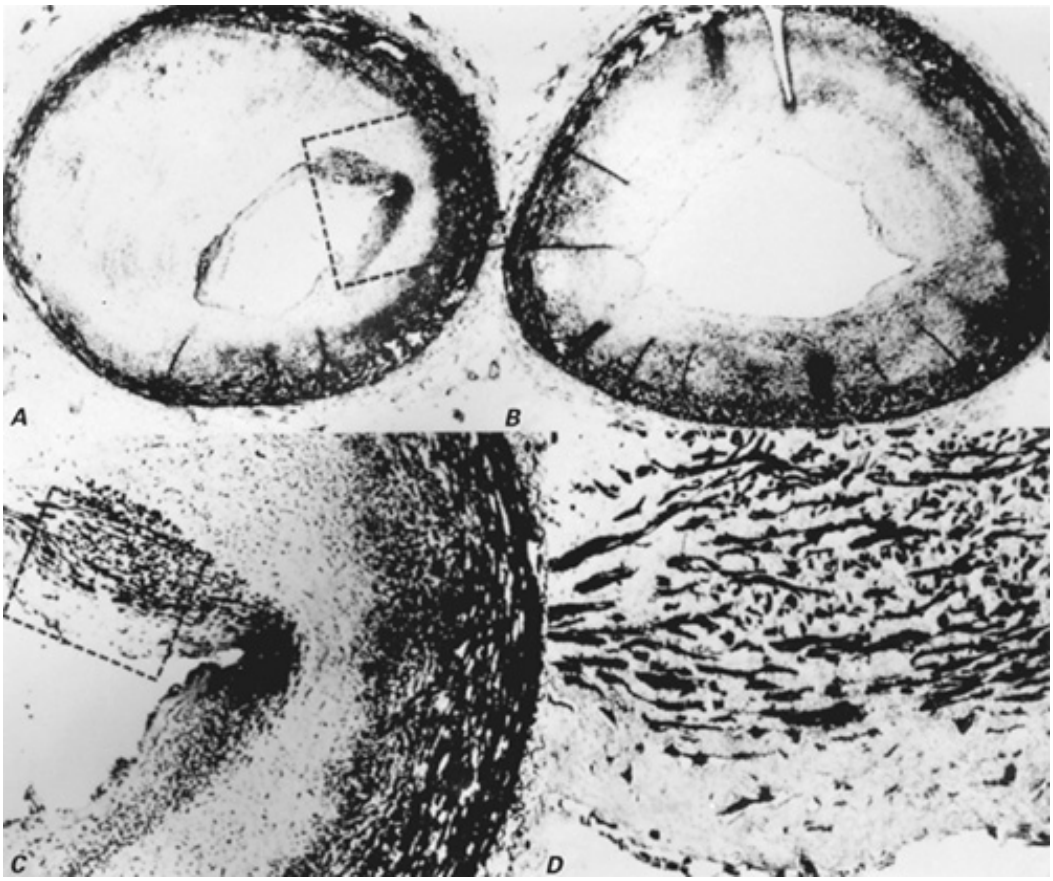


Figure 39-31: Coronary artery spasm. *A*, *B*. Histologic sections of the left anterior descending coronary artery at the approximate site of spasm showing severe luminal narrowing. *C*, *D*. Higher magnifications of the internal plaque showing the predominance of smooth muscle cells. (From Roberts et al.[180] Reproduced with permission from the author, editor, and publisher.)

Most of the 13 previous patients with clinical evidence of spasm had significant fixed coronary luminal narrowing due to atherosclerotic plaque, although coronary angiograms during life did not recognize these lesions found at necropsy.[141,195] In one of the original patients described by Prinzmetal et al.,[169] both major epicardial coronary arteries were "markedly scle rotic," and the "posterior coronary artery" was 80 percent narrowed. Of the subsequent 12 necropsy patients, 10 had at least one major artery severely narrowed by atherosclerotic plaque at necropsy.[169-181] The 3 necropsy patients with clinical spasm[141,180] all had severe luminal coronary narrowing by atherosclerotic plaque at least in the artery in which spasm had been demonstrated during life (see Figs. 39-30 and 39-31). In general, histologic sections of the left anterior descending artery at the

site of spasm disclosed luminal concentric plaque that had a predominance of smooth muscle cells, suggesting that the lesion may have been responsive to pharmacologic and neurologic stimuli compared with "garden variety" fibrotic and calcified atherosclerotic plaque (see Fig. 39-31). In a patient with normal angiograms and documented myocardial infarction, "intimal ridges" were observed on postmortem angiography; these were interpreted as evidence of spasm.[194] Similar ridges have been noted at necropsy in a patient with coronary artery spasm.[195] Histology of the ridges disclosed typical atherosclerotic plaque,[196] suggesting that varying degrees of dynamic muscular contraction may be superimposed on fixed atherosclerotic lesions, presumably related to the amount of smooth muscle present.[141] Coronary artery smooth muscle depletion ("medial attenuation"), which accompanies advanced degrees of luminal narrowing by atherosclerotic plaque, suggests diminished potential for coronary wall spasm.[196] It has been suggested recently that medial "contraction" bands may represent a morphologic-histologic marker for arteries that have spasm during life[197] (see also Chap. 41).

Eccentric atherosclerotic plaques have a segment of disease-free wall with preserved media that presumably has the potential for spasm.[198] In patients with clinical coronary spasm, unstable and stable angina pectoris, and episodes of silent myocardial ischemia, where 448 segments were narrowed by more than 75 percent in cross-sectional area by plaques, 15 percent of these segments had a variable arc of disease-free wall with normal media.[199] Other studies have found a similar 15 to 20 percent of the coronary wall normal in 70 percent of patients studied.[200-205] This disease-free coronary segment represents a site of "vasospastic potential" and could convert a hemodynamically insignificant lesion of less than 50 percent cross-sectional area into a hemodynamically significant one of more than 75 percent narrowing.

Three newly recognized associations and/or causes of coronary artery spasm include general anesthesia,[184] "allergic angina" (histamine-induced),[185] and postpartum bromocriptine use.[186] Acute ST-segment elevation has been noted following induction of general anesthesia in some patients with angiographically normal coronary arteries.[184] In postpartum women receiving bromocriptine in the presence of pregnancy-induced hypertension, acute myocardial infarction has occurred.[186] Coronary spasm also occurs with balloon angioplasty and coronary interventional procedures,[187] catheter-related angiography, and neurofibromatosis.[188]

Endothelial cell dysfunction has been proposed to explain coronary vasospasm.[189] In response to increases in shear stress, platelet products, and other agonists, normal endothelial cells release endothelium-derived relaxing factor (nitric oxide), resulting in vasodilation.[189] When endothelium is damaged, as occurs with hypertension, elevated cholesterol, smoking, or use of cocaine, endothelial nitric oxide is reduced or lost. Thus, when platelets aggregate at such sites with release of vasospastic substances such as serotonin (5HT) and thromboxane A_2, arterial smooth muscle cells contract, causing spasm.[190]

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CORONARY ARTERY TRAUMA

Coronary artery trauma may produce myocardial ischemia and/or acute myocardial infarction. Traumatic injury may result from a nonpenetrating blunt chest wall injury such as a steering-wheel impact, penetration trauma such as a laceration from a stab wound or bullet, coronary artery bypass surgery as from inadvertent ligation, laceration, or intimal dissection, or after coronary angiography or angioplasty resulting in dissection, rupture, or embolus. Nonpenetrating trauma may produce coronary artery injury and subsequent myocardial infarction due to coronary artery dissection, contusion and thrombosis, fistula formation, and/or coronary artery aneurysm formation.[5] Extensive coronary artery dissections occur more commonly as the result of catheter or cannula injury in normal or nearly normal arteries as opposed to coronary arteries with severe atherosclerotic plaque (see also Chap. 79).

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Chapter 39: NONATHEROSCLEROTIC CORONARY HEART DISEASE

CORONARY ARTERY ARTERITIS (VASCULITIS)

Epicardial coronary artery arteritis (vasculitis) is a rare event but has been reported in several conditions (Table 39-7). The resulting coronary artery injury may lead to myocardial ischemia/infarction with or without associated coronary artery thrombosis. This type of coronary artery damage has been classified by route(s) of entry[24]: *direct extension* from adjacent organ or tissue infections, e.g., epicardial or myocardial abscess from aortic valve endocarditis, pericardial infections such as tuberculosis; *hematogenous spread* through the coronary lumen or vasa vasorum; and *unknown* route of entry. In the direct extension route of entry the adventitial layer of the artery is involved initially, whereas in the hematogenous route the coronary intimal layer is involved initially. Evidence of coronary artery arteritis has included[24] the following: (1) focal arterial necrosis with or without calcification, (2) acute coronary artery thrombosis or recanalized thrombus associated with underlying atherosclerotic plaque, (3) rupture of the vessel wall unassociated with trauma or an interventional procedure, (4) coronary artery wall thickening with secondary luminal narrowing, or (5) wall thickening with aneurysm formation.[204] Specific coronary artery lesions also may be seen with systemic diseases such as tuberculosis or polyarteritis (periarteritis).

Table 39-7: Some Conditions Associated with Coronary Artery Arteritis (Vasculitis)

Tuberculosis[24,238,239]
Polyarteritis nodosa[24,205,310-324]
Giant-cell arteritis[205,226-228266-277]
Systemic lupus erythematosus[205,358-362]
Buerger's disease (thromboangiitis obliterans)[205,303-307]
Wegener's granulomatosis[205,342-355]
Salmonella[4,340]
Leprosy[4]
Mucocutaneous lymph node syndrome[326-339]
Takayasu's disease[208,247-265]
Typhus[232]
Infective endocarditis[341]
Rheumatic diseases[205,276-297]
Ankylosing spondylitis[293]
Syphilis[5,114,205,233-237]
Malaria[241]
Schistosoma haematobium[242]
Rickettsial infections[205,242-244]

Viruses[205,245,246]	

SOURCE: Waller.[1] Reproduced with permission from the author, editor, and publisher.

A more recent classification of coronary artery vasculitides has been based on known and unknown causes and involvement of size of vessel (medium-sized, small-sized)[205,206] (Table 39-8). With the exception of infectious angiitis resulting from syphilitic, mycobacterial, or rickettsial infection, the causes and pathogenesis of most coronary artery vasculitides are either unknown or incompletely understood.[207] Vasculitic syndromes may be caused by deposition of immune complexes in the vessel walls.[209-214] The specific antigen has been identified in only a few cases, such as hepatitis B. Circulating immune complexes associated with hepatitis B infection may cause more than one type of vasculitic syndrome,[205] producing periarteritis nodosa in arteries of muscles and hypersensitivity angiitis in venules while eliciting the production of anti-immunoglobulin antibodies, leading to cryoglobulinemia. Thus a classification of vasculitides *based solely* on immunologic studies is incomplete[205] (see also Chap. 76).

General Concepts

The earliest vasculitic syndrome was named *periarteritis nodosa*[215] because of the nodules along the course of small arteries.[205] Because the inflammatory changes are not only periarterial, *polyarteritis* may be a better term.[216] Periarteritis nodosa has become a "wastebasket designation" of any vasculitis whose cause is unknown.[205] The term *necrotizing angiitis*[217] has been used to designate arterial and venous lesions; there are five types[217,218]: (1) hypersensitivity angiitis, (2) allergic granulomatous angiitis, (3) rheumatoid arteritis, (4) periarteritis nodosa, and (5) temporal arteritis. The term *hypersensitivity angiitis* has been considered synonymous with small-vessel vasculitis and is used to imply that the angiitis is due to an allergic response to proteins, drugs, vaccines, or infections.[205] Allergic *granulomatous angiitis* (Churg-Strauss syndrome) is a variant of polyarteritis characterized by necrotizing vasculitis with extravascular granulomas and eosinophilia associated with asthma or allergic rhinitis.[205,219-221] *Rheumatic arteritis*[222] describes vascular lesions in rheumatic diseases with both rheumatic and necrotizing vascular lesions. *Temporal arteritis* (giant-cell arteritis) involves large and small extracranial arteries, including the coronary arteries, and blindness may be a serious complication.[205,223-228] Despite its limitations, this classification[217,218] remains a basis for the diagnosis of vasculitides. The classification of coronary vasculitis is closely tied to that of vasculitides in general[205] and relates to the predominant type and size of vessels affected[229,230] (see Table 39-8 and Chap. 79).

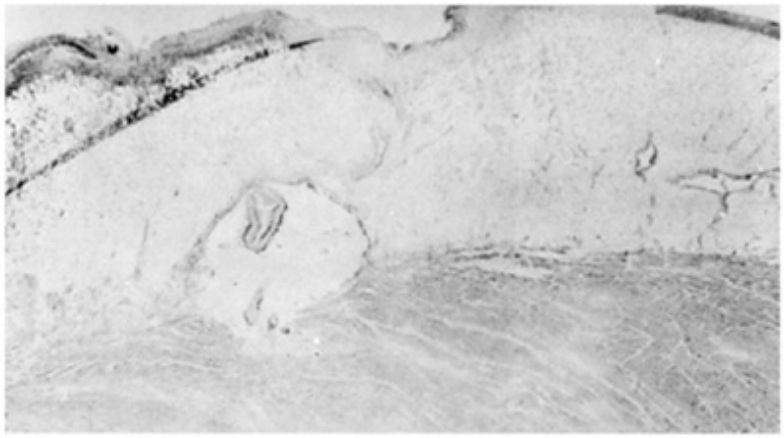
Infectious Angiitis

Various microorganisms may cause vasculitis in vessels of any size and involve the vessel by extension of the acute or chronic infective process from an adjacent tissue or organ[24] or from the lumen by hematogenous spread (see Table 39-8). The inflammatory response produces variable reactions including suppurative inflammation (bacteria),[231] proliferative response (typhoid[232]), hemorrhagic response (anthrax), and histiocytic and granulomatous response (leprosy, syphilis, tuberculosis).[4,205] The most important angiitic infections affecting the coronary arteries include syphilis, tuberculosis, and syphilitic arteritis. All three stages of syphilis show arteritic features. The most important vascular lesion of tertiary syphilis, coronary ostial stenosis, seen in up to 4 percent of patients,[5,233-236] can occur independent of aortic involvement.[205,235] Syphilitic arteritis is characterized by a chronic inflammation with adventitial fibrosis and patchy destruction of media with a lymphoplasmacytic infiltrate. Gummas can be found in 20 percent of patients,[237] but spirochetes are detected rarely.[205] The first 3 to 4 mm of the left and right coronary arteries may be involved with an obliterative arteritis[114]; angina and acute myocardial infarction may result from syphilitic involvement.[236]

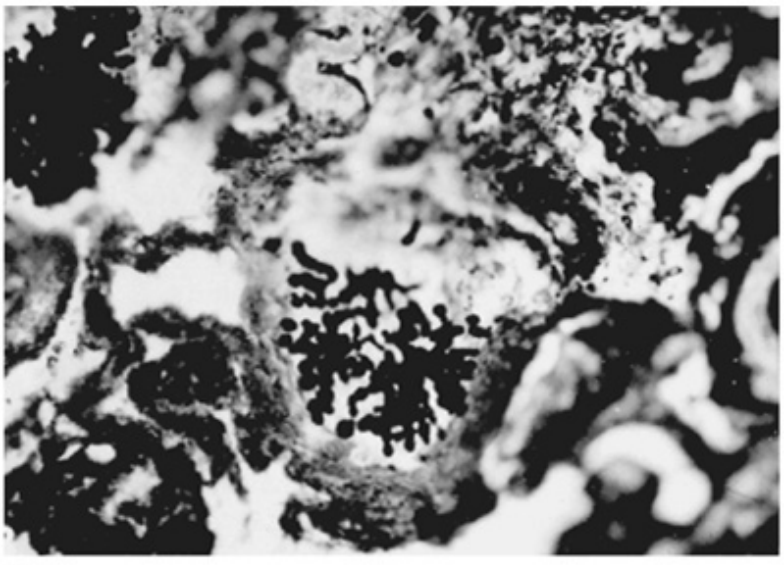
TUBERCULOUS ARTERITIS

Tuberculous coronary arteritis occurs mainly in patients with pericardial and myocardial

tuberculosis.[238,239] Granuloma may involve the adventitia, intima, or entire wall[24,239] and result from several infectious angiitic agents. Endocarditis and septicemia are the most common underlying causes of infectious angiitis and mycotic aneurysm formation.[205,240] Any type of gram-positive or gram-negative organism may be involved. Myocarditis with abscesses and pericarditis frequently accompany infectious coronary angiitis. Mucormycosis, aspergillosis, and *Candida* (Fig. 39-32) are examples of fungi and systemic yeast infections associated with coronary angiitis. Malarial parasites and parasitized red blood cells also may plug larger coronary arteries.[241] *Schistosoma haematobium* has been found in a major epicardial coronary artery associated with myocardial infarction.[242] Rickettsial infections may produce angiitis in small vessels of the heart[205,243]; these infections consist of a lymphomononuclear infiltrate with or without thrombosis. A direct toxic effect from rickettsiae may produce angiitis.[244] Viruses also have been implicated in vasculitis by direct invasion of immunologic mechanisms.[205] Virus-induced vasculitides in humans are represented by polyarteritis associated with hepatitis B antigenemia[205,245,246] and herpes zoster.[205]



A



B

Figure 39-32: Coronary arteritis. *A.* Extensive yeast (*Candida*) pericarditis, which involves the adventitial layer of a branch of a major subepicardial coronary artery. *B.* Close-up shows the budding yeast organisms (GMS stain). (From Waller.1 Reproduced with permission from the author, editor, and publisher.)

Noninfectious Angiitis

Various noninfectious causes of angiitis involve large to medium-sized (predominately medium-sized and

small) blood vessels[205] (see Table 39-8).

TAKAYASU'S ARTERITIS

Takayasu's disease (pulseless disease) is one of the coronary vasculitides associated with aortitis; others are temporal arteritides and rheumatic disease (see also Chaps. 88 and 90). Takayasu's disease is a chronic, occlusive inflammatory disease of unknown etiology[205,247-256] with a worldwide distribution and greater incidence in young to middle-aged female Asians.[249,250] Involvement of the coronary arteries occurs in 15 to 25 percent of patients and may be the lethal complication[248,250-255,257] (Fig. 39-33), commonly involving the coronary ostium[248,257258-263] with segmental involvement of distal coronary arteries.[252-255,264] Rarely, diffuse coronary arteritis is produced by Takayasu's disease.[265]

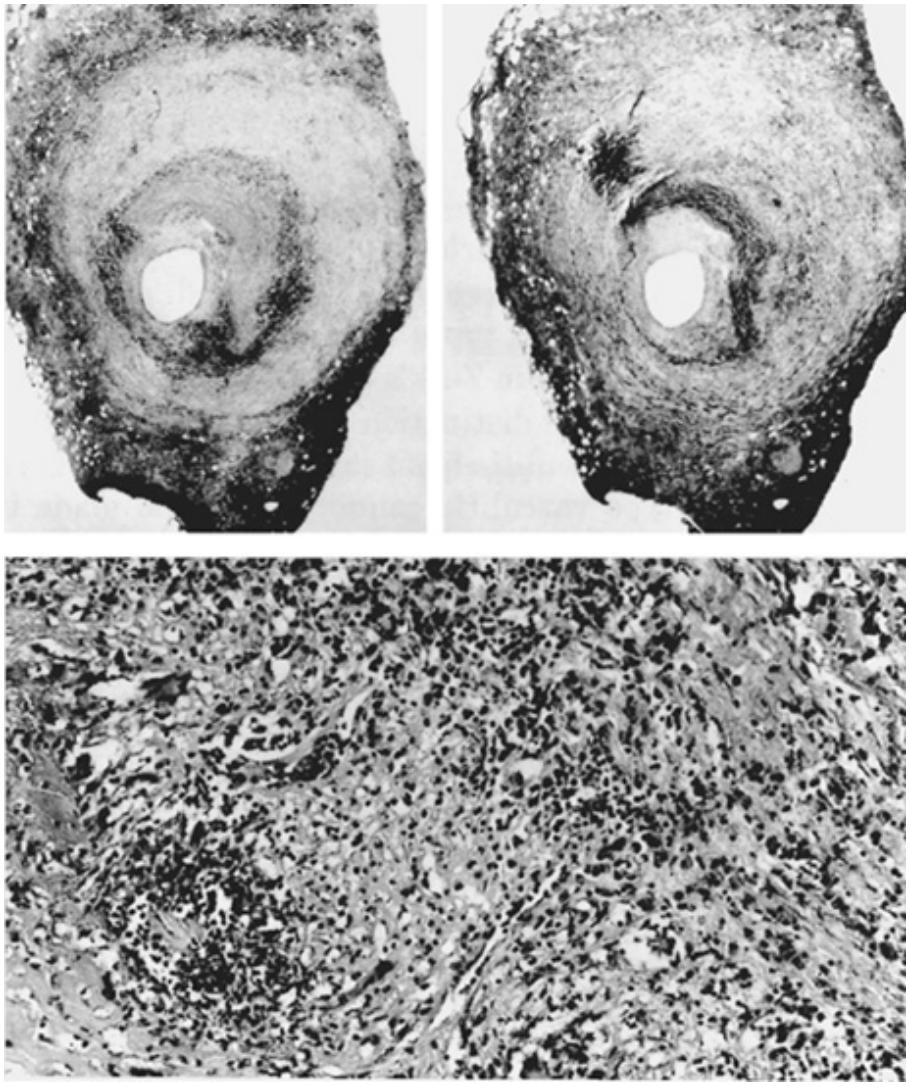


Figure 39-33: (*Top*) Matching hematoxylin-eosin (*left*) and elastic (*right*) stained sections of coronary artery in Takayasu's arteritis. Note transmural fibrosis and inflammatory infiltrate in media of artery (×16). (*Bottom*) Close-up view of lymphoplasmacytic infiltrate with giant cells in media of coronary artery (×160). (From Lie.[205] Reproduced with permission from the author, editor, and publisher.)

GRANULOMATOUS GIANT-CELL ARTERITIS (TEMPORAL ARTERITIS)

Granulomatous giant-cell arteritis may occur independently or, more commonly, may be associated with temporal arteritis in 10 to 15 percent of patients.[205,226-228,266-277] Histologically proven giant-cell coronary

arteritis is rare, and cases leading to fatal myocardial infarction are even rarer[205,266,269-272,274] (Fig. 39-34). The arterial wall lesion is a granulomatous inflammation with giant cells found along degenerative internal elastic membrane.[274] The intima becomes greatly thickened, and ultimately, the vessel is converted into a fibrous cord. Luminal thrombosis also may have been present in 16 patients with temporal arteritis reported by Harrison[275]; only 1 case involved the epicardial coronary arteries. Giant-cell arteritis of the intramural (intramyocardial) coronary arteries (Fig. 39-35) also may occur in association with temporal arteritis and giant-cell arteries[266] (see also Chaps. 76, 88, and 90).

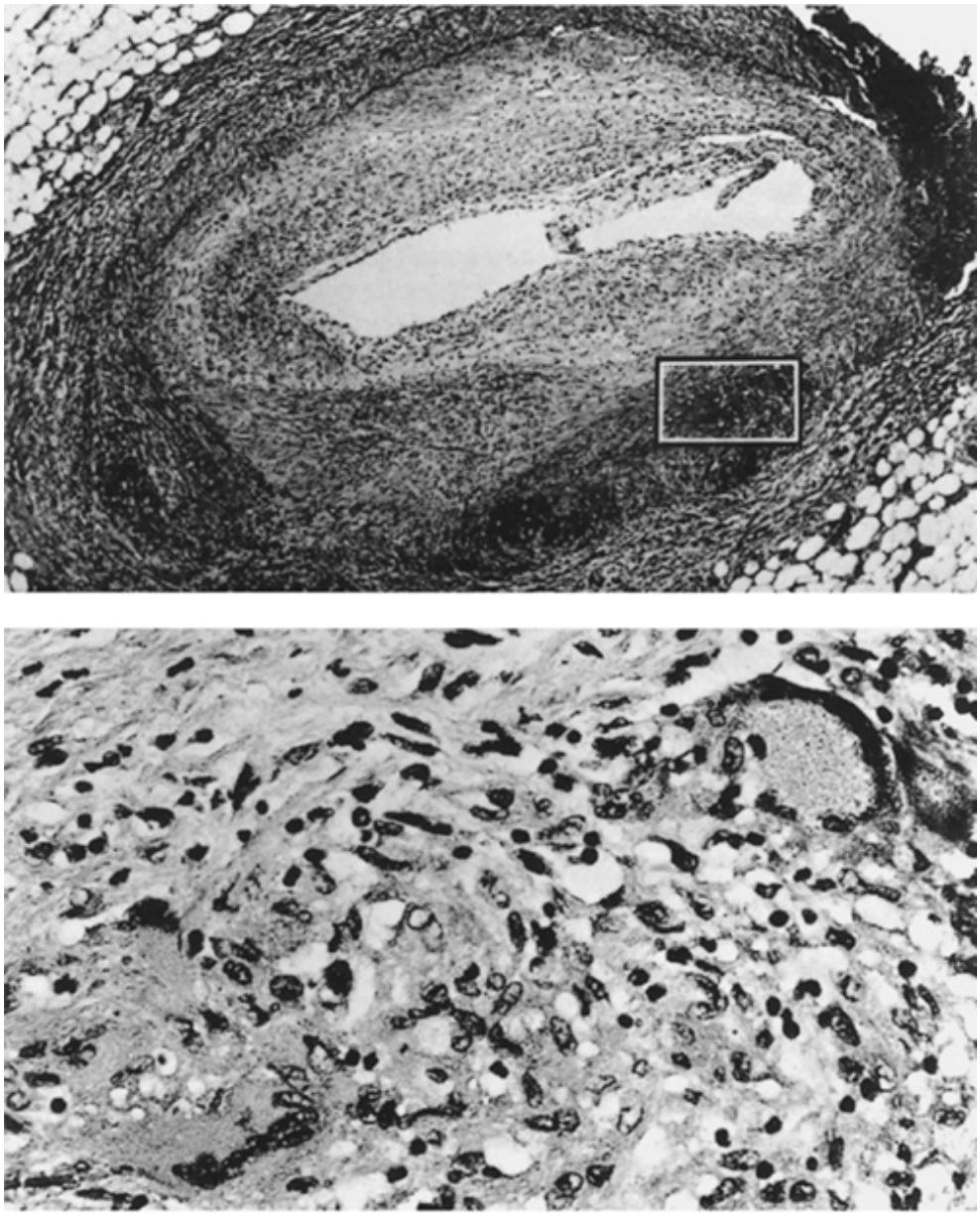


Figure 39-34: (*Top*) Low-power view of granulomatous coronary arteritis associated with giant-cell aortitis (hematoxylin-eosin, ×40). (*Bottom*) Close-up view of boxed area (hematoxylin-eosin, ×400). (From Lie.[205] Reproduced with permission from the author, editor, and publisher.)

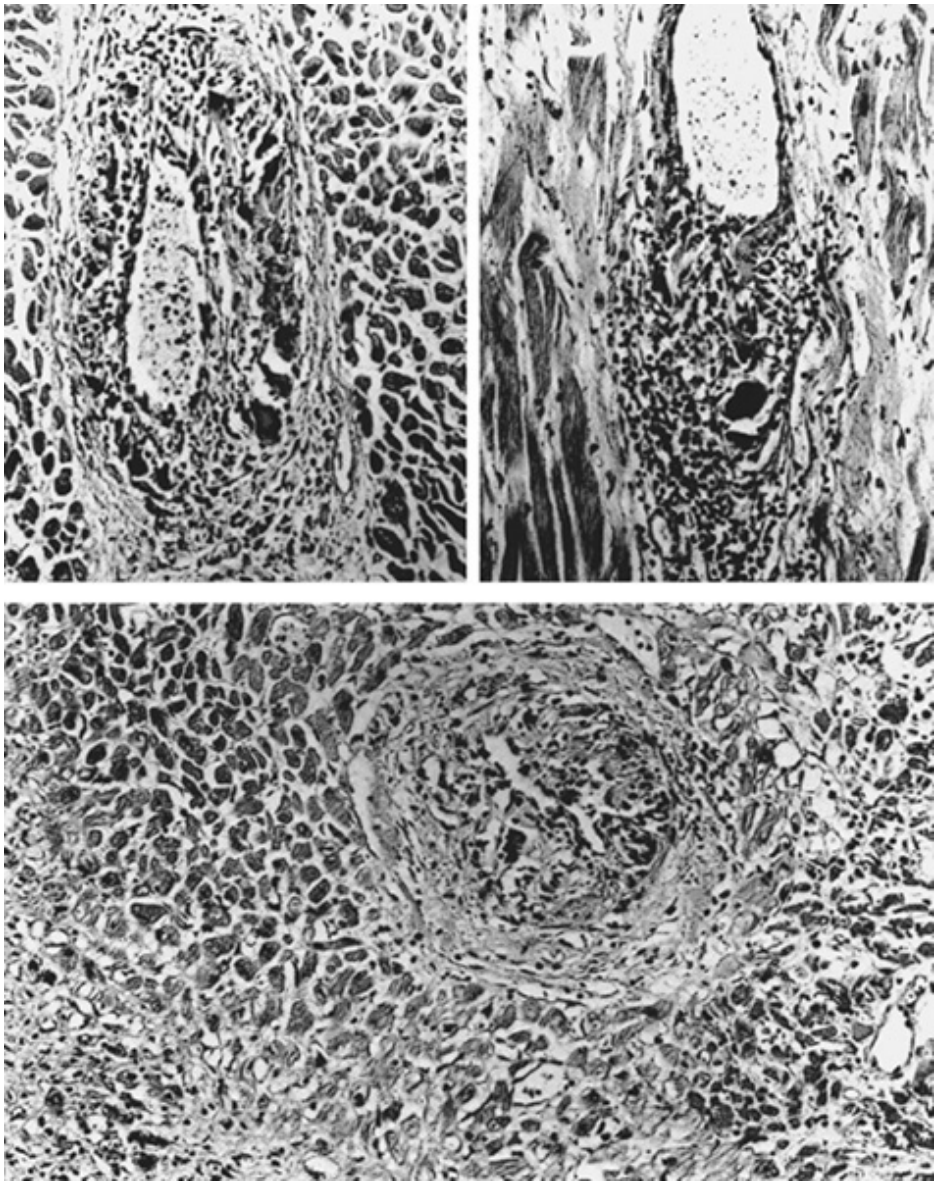


Figure 39-35: (*Top left and right*) Giant-cell arteritis of intramural coronary arteries associated with temporal arteritis and giant cell arteritis (hematoxylin-eosin, ×160). (*Bottom*) Granulomatous coronary arteritis in disseminated visceral giant-cell angiitis (hematoxylin-eosin, ×160). (From Lie.[205] Reproduced with permission from the author, editor, and publisher.)

Rheumatic Arteritis

Rheumatic diseases commonly affect the aorta and are morphologically indistinguishable from granulomatous aortitis.[205,276-293] Coronary arteritis at necropsy has been detected in up to 20 percent of patients with rheumatoid arthritis, usually involving small intramural vessels.[276-297] The small-vessel arteritis also may involve conduction system vessels leading to various forms of heart block.[291-293] Rheumatoid coronary vasculitis producing myocardial infarction is rare.[282-285,296,297] Histologically, extraaortic rheumatoid vasculitis (coronary artery vasculitis) is usually a polyarteritis type of necrotizing angiitis[205,281,286-290] and not a giant-cell arteritis (Fig. 39-36). Small myocardial vessels also may be severely narrowed in ankylosing spondylosis. Occlusion of the left main ostium has been described.[293]

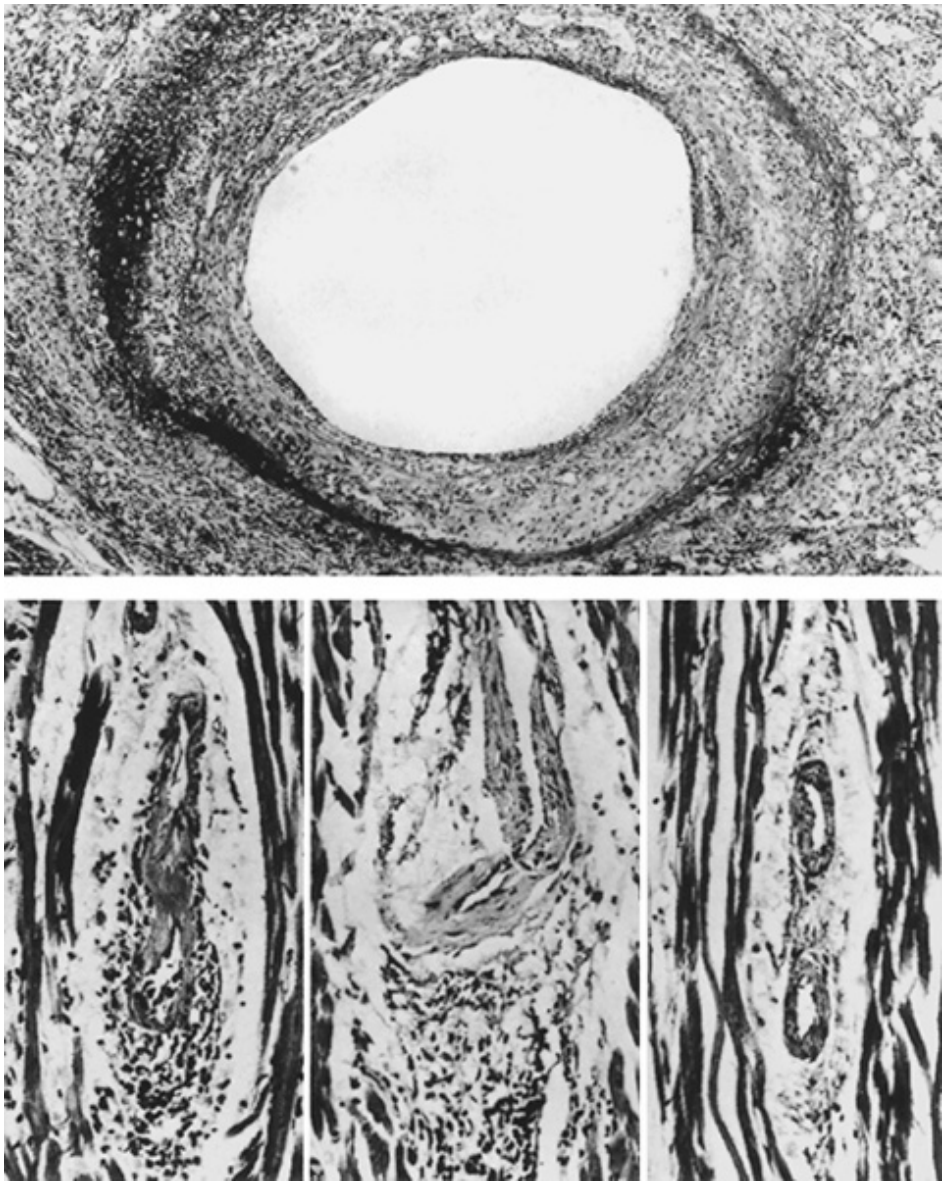


Figure 39-36: (*Top*) Polyarteritis-type necrotizing angiitis of epicardial coronary artery in rheumatoid arthritis (hematoxylin-eosin, ×160). (*Bottom*) Variations of small-vessel coronary artery arteritis in rheumatic fever (hematoxylin-eosin, ×160). (From Lie.[205] Reproduced with permission from the author, editor, and publisher.)

Buerger's Disease

Thromboangiitis obliterans (Buerger's disease), which is very rare[205,298-307] (Fig. 39-37), is a nonatherosclerotic, occlusive, inflammatory vascular disease of unknown cause occurring mainly in young males who are heavy smokers of cigarettes[205] (see also Chap. 90). In a few patients, the coronary arteries have shown focal polymorphonuclear infiltrates, histiocytes, and giant cells with or without coronary artery thrombosis.[304] Coronary involvement is rare,[304] although coronary thrombosis may be seen.[308] Buerger's disease involving a saphenous vein bypass graft also has been documented.[309]

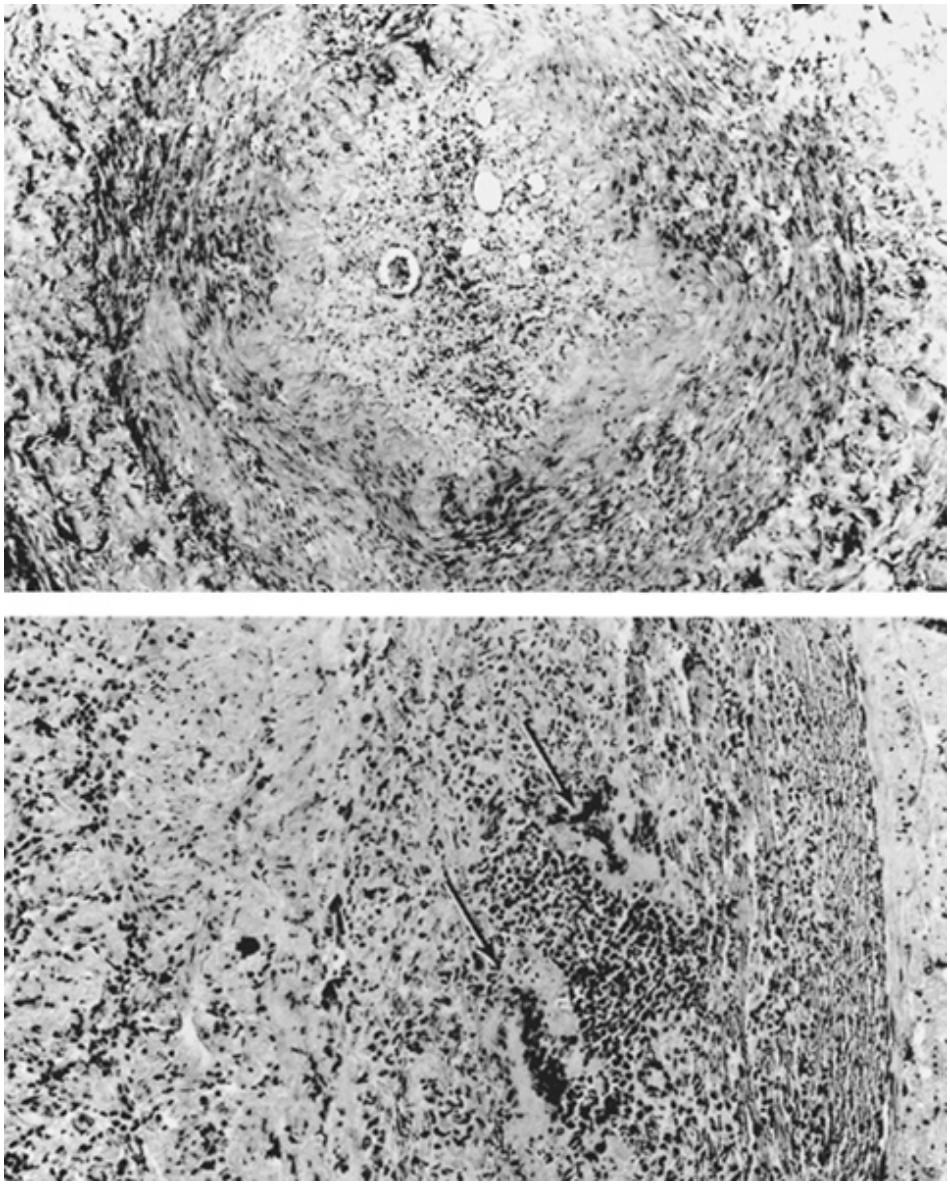


Figure 39-37: (*Top*) Subacute stage of Buerger's disease of coronary artery with organizing thrombus (hematoxylin-eosin, ×160). (*Bottom*) Involvement of coronary vein in Buerger's disease with typical intraluminal microabscesses and giant cells (*arrows*) (hematoxylin-eosin, ×160). (From Lie.[205] Reproduced with permission from the author, editor, and publisher.)

Polyarteritis (Necrotizing) Angiitis

CLASSIC POLYARTERITIS NODOSA

Classic polyarteritis nodosa is a chronic systemic disease manifest by infarction or hemorrhage in various target organs as the result of necrotizing vasculitis.[215] Male patients are affected twice as often as female, with a mean age of 45 years.[205,310-314] It is probably the most common cause of coronary angiitis with both epicardial and intramural coronary arteries being affected[24,310-320] (Fig. 39-38). In a review of 66 necropsy cases,[315] 41 (62 percent) had involvement of the epicardial coronary arteries, including 25 (61 percent) with involvement of both the epicardial and intramural coronary arteries, whereas 16 (39 percent) had only involvement of the intramural arteries. Frequently, various stages of acute disease and healing are seen in the same arterial segment. The acute phase has an acute cellular reaction with destruction of the media and internal elastic membrane.[316] The healing stage results in fibrous internal proliferation. Coronary arteries may dilate to form small berry-like aneurysms (becoming occluded by thrombus), rupture, or produce fatal myocardial infarction,[315,317-320] pericardial tamponade, or sudden death (see also Chap. 76).

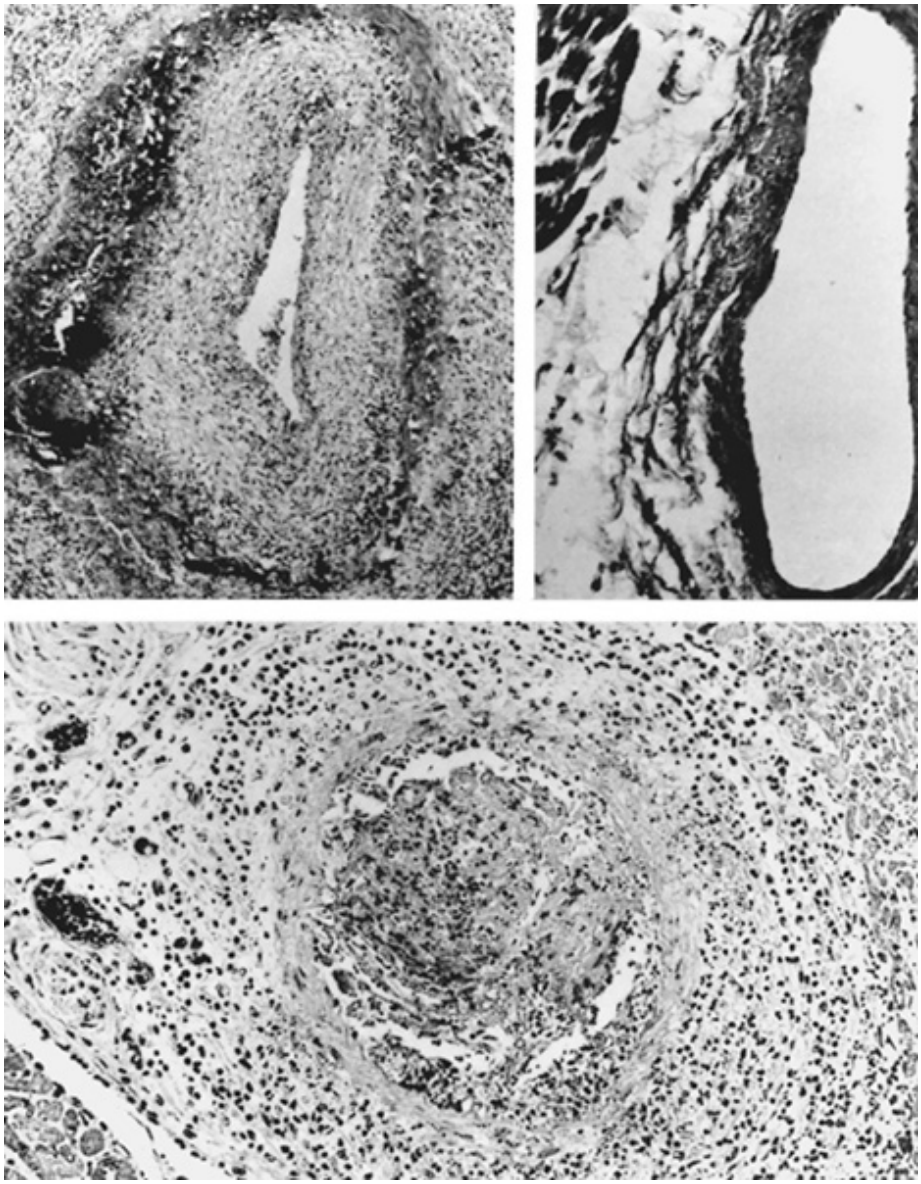


Figure 39-38: (*Top*) Necrotizing angiitis (*left*) and histologically normal (*right*) segments of epicardial coronary arteries in classic polyarteritis nodosa (hematoxylin-eosin, ×16). (*Bottom*) Necrotizing angiitis with fibrinoid necrosis of intramural coronary artery (hematoxylin-eosin, ×160). (From Lie.[205] Reproduced with permission from the author, editor, and publisher.)

INFANTILE POLYARTERITIS

Polyarteritis nodosa occurring in infants under 2 years of age (infantile polyarteritis) differs from the clinical pathologic features of classic polyarteritis nodosa.[205,321-324] Infantile disease involves a higher frequency (79 percent) of coronary vasculitis and aneurysmal disease of the coronary arteries with sparing of vessels in other locations[205,321-324] (Fig. 39-39). Kawasaki's disease may involve children up to 8 or 10 years of age[205] rather than being confined to patients under age 2 as in infantile polyarteritis.[325]

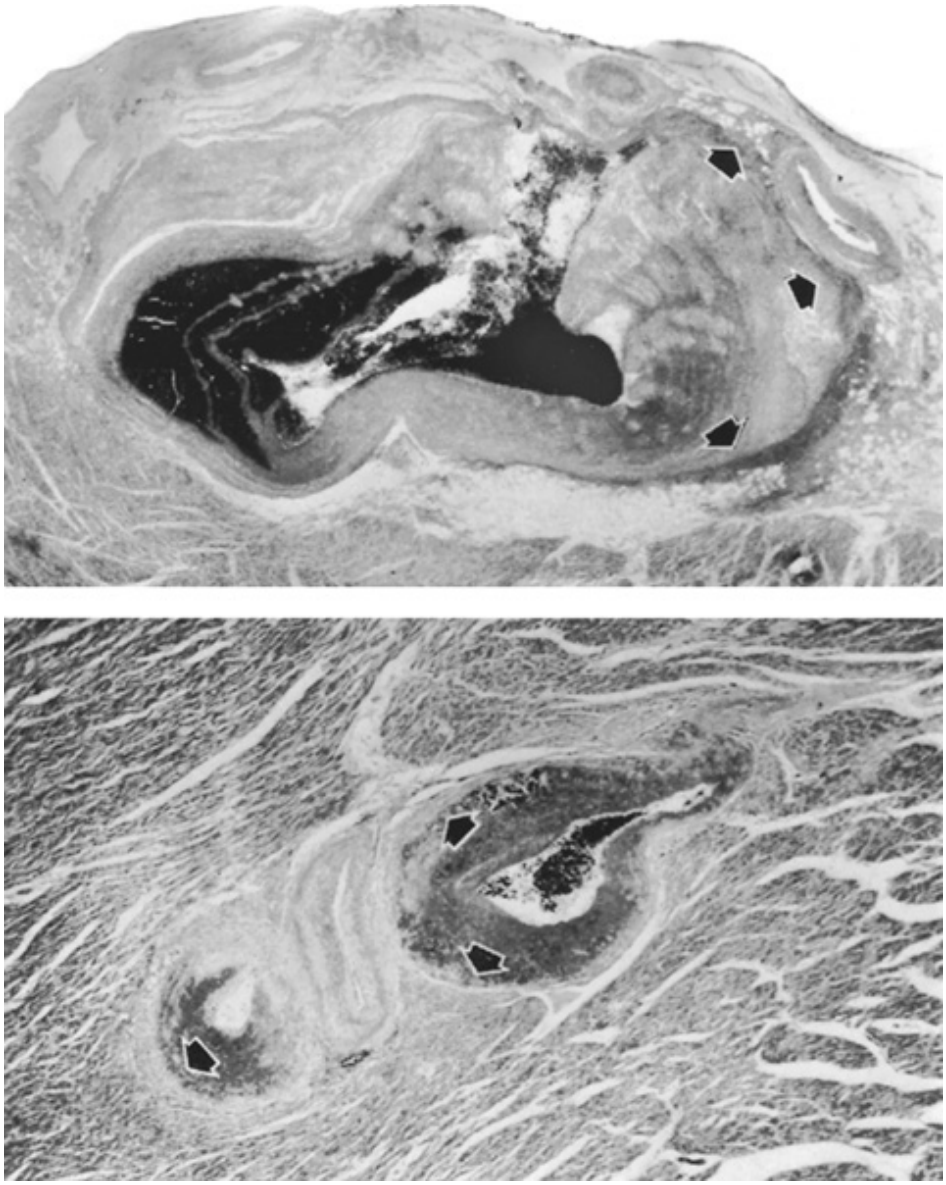


Figure 39-39: Necrotizing angiitis with aneurysmal disruption of epicardial (*arrows, top*) and intramural (*arrows, bottom*) coronary arteries in infantile polyarteritis nodosa (hematoxylin-eosin, ×160). (From Lie.[205] Reproduced with permission from the author, editor, and publisher.)

KAWASAKI'S DISEASE (MUCOCUTANEOUS LYMPH NODE SYNDROME)

Kawasaki's disease, or mucocutaneous lymph node syndrome, is an acute febrile exanthematous illness of children first described in the Japanese literature in 1967 and reported in the English literature in 1974.[326] It has been reported subsequently in children worldwide and in all racial groups.[327] In about 20 percent of children with the acute illness, a vasculitis of the coronary vasa vasorum leads to coronary arterial aneurysm formation, thrombosis, acute myocardial infarction, and sudden death.[326-339] Estimates of death from acute infarction or ventricular fibrillation range from 1 to 2 percent.[332-334] Late presentation with myocardial infarction secondary to dislodged aneurysmal thrombosis also may occur[332,333,335,337] (Figs. 39-40 and 39-41). Pathologically, the acute phase shows a necrotizing angiitis involving media and adventitial layers. Some children have survived into adulthood, with coronary artery aneurysms identified later in life[339] (see Figs. 39-40 and 39-41). The differential diagnosis of coronary artery aneurysms in adults includes previously undiagnosed Kawasaki's disease presumably occurring during childhood. Coronary arteriography results in 1100 children aged 4 months to 13 years identified 262 (24 percent) patients with the disease. In these, coronary occlusion was present in 76 percent, segmental stenosis in 5.7 percent, localized stenosis in 23.7 percent, aneurysms in 35.5 percent, and dilatation in 27.5 percent.[338] The incidence of both occlusion and segmental stenosis was lowest in the group studied shortly after onset of

the illness, whereas the prevalence of coronary aneurysm was highest in this early group.

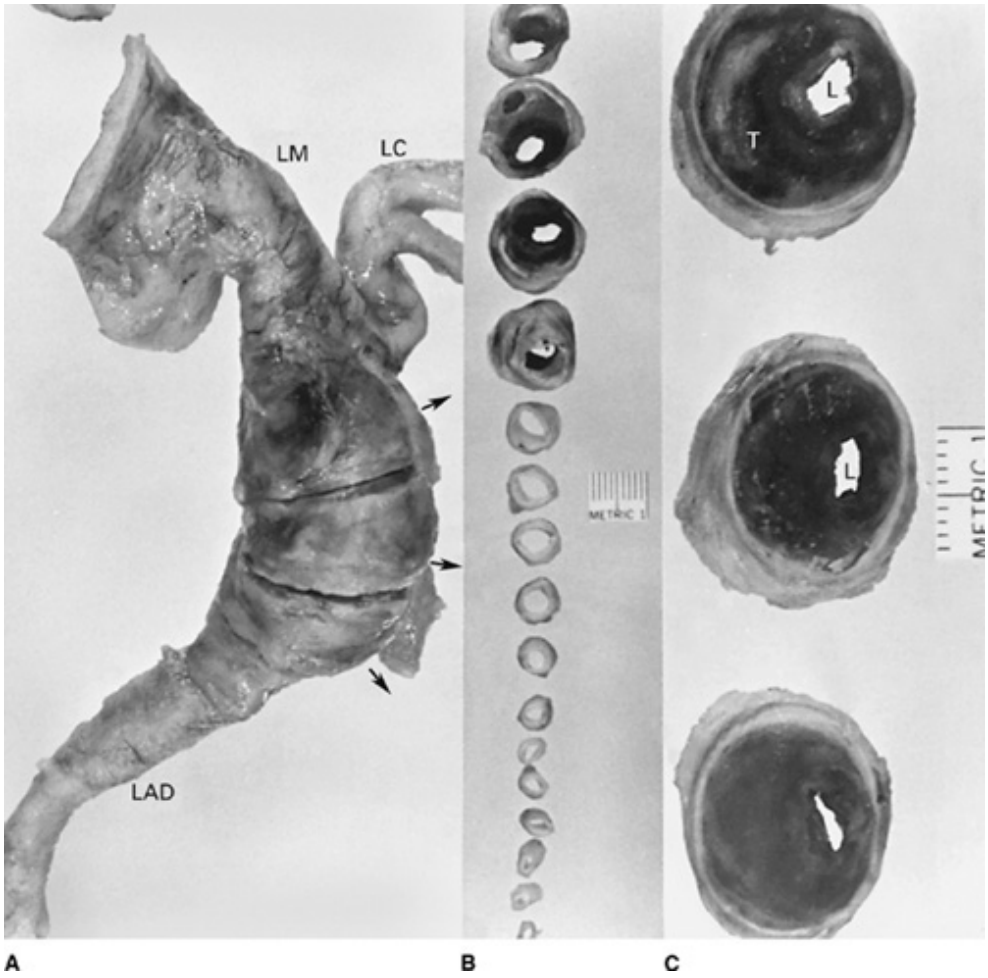


Figure 39-41: *A.* Close-up of left anterior descending (LAD) coronary aneurysm from Fig. 39-40 with cross sections displayed in *B*. Note the intraaneurysmal thrombus. *C*. Close-up of three transverse sections of coronary aneurysm shown in *A* and *B*. LM, left main; LC, left circumflex.

Allergic Granulomatosis and Angiitis: Wegener's Granulomatosis and Churg-Strauss Syndrome

Wegener's granulomatosis is a necrotizing vasculitis of unknown cause classically involving the upper and lower respiratory tracts and the kidneys.[205,342-355] Cardiovascular involvement in Wegener's granulomatosis was described in one of three cases reported in 1936.[345] About 30 additional necropsy cases have been described subsequently, 14 of these (48 percent) showed small-vessel necrotizing coronary vasculitis[205,353,354] (Fig. 39-42). Fibrinoid necrosis of the small and medium-sized coronary arteries[342] and occlusion of larger epicardial coronary arteries with myocardial infarction[343] have been reported. In a large clinical series of patients with Wegener's granulomatosis, 12 percent had cardiac involvement largely manifest by pericarditis and coronary arteritis.[355] Some patients with this disease develop unusual cardiac complications such as pericardial tamponade and later constrictive pericarditis, high-grade atrioventricular block, and atrial tachycardia resistant to usual treatment measures. In this series,[355] all patients improved with cyclophosphamide therapy.

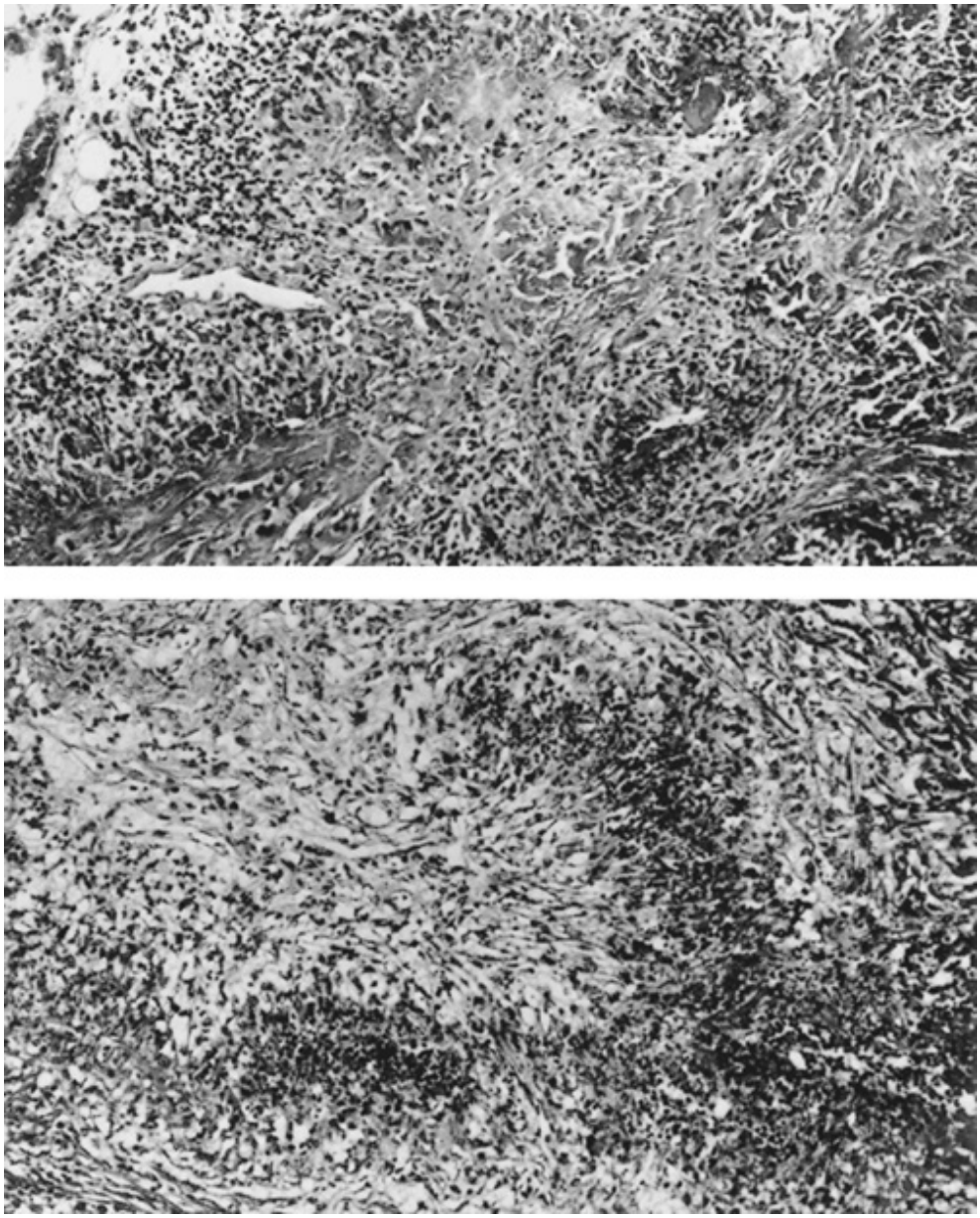


Figure 39-42: Granulomatous necrotizing angiitis of coronary arteries in Wegener's granulomatosis (*top*) and Churg-Strauss syndrome (*bottom*) (hematoxylin-eosin, ×160). (From Lie.[205] Reproduced with permission from the author, editor, and publisher.)

Churg-Strauss syndrome (allergic granulomatosis and angiitis) is a variant of polyarteritis nodosa[205,219] occurring in patients with asthma or an allergy history.[219-221,356] It is characterized by necrotizing angiitis with extravascular granulomas and eosinophilia. The heart is commonly involved with this disease, with granulomatous vasculitis of the coronary arteries (see Fig. 39-42). Granulomatous myocarditis may occur with or without the coronary angiitis[357] (see also Chap. 76).

Collagen Vascular Disease Vasculitis

Collagen vascular diseases generally involve arthritis, myositis, carditis, dermatitis, and inflammatory vascular changes to varying degrees.[358] They include systemic lupus erythematosus, rheumatoid vasculitis, systemic sclerosis, and polymyositis. Rheumatoid vasculitis was discussed earlier. One of the most common conditions with coronary artery vasculitis is systemic lupus erythematosus (Fig. 39-43). Several young patients with this disease and absent coronary atherosclerosis have suffered acute myocardial infarction[359-362] (see also Chap. 76). At necropsy, the coronary arteries in these patients have shown internal fibrous proliferation, possibly representing healed arteritis. Necrotizing vasculitis frequently leads to fatal coronary thrombosis and myocardial infarction,[205,360] rarely associated with thrombotic occlusion

of all three major arteries.[360] Smaller intramural coronary arteries are also involved frequently with fibrinoid necrosis and subsequent fibrosis.[114] Recently, myocardial infarction has been seen with a proximal right coronary artery aneurysm at necropsy. It was postulated that the coronary artery aneurysm represented a sequela of systemic lupus erythematosus arteritis similar to Kawasaki's disease.[362] Necrotizing vasculitis occurs less commonly in other entities of collagen vascular disease such as dermatopolymyositis,[363] systemic sclerosis,[364] Behçet's syndrome,[365] and Cogan's syndrome.[205,366]

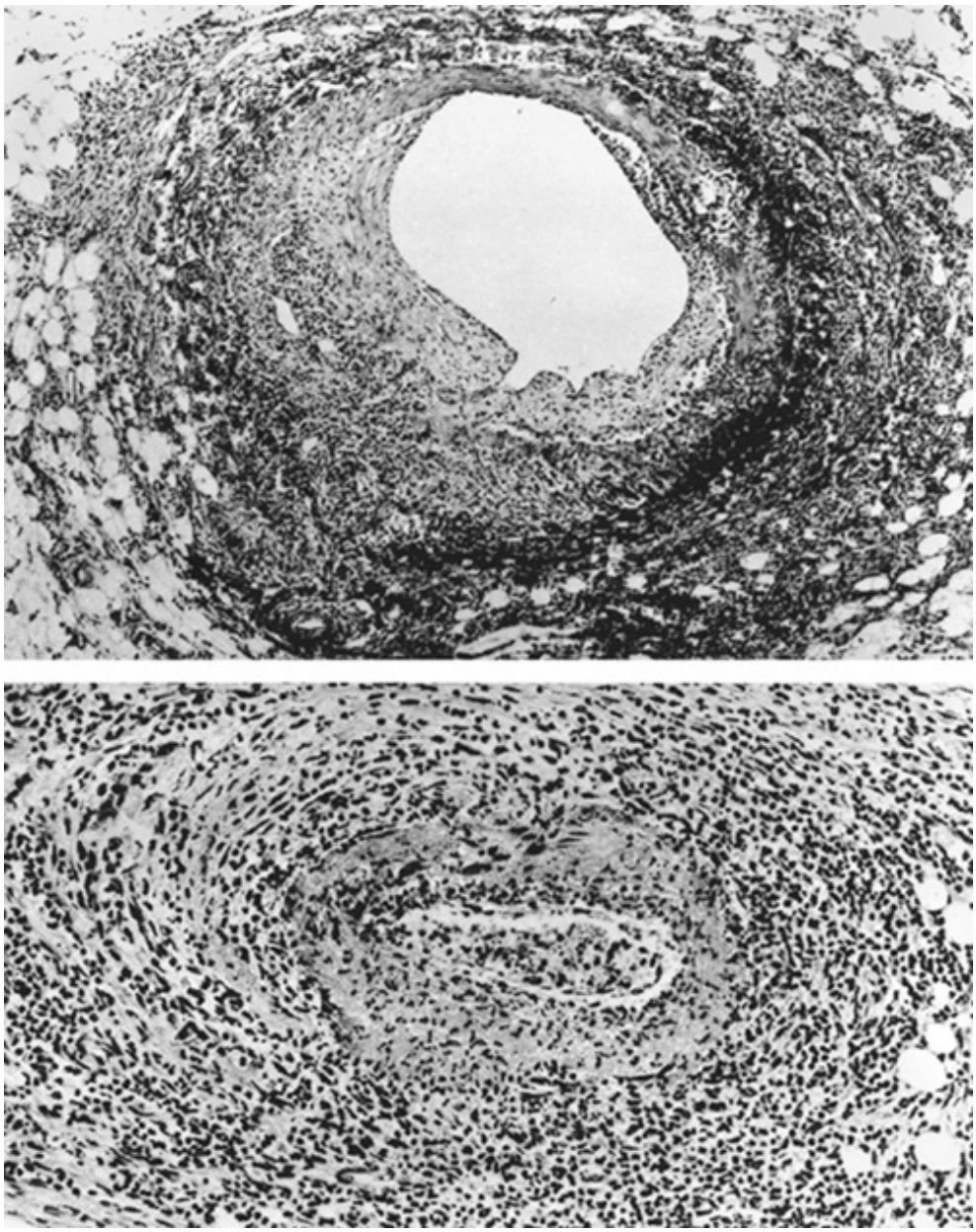


Figure 39-43: Necrotizing angiitis of epicardial (*top*) and intramural (*bottom*) coronary arteries in systemic lupus erythematosus (hematoxylin-eosin, ×160).

Hypersensitivity Angiitis (Allergic Vasculitis)

Hypersensitivity angiitis describes a miscellaneous group of necrotizing vasculitides that involve both epicardial and intramural coronary arteries.[205] This includes drug-induced vasculitis,[367] which, when generalized, may involve the heart. Histologically, drug-induced vasculitis cannot be separated from primary vasculitis or from hypersensitivity angiitis associated with a known underlying disease or malignancy such as serum sickness, mixed cryoglobulinemia, Schönlein-Henoch purpura, etc.[205] (see

Table 39-8). A correct diagnosis cannot be made without clinical information about drug use. Organ-transplantation arteritis[205,368] is also in this category, representing a form of immune-mediated vascular injury (see Chap. 32).

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METABOLIC DISORDERS

Specific metabolic substances may accumulate in the walls of large and small coronary arteries as a result of inborn errors of metabolism. The deposition of this material may severely narrow the coronary artery lumen and produce acute myocardial infarction.[5] Inherited inborn errors of metabolism that are known to affect major epicardial coronary arteries include Hunter's and Hurler's diseases (mucopolysaccharidoses).[293,369-371] The involvement of the coronary arteries in these disorders may be so severe as to totally occlude the vessel and to produce myocardial ischemia/infarction. Other disorders of metabolism such as primary oxalosis,[372] Fabry's disease,[114] Sandhoff's disease (gangliosidoses),[373] and homocystinuria may affect smaller coronary vessels by severe intimal proliferation[374] (see also Chap. 62).

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INTIMAL PROLIFERATION

Fibrous hyperplasia and smooth muscle proliferation in the coronary arteries may narrow the lumen severely and produce myocardial ischemia/infarction. The process may be associated with mediastinal irradiation,[375] fibromuscular hyperplasia of the renal arteries,[5] use of methysergide,[22,376] ostial cannulation during cardiac surgery, aortic valve replacement,[23] and unknown causes.[377,378-380] Up to 50 percent of patients undergoing cardiac transplantation develop significant narrowing of epicardial coronary arteries or total occlusion by intimal fibrous proliferation within 3 to 5 years after transplantation.[381] Myocardial infarction and sudden death may result from this "chronic rejection" process. Fibrosis of the intramural vessels also may occur. Intimal damage from immunologic rejection is believed to be the basis for the accelerated intimal fibrous hyperplasia involving the coronary arteries (see also Chap. 22). A morphologic assessment of 61 human cardiac allografts of short- and long-term survival has been provided.[382] Allographs were divided into two groups: fibrous lesions confined to the proximal region of epicardial arteries and those with diffuse necrotizing vasculitis of the entire system. Disease in the proximal region begins as concentric fibrous thickening. Diffuse disease (necrotizing vasculitis) invariably was associated with acute myocardial rejection with severe intimal lesions of large and small epicardial and intramural arteries.[382] These authors and others[383] have postulated that disease results from healing of a necrotizing vasculitis. Intravascular ultrasound[384] has shown intimal hyperplasia that was detected easily; its severity predicted the development of cardiac events, including myocardial infarction, unstable angina, or sudden death, despite the presence of a normal coronary arteriogram.

A similar histologic picture of intimal fibrous proliferation is seen in epicardial coronary arteries late after undergoing percutaneous balloon angioplasty[143,144] (Fig. 39-44). Intimal fibrous proliferation of the left main coronary artery has been reported late after balloon angioplasty of a lesion in the proximal left anterior descending coronary artery.[385] This may be due to intimal reaction from balloon rubbing of the intimal surface and/or extension of the fibrous process from the angioplasty dilation site (see also Chap. 45).

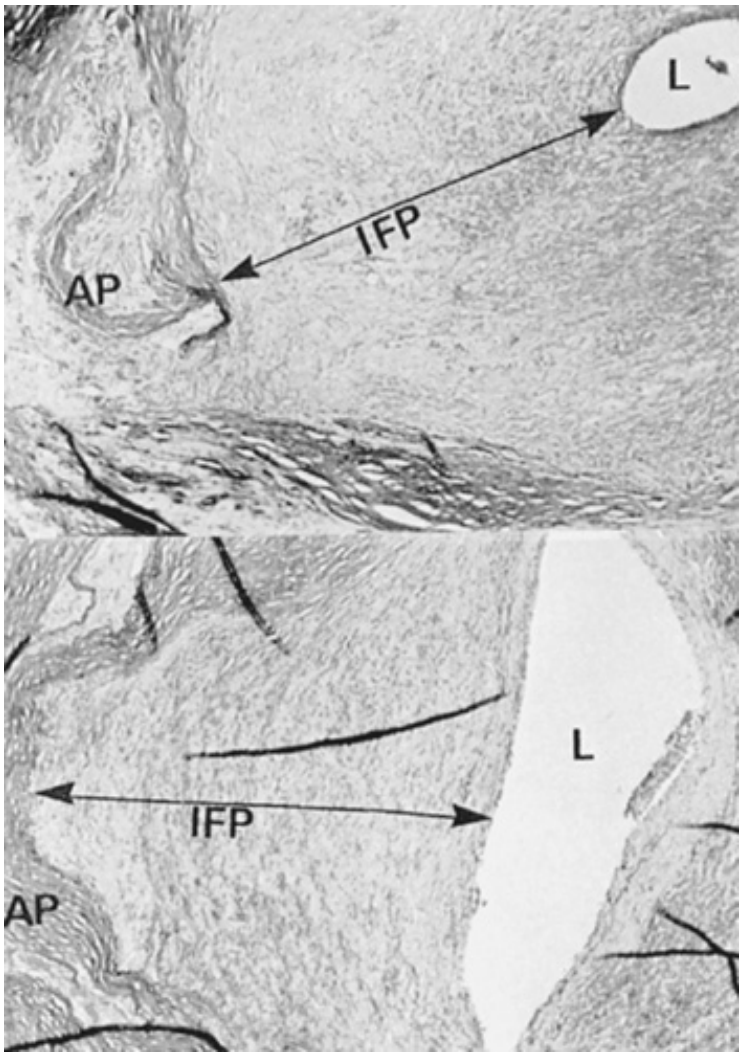

Figure 39-44: Intimal fibrous proliferation. Severe luminal narrowing of the left anterior descending coronary artery by intimal fibrous proliferation (IFP) several months after percutaneous balloon angioplasty. The IFP superimposes underlying atherosclerotic plaque (AP). L, lumen. (From Waller.[1] Reproduced with permission from the author, editor, and publisher.)

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EXTERNAL COMPRESSION

External compression of the epicardial coronary arteries may result in severe luminal narrowing and progressive myocardial ischemia. External compression of a major epicardial coronary artery has been reported in patients with sinus of Valsalva aneurysms, chronic aortic dissection,[386] and epicardial tumor metastases.[387,388] Myocardial bridging (external muscle compression during ventricular systole) was reviewed earlier.

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METASTATIC IMPLANTS

Myocardial metastatic lesions from various tumors-including carcinomas, sarcomas, and lymphomas-may mimic a healed myocardial infarct at necropsy (Fig. 39-45). The discrete location or locations of these metastatic deposits generally are unrelated to specific coronary arterial supply zones, and the lesions usually are surrounded by normal myocardium. These two gross observations suggest the lesions are metastatic tumor implants rather than healed myocardial infarcts (see also Chap. 77).

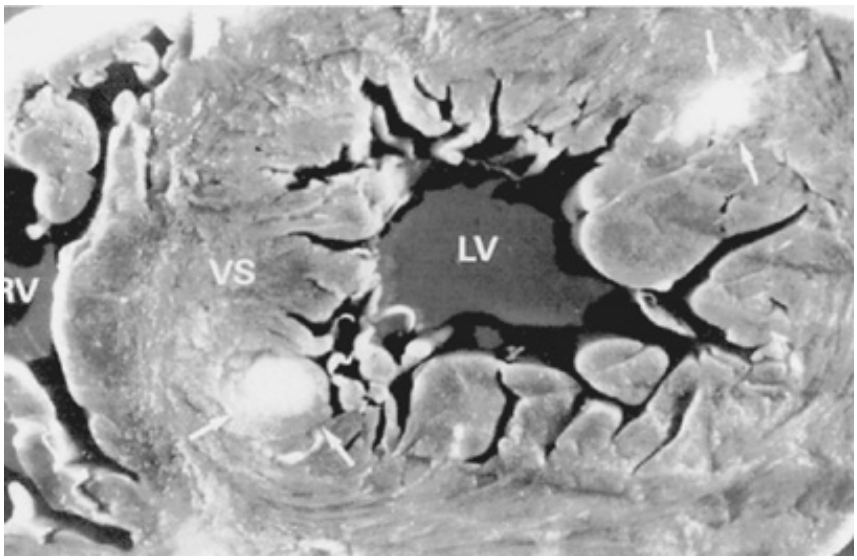

Figure 39-45: Metastatic deposits mimicking myocardial infarction. Transverse section of cardiac ventricle showing two discrete myocardial metastatic deposits of lymphoma. These whitish deposits may be mistakenly interpreted as healed myocardial infarctions in a patient with clean epicardial coronary arteries. LV, left ventricle; RV, right ventricle; VS, ventricular septum. (From Waller.[1] Reproduced with permission from the author, editor, and publisher.)

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RADIATION-INDUCED CAD

Intimal proliferation of epicardial coronary arteries involving the ostium, main segment, or both is well known and increasingly reported.[375,389-400] "Accelerated" or "premature" coronary atherosclerosis has been noted in young individuals undergoing previous mediastinal irradiation for various types of malignancies.[401-404] Internal proliferation following mediastinal radiation 5 to 10 years earlier is described as "intimal thickening *without* medial abnormalities." The intimal lesions (ostial or main segment of artery) consists of fibrous tissue *without* extra cellular lipid deposits.[375,399] Coronary ostial stenosis has an incidence of 0.13 to 2.7 percent of patients undergoing mediastinal irradiation treatment.[375,399] A few patients have developed acute myocardial infarction or unstable angina as a result of the radiation-induced lesions treated by myocardial revascularization[394,398] or angioplasty[398] (see also Chap. 71).

Because of their fibrous nature, many radiation-induced lesions do not provide the best substrate for dilation techniques.[143,144,385] Chemotherapy-induced myocardial infarction in a young man without coronary disease has been reported.[405] Cardiac invasion by tumor, hypercoagulable states, and coronary artery spasm are possible etiologies.[405] Vascular toxicity, including myocardial infarction, has been reported following antineoplastic regimens containing *Vinca* alkaloids.[405]

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CORONARY ARTERY THROMBOSIS WITHOUT UNDERLYING ATHEROSCLEROTIC PLAQUE (THROMBOSIS IN SITU)

Thrombotic occlusion of the coronary system unassociated with underlying atherosclerotic plaque may be seen with several hematologic diseases: thrombocytopenic purpura,[35] leukemia,[406] polycythemia vera,[407] sickle cell anemia,[114] and primary thrombocytosis.[408] Occasionally, acute myocardial infarction may be the initial manifestation of these hematologic disorders. A main factor responsible for the myocardial ischemia in these conditions is blockage of small intramural coronary vessels by platelet aggregates.[409] These platelet aggregates initially may form in the major coronary arteries and then embolize distally.

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SUBSTANCE ABUSE

Cocaine abuse is now a major health hazard; more than 22 million Americans have tried cocaine at least once, and 5 million are current users.[410] Recent reports have documented that cocaine abuse can result in myocardial ischemia and infarction in the absence of CAD,[410-420] and cocaine-induced coronary artery vasoconstriction has been reported in patients following the intranasal administration of cocaine[415,421-424] (see also Chap. 71).

Several instances of coronary artery thrombosis and spasm have been reported in patients who abuse cocaine. Acute coronary thrombosis in association with cardiac events-including angina, acute myocardial infarction, and sudden death-has been reported.[410,413,422-424] In some instances, there is underlying atherosclerotic plaque; in others, the coronary arteries are normal. Coronary thrombosis occurring in coronary arteries free of atherosclerotic plaque suggests the role of cocaine-induced spasm, massive norepinephrine release in the heart, or possible primary thrombogenicity of cocaine or its metabolites.[421] Coronary spasm has been associated with cocaine use and has been postulated as a mechanism of myocardial infarction in cocaine users with clean coronary arteries.[410,425-431] In such cases, fibrointimal proliferation with coronary narrowing was attributed to underlying coronary artery spasm that caused focal vessel endothelial injury, platelet adherence, and aggregation. Platelets liberate platelet-derived growth factor (PDGF), which can induce intimal proliferative lesions. In patients with underlying coronary plaque, cocaine-induced spasm also may produce endothelial disruption at the surface of the plaque and promote platelet aggregation and further vasoconstriction from the release of platelet prostaglandins[432] (see also Chap. 71).

Recently, two drugs have been the center of debate over their potential for abuse versus use as psychotherapeutic agents and their complication in induction of arrhythmias.[433] Use of MDMA ("Ecstasy," 3,4-methylenedioxymethamphetamine) and MDEA ("Eve," 3,4-methylenedioxymethamphetamine) has been associated with five sudden deaths.[433] In three of these, "Eve" and "Ecstasy" may have induced fatal arrhythmias.

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MYOCARDIAL OXYGEN DEMAND-SUPPLY DISPROPORTION

In this category are disease states in which there is failure to deliver adequate oxygen to the myocardium over a prolonged period or increased myocardial wall tension requiring increased oxygen supply. The classic example of the first situation is carbon monoxide poisoning,[4] which has been associated with extensive nontransmural infarction in the presence of normal epicardial coronary arteries. Prolonged shock from any cause also can result in extensive nontransmural necrosis and frequently is associated with transmural necrosis of the papillary muscles. One example of increased myocardial wall tension requiring increased coronary oxygen supply is aortic valve stenosis[4] (see Chap. 56). In the face of increased oxygen demand with increased muscle mass, coronary blood supply may be limited by poor perfusion resulting from the lower coronary arterial pressure. In addition, poor perfusion results from the high coronary arterial resistance caused by increased wall pressure on the intramural coronary arteries and the high LV end-diastolic pressure from a stiff ventricle, with further limitation of the time in diastole for coronary blood flow occasioned by tachycardia.[4] Excessive myocardial oxygen demand exceeding supply and resulting in myocardial ischemia/infarction also may be seen in thyrotoxicosis,[434] which reflects increased metabolic rates and the adverse affects of tachycardia.

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INTRAMURAL CAD (SMALL-VESSEL DISEASE)

Acute myocardial infarction may result from abnormally thickened or totally occluded intramural coronary arteries in the presence of normal extramural (epicardial) coronary arteries. A few of the conditions in this category include (1) hypertrophic cardiomyopathy, (2) diabetes mellitus, (3) amyloid heart disease,[434] (4) neuromuscular disorders (Friedreich's ataxia, progressive muscular dystrophy), (5) cardiac transplantation, (6) rheumatoid arthritis, (7) collagen-vascular disorders (scleroderma, systemic lupus erythematosus), (8) metabolic abnormalities (mucopolysaccharidoses, gangliosidoses), and (9) polyarteritis nodosa.[435-439]

Histologic abnormalities of small-vessel coronary arteries have been reported in individuals who have died from toxic oil syndrome involving rapeseed oil adulterated with aniline.[440] Many of those who later died had scleroderma-like illnesses. Dense fibrosis of the sinus node, resembling scleroderma, was found with cystic degeneration of the sinus node (resembling lupus erythematosus) and fibromuscular dysplasia of small coronary vessels.

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NORMAL EPICARDIAL CORONARY ARTERIES

There have been relatively few necropsy reports of patients with acute myocardial infarction who had angiographically normal coronary arteries and normal coronary arteries at necropsy.[3,4,434,441,442] Of 100 consecutive necropsy cases of acute myocardial infarction,[3] 7 percent had infarcts without evidence of coronary luminal narrowing. In 10 patients with a typical picture of acute myocardial infarction who died within 25 days of onset of symptoms, the coronary arterial systems showed minimal or no luminal narrowing by atherosclerosis. No thrombotic material was observed in the coronary arteries despite the fact that the acute myocardial infarction was 2 days old in 5 patients and 3 to 4 days old in 3. Possible explanations for this have included coronary artery spasm, coronary artery disease in vessels too small to be visualized angiographically, or coronary artery thrombosis or embolus with subsequent clot lysis. Myocardial infarction in postpartum women with normal epicardial coronary arteries has included two additional causes for possible spasm in these patients: bromocriptine used for suppression of lactation[186,443-451] and antiphospholipid syndrome with elevated anticardiolipin antibody levels, false-positive syphilis serology, and a history of deep venous thrombosis.[452]

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Part 6: CORONARY HEART DISEASE
Chapter 40:

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

Authors: Robert A. O'Rourke, Robert C. Schlant, John S. Douglas, Jr.

Ischemic heart disease remains a major public health problem.[1] Chronic stable angina is the first indicator of ischemic heart disease in about 50 percent of patients. The reported annual incidence of angina is 213 per 100,000 population over the age of 30. The number of patients with stable angina in the United States approximates 16.5 million people, not including individuals who do not seek medical attention for their chest pain or who are shown to have a noncardiac cause of chest discomfort. Angina pectoris is a clinical syndrome that consists of discomfort or pain in the chest, jaw, shoulder, back, or arm. Typically it is precipitated or aggravated by exertion or emotional stress and relieved by nitroglycerin. Angina usually occurs in patients with coronary artery disease (CAD) affecting one or more large epicardial arteries. Angina often is present in individuals with valvular heart disease, hypertrophic cardiomyopathy, and uncontrolled hypertension, however. It also occurs in patients with normal coronary arteries and myocardial ischemia due to coronary artery spasm or endothelial dysfunction. The symptom of angina is often observed in patients with noncardiac disorders affecting the esophagus, chest wall, or lungs.

HISTORICAL PERSPECTIVE

In 1768, William Herberden presented his classic description of angina pectoris in a lecture before the Royal College of Physicians; it was published in 1772.[2] This classic description was published again with minor changes in a chapter entitled "Pectoris Dolor" in his *Commentaries on the History and Cure of Diseases*, which was translated from the Latin and published by his son, also named William Herberden, in 1802.[3] The following quotation is from the original lecture:

> There is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and extremely rare, of which I do not recollect any mention among medical authors. The seat of it, and sense of strangling and anxiety, with which it is attended, may make it not improperly be called angina pectoris. Those who are afflicted with it are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or to continue: the moment they stand still all this uneasiness vanishes. In all other respects the patients are at the beginning of this disorder perfectly well, and in particular have no shortness of breath, from which it is totally different.
>
> After it has continued some months, it will not cease so instantaneous upon standing still; and it will come on, not only when the persons are walking, but when they are lying down, and oblige them to rise up from their beds every night for many months together; and in one or two very inveterate cases it has been brought on by the motion of a horse or a carriage, and even by swallowing, coughing, going to stool or speaking, or by any disturbance of mind. I have heard once and only one person, say that he had known it to attack him when he was up and standing still or sitting.

> ... but all the rest, whom I have seen, who are at least twenty, were men, and almost all above 50 years old, and most of them with a short neck, and inclining to be fat. When a fit of this sort comes on by walking, its duration is very short, as it goes off almost immediately upon stopping. If it comes on in the night, it will last an hour or two; and I have met one, in whom it once continued for several days, during all which time the patient seemed to be in imminent danger of death.
>
> But the natural tendency of this illness be to kill the patients suddenly, yet unless it have a power of preserving a person from all other ails, it will easily be believed that some of those, who are afflicted with it, may die in a different manner, since this disorder will last, as I have known it more than once, near twenty years, and most usually attacks only those who are above fifty years of age. I have accordingly observed one, who sunk under a lingering illness of a different nature.
>
> The os sterni is usually pointed to as the seat of this malady, but it seems sometimes as if it was under the lower part of it, and at other times under the middle or upper part, but always inclining more to the left side, and sometimes there is with it a pain about the middle of the left arm. What the particular mischief is, which is referred to these different parts of the sternum, it is not easy to guess, and I have had no opportunity of knowing with certainty. It may be a strong cramp, or an ulcer, or possibly both.

The syndrome of angina pectoris was described as rare in textbooks of medicine in 1866 (Austin Flint) and 1892 (William Osler). Paul Dudley White wrote: "[angina pectoris] was uncommon in my early professional years. But when the automobile came in the 1920s and the population at large became more prosperous and over nourished, the current epidemic of coronary heart disease, as shown mainly by the symptom angina pectoris, began and incidentally involved younger and younger men."[4] In the United States, the peak mortality rate from coronary heart disease (CHD) occurred about 1962 to 1965; since then, it has been decreasing steadily.[5]

NEXT

Chapter 40: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

ETIOLOGY AND CLASSIFICATION

Coronary atherosclerosis is the cause of angina pectoris in most patients (see Chaps. 35 to 38). Many nonatherosclerotic causes of CAD (Tables 39-1 and 39-2) also can produce angina pectoris or myocardial infarction. Other conditions particularly associated with angina pectoris include congenital coronary artery abnormalities (see Chap. 64), aortic stenoses (see Chap. 56) mitral stenoses with resulting severe right ventricular hypertension (see Chap. 52), hypertrophic cardiomyopathy (see Chap. 67), and systemic arterial hypertension[6] (see Chap. 51).

Disorders in which angina occurs less frequently include aortic regurgitation (see Chap. 56), idiopathic dilated cardiomyopathy (see Chap. 66), and luetic heart disease. Mitral valve prolapse (see Chap. 58) rarely causes true angina pectoris. Certain conditions may alter the balance between myocardial oxygen supply-demand and precipitate or aggravate angina pectoris, including severe anemia, tachycardia, fever, hyperthyroidism, and Paget's disease of bone.

The Canadian Cardiovascular Society Grading Scale (see Table 10-2) is commonly used to classify the severity of angina pectoris, with the most severe symptoms occurring at rest and the least severe only with excessive exercise.

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Chapter 40: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

DIAGNOSIS

History and Physical Examination

The first step is to obtain a detailed description of the symptom complex in order to characterize the chest pain or discomfort. Five descriptors typically are considered: (1) location, (2) quality, (3) duration of the discomfort, (4) inciting factors, and (5) factors relieving the pain.[1]

After a description of the chest discomfort is obtained, the physician makes an integrated assessment of various components. The most commonly used classification scheme for chest pain divides patients into three groups: *typical angina*, *atypical angina*, or *noncardiac chest pain*[7,8] (Table 40-1).

Table 40-1: Clinical Classification of Angina

Typical angina (definite)
1. Substernal chest discomfort with a characteristic quality and duration that is 2. provoked by exertion or emotional stress and 3. relieved by rest or NTG.
Atypical angina (probable)
Meets two of the above characteristics.
Noncardiac chest pain
Meets one or none of the typical anginal characteristics.

SOURCE: Modified from Diamond et al.[7]

Angina is further labeled as *stable* when its characteristics are usually unchanged for 60 days or *unstable* (see Chap. 41). The presence of unstable angina predicts a much higher short-term risk of an acute coronary event. *Unstable angina* is defined as angina that presents in one of three major ways: *rest angina*, *severe new-onset angina*, or *prior angina increasing in severity* (see Chap. 41). Recently, the acute coronary syndromes of unstable angina and nonST-segment elevation myocardial infarction have been linked together by their similar presentation and treatment.[8a]

Usually, the discomfort of chronic stable angina pectoris is precipitated by physical activity, emotions, eating, or cold weather. Certain patients are able to describe accurately the extent and type of exercise at which they reproducibly experience their chest pain (see Chap. 10). Many patients with angina will develop chest discomfort if they walk up a hill after a large meal with a cold wind blowing in their face. Emotions, particularly anger, excitation, and frustration, often precipitate angina in patients with CAD. Cigarette smoking induces chest discomfort or lowers the exertion threshold for angina in some patients. A history of cocaine use should be sought because it can precipitate myocardial ischemia with or without infarction by coronary vasoconstriction.[9]

When stable angina pectoris develops, it often increases to a plateau over 10 to 30 s and usually disappears

within minutes if the exertion is discontinued. Occasionally, the angina will disappear despite continued physical activity, so-called walk-through angina. Most patients have discomfort that lasts only several minutes or up to 10 to 15 min, and rarely, up to 30 min (see Chap. 10).

The discomfort of angina is most often located substernally or just to the left of the sternum. Some patients, when describing the discomfort, clench their fist over their upper sternum (Levine's sign), a sign of high diagnostic accuracy. Less often, angina is located over the precordium. The discomfort is rarely localized only to the apex of the heart. Nevertheless, angina can be located anywhere from the epigastrium to the neck, and rarely it may be located only in the neck, throat, arm, or back.

The pain often radiates down the arms or to the neck, jaw, teeth, shoulders, or back. Radiation to the left side is more common, but both sides can be involved. The radiation, characteristically down the ulnar aspect of the arm, often is described as numbness. Increased heat or humidity also may lower the exertional threshold at which angina occurs.

Disorders that increase myocardial oxygen requirement (M_{O_2}) may exacerbate the occurrence of angina pectoris and sometimes may be associated with angina in the absence of moderate or severe CAD stenosis on coronary arteriography.

Patients with stable angina may have many episodes of myocardial ischemia that are asymptomatic or silent. Also, myocardial ischemia may result in symptoms from either systolic or diastolic left ventricular (LV) dysfunction without the chest discomfort characteristic of angina pectoris. Like chest discomfort due to angina, *angina equivalent* symptoms usually are associated with exertion and are relieved by rest and nitroglycerin. *Exertional dyspnea* likely is due to reduced diastolic LV compliance resulting from myocardial ischemia. *Exertional fatigue* or exhaustion probably results from an acute decrease in cardiac output due to diminished systolic LV function and/or associated mitral regurgitation from transient papillary muscle dysfunction.

In general, when myocardial ischemia is produced, an *ischemic cascade* occurs. Regional diastolic and systolic dysfunction precede global diastolic and then systolic dysfunction, which in turn often occurs prior to changes in the electrocardiogram (ECG) and before the symptoms of angina pectoris (Fig. 40-1). Noninvasive testing often is useful in detecting ischemia (see below). The detection of LV diastolic dysfunction by Doppler mitral valve recording or by diastolic filling curves using radionuclide ventriculography has many limitations (see Chaps. 13 and 16). Although diaphoresis and alterations in blood pressure and heart rate may occur, the physical examination is often normal. An examination performed during an episode of pain, however, can be useful. A fourth (most common) or third heart sound, a mitral regurgitant systolic murmur, reversed splitting of the S_2, bibasilar pulmonary rates, or palpable ectopic cardiac impulses that disappear when the pain subsides are all predictive of CAD (see Chap. 10). Carotid sinus pressure often terminates angina chest pain. Evidence of noncoronary atherosclerotic disease such as a carotid bruit, diminished pedal pulse, or abdominal aneurysm increases the likelihood of CAD. An elevated blood pressure, xanthomas, and retinal exudates point to the presence of CAD risk factors[6] (see Chap. 10).

Clinical Assessment of the Likelihood of CAD

The clinicopathologic study performed by Diamond and Forrester[10] demonstrated that it is possible to predict the probability of CAD after the history and the physical examination. By combining data from several angiographic studies performed before 1980, they showed that simple clinical observations of pain type, age, and sex were powerful predictors of the probability of CAD.

The utility of the Diamond and Forrester approach was confirmed subsequently in prospective studies at Duke and Stanford.[11-13] In both men and women referred for cardiac catheterization or for cardiac stress testing, the initial clinical characteristics most helpful in predicting CAD were determined. In these studies, age, sex, and pain type were the most powerful predictors (Table 40-2). Smoking, Q waves, or ST-segment-T-wavechanges on ECG, hyperlipidemia, and diabetes further strengthened the predictive abilities of these

models.[1,13]

Table 40-2: Pretest Likelihood of CAD in Symptomatic Patients According to Age and Sex* (Combined Diamond/Forrester and CASS Data)[7-10]

	NONANGINAL CHEST PAIN		ATYPICAL ANGINA		TYPICALANGINA	
Age, years	Men	Women	Men	Women	Men	Women
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

*Each value represents the percent with significant CAD on catheterization.
SOURCE: Modified from Gibbons et al.[1]

Special Tests for Diagnosis

Most special tests in patients with suspected stable angina are performed either to establish the diagnosis and/or to determine the risk for coronary events.[1] In general, men with a history of classic angina pectoris have a higher probability of having significant CAD on coronary arteriography than do women. Table 40-2 indicates the likelihood for each gender by age and characteristics of the chest discomfort. It also indicates why women have more false-positive responses to ECG exercise testing than do men (see Chap. 14). Terms useful in the evaluation and selection of diagnostic tests for CAD are listed in Table 40-3. Bayes' theorem states that the pretest prevalence of disease influences the posttest likelihood of significant CAD (see Chap. 14). Figure 40-2 illustrates the impact of Bayes' theorem when evaluating several diagnostic tests for CAD. More accurate data on the sensitivity and specificity of noninvasive testing for diagnosis of CAD are provided in Chaps. 13, 14, 16, and 17.

Table 40-3: Glossary of Terms

True positive (TP): Positive result in patient with disease
True negative (TN): Negative result in patient without disease
False positive (FP): Positive result in patient without disease
False negative (FN): Negative result in patient with disease

$$\text{Sensitivity: } \frac{TP}{TP + FN}$$

$$\text{Specificity: } \frac{TN}{TN + FP}$$

$$\text{Predictive value of a positive test: } \frac{TP}{TP + FP}$$

$$\text{Predictive value of a negative test: } \frac{TN}{TN + FN}$$

Bayes' theorem:

$$\text{Probability of disease presence with a positive test} = \frac{\text{sensitivity} \times \text{prevalence}}{(\text{sensitivity} \times \text{prevalence}) + [(1 - \text{specificity}) \times (1 - \text{prevalence})]}$$

$$\text{Probability of disease presence with a negative test} = \frac{(1 - \text{sensitivity}) \times \text{prevalence}}{[(1 - \text{sensitivity}) \times \text{prevalence}] + [\text{specificity} \times (1 - \text{prevalence})]}$$

If an exercise ECG test was performed by a 55-year-old woman with atypical chest pain and a pretest likelihood for coronary disease of 0.46, a positive ECG stress test response would indicate her posttest likelihood to be 0.86. If she had a positive thallium scan, her likelihood of disease would increase to 0.98; however, if her thallium scan were negative, the probability of disease would decrease to 0.63.

On the other hand, diagnostic tests should only be performed when necessary to answer a specific clinical question. Thus a diagnostic test may be of limited additional diagnostic value in patients with either a very high (>0.90) or a very low (<0.10) pretest risk for CAD.[1]

ELECTROCARDIOGRAM AND CHEST ROENTGENOGRAM

A resting 12-lead ECG should be recorded in all patients with symptoms suggestive of angina; however, it will be normal in up to 50 percent of patients with chronic stable angina. ECG evidence of LV hypertrophy or ST-segment-T-wave changes consistent with myocardial ischemia favor the diagnosis of angina pectoris. Evidence of prior Q-wave myocardial infarction (MI) on the ECG makes CAD very likely. Patients with a completely normal resting ECG rarely have significant LV systolic dysfunction.

The presence of arrhythmias (e.g., atrial fibrillation or ventricular tachyarrhythmias) on the ECG in patients with chest pain also increases the probability of underlying CAD; however, these arrhythmias frequently are caused by other types of cardiac disease. Various degrees of atrioventricular (AV) block occur in patients with chronic CAD but have a very low specificity for the diagnosis. Left anterior fascicular block, right bundle-branch block (RBBB), and left bundle-branch block (LBBB) often are present in patients with CAD and frequently indicate multivessel CAD. However, these findings also lack specificity for the diagnosis of chronic stable angina.

An ECG obtained during chest pain is abnormal in about 50 percent of patients with angina and a normal resting ECG. Sinus tachycardia is frequent; bradyarrhythmias are less common. ST-segment elevation or depression establishes a high likelihood of angina and indicates ischemia at a low workload, suggesting an unfavorable prognosis. Many high-risk patients with severe episodes of angina need no further noninvasive testing. Coronary arteriography usually defines the severity of CAD and determines the necessity and feasibility of myocardial revascularization. In patients with ST-segment-T-wave depression or inversion on the resting ECG, pseudonormalization of these abnormalities during pain is another indicator that CAD is likely.[14] The occurrence of tachyarrhythmias, AV block, left anterior fascicular block, or bundle-branch

block during chest pain also increases the probability of CHD and often leads to coronary arteriography.

The *chest roentgenogram* often is normal in patients with stable angina pectoris. Its usefulness as a routine test is *not* well established. It is more likely to be abnormal in patients with previous or acute MI, those with a noncoronary artery cause of chest pain, and those with noncardiac chest pain.

Coronary artery calcification increases the likelihood of symptomatic CAD. *Fluoroscopically detectable* coronary calcification is correlated with major vessel occlusion in 94 percent of patients with chest pain[15]; however, the sensitivity of the test is less than 40 percent.

Electron beam computed tomography (EBCT) (see Chap. 17) is being used with increased frequency. However, the specificity of a positive result may be as low as 49 percent, and the predictive accuracy is less than 70 percent. The role of EBCT in CAD diagnosis and risk stratification has been controversial.[16] A recent report of an ACC/AHA expert consensus writing group does not recommend EBCT for routine screening of asymptomatic patients for CAD or for its use in most patients with chest pain.[17] It also is of little use in detecting vulnerable plaques.[17a]

EXERCISE ECG STRESS TESTING

Exercise ECG stress testing is a well-established procedure that has been in widespread clinical use for many decades.[18] Although usually a safe procedure, both MI and death occur at a rate of up to 1 per 2500 tests[19] (see Chap. 14). Absolute contraindications include acute MI within 2 days, cardiac arrhythmias causing symptoms or hemodynamic compromise, symptomatic and severe aortic stenoses, symptomatic heart failure, acute pulmonary embolus or infarction, acute myocarditis or pericarditis, and acute aortic dissection.

For optimizing the information obtained, the protocol should be tailored to the individual patient, with exercise lasting at least 6 min.[20] Exercise capacity should be reported in estimated metabolic equivalents (METs) of exercise (1 MET is the standard basal oxygen uptake of 3.5 ml/kg/min) as well as in minutes.

The ECG, heart rate, and blood pressure should be monitored carefully and recorded during each stage of exercise, as well as during ST-segment abnormalities and chest pain, as detailed in Chap. 14.

Interpretation of the exercise ECG should include symptomatic response, exercise capacity, hemodynamic response, and ECG changes. The most important ECG abnormalities are ST-segment depression and ST-segment elevation (in leads without diagnostic Q waves) of greater than 1 mm for at least 60 to 80 ms after the end of the QRS complex. Although exercise testing often is terminated when subjects reach a standard percentage (often 85 percent of age-predicted maximum heart rate), there is a *great variability* in maximum heart rate among individuals. Many stress testing laboratories still utilize approaches that are not up to date.

A meta-analysis of 147 published reports describing 24,074 patients who underwent both coronary angiography and exercise testing found wide variation in sensitivity and specificity.[17] The mean sensitivity was 68 percent, and the mean specificity was 77 percent. When only studies that excluded patients with a prior MI were analyzed, the mean sensitivity was 67 percent, and the mean specificity was 72 percent. In the few studies that avoided workup bias by including only patients who agreed in advance to have both exercise testing and coronary angiography, the sensitivity was 50 percent, and the specificity was 90 percent.[1] In the most recent study of 814 men that minimized workup bias, sensitivity was 45 percent, and specificity was 85 percent.[21] Therefore, the true diagnostic value of the exercise ECG relates to its *relatively high specificity*. The modest sensitivity of the exercise ECG is generally lower than that of imaging procedures.

To improve the clinical usefulness of exercise ECG testing in the diagnosis of CAD, a treadmill score[20,22] was developed as well as a prognostic score that predicted 5-year survival using the amount of ST-segment depression, the degree of angina during exercise, and the duration of exercise.[23] Other methods employed include the ST/HR slope, calculated from linear regression of ST-segment depression against heart rate

(HR) during peak exercise,[24] and the simple ST/HR index, in which additional ST-segment depression is divided by the overall change in heart rate throughout the exercise period.[25] The cost-effectiveness of these techniques remains unknown.

Diagnostic testing is most valuable when the pretest probability of obstructive CAD is intermediate. In these conditions, the test result has the largest effect on the posttest probability of disease and thus on clinical decisions. Intermediate probability has been defined arbitrarily as between 10 and 90 percent; this definition has been used in several reports, including the ACC/AHA Exercise Test Guidelines.[18]

Special issues in ECG exercise testing include the effect of digoxin on ST-T wave changes, the usefulness of withholding beta-blocking drugs when possible, changes in ST-segment depression in patients with LBBB or RBBB, changes in the exercise ECG in patients with LV hypertrophy on ECG with or without repolarization abnormalities, and the usefulness of ECG testing in patients with resting ST-segment depression; these are discussed in great detail in Chap. 14 and ref. [18].

Exercise induced ST-depression usually occurs with LBBB and does not necessarily indicate ischemia.[26] However, in RBBB, ST-segment depression in the left chest leads (V_{5-6}) or inferior leads (II, aV_F) during exercise has the same significance as it does when the resting ECG is normal.

The difficulties of using exercise testing for diagnosing obstructive CAD in women have led to speculation that initial stress imaging may be preferable to standard ECG stress testing. There are insufficient data, however, to justify replacing standard exercise testing with stress imaging when evaluating women for CAD, and *women with a completely normal resting ECG* do not have a greater incidence of false-positive tests than men.[1]

REST ECHOCARDIOGRAPHY

Echocardiography can be useful for establishing a diagnosis of CAD and in defining the consequences of CAD in selected patients with chronic chest pain presumed to be chronic stable angina[1] (see Chap. 13). However, most patients undergoing a diagnostic evaluation for angina do not need a resting echocardiogram.[1]

Chronic ischemic heart disease, with or without angina, can result in impaired systolic LV function. The extent and severity of regional and global abnormalities are important considerations in choosing appropriate medical or surgical therapy.[25]

Echocardiographic findings that may help establish the diagnosis of chronic ischemic heart disease include regional systolic wall motion abnormalities, such as hypokinesis, akinesis, dyskinesis, and diminished segmental wall thickening.[27] Chronic CAD as a cause of ventricular septal wall motion abnormalities, however, must be distinguished from other conditions such as LBBB, presence of an intraventricular pacemaker, right ventricular volume overload, or prior cardiac surgery.[27]

Mitral regurgitation demonstrated by Doppler echocardiography may result from global LV systolic dysfunction, regional papillary muscle dysfunction, scarring and shortening of the chordae tendineae, papillary muscle rupture, or other causes.[27]

STRESS IMAGING FOR DIAGNOSIS

Patients who should undergo cardiac stress testing with imaging for the diagnosis of CAD as opposed to exercise ECG alone include those in the following categories: (1) complete LBBB, electronically paced ventricular rhythm, preexcitation syndromes, and other similar ECG conduction abnormalities, (2) patients who have greater than 1 mm of resting ST-segment depression, including those with LV hypertrophy or those taking drugs such as digitalis, (3) patients who are unable to exercise to a level high enough to give meaningful results on routine stress ECG (pharmacologic stress imaging should be considered), and (4)

patients with angina who have undergone prior revascularization, in whom localization of ischemia, establishing the functional significance of lesions, and demonstrating myocardial viability are important considerations. In our experience, false-positive ECG tests often occur in patients with hypertension, no evidence of LV hypertrophy on the ECG, but LV hypertrophy by echocardiography. Stress imaging is utilized in most patients with a history of hypertension even when the resting ECG is normal.

Several methods can be used to induce stress, including (1) exercise (treadmill or bicycle) and (2) pharmacologic techniques (dobutamine or vasodilator drugs). When the patient can exercise to an appropriate level of cardiovascular stress for 6 to 12 min, exercise stress testing generally is preferred to pharmacologic stress.[1]

Myocardial Perfusion Imaging

In patients with suspected or known chronic stable angina, the largest accumulated experience in myocardial perfusion imaging (MPI) has been with the isotope thallium-201; however, the available evidence suggests that the newer isotopes technetium-99m (^{99m}Tc) sestamibi and ^{99m}Tc tetrofosmin provide similar diagnostic accuracy (see Chap. 16). Thus, for the most part, these isotopes can be used interchangeably, with a similar diagnostic accuracy for CAD.[27]

MPI may use either planar or single-photon-emission computed tomography (SPECT), visual analyses, or quantitative techniques (see Chap. 16). Quantification using horizontal or circumferential profiles may improve the test's sensitivity, especially in patients with single-vessel disease. For the less commonly used thallium-201 planar scintigraphy, average reported values of sensitivity and specificity (uncorrected for posttest referral bias) have been in the range of 83 and 88 percent, respectively, for visual analysis and 90 and 80 percent, respectively, for quantitative analyses.[28] Thallium-201 SPECT generally is more sensitive than planar imaging for diagnosing CAD, localizing hypoperfused vascular segments, identifying left anterior descending and left circumflex coronary artery stenoses, and accurately predicting multivessel CAD. The average sensitivity and specificity of exercise thallium-201 SPECT imaging (uncorrected for referral bias) are in the range of 89 and 76 percent, respectively, for qualitative analyses and 90 and 70 percent, respectively, for quantitative analyses.[28]

Pharmacologic stress uses dipyridamole or adenosineinduced coronary vasodilatation as an adjunct to thallium-201 myocardial perfusion imaging.[29] Dipyridamole planar scintigraphy has a high sensitivity (90 percent average) and acceptable specificity (70 percent average) for the detection of CAD. Dipyridamole SPECT with thallium-201 or ^{99m}Tc sestamibi is as accurate as planar imaging, and results of myocardial perfusion imaging during adenosine infusion are similar to those obtained with dipyridamole and exercise imaging[30] (see Chap. 16). Evidence of CAD is demonstrated by redistribution defects comparing stress and resting scintigrams (ischemia), fixed defects at rest (scar), and LV dilatation or lung uptake of isotope during stress[28] (see Chap. 16).

Stress Echocardiography

Stress echocardiography is based on the assessment of myocardial thickening during stress compared with baseline (see Chap. 13). Echocardiographic findings suggestive of myocardial ischemia include (1) decrease in wall motion in one or more LV segments with stress, (2) diminution in systolic wall thickening in one or more segments during stress, and (3) compensatory hyperkinesis in complementary (nonischemic) wall segments.[27] The use of digital acquisition and storage, as well as side-by-side display of cine loops of LV images acquired at rest and at different levels of stress, has improved efficiency and accuracy in interpretation of stress echocardiograms.[27]

In 36 studies including 3210 patients, the reported overall sensitivities (uncorrected for referral bias) ranged from 70 to 97 percent. The average overall sensitivity was 85 percent for exercise echocardiography and 82 percent for dobutamine stress echocardiography.[24] The reported sensitivity of exercise echocardiography for multivessel disease was higher (approximately 90 percent) than the sensitivity for single-vessel disease (approximately 79 percent). In this series of studies, specificity averaged approximately 86 percent for

exercise echocardiography and 85 percent for dobutamine echocardiography.[27]

Pharmacologic stress echocardiography is best accomplished using dobutamine because it enhances myocardial contractile performance and wall motion, both of which can be evaluated directly by echocardiography (see Chap. 13). In 36 studies, average sensitivity and specificity (uncorrected for referral bias) of dobutamine stress echocardiography in the detection of CAD were 82 and 85 percent, respectively.[27]

Additional information concerning the sensitivity of exercise imaging in patients receiving beta blockers, the need for pharmacologic stress imaging in patients with LBBB, and the accuracy of myocardial perfusion and echocardiographic imaging in selected patient subgroups is included in Chaps. 13, 14, and 16.

Echocardiographic and MPI have complementary roles, and both add value to routine stress ECG under appropriate circumstances, as outlined earlier. The choice of which test to perform depends importantly on issues of local expertise, available facilities, and considerations of cost-effectiveness. A summary of the comparative advantages of stress myocardial perfusion imaging and stress echocardiography is provided in Table 40-4.

Table 40-4: Comparative Advantages of Stress Echocardiography and Stress Radionuclide Perfusion Imaging in Diagnosis of CAD

Advantages of stress echocardiography

1. Higher specificity
2. Versatility. More extensive evaluations of cardiac anatomy and function
3. Greater convenience/efficacy/availability
4. Lower cost

Advantages of stress perfusion imaging

1. Higher technical success rate
2. Higher sensitivity, especially for single-vessel coronary disease involving the left circumflex
3. Better accuracy in evaluating possible ischemia when multiple resting LV wall motion abnormalities are present
4. More extensive published data base, especially in evaluation of prognosis

SOURCE: From Gibbons et al.[1]

Coronary Angiography for Diagnosis

Direct referral for diagnostic coronary angiography in patients with chest pain, possibly due to myocardial ischemia, is appropriate when noninvasive tests are contraindicated or likely to be inadequate due to illness, disability, or physical characteristics.[1] Many patients with obesity, chronic obstructive pulmonary disease, bronchospasm, and heart failure are likely to have suboptimal imaging tests; diagnostic coronary angiography will provide accuracy diagnostic information with minimal risk.

Patients with noninvasive tests that are abnormal but not clearly diagnostic often require clarification of an uncertain diagnosis by coronary angiography. In certain cases, a second noninvasive test (imaging modality) may be recommended for a patient with a low likelihood of CAD but an intermediate risk treadmill result. Coronary angiography is likely to be most appropriate for a patient with a high-risk treadmill outcome.[1]

In individuals with symptoms consistent with but not diagnostic of stable angina, coronary angiography may be a necessity when the patient's occupation or activity could constitute a risk to themselves or others (e.g., pilots, firefighters, professional athletes).[1] When typical or atypical symptoms suggest stable angina and there is high clinical probability of severe CAD, direct referral for coronary angiography may be indicated and cost-effective.[31] In diabetic patients, the diagnosis of chronic stable angina can be particularly difficult because of the absence of characteristic symptoms of myocardial ischemia due to the autonomic and sensory neuropathy (see also Chap. 78). Thus a lower threshold for coronary angiography is appropriate. Special groups for the consideration of coronary angiography include women, who more often have atypical chest discomfort, and the elderly, in whom symptoms are common, noninvasive testing may be difficult, and comorbid conditions that mimic angina pectoris are frequent.[1] Coronary angiography is useful in patients in whom coronary artery spasm is suspected, in younger patients with signs or symptoms of myocardial ischemia possibly due to coronary anomalies, in patients with a history of cocaine use, and in patients experiencing sudden death or ventricular arrhythmias.[1,32] The ACC/AHA recommendations concerning the value of coronary angiography are listed in Table 40-5. Coronary angiographic findings in patients with chronic stable angina are depicted in Fig. 40-3.[32]

Table 40-5: Invasive Testing: Coronary Angiography (Recommendations for Coronary Angiography to Establish a Diagnosis in Patients with Suspected Angina, Including Those with Known CAD Who Have a Significant Change in Anginal Symptoms)

Class I

1. Patients with known or possible angina pectoris who have survived sudden cardiac death

Class IIa

1. Patients with an uncertain diagnosis after noninvasive testing in whom the benefit of a more certain diagnosis outweighs the risk and cost of coronary angiography
2. Patients who cannot undergo noninvasive testing due to disability, illness, or morbid obesity
3. Patients with an occupational requirement for a definitive diagnosis
4. Patients who by virtue of young age at onset of symptoms, noninvasive imaging, or other clinical parameters are suspected of having a nonatherosclerotic cause of myocardial ischemia (coronary artery anomaly, Kawasaki disease, primary coronary artery dissection, radiation-induced vasculoplasty)
5. Patients in whom coronary artery spasm is suspected and provocative testing may be necessary
6. Patients with a high pretest probability of left main or 3-vessel CAD

Class IIb

1. Patients with recurrent hospitalization for chest pain in whom a definite diagnosis is judged necessary
2. Patients with an overriding desire for a definitive diagnosis and a greater than low probability of CAD

Class III

1. Patients with significant comorbidity in whom the risk of coronary arteriography outweighs the benefits of the procedure
2. Patients with an overriding personal desire for a definitive diagnosis and a low probability of CAD

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful and in some cases may be harmful.
SOURCE: From Gibbons et al.[1]

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Chapter 40: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

DIFFERENTIAL DIAGNOSIS

Table 40-6 lists the differential diagnoses of angina pectoris. Usually, the distinction is clear if an accurate history is obtained and a complete, accurate physical examination is performed (see Chap. 10).

Table 40-6: Differential Diagnosis of Angina Pectoris

Cardiovascular

- Myocardial ischemia
  - Coronary atherosclerosis
  - Coronary vasospasm
  - Congenital coronary artery disease
    - Anomalous origin
    - Aberrant coronary artery
    - Coronary arteriovenous fistula
- Kawasaki's disease
- Small vessel disease
- Microvascular angina (syndrome X)
- Systemic arterial hypertension
- Hypertrophic cardiomyopathy
- Idiopathic dilated cardiomyopathy
- Aortic valve disease
- Coronary artery dissection(Marfan's syndrome)
- Pulmonary hypertension
- Right ventricular hypertension
- Chronic obstructive pulmonary disease
- Syphilitic aortitis coronary ostial disease
- Collagen vascular disease
  - Periarteritis nodosa
  - Systemic lupus
  - Erythematosus
  - Rheumatoid arthritis
- Cardiac amyloid
- Cardiac tumors
- Hereditary connective tissue
  - Pseudoxanthoma Elasticum
  - Cystic medial necrosis
  - Homocystinuria
  - Gargoylism
  - Severe anemia, hypoxia
  - High-dose x-irradiation
  - Withdrawal from chronic nitroglycerin exposure
- Nonmyocardial ischemia
  - Aortic dissection

- Discrete thoracic aortic aneurysm
- Mitral valve prolapse
- Tachycardia, bradycardia
- Palpitations
- Pericarditis

Thoracic-respiratory

- Pulmonary embolism, infarction
- Pneumothorax
- Pneumomediastinum (mediastinal emphysema)
- Pleuritis
- Epidemic pleurodynia (Bornholm's disease)
- Mediastinitis
- Intrathoracic malignancy
- Café Coronary

Gastrointestinal

- Gastroesophageal reflux, esophagitis
- Esophageal spasm
- Esophageal rupture(Mallory-Weiss syndrome; Boehaave's syndrome)
- Esophageal impaction
- Hiatal hernia
- Cholecystitis, gallstones
- Gastritis
- Peptic ulcer disease
- Pancreatitis
- Splenic infarction
- Splenic flexure syndrome

Neuromuscular/skeletal

- Chest wall pain
- Costochondritis (Tietze's syndrome)
- Cervical or thoracic degenerative arthritis, nerve compression,radiculopathy
  - Cervical vertebral disk
  - Intercostal neuralgia
- Thoracic outlet(scalenus anticus)syndrome
- Shoulder arthropathies
- Shoulder hand syndrome
- Fibromyalgia (myofascial pain syndrome; fibromyositis)
  - Pectoral, intercostal, seratus anterior
  - Precordial catch syndrome
- Cardiac causalgia
- Bursitis
- Superficial thrombophlebitis of thoracicveins (Mondor's syndrome)
- Xiphoidalgia
- Diaphragmatic flutter

Neurocutaneous

- Herpes zoster

Breast

- Pendulous breast syndrome
- Brassiere syndrome

Psychologic

- Anxiety
- Hyperventilation
- Panic attacks
- Depression
- Self-gain
- Munchausen syndrome

Patients with hypertensive or valvular heart disease may have chest pain that is located at the apex rather than substernally and that is often associated with hyperesthesia of the left breast or precordium.[6] Many patients with no functional heart disease have pain over the LV apex that often occurs at rest. Chest wall pain, cervical arthritis, and subdeltoid bursitis can occur with exertion and are relieved by rest. Importantly, patients frequently have more than one type of chest pain.[1]

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Chapter 40: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

PATHOPHYSIOLOGY

In patients with stable angina pectoris due to atherosclerotic CAD, the correlation between the severity or extent of atherosclerosis and the magnitude of angina symptoms is poor. Also, no definite relation exists between the location of the chest discomfort and the site of the myocardial ischemia. Women have angina as the initial manifestation of CAD more often than men, who often present with acute MI. The pathology of coronary atherosclerosis is discussed in detail in Chap. 36. The nonatherosclerotic causes of CHD are discussed in Chap. 39.

A disparity between the supply of coronary blood flow (CBF) and the metabolic demands of the myocardium (M_{O_2}) is the primary factor in ischemic heart disease. This imbalance may result in clinical manifestations of ischemia when myocardial demand exceeds the capacity of the coronary arteries to deliver an adequate supply of oxygen. In normal hearts there is an excess CBF reserve so that ischemia does not occur even with very vigorous exercise.[34]

Arteriosclerotic disease in either the epicardial coronary arteries or in the coronary microvasculature may cause an imbalance between supply and demand at even modest levels of exercise. An understanding of the determinants of CBF and myocardial metabolic demand is important in the management of chronic ischemic heart disease.[6]

Myocardial Oxygen Demand

The major relevant determinants of M_{O_2} are heart rate, contractility, and systolic wall stress (Fig. 40-4). A detailed discussion of the major and minor determinants of myocardial oxygen demand is presented in Chaps. 3 and 37. Heart rate is one of the most important determinants of M_{O_2} and can be altered easily by medical therapy in most patients.[35]

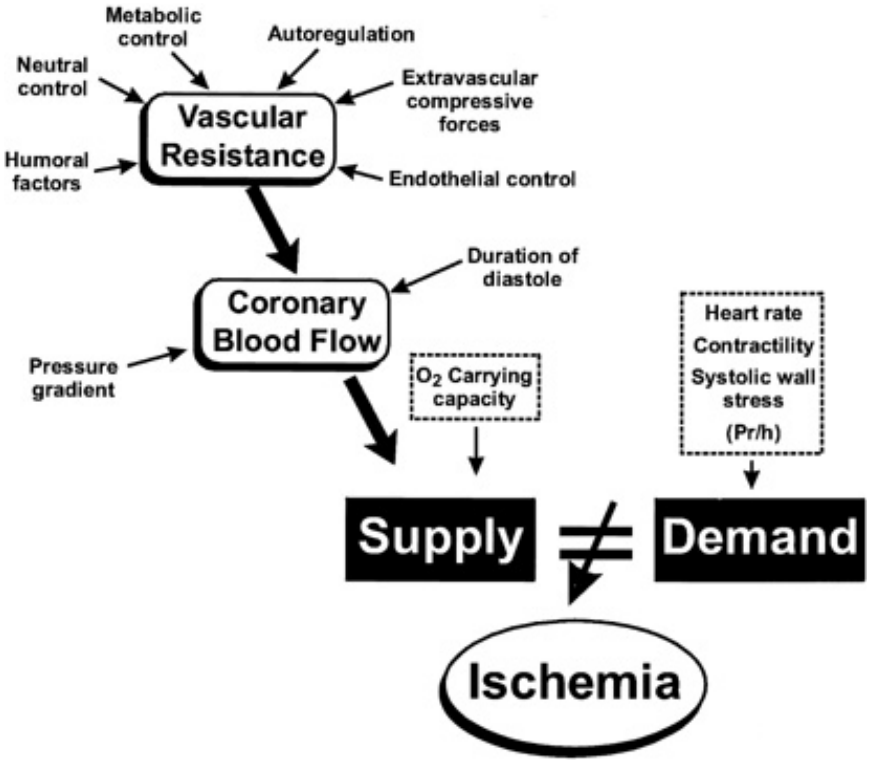

Figure 40-4: Factors controlling myocardial oxygen demand. *P*, systolic pressure; *r*, radius; *h*, wall thickness. (Modified from Ardehali A, Ports TA. Myocardial oxygen supply and demand. *Chest* 1990; 98:699-705. Reproduced with permission from the publisher and authors.)

Myocardial contractility, partially reflected in the isovolumic rate of change of LV pressure (*dP/dt*), is a major determinant of M_{O_2} but not usually a primary factor for therapeutic intervention. However, LV systolic wall stress is an important consideration in the medical treatment of angina pectoris.

Systolic wall stress is directly related to the LV systolic pressure (*P*) and radius (*r*) and inversely related to wall thickness (*h*). Thus, reducing systolic pressure afterload (i.e., treating hypertension) can decrease M_{O_2}. Decreasing preload by venodilation, and thus reducing LV size and oxygen consumption, is an important mechanism for the efficacy of nitrate therapy in angina pectoris. Positive inotropic agents actually may decrease M_{O_2} in patients with an enlarged left ventricle if the results of a diminished LV radius outweigh those of increasing contractility.

Myocardial Oxygen Supply

Oxygen supply to the myocardium depends on the oxygen-carrying capacity of the blood and on CBF (see Fig. 40-4). Although a decrease in oxygen-carrying capacity may contribute to the development or exacerbation of myocardial ischemia in severe anemia, myocardial ischemia related to oxygen supply usually results from inadequate CBF.

The arteriolar resistance vessels are normally the primary regulators of CBF because the epicardial arteries are low-resistance conduits. Narrowing of the large coronary arteries transiently by vasospasm or permanently by obstructive lesions may increase the coronary resistance sufficiently to reduce CBF.

In the past decade, the pathophysiologic role of the coronary microvasculature has been recognized,[36,37] either concomitantly with atherosclerotic narrowing of the large-conduit arteries

or predominantly in anginal syndromes with normal epicardial arteries (syndrome X).[38,39]

The determinants of CBF are relatively complex and include (1) metabolic control, (2) autoregulation, (3) extravascular compressive forces, (4) duration of diastole, (5) humoral agents composed of both circulating hormones and autocrine and paracrine factors produced within the arterial wall and in particular by the endothelium, (6) neural control, and (7) the difference between aortic diastolic pressure and right atrial pressure[6] (see Fig. 40-4).

CBF is relatively constant, being autoregulated during perfusion pressures between 60 and 160 mmHg.[40] Below a perfusion pressure of 60 mmHg, vasodilator reserve disappears, and blood flow is directly related to perfusion pressure. Experimentally, loss of vasodilator reserve occurs distal to lesions with an 85 percent decrease in diameter.[41] A decrease in CBF, likely due to vasoconstriction and loss of vasodilator reserve, has been observed despite an increase in blood pressure during cold pressor stimulation in patients with significant CAD.[42]

Extravascular compressive forces, including intrapericardial, intramyocardial, and intraventricular pressures, are important in the control of CBF and account for 30 to 50 percent of the vascular resistance.[6] Since intramyocardial and intraventricular pressures are maximal during systole and are exerted maximally on the subendocardium, LV subendocardial blood flow decreases during systole. Thus subendocardial blood flow is most vulnerable whenever total blood flow is decreased or M_{O_2} is increased and blood flow is limited. Because of the systolic compressive forces, the subendocardium is also critically dependent on the duration of diastole for its blood flow (see Chap. 37).

CBF is regulated by systemic hormones and by neural control mechanisms similar to other vascular beds. Angiotensin II is a coronary vasoconstrictor; beta-adrenergic agonists dilate and alpha-adrenergic agonists constrict coronary arteries, although there are some regional differences in distribution of receptors in vessels of different sizes.[6] Importantly, the integrated vasomotor response to the various vasoactive stimuli affecting a coronary artery or arteriole appears greatly influenced by the functional state of the endothelium (see Chaps. 6 and 37).

Endothelial Function and Coronary Vasomotor Control

The phenomenon of endothelial-dependent relaxation[43] and the identification of endothelial-derived relaxing factor as nitric oxide[44] are discussed in detail in Chap. 6. The defect in endothelial-dependent dilatation in atherosclerotic epicardial coronary arteries that vasoconstrict in response to stimuli that normally cause vasodilation, such as acetylcholine, exercise, or cold pressure testing, is discussed in Chap. 37, as is the role of dysfunctional endothelium in both the stable and unstable coronary artery syndromes.

The majority view is that endothelium-dependent vasodilator mechanisms are predominant in nondiseased epicardial coronary arteries. Thus interventions such as exercise,[45] mental stress,[46] cold pressure testing,[47] or even pacing-induced tachycardia,[48] which normally induce increases in M_{O_2} and flow, are associated with epicardial dilatation that is at least partially endothelial-dependent. The presence of even nonocclusive, early atherosclerosis appears to attenuate this vasodilator mechanism and results in prevailing constrictor forces.[6]

The local infusion of the alpha-adrenergic agonist phenylephrine does not constrict normal coronary arteries of patients with intact endothelial-dependent dilatation.[49] However, vasoconstriction occurs in even minimally diseased coronary arteries at low concentrations of phenylephrine. Thus in CAD there appears to be both loss of endothelial-dependent dilatation and

an enhanced vasoconstrictor sensitivity to catecholamines. This disordered vasomotor control is an important contributor to the variability in anginal threshold commonly observed in many patients.[50]

Moderate vasoconstriction of a minimal stenosis may have little hemodynamic importance, whereas the same degree of vasoconstriction of a higher-grade stenosis may markedly decrease blood flow and induce ischemia.

The Microvasculature and Coronary Ischemia

The recognition of the likely importance of the coronary microvascular resistance vessels in the pathogenesis of angina pectoris resulted from studies of patients with angina-like chest pain and angiographically normal epicardial coronary arteries.[51-55]

The coronary etiology of the chest pain is supported by the frequent but not universal evidence of ischemia in these patients during exercise testing[56]; many were found to have abnormal vasodilator reserve.[56] Specifically, in patients with angina and angiographically normal coronary arteries, endothelial-dependent vasodilatation of the resistance arteries, as reflected in the responses of CBF to infusion of the endothelial-dependent vasodilator acetylcholine, was diminished relative to controls.[58]

In contrast, the flow responses to the non-endothelial-dependent dilators, isosorbide dinitrate and papaverine were no different between patients and controls, suggesting that the intrinsic vasodilator capacity of the resistance arteries was not defective. Similar defects in endothelial-dependent increases in CBF have been observed in LV hypertrophy associated with hypertension, another condition that may be associated with angina pectoris with angiographically normal epicardial coronary arteries.[58]

The histopathology of biopsy specimens from patients with normal epicardial coronaries but with anginal syndromes has demonstrated capillary narrowing with swollen endothelium encroaching on the lumen as well as decreased capillary density. Thus the coronary microvasculature can develop dysfunction of vasomotor control mechanisms and of endothelial-dependent vasodilation that may become clinically significant in the setting of increased demand or M_{O_2}. In this situation, the loss of vasodilator reserve and/or the actual constriction of resistance arterioles may induce ischemia and chest pain.[6]

Spectrum of Pathophysiologic Mechanisms Associated with the Stable Coronary Ischemia Syndromes

Symptomatic myocardial ischemia due primarily to microvascular abnormalities in the control of coronary vascular tone partially explains the characteristics of stable angina syndromes. Angina pectoris or anginal equivalents, with a *relatively constant* threshold for inducing ischemic symptoms due to a fixed stenoses of an epicardial coronary artery, also in part determine the spectrum of angina symptoms. Most patients have a somewhat variable threshold for inducing angina from day to day or even at different times of the day.

Interestingly, the same activity that causes chest discomfort in the early morning may not do so in the afternoon or evening. Yet the patient may have a consistent level of exercise for inducing ischemia on protocol exercise testing because of the augmented M_{O_2} that is due to increases in heart rate, contractility, and blood pressure and the associated increment in systolic wall stress. This is explained by the presence of both flow-limiting epicardial coronary stenosis and associated episodic vasoconstriction.

Maseri et al.[50] have termed have termed this phenomenon *mixed angina*. Myocardial ischemia is induced by both an increase in M_{O_2} and a decrease in CBF. The site(s) of vasoconstriction may be at an epicardial stenoses, in the microvasculature, or at both locations.[61] The concept of a *variable flow reserve* that interacts with differing metabolic demands to produce intermittent ischemia is depicted in Fig. 40-5*A* and *B*.

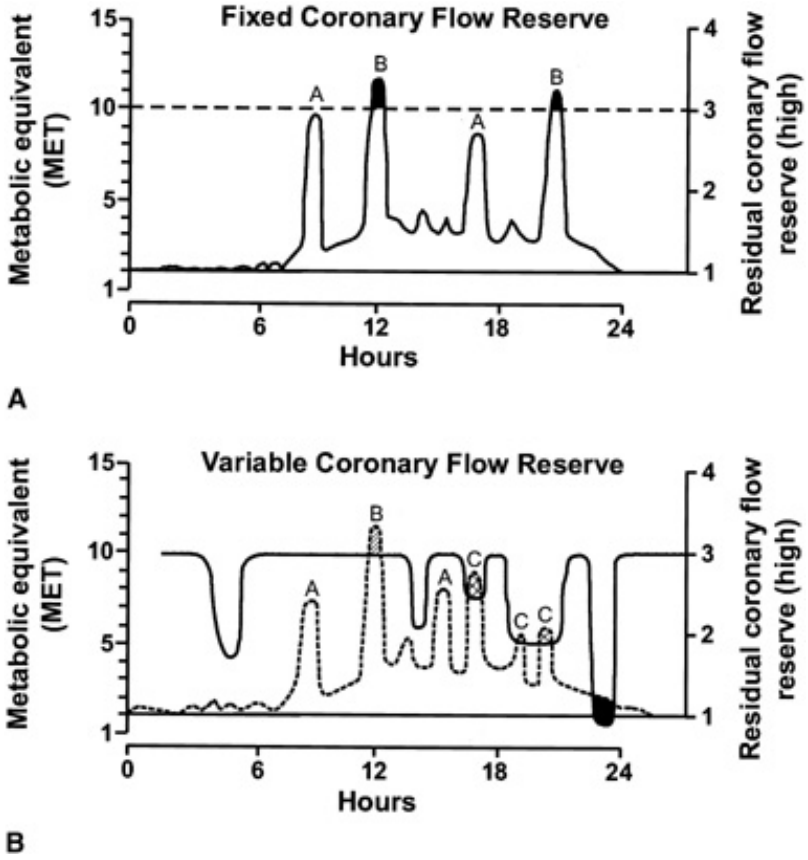

Figure 40-5: Concept of variable coronary flow reserve in the presence of variable atherosclerotic obstruction. *A*. Episodes not associated with ischemia. *B*. Ischemic episode occurring at levels of exercise exceeding threshold of residual coronary flow reserve. *C*. Ischemic episodes occurring at lower levels of exercise when residual coronary flow is reduced. *D*. Ischemic episodes occurring at rest in the presence of maximal reduction in residual coronary flow reserve. --, residual coronary flow reserve; - - -, variable atherosclerotic obstruction as measured by MED. (Modified from Cohn PF. Mechanisms of myocardial ischemia. *Am J Cardiol* 1992; 70:14G-18G; and Maseri A. Role of coronary artery spasm in symptomatic and silent myocardial ischemia. *J Am Coll Cardiol* 1987; 9:249-262. Reproduced with permission from the authors and publishers.)

In the stable anginal syndromes, the predominant vasoconstrictors are likely neural and hormonal, whereas in the unstable (acute) coronary syndromes, platelet and coagulation products as well as inflammatory mediators are important contributors (see Chap. 41). Patients with predominantly vasoconstrictor pathophysiology in an epicardial vessel have been classified as having *vasospastic angina* or *Prinzmetal's variant angina* (see Chap. 41).

Cellular Bases for the Clinical Manifestations of Ischemia

The cellular effects of myocardial ischemia are discussed in detail in Chaps. 36 and 37. The rapid decreases in systolic function and diastolic compliance that are associated with creatine phosphate

depletion and ionic shifts will increase LV enddiastolic pressure. Elevated pulmonary vascular pressures often stimulate mechanoreceptors and mediate the dyspnea response. Dyspnea may be associated with angina or may be present as an anginal equivalent in patients who do not develop chest discomfort.

The metabolic abnormalities due to ischemia cause cellular depolarization and the flow of electric currents between normal and ischemic areas that are reflected on the ECG.[6] ST-segment depression reflecting subendocardial underperfusion is the most common ECG manifestation of ischemia in chronic stable angina during ambulatory recordings or exercise testing.[62] The ST-segment depression observed during exercise testing or ambulatory ECG recordings is not commonly associated with complex or life-threatening ventricular arrhythmias; exercise-induced ventricular ectopic activity is not a reliable predictor of cardiac events in asymptomatic persons.[63]

The Coronary Ischemia Cascade

Studies in which hemodynamic and ECG recordings have been performed during spontaneous episodes of ischemia, either in unstable patients or during balloon inflation at angioplasty, have provided insights into the sequential responses evoked at the onset of ischemia and are consistent with those described in animals undergoing acute coronary artery ligation[64] (see Fig. 40-1).

After balloon inflation, impaired LV compliance occurs within a few seconds and is followed rapidly by systolic contractile dysfunction causing a decrease in LV ejection fraction of up to 30 percent within 10 s.[64] ECG changes occur at about 20 s, and angina, if it occurs, appears at between 25 and 30 s.

Considering this "ischemic cascade," there are likely to be episodes that do not progress to angina. Since many patients do not perceive coronary ischemic pain or have high pain thresholds, the common occurrence of asymptomatic (silent) ischemia in individuals with CAD is not surprising.

Hemodynamic measurements and ECG recording of patients with spontaneous or exercise-induced ischemia provide physiologic explanations for many of the classic clinical observations about angina.

As noted earlier, an anginal episode may be associated with new physical findings, including the development of an S_4, systolic bulging of the precordium, mitral regurgitation due to papillary muscle dysfunction, and reversed splitting of S_2. The fourth heart sound (S_4) reflects diastolic ventricular dysfunction and decreased ventricular compliance, whereas the remaining features reflect ventricular systolic dysfunction, including a prolonged LV ejection time accounting for the reversed splitting of S_2.

In addition, the crescendo-decrescendo nature of anginal pain is reflected in the crescendo-decrescendo pattern of the development and resolution of ischemic ST-segment changes and elevations in LV filling pressure recorded during exercise-induced angina.

Circadian Rhythm of Coronary Ischemia

The prevalence of MI, unstable angina, variant angina, and silent ischemia is greatest in the morning during the first few hours after awakening, and the threshold for precipitating anginal attacks in patients with stable angina also appears to be lowest in the morning.[65,66] Patients often develop ST-segment depression and angina at lower thresholds during exercise testing in the morning than later in the day. Studies with ambulatory ECG recordings have confirmed that the

incidence of both painful and painless episodes of ST-segment depression is highest in the morning[66] and, in particular, in the first few hours after awakening (Fig. 40-6).

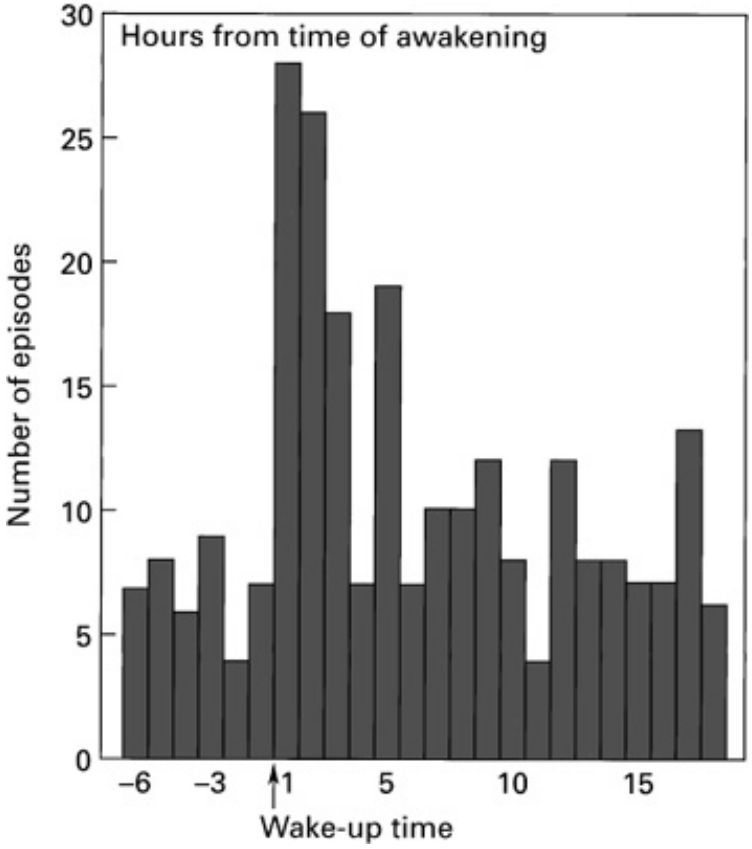

Figure 40-6: When the frequency of episodes is displayed hourly from the time of awakening, the peak activity occurs in the first and second hour after arising. (From Rocco et al.[67] Reproduced with permission from the authors and publishers.)

The diurnal variation in ischemic threshold is attributed to the endogenous rhythms of catecholamine secretion and to the sensitivity to coronary vasoconstrictors, both of which appear to peak in the morning. The increase in sympathetic nervous system activity is associated with increases in heart rate, blood pressure, contractility, and M_{O_2}. The lowered morning anginal threshold and the higher morning systolic blood pressure have *important therapeutic implications*. A decrease in the frequency of ischemia can be achieved by blunting the morning surge of beta-adrenergic stimulation by the administration of beta blockers. The control of hypertension by the *early morning use of antihypertensive drugs* is also important. In patients with recurrent morning angina, the use of nitroglycerin (TNG) soon after awakening may prevent angina in many instances.

Mechanisms of Anginal Pain

Angina pain is a useful warning system, but it is often too insensitive. Pain stimuli arise within the myocardium and most likely stimulate free nerve endings in or near small coronary vessels. Impulses travel in afferent unmyelinated or small myelinated cardiac sympathetic nerves through the upper five thoracic sympathetic ganglia to dorsal horn cells and through the spinothalamic tract of the thalamus and then to the cortex.[67]

Integration and modification of these impulses occur at several levels, including the cerebral

cortex. This modulation also may contribute importantly to the variability in anginal threshold. At the cortical level, psychosocial and cultural factors may alter the perception of pain. The radiation patterns of angina are determined by the levels of the thoracic spinal cord that share the sensory inputs from the heart and from somatic structures.

The nature of the stimuli causing angina has been difficult to delineate. The causes are probably chemical, and several molecules, including kinins, serotonin, hydrogen ions, and inflammatory mediators, have been proposed. By contrast, adenosine, which is increased during ischemia, has been shown to cause anginal-type pain during intravenous infusion in normal volunteers.[68] The precise mechanisms causing angina pain are yet to be defined.

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Chapter 40: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

ASYMPTOMATIC (SILENT) ISCHEMIA IN STABLE CAD

The presence of unrecognized myocardial infarction due to the absence of pain was mentioned by Herrick in 1912.[69] The frequent presence of extensive CAD and MI at autopsies of apparently asymptomatic persons was recognized later.[70] Direct evidence of asymptomatic (silent) ischemia during ECG exercise testing and during ambulatory ECG recording stimulated interest in this clinical entity.[71]

Prevalence of Silent Ischemia

Asymptomatic ischemic episodes may be present in patients with any of the ischemic coronary syndromes, including unstable angina and silent ischemia after MI; they may be observed in patients who are totally asymptomatic or who have chest discomfort with some episodes of ischemia but not with others.[72] The prevalence of silent ischemic episodes approaches 40 percent in patients with chronic stable angina or in those with a history of instability.[73] The incidence of asymptomatic ischemia occurring in individuals with extensive CAD has been estimated at 5 percent.[74] ST-segment depression of 60 s or more on ambulatory recordings is uncommon in patients with no evidence of CAD.[75,76]

A prospective study of 68-year-old men with a 9.9 and a 6.6 percent prevalence of a history of angina pectoris or MI, respectively, demonstrated ST-segment depression on ambulatory ECG recordings. In 25 percent[77]; 92 percent of the "ischemic" episodes were asymptomatic, but ST-segment depression was associated with an increased risk of coronary events.

The true prevalence of silent ischemia is difficult to determine and obviously will depend on age and the presence and extent of CAD. In the presence of CAD, however, it is apparent that episodes of asymptomatic ischemia are often more common than are painful episodes.[78]

Pathophysiology of Silent Ischemia

An obvious possible explanation for painful as opposed to asymptomatic ischemia is that the ischemia, and thus the noxious stimulus, is more severe in the former. The correlation between the duration and severity of an ischemic episode and the development of anginal pain in chronic stable angina, however, is only fair.[79] Symptomatic episodes last slightly longer and have a slightly higher frequency of severe ST-segment depression than do painless ones, but there is considerable overlap. In several clinical studies, the intensity of the ischemic stimulus did not appear to account for the variability in the perception of pain in chronic ischemic heart disease.[80]

An alternative reason for lack of pain with myocardial ischemia is neurologic.[81] Neuropathy with defective sensory efferent nerves definitely occurs in some patients and is particularly prevalent in diabetics. Modification of pain stimuli in the central nervous system (CNS) may contribute importantly to the variable expression of ischemic pain. This modulation may occur in spinal centers because transcutaneous nerve,[81] esophageal,[82] and dorsal column stimulation[83] can increase anginal threshold. Modulation of pain-mediating efferent messages also may occur at

supraspinal centers. Psychological or cultural factors also may affect pain perception. Subsets of patients with predominantly painless ischemic episodes tend to have a higher threshold and tolerance for painful stimuli than those who experience pain.[84-86] Thus processing of pain signals in the CNS likely contributes to the variability of anginal threshold or to the absence of pain.

Diabetic patients have a relatively high incidence of painless MI and definite silent ischemic episodes as documented by exercise testing and ambulatory ECG recordings (also Chap. 78).[87-90]

Causes and Functional Consequences of Asymptomatic Ischemia

Ischemia caused by the increased M_{O_2} associated with exercise testing often is silent.[91] Ambulatory ECG recordings have provided insights into potential mechanisms of many episodes of painless or painful ischemia during daily living. The heart rate at the onset of ischemia is generally lower with ambulatory ECG recordings than with exercise testing.[92] These observations suggest that coronary vasoconstriction likely contributes to many episodes of silent ischemia.

Clinical Implications of Silent Ischemia

Asymptomatic silent ischemia is a common component of both acute and chronic coronary artery syndromes. Thus it may have the same clinical importance as symptomatic ischemia.[93] The important indicators of risk are the extent and severity of ischemia, regardless of how it is detected or manifested, and whether the disease is in a stable or unstable phase. Whether ECG monitoring for silent ischemia and changing therapy to decrease or eliminate it diminish morbidity and mortality in a cost-effective manner is unproven.[76]

Evidence of high-risk ischemia detected by exercise ECG testing, with or without myocardial imaging, and implications for treatment are discussed later. Therapeutically, it is appropriate to treat high-risk ischemia whether or not it is associated with pain. Persistent severe ischemia despite medical therapy should lead to consideration of myocardial revascularization.

The role of ambulatory ECG recordings *alone* without stress testing to detect asymptomatic ischemia in routine patient care is *minimal*, and ACC/AHA practice guidelines on this topic have been published recently.[76]

Treatment of Silent Ischemia

Most medical or interventional strategies that reduce symptomatic ischemia also will reduce asymptomatic ischemia.[94-96] The available data from early clinical trials of the treatment of asymptomatic (silent) ischemia in stable CAD have been summarized recently.[94-96] Nitroglycerin (TNG) is highly effective, and beta blockers appear to be somewhat more effective than calcium antagonists. Calcium antagonists may be most effective in preventing ischemia occurring at lower heart rates because coronary artery vasoconstriction may be a predominant factor in this situation. In patients with ischemic CAD, the total ischemic burden, and not just symptoms, may be the appropriate therapeutic target.

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RISK STRATIFICATION OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

The prognosis for the patient with chronic CHD is usually related to four patient factors.[1] *LV performance* is the strongest predictor of long-term survival in patients with CHD, and the ejection fraction (EF) is the most often used measure of the presence and the degree of LV dysfunction. The second predictive factor is the *anatomic extent and severity* of atherosclerotic involvement of the coronary arteries. The number of stenosed coronary arteries is the most common measure of this factor. The third patient factor affecting prognosis is evidence of a *recent coronary plaque rupture* indicating a much higher short-term risk for cardiac death or nonfatal MI. Worsening clinical symptoms with unstable features are an important clinical marker of a complicated plaque (see Chap. 41). The fourth prognostic factor is *general health and noncoronary comorbidity*.

History and Physical Examination for Prognosis

Useful information relative to *risk stratification* can be obtained from the history. This includes demographics such as age and gender, as well as a medical history focusing on hypertension, diabetes, hypercholesterolemia, smoking, peripheral vascular disease, and previous MI.

The physical examination can be useful in risk stratification by defining the presence or absence of signs that may alter the probability of *severe* CAD.[1] Useful physical findings include those suggesting vascular disease (abnormal fundi, decreased peripheral pulses, bruits), long-standing hypertension (high blood pressure, abnormal fundi), aortic valve stenoses or hypertrophic obstructive cardiomyopathy (systolic murmur, abnormal carotid arterial pulse, abnormal LV impulse), left-sided heart failure (third heart sounds, displaced LV impulse, bibasilar rales), and right-sided heart failure (elevated jugular venous pressure, hepatomegaly, ascites, peripheral edema).[1] Hubbard et al.[97] identified five clinical markers that independently predicted severe three-vessel and left main CAD, including age, typical angina, diabetes, male gender, and prior MI, which were used to develop a five-point cardiac risk score.

ECG and Chest Roentgenogram for Prognosis

Patients with chronic stable angina who have abnormalities on resting ECG are at greater risk than those with normal ECGs.[98] Evidence of one or more prior MIs on ECG indicates a greater risk for cardiac events. The presence of Q waves in multiple ECG leads, often accompanied by an R wave in lead V_1 (posterior infarction), commonly is associated with a markedly reduced left ventricular ejection fraction (LVEF), an important factor in the natural history of patients with CAD.[99] Persistent ST-segment-T-wave inversions, particularly in V_1 to V_3, are associated with an increased prevalence of future coronary events and a poor prognosis.[99]

On the chest roentgenogram the presence of cardiomegaly, a LV aneurysm or pulmonary venous congestion is associated with a poorer long-term prognosis than occurs in patients with a normal chest x-ray.

The presence of calcium in the coronary arteries on chest x-ray or fluoroscopy in patients with symptomatic CAD suggests an increased risk of cardiac events. Although the presence and amount of coronary artery calcification by electron beam computed tomography correlate to some extent with the severity of CAD, there is considerable patient variation.[16] Also, placques vulnerable to rupture with resulting acute coronary syndromes rarely contain much calcium.

Noninvasive Testing for Prognosis

ASSESSMENT OF LV FUNCTION

LV global systolic function and volumes are important predictors of prognosis in patients with cardiac disease.[1] In patients with chronic CHD, LVEF measured at rest by either echocardiography (usually qualitative and less reliable) or radionuclide ventriculography (RVG) is predictive of long-term prognosis. As LVEF decreases, subsequent mortality increases; a resting ejection fraction of greater than 35 percent is associated with an annual mortality rate of more than 3 percent per year.[1]

Radionuclide LVEF may be measured at rest using a gamma camera, a ^{99m}Tc tracer, and first-pass or gated equilibrium blood pool angiography (RVG) or by gated SPECT perfusion imaging using a technetium-based isotope[27] (see Chap. 16). LV diastolic function also can be estimated from RVG diastolic filling curves. LV systolic function can be measured by quantitative two-dimensional echocardiography (see Chap. 13), and LV diastolic function can be assessed by transmitral valve Doppler recording.[13]

In patients with chronic stable angina and a history of previous MI, segmental wall motion abnormalities are apparent not only in the zone(s) of prior infarction but also in areas with ischemic "stunning" or "hibernation" of myocardium that are nonfunctional but still viable.[100] In patients with CHD, the presence, severity, and mechanism of mitral regurgitation can be detected reliably using transthoracic and transesophageal two-dimensional imaging and Doppler echocardiographic techniques (see Chap. 13).

Echocardiography is the definitive test for detecting intracardiac thrombi.[27] LV thrombi are most common in stable angina pectoris patients who have significant LV wall motion abnormalities. In patients with anterior and apical infarctions, the presence of LV thrombi denotes an increased risk of both embolism and death (see Chap. 41).

ECG EXERCISE TESTING

Unless cardiac catheterization is clearly indicated, symptomatic patients with suspected or known CAD usually should undergo exercise testing to assess the risk of future cardiac events, unless they have confounding features on their resting ECG or are unable to exercise[1] (see Chap. 14). Also, demonstration of exercise-induced ischemia is desirable for most patients who are being evaluated for revascularization.

Several studies have shown that risk assessment in patients with a normal ECG who are not taking digoxin and who are physically capable *usually* should start with the exercise test[1,102] (see Chap. 14). In contrast, a stress-imaging technique should be used for patients with ECG evidence of LV hypertrophy, widespread resting ST-segment depression (>1 mm), complete LBBB, ventricular paced rhythm, or preexcitation.[17] The primary evidence that ECG exercise testing can be used to estimate prognosis and assist in management decisions consists of seven observational studies.[1,18] One of the strongest and most consistent prognostic markers is the *maximum exercise capacity*.[103,104]

A second group of *prognostic markers* relates to exercise-induced ischemia (see Chap. 14). ST-segment depression and ST-segment elevation (in leads without pathologic Q waves and not in aV_R) best summarize the prognostic information related to ischemia. Other variables are less powerful, including angina, the number of leads with ST-segment depression, and the configuration of the ST-segment depression and the duration of ST-segment deviation into the recovery phase.

The *Duke treadmill score* combines this information and provides a way to calculate risk.[103,105] The Duke treadmill score equals the exercise time in minutes minus five times the peak ST-segment deviation during or after exercise (in millimeters) minus four times the angina index (which has a value of 0 if there is no angina, 1 if angina occurs, and 2 if angina is the reason for stopping the test). Among outpatients with suspected CAD, two-thirds of patients with scores indicating low risk had a 4-year survival of 99 percent

(average annual mortality of 0.25 percent), and the 4 percent who had scores indicating high risk had a 4-year survival of 79 percent (average annual mortality rate of 5 percent) (Table 40-7). Recent studies indicate that this approach is equally applicable in men and women.[106]

Table 40-7: Survival According to Risk Groups Based on Duke Treadmill Scores

Risk Group (Score)	Percentage of Total	Four-Year Survival	Annual Mortality (percent)
Low (≥ +5)	62	0.99	0.25
Moderate (-10 to +4)	34	0.95	1.25
High (< -10)	4	0.79	5.0

SOURCE: From Gibbons et al.[1]

STRESS IMAGING FOR PROGNOSIS

Stress-imaging studies using radionuclide MPI techniques or two-dimensional echocardiography at rest and during stress are beneficial for risk stratification and determining the most effective treatment strategy for patients with chronic stable angina.[1] Whenever feasible, treadmill or bicycle exercise should be used as the most desirable forms of stress because exercise provides the most information concerning patient's symptoms, cardiovascular function, and hemodynamic response during usual activity (see Chap. 16). The inability to perform a bicycle or exercise treadmill test has been shown to be a serious and negative prognostic factor for patients with chronic CAD.[1]

In patients unable to exercise adequately, various types of pharmacologic stress (as discussed under diagnosis) are commonly used for *risk stratification*. The type of pharmacologic stress selected will depend on specific patient factors, including the patient's heart rate and blood pressure, evidence of bronchospastic disease, the presence of LBBB or a pacemaker, and the likelihood of ventricular arrhythmias. Pharmacologic agents often are used to increase workload or to cause an increase in overall CBF.[107,108]

MPI has played a major role in the risk stratification of patients with CAD.[27] Either planar (less common) or SPECT imaging using thallium-201 or ^{99m}Tc perfusion tracers, with images obtained at stress and during rest, provides important information concerning the severity of functionally significant CAD (see Chap. 16).

Stress echocardiography has been used more recently for detecting the presence and amount of ischemia in patients with chronic stable angina. Accordingly, the amount of prognostic data obtained with this approach is less extensive. The presence or absence of inducible myocardial wall motion abnormalities, however, has useful predictive value in patients undergoing exercise or pharmacologic stress echocardiography.[27,109-112] A negative stress echocardiographic study denotes a low cardiovascular event rate during follow-up.

MYOCARDIAL PERFUSION IMAGING FOR PROGNOSIS

Normal poststress thallium scan results are highly predictive of a benign prognosis even in patients with known CAD.[1] An analysis of 16 studies involving 3594 patients followed for an average of 29 months indicated a rate per year of cardiac death and MI of 0.9 percent, little different from that of the general population.[113,114] In a recent prospective study of 5183 consecutive patients undergoing myocardial perfusion imaging during stress and later at rest, patients with normal scans were at low risk (<0.5 percent per year) for the composite end point of cardiac death and MI during 642 ± 226 days of mean follow-up[115] (see Chap. 16).

The number, extent, and site of abnormalities on stress MPI reflect the location and severity of functionally significant coronary artery stenoses (see Chap. 16). Lung uptake of thallium-201 on postexercise or pharmacologic stress images is an indicator of stress-induced global LV dysfunction and is associated with pulmonary venous hypertension in the presence of multivessel CAD.[115] Transient poststress ischemic LV dilatation also correlates with severe two- or three-vessel CAD (see Chap. 16). SPECT may be more accurate than planar imaging for determining the size of defects, for detecting particularly left circumflex CAD, and for localizing abnormalities in the distribution of individual coronary arteries. More false-positive results are likely to result from photon attenuation during SPECT imaging, however.

The determination of both myocardial perfusion and LV function at rest may help determine the extent and severity of CAD.[1] This combined information can be obtained by performing two separate exercise tests (e.g., stress MPI and stress RVG), or by combining the studies after a single exercise test (first-pass RVG) with ^{99m}Tc-based agents followed by MPI, or by perfusion imaging using ECG gating. The use of ECG gated ^{99m}Tc sestamibi SPECT imaging at rest and with exercise or pharmacologic stress provides important prognostic information concerning LVEF and the extent of reversible ischemia (see Chap. 16).

Pharmacologic stress perfusion imaging for risk stratification is preferable to *exercise perfusion* imaging in patients with LBBB.[116] Recently, 245 patients with LBBB underwent SPECT imaging with thallium-201 (n = 173) or ^{99m}Tc sestamibi (n = 72) during dipyridamole (n = 153) or adenosine (n = 92) stress.[134] The 3-year survival was 57 percent in the high-risk group compared with 87 percent in the low-risk group (p = 0.001).

STRESS ECHOCARDIOGRAPHY FOR PROGNOSIS

Stress echocardiography is both sensitive and specific for detecting inducible myocardial ischemia in patients with chronic stable angina.[27] Compared with standard exercise treadmill testing, stress echocardiography provides additional clinical value for detecting and localizing myocardial ischemia. Several studies indicate that patients at low, intermediate, and high risk for cardiac events can be stratified by the presence or absence of inducible wall motion abnormalities on stress echocardiography testing.[109-112] The presence of ischemia on the exercise echocardiogram is independent and additive to clinical and exercise data in predicting cardiac events in both men and women.[117,118]

The prognosis is not benign in patients with a positive stress echocardiographic study, and morbid or fatal cardiovascular events are more likely. The overall event rates, however, are rather variable, and the cost-effectiveness of using routine stress echocardiographic testing to establish prognosis is uncertain.[1]

Coronary Angiography for Prognosis

The availability of powerful but expensive therapeutic strategies to reduce the long-term morbidity and mortality of CAD dictate that the patients most likely to benefit because of increased risk be determined. The assessment of cardiac risk and the need for further testing usually begin with simple, repeatable, and inexpensive assessments of history and physical examination that lead to noninvasive or invasive testing depending on outcome. Clinical risk factors generally are additive, and a crude estimate of 1-year mortality can be obtained from these variables. Methods for the accurate identification of vulnerable plaques, however, are lacking. Magnetic resonance imaging (MRI) offers significant promise in this regard.[1]

Risk stratification of patients with chronic stable angina by stress testing with exercise or pharmacologic agents has been shown to permit identification of groups of patients with low, intermediate, or high risk for subsequent cardiac events[1,27,28] (see ).

The randomized trials of coronary artery bypass grafting (CABG) demonstrated that patients randomized to initial CABG had a lower mortality than those assigned to medical therapy only if they were at substantial risk (annual mortality > 3 percent).[119,120] Coronary angiography is appropriate for patients whose mortality risk is in this range. Noninvasive test findings that identify high-risk patients are listed in Table 40-8.

Patients identified as at high risk generally are referred for coronary arteriography independent of their symptomatic status. The ACC/AHA guidelines for risk stratification using coronary angiography in patients with stable angina are listed in Table 40-9.

Table 40-8: Noninvasive Risk Stratification

High risk (greater than 3% annual mortality rate)

1. Severe resting left ventricular dysfunction (LVEF < 35%)
2. High-risk treadmill score (score ≤ -11)
3. Severe exercise left ventricular dysfunction (exercise LVEF < 35%)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilatation or increased lung uptake (thallium-201)
7. Stress-induced moderate perfusion defect with LV dilatation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving greater than two segments) developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min)
9. Stress echocardiographic evidence of extensive ischemia

Intermediate risk (1% < 3% annual mortality rate)

1. Mild/moderate resting left ventricular dysfunction (LVEF = 35%-49%)
2. Intermediate-risk treadmill score* (-11 < score < 5)
3. Stress-induced moderate perfusion defect without LV dilatation or increased lung intake (thallium-201)
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving less than or equal to two segments

Low risk (less than 1% annual mortality rate)

1. Low-risk treadmill score (score ≥ 5)
2. Normal or small myocardial perfusion defect at rest or with stress
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress

*Duke treadmill score; see text.

SOURCE: From Gibbons et al.[1]

Table 40-9: Recommendations for Coronary Angiography for Risk Stratification in Patients With Chronic Stable Angina

Class I

1. Patients with disabling [Canadian Cardiovascular Society (CCS) classes III and IV] chronic stable angina despite medical therapy
2. Patients with high-risk criteria on noninvasive testing regardless of anginal severity
3. Patients with angina who have survived sudden cardiac death or serious ventricular arrhythmia
4. Patients with angina and symptoms and signs of congestive heart failure
5. Patients with clinical characteristics that indicate a high likelihood of severe CAD

Class IIa

1. Patients with significant LV dysfunction (ejection fraction < 45%), CCS class I or II angina, and demonstrable ischemia but less than high-risk criteria on noninvasive testing
2. Patients with inadequate prognostic information after noninvasive testing

Class IIb

1. Patients with disabling CCS class I or II angina, preserved LV function (ejection fraction > 45%), and less than high-risk criteria on noninvasive testing

Class III

1. Patients with disabling CCS classes I or II angina who respond to medical therapy and have no evidence of ischemia on noninvasive testing
2. Patients who prefer to avoid revascularization

NOTE: See classes I-III as described at bottom of Table 40-5.
SOURCE: From Gibbons et al.[1]

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Chapter 40: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

TREATMENT OF CHRONIC STABLE ANGINA

There are two major purposes in the treatment of stable angina. The first is to prevent MI and death and thereby *increase the quantity of life*. The second is to reduce symptoms of angina and the frequency and severity of ischemia, which should *improve the quality of life*. Therapy directed toward preventing death has the highest priority. The choice of therapy often depends on the clinical response to initial medical therapy, although some patients (and many physicians) prefer coronary revascularization in situations where either may be successful. It must be stressed that the pharmacologic treatment of chronic CAD has greatly improved and may even be superior to revascularization therapy for many patients.[120a] Patient education, cost-effectiveness, and patient preference are important components in this decision-making process.

Pharmacotherapy to Prevent MI

ANTIPLATELET AGENTS

Aspirin exerts an antithrombotic effect by inhibiting cyclooxygenase and synthesis of platelet thromboxane A_2. In the Physicians' Health Study, aspirin given on alternative days to asymptomatic individuals was associated with a decreased incidence of MI.[121] In the Swedish Angina Pectoris Aspirin Trial (SAPAT), in patients with stable angina, the addition of 75 mg aspirin to sotalol resulted in a 34 percent reduction in primary outcome events of MI and sudden death and a 32 percent decrease in secondary vascular events.[122]

Ticlopidine is a thienopyridine derivative that inhibits platelet aggregation induced by adenosine diphosphate and low concentrations of thrombin, collagen, thromboxane A_2, and platelet-activating factor.[123] It has *not* been shown to decrease adverse cardiovascular events and may induce neutropenia and often thrombotic thrombocytopenia purpura (TTP).

Clopidogrel, also a thienopyridine derivative, is chemically related to ticlopidine, but it appears to possess a greater antithrombotic effect than ticlopidine. In a randomized trial that compared clopidogrel with aspirin in patients with previous MIs, stroke, or peripheral vascular disease, clopidogrel was slightly more effective than aspirin in decreasing the combined risk of MI, vascular death, or ischemic stroke.[124] Aspirin, 75 to 325 mg per day, should be used routinely in all patients with acute and chronic ischemic heart disease with and without clinical symptoms in the absence of contraindications. In those unable to take aspirin, clopidogrel may be used instead. Warfarin is the third choice.

ANTITHROMBOTIC THERAPY

Disturbed fibrinolytic function after exercise appears to be associated with an increased risk of subsequent cardiovascular death in patients with chronic stable angina, providing the rationale for long-term antithrombotic therapy. In small placebo-controlled trials among patients with chronic stable angina, daily subcutaneous administration of low-molecular-weight heparin deceased the fibrinogen level and improved the exercise time to ST-segment depression.[125] The clinical experience of such therapy, however, is extremely limited. The efficacy of newer antiplatelet and antithrombotic agents such as glycoprotein IIIb/IIa inhibitors and recombinant hirudin in the management of patients with chronic stable angina has not been established. Low-intensity oral anticoagulation with warfarin decreased the risk of ischemic events in a randomized trial of patients with risk factors for atherosclerosis but without symptoms of angina.[126]

LIPID-LOWERING AGENTS

Recent clinical studies have conveniently demonstrated that low-density lipoprotein (LDL)-lowering agents can decrease the risk of adverse ischemic events in patients with established CAD (see Chap. 38). In the Scandinavian Simvastatin Survival Study (4S),[127] treatment with an HMG-CoA reductase inhibitor in patients with documented CAD (including stable angina) and a baseline total cholesterol concentration between 212 and 308 mg/dL was associated with 30 to 35 percent reduction in both mortality rate and major coronary events. In the Cholesterol And Recurrent Events (CARE) study,[128] in men and women with previous MI and total cholesterol levels of less than 240 mg/dL and LDL-cholesterol levels of 115 to 174 mg/dL, treatment with a HMG-CoA reductase inhibitor (statin) was associated with a 24 percent reduction in risk for nonfatal MI. Thus lipid-lowering therapy should be recommended even in the presence of mild to moderate elevations of LDL-cholesterol in patients with chronic stable angina. Ongoing studies[128a,128b] suggest that a reduction of LDL-cholesterol below 100 mg/dL will further reduce cardiac events (see Chap. 38).

Antianginal and Anti-ischemic Therapy

Antianginal and anti-ischemic drug therapy consists of beta-adrenoreceptor blocking agents (beta blockers), calcium antagonists, and nitrates. Drug interactions are described in Chap. 81. There is a tendency for physicians to give *lower doses* of antianginal medications than those proven to be effective in clinical trials and after higher doses or combined therapy are neglected in patients who could be "angina-free," if treated more appropriately; this is particularly true with beta-blocker therapy. For example, the usual dose for angina is 50 to 200 mg of metoprolol twice daily.

BETA BLOCKERS

The decrease in heart rate, contractility, arterial pressure, and usually LV wall stress with beta blockers is associated with decreased M_{O_2}. A reduction in heart rate also increases diastolic coronary artery perfusion time, which may enhance LV perfusion. Although beta blockers have the potential to increase coronary vascular resistance by the formation of cyclic AMP, the clinical relevance of this pharmacodynamic effect remains to be demonstrated.

All beta blockers without intrinsic sympathetic activity appear to be equally effective in angina pectoris. In patients with chronic stable exertional angina, these agents decrease the heart rate-blood pressure product during exercise, and the onset of angina or the ischemic threshold during exercise is delayed or avoided.[1] When treating stable angina, it is essential that the dose of beta blockers be adjusted to lower the resting heart rate to 55 to 60 beats per minute. In patients with more severe angina, the heart rate can be reduced to less than 50 beats per minute if there are no symptoms associated with bradycardia and AV block does not develop (see Chap. 81). In patients with exertional angina, beta blockers attenuate the increase in heart rate during exercise, which ideally should not exceed 75 percent of the heart rate response associated with the onset of ischemia. It is often useful for the patient to perform exercise (sit-ups, running in place) before and after the institution of beta-blocker therapy. If the heart rate increase with exercise is not significantly reduced by therapy, the dose of the beta blocker is inadequate. Beta blockers are definitely effective in reducing exercise-induced angina. Three controlled studies comparing beta blockers with calcium antagonists[129-132] report equal efficacy in the treatment of chronic stable angina.

In patients with postinfarction stable angina and those who require antianginal therapy after revascularization, treatment with beta blockers appears to be effective in controlling symptomatic and asymptomatic ischemic episodes. Beta blockers are still the anti-ischemic drugs of choice in elderly patients with stable angina.[1]

Beta blockers frequently are combined with nitrates for treating chronic stable angina. This combination of therapy appeared to be more effective in several studies than nitrates or beta blockers alone.[133-135] Beta blockers also may be combined with calcium antagonists. For combination therapy, slow-released dihydropyridine derivatives or new-generation long-acting dihydropyridine derivatives are the calcium antagonists of choice.[1]

In the International Multicenter Angina Exercise (IMAGE) study,[132] both metoprolol and nifedipine were effective as monotherapy in increasing exercise time, although metoprolol was more effective than nifedipine. The combination therapy also increased the exercise time to ischemia compared with either drug alone. The absolute contraindications to the use of beta blockers are severe bradycardia, preexisting high-degree AV block, sick sinus syndrome, and severe, unstable LV failure (see Chap. 81). Asthma and bronchospastic disease, severe depression, and peripheral vascular disease are relative contraindications (see Chap. 81). Fatigue, inability to perform exercise, lethargy, insomnia, nightmares, worsening claudication, and impotence are frequently experienced side effects. Most patients with chronic CAD and diabetes can be treated with beta blockers (see Chap. 78).

CALCIUM ANTAGONISTS

These agents, also considered in Chap. 81, reduce the transmembrane flux of calcium by the calcium channels. There are three types of voltage-dependent calcium channels: L type, T type, and N type.

All calcium antagonists exert a negative inotropic effect, depending on dosage. In smooth muscle, calcium ions also regulate the contractile mechanism, and calcium antagonists reduce smooth muscle tension in the peripheral vascular bed, thus causing vasodilation. All the calcium antagonists cause dilatation of the epicardial conduit vessels and the arterial resistance vessels, the former being the primary mechanism for the beneficial effect of calcium antagonists for relieving vasospastic angina. Calcium antagonists also decrease M_{O_2} demand primarily by reducing the systemic vascular resistance and arterial pressure. The negative inotropic effect of calcium antagonists also decreases the M_{O_2}.

Randomized clinical trials comparing calcium antagonists and beta blockers have demonstrated that calcium antagonists are equally effective as beta blockers in relieving angina and improving exercise time to onset of angina or ischemia.[1] The calcium antagonists are effective in reducing the incidence of angina in patients with vasospastic angina.[136,137]

In a *retrospective case-controlled study* reported in patients with hypertension, treatment with immediate-acting nifedipine, diltiazem, and verapamil was associated with an increased risk of MI of 31 to 61 percent.[138] Although a subsequent meta-analysis of immediate-release and short-acting nifedipine in patients with MI and unstable angina reported a dose-related influence on excess mortality,[139] further analysis of the published reports failed to confirm an increased risk of adverse cardiac events with calcium antagonists.[140,141] Importantly, long-acting calcium antagonists, including slow-release and long-acting dihydropyridine and nondihydropyridine derivatives, are effective in relieving symptoms in patients with chronic stable angina. They should be used in combination with beta blockers when initial treatment with beta blockers is not successful or as a substitute for beta blockers when initial treatment leads to unacceptable side effects. Many patients with two- or three-vessel CAD are asymptomatic on combined beta blocker and calcium antagonist therapy. Some have further improvement on triple therapy (combined beta blocker, calcium antagonist, and long-acting nitrates). Further information concerning the potential side effects of the calcium antagonists is given elsewhere (see Chap. 81).

NITROGLYCERIN AND NITRATES

Nitrates are endothelium-independent vasodilators that produce beneficial effects by both reducing the M_{O_2} and improving CBF perfusion. The decreased M_{O_2} results from the reduction of LV volume and arterial pressure primarily due to reduced preload. Nitroglycerin also exerts antithrombotic and antiplatelet effects in patients with stable angina.[1]

Nitrates dilate large epicardial arteries and collateral vessels. The vasodilating effect on epicardial coronary arteries with or without atherosclerotic CAD is beneficial in relieving coronary vasospasm in patients with vasospastic angina.

In patients with exertional stable angina, nitrates improve exercise tolerance, time to onset of angina, and time to ST-segment depression during treadmill exercise testing. In combination with beta blockers or

calcium antagonists, nitrates produce greater antianginal and anti-ischemic effects in patients with stable angina.[142-145]

The interaction between nitrates and sildenafil (Viagra) is discussed in detail elsewhere.[146] The coadministration of nitrates and sildenafil significantly increases the risk of potentially life-threatening hypotension (see Chap. 81).

The major problem with long-term use of nitroglycerin and long-acting nitrates is development of nitrate tolerance.[147] Tolerance develops not only to antianginal and hemodynamic effects but also to platelet antiaggregatory effects.[148] The mechanism for development of nitrate tolerance remains unclear. For practical purposes, the administration or nitrates with an adequate nitrate-free interval (8-12 h) appears to be the most effective method of preventing nitrate tolerance. Unfortunately, this means that patients with unpredictable episodes of myocardial ischemia should not be treated with nitrate therapy alone because for part of each 24 h they will be "unprotected."

The primary consideration in the choice of pharmacologic agents for treatment of angina should be to *improve prognosis*. Aspirin and lipid-lowering therapies have been shown to reduce the risk of death and nonfatal myocardial infarction in both primary and secondary prevention trials. Beta blockers also reduce cardiac events when used as secondary prevention in postinfarction patients and reduce mortality and morbidity among patients with hypertension. Nitrates have not been shown to reduce mortality with acute infarction or in patients with chronic CAD.

Recommended drug therapy using calcium antagonists versus beta blockers in patients with angina-associated conditions are listed in Table 40-10.

Table 40-10: Recommended Drug Therapy (Calcium Antagonist versus Beta Blocker) in Patients with Angina and Associated Conditions

Condition	Recommended Treatment and Alternative	Avoid
Medical conditions		
Systemic hypertension	Beta blockers (calcium antagonists)	
Migraine or vascular headaches	Beta blockers (verapamil or diltiazem)	
Asthma or chronic obstructive pulmonary disease with bronchospasm	Verapamil or diltiazem	Beta blockers
Hyperthyroidism	Beta blockers	
Raynaud's syndrome	Long-acting slow-release calcium antagonists	Beta blockers
Insulin-dependent diabetes mellitus	Beta blockers (particularly if prior myocardial infarction) or long-acting slow-release calcium antagonists	
Non-insulin-dependent diabetes mellitus	Beta blockers or long-acting slow-release calcium antagonists	
Depression	Long-acting slow-release calcium antagonists	Beta blockers

Mild peripheral vascular disease	Beta blockers or calcium antagonists	
Severe peripheral vascular disease with rest ischemia	Calcium antagonists	Beta blockers
Cardiac arrhythmias and conduction abnormalities		
Sinus bradycardia	Long-acting slow-release calcium antagonists that do not decrease heart rate	Beta blockers, diltiazem, verapamil
Sinus tachycardia (not due to heart failure)	Beta blockers	
Supraventricular tachycardia	Verapamil, diltiazem, or beta blockers	
Atrioventricular block	Long-acting slow-release calcium antagonists that do not slow AV conduction	Beta blockers, verapamil, diltiazem
Rapid artrial fibrillation (with digitalis)	Verapamil, diltiazem, or beta blockers	
Ventricular arrhythmias	Beta blockers	
Left ventricular dysfunction		
Congestive heart failure		
Mild (LVEF ≥ 40%)	Beta blockers	
Moderate to Severe (LVEF < 40%)	Amlodipine or felodipine (nitrates)	Verapamil, diltiazem
Left-sided valvular heart disease		
Mild aortic stenosis	Beta blockers	
Aortic insufficiency	Long-acting slow-release dihydropyridines	
Mitral regurgitation	Long-acting slow-release dihydropyridines	
Mitral stenosis	Beta blockers	
Hypertrophic cardiomyopathy	Beta blockers, nondihydropyridine calcium antagonist	Nitrates, dihydropyridine, calcium antagonists

SOURCE: From Gibbons et al.[1]

Treatment of Risk Factors

The recommendations of the AHA for the treatment of risk factors are detailed in Chap. 38. *The risk factors to which interventions have been shown to reduce the incidence of CAD events include* (1) cigarette smoking, (2) LDL-cholesterol, (3) systemic hypertension, (4) LV hypertrophy, and (5) thrombogenic

factors (see Chap. 38).

The causal role of *LDL-cholesterol* in the pathogenesis of atherosclerotic CAD has been enhanced by recent randomized, controlled clinical trials of lipid-lowering therapy. Several primary and secondary prevention trials have shown that LDL-cholesterol lowering is associated with a reduced risk of CAD (see Chap. 38). Angiographic trials provide firm evidence linking cholesterol reduction to favorable trends in coronary anatomy.

Data from numerous observational studies indicate a continuous and graded relation between blood pressure and cardiovascular disease risk.[149,150] Hypertension predisposes patients to coronary events both as a result of the direct vascular injury caused by increases in blood pressure and by its effects on the myocardium, including increased wall stress and M_{O_2}.

CAD, diabetes, LV hypertrophy, heart failure, retinopathy, and nephropathy are indicators of increased cardiovascular disease risk in hypertensive patients. The target of therapy is a reduction in blood pressure to less than 130 mmHg systolic and less than 85 mmHg diastolic in patients with CAD and coexisting diabetes, heart failure, or renal failure.[149]

Treatment of *hypertension* begins with nonpharmacologic means. When lifestyle modifications and dietary alterations adequately reduce blood pressure, pharmacologic intervention may be unnecessary (see Chaps. 38 and 51).

When pharmacologic treatment is necessary (usually the case), beta blockers or calcium antagonists may be especially useful in patients with hypertension and angina pectoris; however, short-acting calcium antagonists should not be used.[151]

Epidemiologic studies have implicated *LV hypertrophy* as a risk factor for development of MI, congestive heart failure, and sudden death.[152] LV hypertrophy also has been shown to predict a poorer prognosis in patients with definite CAD.[153] In the Framingham Heart Study,[154] the subjects who demonstrated ECG evidence of LV hypertrophy regression on follow-up were at a substantially reduced risk for cardiovascular events.

Coronary artery thrombosis is a trigger of acute MI. Aspirin has been documented to reduce the risk for CHD in both primary and secondary prevention settings.[1] Elevated plasma fibrinogen levels predict CAD risk in prospective observational studies[155] (see Chap. 38).

Risk factors for which interventions are likely to reduce the incidence of coronary disease events include diabetes mellitus, high-density lipoprotein (HDL)-cholesterol, obesity, physical inactivity, and postmenopausal status (see Chap. 38).

Diabetes mellitus, which is defined as a fasting blood sugar level of more than 126 mg/dL,[156] is present in a significant minority of adult Americans. Data supporting an important role of diabetes mellitus as a risk factor for cardiovascular disease comes from a number of observational settings. This is true for both type I and type II diabetes. Atherosclerosis accounts for 80 percent of all diabetic mortality,[157,158] with CAD alone responsible for 75 percent of total atherosclerotic deaths (see Chaps. 38 and 78). The goal is to maintain a blood glucose HbA_1c level of less than 7 percent and a blood glucose level of less than 140 mg/dL. In diabetic patients with hypertension, microalbuminuria, or decreased LV systolic function, angiotensin converting enzyme (ACE) inhibitors appear indicated. This may apply to most diabetics with CAD.[158a]

Observational studies and clinical trials have demonstrated a strong inverse association between *HDL-cholesterol* and CAD risk (see Chap. 38). This inverse relation is observed in both men and women and among asymptomatic persons as well as patients with established CAD.[1] The National Cholesterol Adult Treatment Panel II has defined a low HDL-cholesterol level as less than 35 mg/dL.[159]

Obesity is a common condition associated with increased risk for CHD and mortality (see Chap. 38). New AHA guidelines for weight control have been published recently.[160]

Multiple randomized, controlled trials comparing exercise training with a "no exercise" control group have demonstrated a statistically significant improvement in exercise tolerance for the exercise group versus the control group.[1] The threshold for ischemia is likely to increase with exercise training because training reduces the heart rate-blood pressure product at a given submaximal exercise workload[1] (see Chap. 38).

When hormone production decreases in the perimenopausal period over several years, the risk of CAD rises in postmenopausal women. By age 75, the risk of atherosclerotic cardiovascular disease among men and women is equal.[1] The first published randomized trial of estrogen plus progestin therapy in postmenopausal women with known CAD did not show any reduction in cardiovascular events over 4 years of follow-up[161] despite an 11 percent lower LDL-cholesterol level and a 10 percent higher HDL-cholesterol level in those women receiving hormone replacement. Other randomized trials of hormone-replacement therapy in primary and secondary prevention of CAD in postmenopausal women are in progress.

Risk factors for which interventions may reduce the incidence of coronary disease events include psychosocial factors, triglycerides, lipoprotein (a), homocysteine, oxidative stress, and consumption of alcohol (see Chap. 38).

Triglyceride levels are predictive of CHD in a variety of observational studies and clinical settings.[162] However, much of the association of triglycerides with CHD risk is related to other factors, including diabetes, obesity, hypertension, high LDL-cholesterol, and low HDL-cholesterol[163] (see Chap. 38).

Lipoprotein(a) is a lipoprotein particle that has been linked to CHD risk in observational studies. Elevated lipoprotein(a) levels are largely genetically determined and found in 15 to 20 percent of patients with premature CHD.[164,165] Increased *homocysteine* levels are associated with increased risk of CAD, peripheral arterial disease, and carotid disease.[166,167] Elevated homocysteine levels can occur as a result of inborn errors of metabolism such as homocysteinuria, and homocysteine levels also can be increased by deficiencies of vitamin B_6, vitamin B_{12}, and folate, which commonly occur in older patients[167] (see Chap. 38).

Extensive laboratory data indicate that oxidation of LDL-cholesterol promotes and accelerates the atherosclerosis process.[168] Observational studies have documented an association between dietary intake of antioxidant vitamins (vitamin C, vitamin E, and β-carotene) and reduced risk for CHD[169] (see Chap. 38).

Observational studies have shown repeatedly an inverse relation of *moderate alcohol intake* to the risk of CHD events.[170] However, excessive alcohol intake can promote many other medical problems that outweigh its beneficial effects on CHD risk.

Risk factors associated with increased risk but that cannot be modified or when modified are unlikely to change the incidence of CHD events include age, male gender, and a positive family history of premature CHD. The latter is defined as definite MI or sudden death before age 55 in a father or other male first-degree relative or before age 65 in a mother or other female first-degree relative[1] (see Chap. 38).

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Chapter 40: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE

MYOCARDIAL REVASCULARIZATION

There are currently two well-established revascularization approaches to treatment of chronic stable angina caused by coronary atherosclerosis. One is CABG surgery, in which segments of autologous arteries or veins are used to reroute blood around relatively stenotic segments of the proximal coronary artery. The other is percutaneous coronary interventions (PCIs) using catheter-borne or laser techniques to open usually short areas of stenoses from within the coronary artery. These techniques are described in greater detail in Chaps. 45 and 48. Revascularization is also potentially feasible with transthoracic (laser) myocardial revascularization in patients in whom neither CABG nor PCI is feasible (see Chap. 48). The recommendations of the ACC/AHA/ACP-ASIM for revascularization with PCIs or CABG in patients with stable angina are listed in Table 40-11.

Table 40-11: Revascularization for Chronic Stable Angina (Recommendations for Revascularization with PTCA or Other Catheter-Based Techniques and CABG in Patients with Stable Angina)

Class I

1. CABG for patients with significant left main coronary disease.
2. CABG for patients with three-vessel disease. The survival benefit is greater in patients with abnormal LV function (ejection fraction < 50%).
3. CABG for patients with two-vessel disease with significant proximal left anterior descending CAD and either abnormal LV function (ejection fraction < 50%) or demonstrable ischemia on noninvasive testing.
4. PCI for patients with two- or three-vessel disease with significant proximal left anterior descending CAD, who have anatomy suitable for catheter-based therapy, normal LV function and who do not have treated diabetes.
5. PCI or CABG for patients with one- or two-vessel disease CAD without significant proximal left anterior descending CAD, but with a large area of viable myocardium and high risk criteria on noninvasive testing.
6. CABG for patients with one- or two-vessel disease CAD without significant proximal left anterior descending CAD who have survived sudden cardiac death or sustained ventricular tachycardia.
7. In patients with prior PCI, CABG, or PCI for recurrent stenosis associated with a large area of viable myocardium or high-risk criteria on noninvasive testing.
8. PTCA or CABG for patients who have not been treated successfully by medical therapy and can undergo revascularization with acceptable risk.

Class IIa

1. Repeat CABG for patients with multiple saphenous vein graft stenoses, especially when there is significant stenosis of a graft supplying the LAD. It may be appropriate to use PTCA for focal saphenous vein graft lesions or multiple stenoses in poor candidates for reoperative surgery.
2. Use of PCI or CABG for patients with one- or two-vessel disease CAD without significant proximal LAD disease but with a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing.
3. Use of PCI or CABG for patients with one-vessel disease with significant proximal LAD disease.

Class IIb

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1. Compared with CABG, PCI for patients with two- or three-vessel disease with significant proximal left anterior descending CAD, who have anatomy suitable for catheter-based therapy, and who have treated diabetes or abnormal LV function.
2. Use of PCI for patients with significant left main coronary disease who are not candidates for CABG.
3. PCI for patients with one- or two-vessel disease CAD without significant proximal left anterior descending CAD, who have survived sudden cardiac death or sustained ventricular tachycardia.

Class III

---

1. Use of PCI or CABG for patients with one- or two-vessel CAD without significant proximal left anterior descending CAD, who have mild symptoms that are unlikely due to myocardial ischemia or who have not received an adequate trial of medical therapy and
    a. Have only a small area of viable myocardium or
    b. Have no demonstrable ischemia on noninvasive testing
2. Use of PCI or CABG for patients with borderline coronary stenoses (50% to 60% diameter in locations other than the left main coronary artery) and no demonstrable ischemia on noninvasive testing.
3. Use of PCI or CABG for patients with insignificant coronary stenosis (<50% diameter).
4. Use of PCI in patients with significant left main coronary disease who are candidates for CABG.

NOTE: PTCA is used in these recommendations to indicate PTCA or other catheter-based techniques, such as stents, atherectomy, and laser therapy. See classes I-III as described at the bottom of Table 40-5.

Patients with stable angina pectoris may be appropriate candidates for revascularization either by CABG surgery or PCIs. In general, this is an individual decision to be made by the patient with knowledge of the advantages or disadvantages either of medical therapy alone or revascularization with either CABG or PCIs.

There are two general indications for revascularization procedures: the presence of symptoms that are not acceptable to the patient either because of (1) restriction of physical activity and lifestyle as a result of limitations or side effects from medications or (2) the presence of findings that indicate clearly that the patient would have a better prognosis for revascularization than with medical therapy. Considerations regarding revascularization are based on an assessment of the grade or class of angina experienced by the patient, the presence and severity of myocardial ischemia on noninvasive testing, the degree of LV function, and the distribution and severity of coronary artery stenoses.

A recent meta-analysis of three major large multicenter randomized trials of initial surgery versus medical management (performed in the 1970s) as well as other smaller trials has confirmed the surgical benefits achieved by surgery at 10 postoperative years for patients with three-vessel disease, two-vessel disease, or even one-vessel disease that included a severe stenoses of the proximal left anterior descending coronary artery[119] (see Chap. 48).

The advantages of PCIs for the treatment of CAD include a low level of procedure-related morbidity, a low procedure-related mortality rate in properly selected patients, a short hospital stay, early return to activity, and the feasibility of multiple procedures. However, PCIs are not feasible in all patients; they are accompanied by a significant incidence of restenoses, and there is an occasional need for emergency CABG surgery (see Chap. 45).

Three randomized studies have compared PCIs with medical management alone for the treatment of chronic stable angina.[171-173] All these randomized studies of PCIs versus medical management have involved patients at a low risk of mortality even with medical management and did not assess patients with moderate to severe CAD (see Chap. 45). Multiple trials have compared the strategy of an initial PCI with initial CABG surgery for treatment of multivessel CAD (see Chaps. 45 and 48). The results of all these trials have shown that early and late survival rates have been equivalent for the PCI and CABG surgery groups. In the Bypass Angioplasty Revascularization Intervention (BARI) trial, the subgroups of patients with treated diabetics had a significantly better survival rate with CABG surgery.[174] This was true, however, on post hoc analysis of the clinical variables, including diabetes, which was not a prerandomization blocking variable.

The randomized studies of invasive therapy for chronic angina have all excluded patients who developed recurrent angina after previous CABG surgery. Few existing data define outcomes for risk-stratified groups of patients who develop recurrent angina after bypass surgery. Those which do indicate that patients with ischemia produced by late atherosclerotic stenoses in vein grafts are at a higher risk with medical management alone than those with ischemia produced by native-vessel disease.

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FOLLOW-UP OF PATIENTS WITH CHRONIC STABLE ANGINA

Published evidence of the efficacy of specific strategies for the follow-up of patients with chronic stable angina on patient outcome are nonexistent. The ACC/AHA/ACP-ASIM guidelines[1] for monitoring of symptoms and antianginal therapy during patient follow-up are as follows:

For the patient with successfully treated chronic stable angina, a follow-up evaluation every 4 to 12 months is appropriate. During the first year of therapy, evaluations every 4 to 6 months are recommended. After the first year of therapy, annual evaluations are recommended if the patient is stable and reliable enough to return for evaluation when anginal symptoms become worse or other symptoms occur.[1] At the time of follow-up, a general assessment of the patient's functional and health status and quality of life may reveal additional issues that affect angina. Symptoms that have worsened should follow reevaluation as outlined above. A detailed history of the patient's daily activity is critical because angina symptoms may remain stable only because stressful activities have been eliminated.

A careful history of the characteristics of the patient's angina including provoking and alleviating factors must be repeated at each visit. Detailed questions should be asked about common drug side effects. The patient's adherence to the treatment program must be assessed.

The physical examination should be determined by the patient's history. Every patient should have weight, blood pressure, and pulse noted. The jugular venous pressure, carotid pulse magnitude and upstroke, and presence or absence of carotid bruits should be noted. Pulmonary examination with special attention to rales, rhonchi, wheezing, and decreased breath sounds is required. A cardiac examination should note the presence of fourth and third heart sounds, a new or changed systolic murmur, the location of the LV impulse, and any change from previous examinations. Clearly, the vascular examination should identify any change in peripheral pulses and new bruits; the abdominal examination should identify hepatomegaly and the presence of any pulsatile mass suggesting abdominal aortic aneurysm. The presence of new or worsening peripheral edema should be noted.

The American Diabetes Association recommends that patients not known to have diabetes should have a *fasting blood glucose* measured every 3 years and an annual measurement of glycosylated hemoglobin for individuals with established diabetes. Fasting blood work 6 to 8 weeks after initiating lipid-lowering drug therapy should include liver function testing and assessment of the cholesterol profile. This should be repeated every 8 to 12 weeks during the first year of therapy and at 4- to 6-month intervals thereafter.

An ECG should be repeated when medications affecting cardiac conduction are initiated or changed. A repeat ECG is indicated for a change in the anginal pattern, symptoms or finding suggestive of an arrhythmia or conduction abnormality, and near or frank syncope. There is no clear evidence showing that routine, periodic ECGs are useful in the absence of a change in history or physical examination.

In the absence of a change in clinical status, low-risk patients with an estimated annual mortality rate of less than 1 percent over each year of the interval do not require repeat stress testing for 3 years after the initial evaluation.[1] These include those with low-risk Duke treadmill scores either without imaging or with negative imaging, those with normal LV function and normal coronary angiograms, and those with normal LV function and insignificant CAD. *Annual follow-up for noninvasive testing in the absence of a change in symptoms* has not been studied adequately; it may be useful in high-risk patients with an estimated annual mortality rate of greater than 5 percent. Follow-up testing should be performed in a stable high-risk patient only if the initial decision not to proceed with revascularization may change if the patient's estimated risk worsens. Patients with an immediate-risk (>1 and <3 percent) annual mortality rate are more problematic because of limited data. They may need testing at an interval of 1 to 3 years depending on the individual

circumstances. The ACC/AHA/ACP-ASIM recommendations for echocardiography, treadmill exercise testing, stress imaging studies and coronary angiography during patient follow-up are also listed in Table 40-12.

Table 40-12: Recommendations for Echocardiography, Treadmill Exercise Testing, Stress Imaging Studies, and Coronary Angiography during Patient Follow-Up

Class I

1. Chest x-ray for patients with evidence of new or worsening congestive heart failure.
2. Assessment of LV ejection fraction and segmental wall motion in patients with new or worsening congestive heart failure or evidence of intervening MI by history or ECG.
3. Echocardiography for evidence of new or worsening valvular heart disease.
4. Treadmill exercise test for patients without prior revascularization who have a significant change in clinical status, are able to exercise, and do not have any of the ECG abnormalities listed below in number 5.
5. Stress imaging procedures for patients without prior revascularization who have a significant change in clinical status and are unable to exercise or have one of the following ECG abnormalities:
    a. Preexcitation (Wolff-Parkinson-White) syndrome.
    b. Electronically paced ventricular rhythm.
    c. More than 1 mm of rest ST-segment depression.
    d. Complete left bundle-branch block.
6. Stress imaging procedures for patients who have a significant change in clinical status and required a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results.
7. Stress imaging procedures for patients with prior revascularization who have a significant change in clinical status.
8. Coronary angiography in patients with marked limitation of ordinary activity. (CCS class III despite maximal medical therapy).

Class IIb

Annual treadmill exercise testing in patients who have no change to clinical status, can exercise, have none of the ECG abnormalities listed in number 5 above, and have an estimated annual mortality of >1%.

Class III

1. Echocardiography or radionuclide imaging for assessment of LV ejection fraction and segmental wall motion in patients with a normal ECG, no history of MI, and no evidence of congestive heart failure.
2. Repeat treadmill exercise testing in <3 years in patients who have no change in clinical status and an estimated annual mortality ≤1% on their initial evaluation as demonstrated by one of the following:
    a. Low-risk Duke treadmill score (without imaging).
    b. Low-risk Duke treadmill score with negative imaging.
    c. Normal LV function and a normal coronary angiogram.
    d. Normal LV function and insignificant CAD.
3. Stress imaging procedures for patients who have no change in clinical status and a normal rest ECG, are not taking digoxin, are able to exercise, and did not require a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results.
4. Repeat coronary angiography in patients with no change in clinical status, no change on repeat exercise testing or stress imaging, and insignificant CAD on initial evaluation.

NOTE: See classes I-III as described at the bottom of Table 40-5.

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MANAGEMENT OF SPECIAL CATEGORIES

Systemic Arterial Hypertension

Patients with systemic arterial hypertension (SAH) often have angina pectoris. In most patients, significant coronary atherosclerosis of the epicardial blood vessels is present, but some patients with SAH may have angina pectoris or even fatal MI without significant obstruction of the large epicardial vessels. A major mistake is to send a patient for noninvasive testing when his or her hypertension has not been treated. In some patients there may be a marked increase in M_{O_2} that exceeds the CBF reserve, whereas others may have microvascular angina (syndrome X).

In many patients, treatment of the hypertension with a beta blocker, calcium antagonist, or angiotension-converting enzyme inhibitor also will decrease M_{O_2} and prevent the development of angina pectoris. In general, efforts should be made to control the blood pressure both at rest and during exercise. It is now know that many patients with an elevated systolic and/or diastolic blood pressure above the normal variation during exercise will develop severe fixed SAH. Efforts should be made to control the blood pressure both at rest and during exertion.

Chronic Obstructive Pulmonary Disease/Asthma

Beta blockers should be avoided in the subset of patients who have true bronchospastic lung disease, and the use of nitrates and calcium antagonists is preferred. Since many of these patients receive medications for their pulmonary disease that may increase their heart rate or even produce supraventricular tachycardia, it is preferable to use a heart rate-slowing calcium antagonist such as diltiazem or verapamil. Many patients with a history of only asthma or mild chronic obstructive pulmonary disease may be able to tolerate small doses of cardioselective beta blockers with careful monitoring.

Elderly Patients

In general, elderly patients tolerate calcium antagonists better than beta blockers. The presence of sinus tachycardia or atrial fibrillation is a relative contraindication to the selection of dihydropyridines such as nifedipine or amlodipine. In such patients, diltiazem or verapamil or even a beta blocker is preferable. On the other hand, beta blockers, verapamil, and diltiazem can exacerbate AV block, and verapamil produces constipation in many elderly patients. Also, some elderly patients develop postural hypotension from short-acting nitrates.

Peripheral Vascular Disease

Patients with peripheral vascular disease may have a worsening of their symptoms when treated with a nonselective beta blocker, permitting unopposed alpha-induced vasoconstriction. Alternatively, the worsening symptoms may be due to a decrease in arterial perfusion pressure. In general, it is preferable to treat patients with chronic stable angina who have peripheral vascular disease with nitrates and a calcium antagonist.

Diabetes Mellitus

Patients with chronic stable angina who have diabetes mellitus and hypoglycemic episodes due to insulin probably should be treated with nitrates and calcium antagonists (see Chap. 78). If it is necessary to use a beta blocker, a cardioselective agent should be chosen, since it is less likely to impair the recognition of and recovery from insulin-induced hypoglycemia. In most diabetics, cardioselective beta blockers are well tolerated. The BARI-II Diabetes Study is evaluating the efficacy at *early* myocardial revascularization in diabetes with CAD.

Chronic Renal Disease

While beta blockers and calcium antagonists normally can be used effectively in patients with chronic angina and chronic renal insufficiency, careful monitoring may be necessary because many beta blockers and calcium antagonists (see Chap. 84) are excreted primarily by the kidneys.

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CHRONIC MANIFESTATIONS OF CHRONIC ISCHEMIC HEART DISEASE

Heart Failure

Patients with severe CAD that produces a loss of 20 percent or more of the myocardium or that results in a ventricular septal defect or significant mitral regurgitation may cause important LV failure. While there may be significant hypertrophy of the remaining myocytes and interstitium (see Chap. 20), the ventricle is unable to compensate completely, and heart failure often results with a decreased stroke volume and elevated diastolic filling pressures. A syndrome of heart failure may result that is clinically predominant and often more incapacitating than any symptom of angina pectoris (see Chap. 66).

Patients with severe LV dysfunction due to CAD have a poor prognosis. Usually it reflects permanent, irreversible loss of myocytes. In some patients severe chronic CAD is associated with persistently impaired LV function at rest due to reduced CBF that can be partially or completely restored to normal either by improving blood flow (more common) or by reducing oxygen demand. This concept of "hibernating" myocardium is important because there can be significant improvement following good LV revascularization. While this does not occur routinely, it must be considered before concluding that the LVEF of an individual patient is too low to consider revascularization surgery or that the etiology of the heart failure is not CHD. MPI imaging techniques, magnetic resonance imaging (MRI), dobutamine echocardiography, and positron-emission tomography (PET) are useful in detecting myocardial viability (see Chap. 19).

The treatment of patients with heart failure due to CHD is the same as for most patients with combined systolic and diastolic LV failure and includes diuretics, an ACE inhibitor, digitalis, beta blockers, and spironolactone (see Chap. 28).

Cardiac transplantation is also frequently performed for severe heart failure due to CAD (see Chap. 22). A patient with heart failure who has a large LV aneurysm may benefit from aneurysmectomy if there is sufficient remaining functioning LV tissue. Similarly, heart failure due to severe mitral regurgitation sometimes can be improved significantly by corrective mitral valve surgery, which is often combined with myocardial revascularization. The operative mortality for this procedure can be high; in patients with severe functional mitral regurgitation, mitral valve repair with a reduced annular size can improve patient symptoms considerably (see Chap. 48).

Cardiac Arrhythmias, Conduction Disturbances

Chronic ischemic heart diseases causes many cardiac arrhythmias. The basic management is discussed in Chap. 24. In general, beta blockers should be employed whenever there is no strong contraindication, and type IC antiarrhythmic agents should be avoided unless the patient is symptomatic. In patients with atrial fibrillation, the ventricular response rate should be controlled with digoxin.

Patients with chronic atrial fibrillation also should be maintained on warfarin (INR = 2-3) unless

there is a contraindication, in which case aspirin (80-325 mg/day) should be used. Patients in heart failure who have atrial fibrillation may benefit from an effective atrial contraction restored by electrical cardioversion. Unfortunately, large percentages revert to atrial fibrillation in the next few months. Nonetheless, cardioversion sometimes can improve overall function significantly even though for a short time. Patients with recurrent symptomatic ventricular tachycardia or ventricular fibrillation can be treated with an implantable cardioverter-defibrillator. The use of these devices is discussed in Chap. 29.

Embolic Disease

Patients with ischemic disease are likely to have systemic emboli, particularly patients with a history of systemic embolus, chronic atrial fibrillation, ventricular aneurysm, a large dyskinetic or hypokinetic area of myocardium, or a severely depressed LVEF. Such patients should be considered for chronic, long-term, low-dose warfarin therapy (INR = 2-3).

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CHEST PAIN WITH NORMAL CORONARY ARTERIES

The combination of chest pain with many of the features of angina pectoris, although frequently atypical, and normal epicardial coronary arteries at cardiac catheterization has been known since the entity was first described in the 1960s. The early studies identified many of the features of what was subsequently characterized as a syndrome: female predominance, the frequent presence of ischemic ST-segment changes on the exercise ECG, inconsistent relationship between ECG changes and metabolic or hemodynamic evidence of ischemia, and pain that could be very severe, prolonged, variable in location, precipitated by unusual events, and unresponsive to usual antiischemic therapy.

The term *syndrome X* was applied to this diagnostic combination in 1973[175]; it is usually used to describe patients with the common features of angina-like pain and normal epicardial coronaries, but the term is also used to categorize groups that undoubtedly are pathophysiologically heterogeneous.[176-178] The continued use of this term is unfortunate and has been discouraged,[179] especially since there is a *metabolic syndrome X*, characterized by insulin resistance, hyperinsulinemia, and diabetes, that is associated with abnormal lipids, hypertension, and abdominal obesity[179] (see Chap. 78). A more specific term such as *angina with normal coronary arteriography* is preferable.

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Part 6: CORONARY HEART DISEASE
Chapter 41:

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

Author: David D. Waters

Unstable angina is an acute coronary syndrome that does not involve myocardial necrosis. It is characterized clinically by new-onset or worsening angina. The usual underlying pathophysiologic mechanism involves the rupture or erosion of an atherosclerotic plaque with thrombus formation that severely obstructs the coronary artery lumen. In 1996, 1,367,000 patients were hospitalized with this diagnosis in the United States.[1]

Important advances in the management of unstable angina have occurred in the last decade. Serum markers such as C-reactive protein and the troponins facilitate more accurate risk stratification. New therapies, specifically low-molecular-weight heparins and platelet glycoprotein (GP) IIb/IIIa receptor antagonists, have improved outcomes in high-risk patients. The introduction of coronary stents has reduced the incidence of acute vessel closure and restenosis. The exact indications for these newer therapies have not been defined completely across different strata of risk in patients with unstable angina. Physicians therefore must continue to integrate the results of new trials into their practice and exercise finely tuned judgment in the management of these patients. Unstable angina and the closely related condition non-ST-segment elevation myocardial infarction (NSTEMI) are very common manifestations of coronary artery disease.[1]

DEFINITION AND CLASSIFICATION

The term *unstable angina* has superseded older labels such as *preinfarction angina, acute coronary insufficiency*, and *intermediate coronary syndrome*. Unstable angina can be defined conveniently as new-onset or worsening angina within the previous 60 days or postinfarction angina (after the first 24 h from the onset of infarction).

Several systems have been proposed for classifying unstable angina. Distinguishing *primary* from *secondary* unstable angina is of clinical value. Acute worsening of a coronary stenosis (as described below) causes primary unstable angina by limiting coronary blood flow. Secondary unstable angina arises as a consequence of increased myocardial oxygen demand superimposed on severe underlying coronary disease. The major determinants of myocardial oxygen demand are heart rate, inotropic state, and the loading conditions of the left ventricle, primarily afterload. Thus, conditions with the potential to provoke secondary unstable angina include tachyarrhythmia, fever, hypoxia, anemia, hypertensive crisis, and thyrotoxicosis. Secondary unstable angina should resolve after successful treatment of the precipitating condition. Various classifications have been proposed for primary unstable angina, based on the presenting symptoms.[2-4] In 1973, Gazes and associates[2] defined three subgroups: (1) initial onset of progressive, crescendo angina and pain at rest in a patient previously free from symptoms, (2) the same presentation occurring suddenly in a patient with previously stable angina, and (3) episodes of prolonged pain at rest, lasting more than 15 min, not related to obvious precipitating factors.

The classification proposed by Braunwald (Table 41-1) includes three levels of severity and three clinical circumstances, yielding nine categories in all.[4] The presence or absence of electrocardiographic (ECG) changes and the intensity of medical therapy also were considered. A

higher clinical category was more commonly associated with intracoronary thrombus and complex lesions in one study.[5] The components of the Braunwald classification have been shown to correlate with clinical outcomes. Specifically, a 48-h pain-free interval and the absence of ECG changes are associated with decreased risk, while postinfarction unstable angina and the need for maximal medical therapy carry a higher risk.[6,7] The Braunwald classification sometimes is used to categorize patients for research purposes, but no system is widely used in clinical practice. Braunwald has proposed a pictographic system to display the pathophysiologic components that contribute to unstable angina in a specific patient (Fig. 41-1).[8]

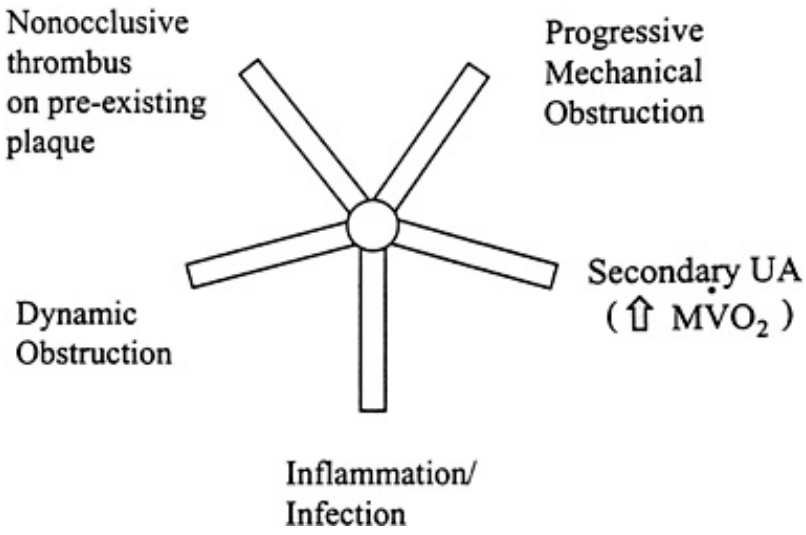

Figure 41-1: Framework for considering the pathophysiologic components that contribute to unstable angina in a specific patient. Varying contributions are possible from each of the five arms. Some patients will have predominantly one cause, while in others two or more mechanisms will contribute significantly. (From Braunwald,[8] with permission.)

The recognition of three specific forms of primary unstable angina is worthwhile because the pathophysiology, prognosis, and management of those forms are different. Variant, or Prinzmetal's, angina (discussed later in this chapter) is caused by coronary spasm and usually can be controlled with calcium channel blockers. Unstable angina within 6 months after coronary angioplasty almost invariably is caused by restenosis. Since the underlying mechanism is cellular proliferation instead of plaque rupture, antithrombotic drugs are not needed and intravenous nitroglycerin provides effective treatment.[9] Unstable angina in a patient with previous coronary bypass surgery often involves advanced atherosclerosis of venous bypass grafts and a lower likelihood of long-term symptomatic relief compared with other patients with unstable angina.[10,11] As is discussed below, patients with unstable angina should be classified according to their level of short-term risk. High-, intermediate-, and low-risk categories have been established on the basis of clinical and ECG data available at the time of the first assessment.[12]

NEXT

Chapter 41: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

PATHOPHYSIOLOGY

Progression of coronary atherosclerotic plaque can be divided into five phases and different lesions (Fig. 41-2).[13] Disruption of a type IV or type VA lesion exposes the underlying thrombogenic substrate, leading to the formation of a thrombus. This acute type VI lesion can heal without producing symptoms. However, when the thrombus totally or subtotally occludes the lumen, an acute coronary syndrome may result. The factors that contribute to the development of an acute coronary syndrome (Table 41-2) also represent potential targets for therapy.

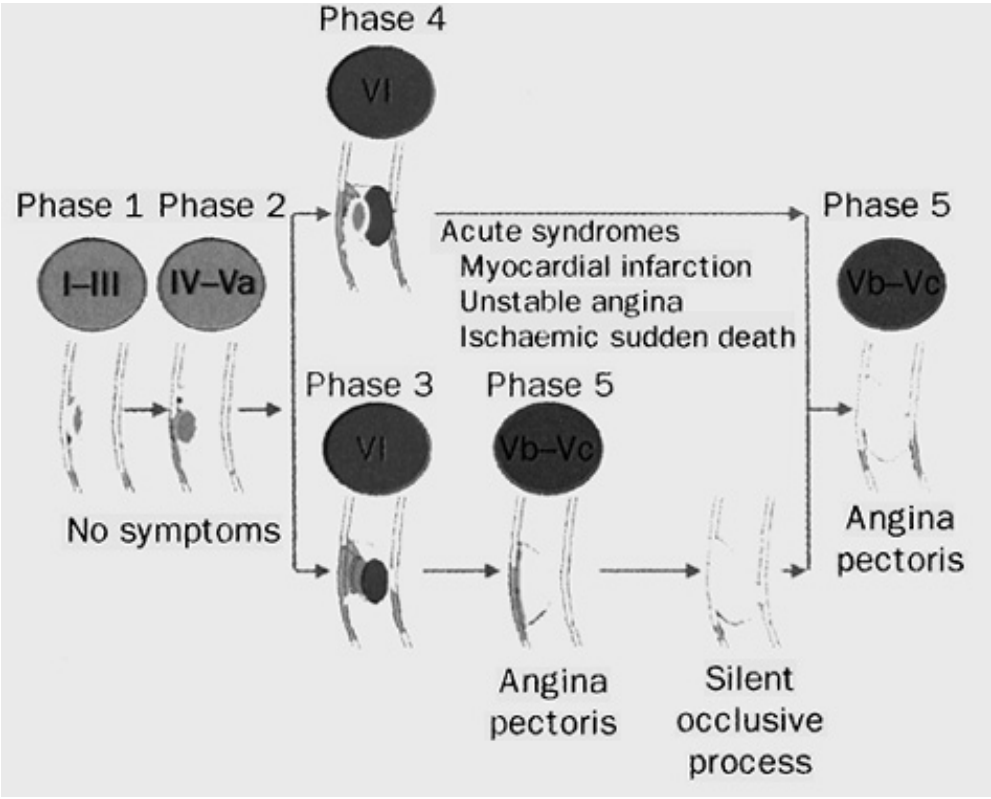

Figure 41-2: Phases of coronary lesion morphology and progression, with correlation to clinical syndromes. Unstable angina is caused by phase 2, type IV and type Va, lesions that are disrupted and progress to phases 3 and 4, type VI. (From Fuster et al.,[13] with permission.)

Table 41-2: Factors That Modulate the Development of Acute Coronary Syndromes

Coronary factors
Location of the culprit coronary lesion
Stenosis length, contour, and severity
Extent of plaque rupture or erosion
Inflammatory substrate
Endothelial function
Degree of coronary vasoconstriction
Extent of collaterals
Thrombotic factors
Platelet aggregability and reactivity
Leukocyte activation
Intrinsic clotting factors
Plaque tissue factor levels
Level of fibrinolytic activity
Blood viscosity
Systemic factors
Heart rate and blood pressure
Catecholamine levels (smoking, cocaine, stress)
Cholesterol levels, including Lp(a)

Plaque Disruption

The mechanisms involved in plaque disruption and the transformation of coronary atherosclerosis from a stable phase to an unstable phase have been studied intensively in recent years. Mechanical factors contribute to plaque disruption: A thin fibrous cap is more prone to rupture than is a thick one, and plaque rupture occurs commonly at the shoulders, where the plaque joins the adjacent vessel wall.[14] A lipid pool within a plaque influences the biomechanical properties of the plaque and increases the risk of rupture; conversely, fibrosis and calcification appear to decrease the risk of rupture.[14,15]

Plaque erosion, as well as plaque rupture, can initiate an acute coronary syndrome.[16] Erosion usually occurs centrally through a thinning cap as opposed to taking place at the plaque shoulders. Plaque erosion appears to be more common in women smokers, and plaque rupture in hyperlipidemic men.[17,18] In a study of women who died from sudden coronary death, plaque erosion was common in the premenopausal age group and plaque rupture was common in older women with hyperlipidemia.[18] Diabetes and hypertension were most common in women with healed infarcts. Macrophages and T cells invariably are found in close proximity to sites of plaque

rupture but are not prominent features of plaque erosion.

Inflammation

In addition to biomechanical factors, inflammation appears to play a key role in plaque disruption. Macrophages and T lymphocytes accumulate in atherosclerotic plaques because of the expression of adhesion molecules on monocytes, endothelial cells, and leukocytes.[19,20] Once within the plaque, these cells release growth and chemotactic factors and are involved in the local oxidation of low-density lipoprotein (LDL) cholesterol and other products. These processes stimulate smooth muscle cell proliferation and the production of foam cells.

T lymphocytes produce interferon-gamma (INF-gamma), a cytokine that markedly inhibits the production of collagen by smooth muscle cells in vulnerable regions of the plaque cap.[21] INF-gamma also inhibits the proliferation of smooth muscle cells. In addition to impaired synthesis of collagen, accelerated degradation of collagen and other components of the matrix contributes to weakening of the fibrous cap. The matrix metalloproteinases, a family of enzymes that includes collagenases and gelatinases, are released by foam cells and are able to degrade the collagen that provides strength to the fibrous cap.[21] Tissue inhibitors of metalloproteinases (TIMPs) normally are expressed by vascular smooth muscle cells; however, in the critical areas of the fibrous cap, foam cells predominate and smooth muscle cells are sparse. Under the influence of cytokines, smooth muscle cells produce a different form of gelatinase, with no increase in the production of TIMPs.

Elevated peripheral blood levels of specific matrix metalloproteinases have been reported in patients with acute coronary syndromes.[22] Furthermore, atherectomy specimens from patients with unstable angina, but not stable angina, exhibit active synthesis of a specific gelatinase.[23] Nuclear factor-κB (NF-κB) also has been found in the peripheral blood of patients with unstable angina but not stable angina.[24] NF-κB resides inactive in the cytoplasm of lymphocytes, monocytes, endothelial cells, and smooth muscle cells, where after stimulation it transcriptionally activates interleukins, interferon, tumor necrosis factor-alpha, and adhesion molecules. It is thus a specific marker of inflammation.

In a detailed study of 20 culprit lesions, macrophages and T lymphocytes were found to be clustered at the immediate site of plaque rupture.[25] These cells and nearby smooth muscle cells expressed high levels of the same human leukocyte antigen (HLA)-DR transplantation antigen, indicating both activation and "cross-talk" among the cells. Mast cells also have been found in culprit lesions of unstable angina patients but not stable angina patients.[26] These mast cells stained positively for TNF-alpha and were in proximity to macrophages containing matrix metalloproteinase and gelatinase. Taken together, these findings indicate that an inflammatory stimulus unleashes a biochemical storm within the susceptible plaque, leading to rupture of the fibrous cap.

C-reactive protein (CRP) is a nonspecific acute-phase reactant. Increased serum levels of CRP[27,28] were reported to be elevated in most patients with unstable angina and myocardial infarction but not in those with stable angina. The short-term prognosis was worse in unstable angina patients with elevated levels.[28] In a larger study of stable and unstable angina patients undergoing coronary arteriography,[29] CRP levels averaged slightly higher than normal in both groups, and an elevated CRP level was a strong predictor of coronary events over the subsequent 2 years. The cytokine interleukin-6, which is the main producer of CRP in the liver, is elevated in unstable angina but not in stable angina.[30] Interleukin-6 and interleukin-1 receptor antagonist levels were higher on admission in unstable angina patients who were destined to have a complicated course than in unstable angina patients without complications in a recent study.[31]

Infection

The stimulus that initiates the acute inflammatory process in unstable angina has not been identified. Atherosclerosis itself, as defined by the "response to injury" hypothesis, is a chronic, low-grade inflammatory condition.[32] Considerable controversy exists about whether infectious agents play a role either in atherogenesis or in the transformation of stable to unstable coronary disease.[33,34]

Chlamydia pneumoniae, cytomegalovirus, and *Helicobacter pylori* have been identified within human atherosclerotic lesions.[33] Mechanisms by which chlamydia may contribute to atherogenesis or plaque disruption have been identified: Chlamydia heat shock protein and human heat shock protein are located together within macrophages, where they stimulate TNF-alpha and matrix metalloproteinase production.[35] Also, antibodies against chlamydia heat shock proteins could cross-react against heat shock proteins produced by endothelium, resulting in endothelial damage and accelerated atherosclerosis.[36]

Antibodies to chlamydia, cytomegalovirus, and *Helicobacter* are found more often in patients with atherosclerosis than in controls.[33,34] However, these associations do not prove causality. Antibodies to these agents are found in a high proportion of the population, particularly in members of the lower socioeconomic classes.[37] In prospective studies, antibodies to cytomegalovirus or *Helicobacter* did not predict future cardiovascular events, although total mortality was higher in subjects with antibodies to *Helicobacter*.[37,38]

If infection contributes to the initiation of acute coronary syndromes, appropriate antibiotic treatment should reduce coronary events in infected individuals. In a small study of postinfarction patients, adverse cardiovascular events during follow-up increased with increasing antibody titers to chlamydia.[39] Patients with high titers were randomized to azithromycin or placebo, and events were reduced significantly in the antibiotic-treated group. However, in another small trial of azithromycin in coronary patients with a seropositive reaction to chlamydia, no reduction in events was seen despite a significant reduction in the levels of inflammatory markers.[40] In the ROXIS pilot study, patients with unstable angina or non-Q-wave infarction were randomized to either roxithromycin or placebo for 1 month, with a total follow-up of 6 months.[41] The drug reduced end point events significantly. Larger, more definitive trials to assess the effect of antibiotics in coronary patients are under way.

Platelets and Leukocytes

Platelet deposition onto the exposed, thrombogenic surface of a ruptured plaque represents an important step in the pathogenesis of unstable angina. Autopsy studies in accident victims with coronary atherosclerosis suggest that plaque ruptures are common.[42] Only a small fraction of disrupted plaques culminate in an acute coronary syndrome. The surface area exposed by plaque rupture or erosion and the features of the exposed surface determine in part the propensity for the development of thrombus. For example, atheromatous core may be up to six times as thrombogenic as are other substrates, such as collagen-rich matrix.[43]

Platelet function is also an important determinant of the outcome of plaque disruption and as such is a major target of therapy. Patients with stable coronary or peripheral vascular disease already have increased platelet reactivity compared with normal controls.[44,45] Healthy endothelium releases nitric oxide, which inhibits platelet aggregation. This protective mechanism is attenuated in patients with atherosclerosis.[46]

In unstable angina, platelets are activated and generate thromboxane and prostaglandin metabolites.[47] Severe or persistent unstable angina is associated with the highest thromboxane

output, and stabilization of unstable angina is accompanied by a return to normal levels.[48,49] Not only is the release of nitric oxide by the endothelium attenuated, the platelets themselves exhibit impaired nitric oxide production in patients with unstable angina.[50]

P-selectin is a membrane glycoprotein found both in the alpha granules of platelets and in endothelial cells. P-selectin mediates both platelet-leukocyte and endothelial cell-leukocyte adhesive interactions. Plasma P-selectin levels increase significantly in unstable angina and myocardial infarction but not in stable angina.[51] Neutrophils also are activated in unstable angina, and neutrophil-platelet adhesion is increased.[52] Neutrophil and monocyte adhesion molecules have been reported to increase in unstable angina,[20] particularly when measured in the coronary sinus soon after an episode of rest angina.[53]

Activated platelets and activated leukocytes thus interact in the acute phase of unstable angina to facilitate platelet-thrombus deposition. The interaction involves not only cellular elements but also the coagulation cascade.

Thrombosis and Fibrinolysis

Activated platelets and leukocytes interact to stimulate the coagulation system. Monocytes release tissue factor, a small glycoprotein that initiates the extrinsic clotting cascade, leading to an increase in thrombin generation.[54,55] Transient increases in thrombin-antithrombin III and prothrombin fragment 1+2 can be demonstrated in the hour after an ischemic attack in most patients with unstable angina.[56] This finding indicates that intermittent thrombus deposition, stimulated by all the mechanisms discussed above, causes transient coronary flow reductions and thus the symptoms of ischemia at rest.

Tissue factor is also present in the lipid-rich core of atherosclerotic plaque and may be one of the major determinants of the thrombogenicity of plaques when they rupture.[57] When tissue factor is specifically inhibited, platelet and fibrin deposition onto the ruptured plaque is reduced.[58] Tissue factor content is higher in unstable than in stable angina culprit lesions and correlates with areas of macrophages and smooth muscle cells.[59] Unstable angina patients with high circulating levels of tissue factor have unfavorable outcomes.[60] This finding implies that tissue factor plays a key role in the evolution of the unstable plaque.

Overactivity of other components of the coagulation system has been reported in unstable angina, including levels of factor XII, bradykinin precursor, and fibrinogen.[61] Lower tissue-type plasminogen activator (TPA) and plasminogen activator inhibitor-1 (PAI-1) levels indicate that impairment of the fibrinolytic system also is present in unstable angina.[61]

Vasoconstriction

Culprit lesions in unstable angina exhibit a heightened response to vasoconstrictor stimuli.[62] This response is not present in other coronary segments and also is not seen in the culprit lesions of patients with stable angina. One explanation for this is that endothelin levels are higher in culprit lesions in unstable angina patients as a result of the inflammatory component of those patients' condition.[63] However, under experimental conditions, the degree of vasoconstriction varies directly with the amount of platelet deposition.[64] The process of platelet aggregation and thrombus formation releases potent vasoconstrictors such as thromboxane A_2 and serotonin. Vasoconstriction, or the absence of appropriate vasodilation, probably contributes significantly to the development of ischemic episodes in patients with unstable angina and represents a potential target for therapy.

Evolution of the Culprit Lesion

The angiographic aspects of the culprit lesion have been defined before, during, and after an episode of unstable angina. If a patient with unstable angina has previously had a coronary angiogram, the culprit lesion usually can be documented to have progressed markedly since that time.[65] Lesions that progress to cause acute coronary events are usually not severely stenotic; in fact, two-thirds of them are less than 50 percent in diameter stenosis and thus would not be targets for revascularization.[66] Angiographic features of a lesion that predict that it will precipitate an acute coronary event include greater asymmetry, greater length, and a steeper outflow angle.[67]

At the time of an episode of unstable angina, the culprit lesion is likely to be asymmetric or eccentric, with a narrow base or neck, compared with control lesions.[68] These angiographic features reflect the underlying pathology: plaque disruption with thrombus. Obvious thrombus is visible at angiography in a minority of unstable angina patients. However, coronary angioscopy reveals plaque rupture with overlying thrombus in most culprit lesions.[69,70]

During the months after an episode of unstable angina, the culprit lesion is far more likely to progress and precipitate another coronary event than are other lesions in the same patient or lesions in stable patients.[71,72] Lesions with irregular borders, overhanging edges, or obvious thrombus at angiography are more likely to precipitate another event in the ensuing months than smooth lesions are. Whether more aggressive treatment with antiplatelet or antithrombotic drugs can modify the evolution of such complex lesions is not known.

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Chapter 41: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

DIAGNOSIS

A patient with unstable angina seeks medical attention because he or she has recognized either that new symptoms have appeared or that a previously stable pattern of symptoms has become unstable. The diagnostic difficulty usually lies in determining whether the chest pain is due to myocardial ischemia. Patients with suspected unstable angina must be evaluated rapidly and efficiently. A prompt and accurate diagnosis permits the timely initiation of appropriate therapy, which is important because complications are clustered in the early phases of acute coronary syndromes and because appropriate treatment reduces the rate of complications.

Patients with chest pain lasting for longer than 20 min, hemodynamic instability, or recent syncope or presyncope should be referred to a hospital emergency department.[1] Other patients with suspected unstable angina may be seen initially either in an emergency department or in an outpatient facility where a 12-lead ECG can be obtained quickly.

Initial Evaluation

The initial assessment should be directed toward determining whether the symptoms are caused by myocardial ischemia and, if so, the level of risk. If chest pain and ST-segment elevation >1 mm in two contiguous leads are present, reperfusion with thrombolytic therapy or primary angioplasty should be considered without delay. In the absence of these findings, the patient's clinical features should indicate whether the probability that symptoms are due to myocardial ischemia is high, intermediate, or low (Table 41-3). In a patient known to have coronary disease, typical symptoms are highly likely to be caused by myocardial ischemia, particularly if the patient confirms that the symptoms are identical to previous episodes with objective documentation. However, even if chest pain has some typical features, it is unlikely to be related to myocardial ischemia in a young individual who is known not to have risk factors for coronary disease. In one prospective multicenter study, older age, male sex, and the presence of chest or left arm pain or pressure as the presenting symptom all increased the likelihood that a patient was experiencing acute myocardial ischemia.[73]

Table 41-3: Likelihood That Unstable Angina Symptoms Are Caused by Myocardial Ischemia

HIGH LIKELIHOOD
Any of the following features:
Known coronary disease
Definite angina in men age 60 years or older or women 70 years or older
Hemodynamic or ECG changes during pain
Variant angina
ST elevation or depression of at least 1 mm
Marked symmetric T-wave inversion in multiple precordial leads
INTERMEDIATE LIKELIHOOD
Absence of high-likelihood features and any of the following:

Definite angina in men younger than age 60 or women younger than 70 years
Probable angina in men 60 years or older or women 70 years or older
Probably not angina in diabetics or in nondiabetics with two or more other risk factors[a]
Extracardiac vascular disease
ST depression of 0.05 to 1 mm
T-wave inversion of at least 1 mm in leads with dominant R waves
LOW LIKELIHOOD
Absence of high- or intermediate-likelihood features but may have:
Chest pain, probably not angina
One risk factor but not diabetes
T waves flat or inverted <1 mm in leads with dominant R waves
Normal ECG

[a]Risk factors include diabetes, smoking, hypertension, and hypercholesterolemia.

SOURCE: Adapted from Braunwald et al.,[12] with permission.

When unstable angina is suspected in a patient younger than age 50, it is particularly important to ask about cocaine use regardless of social class or ethnicity.[1] As is discussed in Chap. 71, cocaine can cause coronary vasospasm and thrombosis in addition to its direct effects on heart rate and arterial pressure and has been implicated as a cause of acute coronary syndromes. Unstable angina may be more difficult to diagnose than is stable angina because of the absence of some of the distinguishing features. The characteristic relation between stable angina and physical exertion or other stressful activities is a key diagnostic feature of stable angina that is lacking in unstable angina. Unstable angina may be poorly relieved by nitroglycerin, whereas this is rarely true for stable angina. The duration of an episode of chest discomfort is usually longer and more variable in unstable angina than in stable angina.

The sensation of myocardial ischemia usually is located in the retrosternal area but may be felt only in the epigastrium, back, arms, or jaw. The description may include adjectives such as *burning, squeezing, pressurelike,* or *heavy* but rarely includes *sharp, jabbing,* or *knifelike*. The physician should be cautioned that atypical features do not completely rule out the possibility of unstable angina. For example, in one study of patients presenting to the emergency department, acute ischemia ultimately was found to be present in 22 percent of patients who used the terms *sharp* and *stabbing* to describe their symptoms and 7 percent of patients whose pain was reproduced on palpation.[74]

Nausea, sweating, or shortness of breath may accompany episodes of unstable angina. In elderly or diabetic patients, these symptoms may be the only indication that myocardial ischemia is present. Elderly and diabetic patients also have a greater likelihood of having multivessel disease. Women who present with unstable angina are more likely to have diabetes, hypertension, hyperlipidemia, and heart failure and to be older than men; they are less likely to be smokers and to have had a previous infarction or a previous coronary revascularization (Table 41-4).[75] At coronary angiography, they are less likely to have significant coronary lesions.[75] In a recent large series of unstable angina patients, female sex had an independent protective effect against death or myocardial infarction within the first 30 days, with an odds ratio of 0.65 (95 percent confidence interval of 0.49 to 0.87).[75]

Table 41-4: Clinical Features in Men and Women Presenting with Unstable Angina

	Men	Women	*p* value
Number of patients	2801	1690	
Age (median, 25th, 75th percentile)	64 (54, 71)	68 (60, 75)	<.001
Hypertension	45%	57%	<.001
Diabetes	17%	23%	<.001
Current or former smoker	74%	38%	<.001
Hypercholesterolemia	39%	47%	<.001
Prior myocardial infarction	38%	27%	<.001
Prior angina	82%	82%	.54
Prior congestive heart failure	6.1%	10.2%	<.001
Prior bypass surgery	16.6%	9.2%	<.001
Heart rate (median, 25th, 75th percentile)	71 (62, 83)	76 (67, 86)	<.001
Systolic blood pressure (mmHg)	138 (120, 150)	140 (125, 160)	<.001
Killip class 2-4 on presentation	9.6%	12.5%	<.001

SOURCE: Adapted from Hochman et al.,[75] with permission.

On physical examination, transient signs of left ventricular dysfunction such as basilar rales or a ventricular gallop may accompany or follow shortly after an episode of unstable angina. More ominous signs of severe transient left ventricular dysfunction, such as hypotension and peripheral hypoperfusion, fortunately are not encountered commonly. Physical examination may reveal precipitating causes of or contributing factors to unstable angina, such as pneumonia and uncontrolled hypertension.

The Electrocardiogram

An ECG must be obtained as part of the initial evaluation of a patient with suspected unstable angina. The diagnostic yield is enhanced greatly if a tracing also can be recorded during an episode of chest pain. A normal ECG during chest pain does not rule out unstable angina as a likely diagnosis; however, it does indicate that an ischemic area, if present, is not extensive or severe enough to induce ECG changes and thus is a favorable prognostic sign.

Transient ST depression of at least 1 mm (Fig. 41-3) that appears during chest pain and disappears after relief represents objective evidence of transient myocardial ischemia. When ST depression is a persistent feature of ECGs recorded with or without chest pain, the finding is less specific. A common ECG pattern in patients with unstable angina is a persistently negative T wave over the involved territory (Fig. 41-4). This usually indicates that a severe stenosis is present in the corresponding coronary artery.[76] Myocardial stunning distal to the culprit lesion probably accounts for this ECG abnormality.[77] Deeply negative T waves occasionally are seen across all the precordial leads and point to a proximal, severe left anterior descending (LAD) coronary artery stenosis as the culprit lesion.[78]

In unstable angina patients, the ECG may show Q waves from an old infarct or a left bundle branch block resulting from extensive prior left ventricular damage. Patients with such findings are at increased risk because they are less likely than other patients to be able to tolerate an additional insult to the myocardium.[79,80] Myocardial ischemia is less likely to induce ST-segment changes in a territory that has Q

waves, and when it does, the change usually consists of ST elevation.

ECG abnormalities may appear or evolve in the absence of new symptoms in patients with acute coronary syndromes. For example, the development of significant Q waves may be the first indicator that the diagnosis is myocardial infarction, not unstable angina. T-wave abnormalities may appear, worsen, or resolve. It is therefore worthwhile to obtain serial ECGs during the first 48 h as well as during episodes of chest pain. Continuous 12-lead ECG monitoring can be performed using new multiprocessor-controlled, programmable devices. The limited clinical experience with this technology suggests that it can detect episodes of ST depression when the presenting ECG is normal and that this information has prognostic as well as diagnostic value.[81] Continuous vector cardiography ST-segment monitoring has been used by investigators who have reached the same conclusion.[82]

Serum Cardiac Markers

In the traditional paradigm, elevated serum levels of cardiac enzymes or the MB isoenzyme of creatine kinase (CK) could be used to distinguish between unstable angina and acute myocardial infarction. The diagnosis of unstable angina could be retained when minor elevations in CK or CK-MB were detected by serial sampling, but it was recognized that this was a negative prognostic sign.[83]

The widespread availability of other serum cardiac markers, particularly the troponins, has enriched this paradigm. One-fifth to one-quarter of patients with unstable angina will have elevated levels of troponin T or troponin I on admission or soon thereafter, and most of them will have normal levels of CK-MB. Several large studies have demonstrated that elevations of either troponin T or troponin I are independent predictors of adverse events in populations with either unstable angina alone or unstable angina and non-Q-wave infarction.[80,82,84-88] The troponin complex in cardiac and skeletal muscle consists of three subunits, which have been termed T, I, and C. The amino acid sequence of troponins T and I but not troponin C differ in cardiac muscle versus skeletal muscle. Immunoassays based on monoclonal antibodies have been developed to detect cardiac troponin T and cardiac troponin I. The sensitivity and specificity of these two markers appear to be roughly equal when used in populations with a high prevalence of acute coronary syndromes.[88] However, troponin I theoretically could be more specific because it is less likely to be generated by skeletal muscle disease or injury.[88] A rapid bedside assay for cardiac troponin T has been developed,[89] and a positive result of this test has been shown to be predictive of in-hospital adverse events among patients with unstable angina or non-Q-wave infarction.[90] Early positivity indicates higher troponin levels and a worse prognosis than does later positivity.[90]

Troponin T or troponin I measurements may be normal early after the onset of an acute coronary syndrome and become positive later. Myoglobin, a low-molecular-weight heme protein found in both skeletal and cardiac muscle, may be detected as early as 2 h after the onset of symptoms but is not specific for myocardial damage.[91] CK-MB subforms are usually positive within 6 h, and troponin T or troponin I within 12 h.[91] Troponin levels remain elevated for 1 week and thus are useful in making a diagnosis when a patient presents late after a coronary event.

The pathophysiologic basis for troponin release in unstable angina has not been defined adequately. Some patients probably have non-Q-wave infarcts that are not extensive enough to result in CK-MB release. A total occlusion of the culprit lesion with early spontaneous reperfusion could be the usual underlying substrate. In other unstable angina patients, elevated troponin levels may reflect mild myocardial damage caused by platelet microemboli from the culprit lesion.[92] Whether troponin can be released without irreversible damage to cardiac myocytes is not known.

With respect to terminology, patients with unstable angina, elevated troponin, and normal CK-MB levels could be classified as having either unstable angina or non-Q-wave infarction. It seems reasonable to continue to label them as having unstable angina to distinguish them from patients with elevated CK-MB levels. These patients should, however, be treated as high risk compared with unstable angina patients with normal troponin levels.

Cardiac troponins are less useful for the diagnosis of unstable angina than they are for risk stratification.

Only a minority of unstable angina patients will have elevated troponin levels on admission, and so the diagnosis usually is made by other means. However, an elevated level may be the only objective evidence of the presence of an acute coronary syndrome in some patients.

Acute Myocardial Perfusion Imaging

Intermittent reductions in coronary blood flow distal to the culprit lesion theoretically could occur in unstable angina without either ECG abnormalities or release of serum cardiac markers. Acute rest myocardial perfusion imaging with either thallium or sestamibi therefore might be a sensitive and specific diagnostic test for unstable angina. In practice, sestamibi is more useful than thallium for this purpose because imaging can be delayed for up to several hours after injection as a result of the minimal redistribution of this imaging agent. ECG-gated images provide an assessment of wall motion in addition to perfusion.

Several groups of investigators have shown that acute rest sestamibi imaging is useful in risk stratifying patients who present with chest pain.[93-96] A perfusion defect indicates either unstable angina or myocardial infarction. Imaging cannot distinguish between an acute infarct and one that is old. An example of a patient with unstable angina and a positive acute rest sestamibi image is shown in Fig. 41-5. An imaging study may be interpreted as equivocal if a perfusion defect cannot be distinguished from soft tissue attenuation in a myocardial segment with normal wall motion.

The sensitivity and specificity of acute rest imaging are very high if sestamibi is injected during an episode of chest pain, but sensitivity decreases if the injection is done within the ensuing hours.[97] The negative predictive value of a normal perfusion study is extremely high when the injection is done during symptoms. However, acute rest imaging will miss a few patients with acute coronary syndromes (less than 5 percent with experienced readers) and so patient management decisions cannot be made solely on the basis of one test result.

Chest Pain Units

The evaluation of patients with chest pain who may have unstable angina or myocardial infarction is often fraught with uncertainty. Hospitalizing all such patients for an extensive workup when the probability that active coronary disease accounts for their symptoms is neither cost-effective nor necessary. However, missing the diagnosis of unstable angina may result in unnecessary myocardial infarction or death. The chest pain unit has been developed as a solution to this problem.

Most chest pain units are in or adjacent to the emergency department and employ a set of criteria designed to select low-risk patients.[98-100] These criteria usually include chest pain that may indicate myocardial ischemia but with a normal or unchanged ECG and a normal first set of cardiac enzymes.[100] In a study of over 10,000 patients presenting to emergency departments with chest pain, the likelihood of a major cardiovascular event declined over time, with 41 percent occurring within 12 h and 62 percent within 24 h.[101] Events could be predicted by a set of simple clinical measures available at baseline and updated at 12 h.[101] This information provides a rationale for the design of chest pain units.

In most units, CK-MB is measured at 3- to 4-h intervals for 9 to 12 h, sometimes with other serum markers. Patients receive an aspirin, an intravenous line, ECG monitoring, and 12-lead ECGs during chest pain and at specific intervals. If no evidence of active coronary disease is detected at the end of this observation period, a stress test may be performed for diagnostic and prognostic purposes.

Chest pain units have been reported to reduce the rate of missed infarctions from approximately 5 percent to 0.5 percent of patients, as estimated from return visits within 72 h.[100] Missed diagnoses of unstable angina probably are reduced as well, although this rate is difficult to measure. Hospitalizations, hospital days, and total costs are reduced because approximately 75 percent of patients are discharged directly from the unit.[99,100]

Although most chest pain units accept only patients at low risk for an acute coronary event, a randomized trial has demonstrated that patients with unstable angina who are judged to be at intermediate risk also can

be managed in this environment.[102] Nearly half the patients randomized to the chest pain unit strategy completed the observation period, had a negative stress test, and were discharged home, to be evaluated further as outpatients. The rate of serious complications, mainly myocardial infarction, was not significantly different at 30 days and 6 months between the two groups.

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Chapter 41: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

RISK STRATIFICATION

The evaluation of a patient with unstable angina requires not only the establishment of the diagnosis but also an assessment of the short-term risk. This risk assessment determines the appropriate intensity of therapy. At the low end of the risk scale, a patient may be discharged home with aspirin and a beta blocker, to be followed as an outpatient. At the opposite end of the scale, a patient may be hospitalized in a coronary care unit, be treated with multiple drugs, and undergo coronary arteriography urgently as a prelude to revascularization.

Clinical Features

The 1994 report of the Agency for Health Care Policy and Research (Table 41-5) categorized unstable angina patients into low-, intermediate-, and high-risk groups on the basis of the data available at the time of the first assessment.[12] High-risk patients have ongoing chest pain that lasts longer than 20 min, reversible ST changes of at least 1 mm, or signs of serious left ventricular dysfunction. Low-risk patients have worsening angina without rest pain, are not older than age 65, and have a normal or unchanged ECG without evidence of a previous infarct.

The risk assessment should be updated during hospitalization because patients frequently change categories. Continuing angina with ST changes despite medical therapy is an ominous sign that should precipitate urgent coronary arteriography with a view to revascularization, because the risk of myocardial infarction is high. Most episodes of myocardial ischemia are silent, and some investigators have reported that episodes of ST depression detected by Holter monitoring are a better predictor of an unfavorable outcome.[103]

Serum Cardiac Markers

Troponin measurements should be used in the risk stratification of patients with unstable angina to supplement the assessment from clinical features and the results of the ECG. Elevated troponin levels strongly predict coronary events over the short term. The odds ratio for cardiac death or myocardial infarction within 30 days for an elevated troponin T was 2.7 (95 percent confidence interval of 2.1 to 3.4), based on 12 studies including a total of 2847 unstable angina patients.[88] The odds ratio for an elevated troponin I was 4.2 (95 percent confidence interval of 2.7 to 6.4), based on 9 studies of 1901 unstable angina patients.[88] The sensitivity and specificity of troponin T and troponin I are not significantly different.[88]

A major advantage of troponin measurements is that troponins contribute to risk independently of most of the other major predictors. For example, in one large study, elevated troponin T, age, hypertension, number of antianginal drugs, and ECG changes at baseline predicted cardiac death or myocardial infarction in a multivariate analysis.[84] In that study, the amount of troponin T elevation was also a predictor, with risk increasing for each quintile of troponin T elevation. The combination of troponin T elevation and ST depression identified a group at particularly high risk.

Measuring troponin not just at baseline but also at 8 and 16 h after admission has been shown to add useful prognostic information.[104] Elevated troponin levels predict an adverse outcome not just

in unstable angina patients but also in the broader population of patients with chest pain presenting to emergency departments.[105] Evidence from a trial of a low-molecular-weight heparin suggests that elevated troponin may be a marker that identifies patients who will benefit from antithrombotic therapy.[106]

High levels of the inflammatory markers CRP, serum amyloid A, and interleukin-6 are associated with a poorer prognosis in unstable angina patients.[28,31,107] Markers of activation of the coagulation system also have been reported to predict risk, including fibrinopeptide A[108] and fibrinogen.[109] The early rise in von Willebrand factor was an independent predictor of events within 30 days in one study.[110] However, in practice, the only serum marker that should be measured routinely for risk stratification in unstable angina is troponin T or I.

Stress Testing

Stress testing often is used as a risk assessment tool in patients with unstable angina. Low-risk and some intermediate-risk patients whose symptoms stabilize with medical therapy undergo stress testing for advanced risk stratification. Those with high-risk findings (Fig. 41-6) such as reversible perfusion defects or ST depression at low exercise levels undergo coronary arteriography, and those with negative or low-risk results are managed medically. This approach has been validated by studies in unstable angina patients demonstrating that these abnormalities correlate with a higher event rate during follow-up.[111-114] For example, in one study, 60 percent of patients with a reversible perfusion defect compared with 12 percent of those with a normal exercise sestamibi scan experienced cardiac death, nonfatal infarction, or rehospitalization for unstable angina during a 12-month follow-up.[114] Patients with low exercise tolerance, exercise-induced ST depression, and larger perfusion defects are more likely to have three-vessel coronary disease than are patients without these high-risk findings.[115]

Patients who complete a stay in a chest pain unit without objective evidence of myocardial ischemia can safely undergo stress testing for diagnostic and prognostic purposes.[116] In one study, 71 percent of chest pain unit patients completed stage 1 of a Bruce protocol without evidence of myocardial ischemia, and their rate of infarction or coronary revascularization over the next 6 months was only 2 percent.[116]

In patients who are unable to exercise, dipyridamole or dobutamine can be used as the stress and sestamibi imaging or echocardiography can be used as the method of assessment. Stress testing is not needed in patients whose clinical features already put them at high risk. Patients with continuing angina despite medical therapy. ST depression, or hemodynamic impairment during spontaneous attacks of rest angina or elevated troponin levels should proceed directly to coronary arteriography.

Coronary Angiography

Risk in coronary patients traditionally has been assessed according to the number of vessels with at least 50 percent diameter stenosis and the presence and severity of left ventricular dysfunction. Older studies indicate that these variables are important predictors of outcome in unstable angina.[117-119] However, their prognostic impact is probably less than it is in stable coronary disease because the risk of short-term events in unstable angina is dominated by features of the culprit lesion, such as whether it induces ST depression or troponin release. Culprit lesions are far more likely to progress and initiate other coronary events in the months after an episode of unstable angina than are other coronary lesions in the same patients.[71,72]

Among patients with unstable angina who undergo coronary arteriography, approximately one-quarter will have one-vessel, one-quarter two-vessel, and one-quarter three-vessel involvement; 10

percent will have significant left main stenosis; and the other 15 percent will have narrowings of less than 50 percent or normal vessels on angiography. Patients with left main stenosis of at least 50 percent or three-vessel disease with left ventricular dysfunction will obtain a survival benefit from coronary bypass surgery.[120,121] Although noninvasive testing is sensitive and specific enough to detect many of these patients, the only certain method for diagnosing these conditions is angiography.

At the other extreme, patients without significant lesions at angiography benefit from a reorientation of their management. Noncardiac causes of chest pain should be considered, as well as other potential diagnoses, such as syndrome X and variant angina. Antithrombotic and antiplatelet drugs often can be discontinued, and the need for antianginal medication can be reassessed. The unstable angina patients who are most likely to have no significant lesions at angiography tend to be women with no ST-segment abnormalities on ECG.[122] Nevertheless, the finding of no significant lesions at angiography is usually a surprise. These patients have a low coronary event rate during follow-up even though their symptoms often persist.[122]

Risk Stratification with Combinations of Predictors

In clinical practice, several variables usually are integrated into a global assessment of risk. The combination of ST-segment abnormalities and elevated troponin levels has been shown to be useful. In one study that used these two indicators, the risk of death or infarction within 30 days was 25.8 percent, 3.1 percent, and 1.7 percent in high-, intermediate-, and low-risk groups, respectively.[24] In a Thrombin Inhibition in Myocardial Ischemia (TRIM) substudy, the composite end point of death, myocardial infarction, or refractory angina within 30 days was predicted by ST depression, inverted T waves in at least five leads, elevated troponin or myoglobin levels, female sex, and age of 65 or higher.[123] Death or infarction occurred in 14 percent, 6 percent, and 3 percent of high-, intermediate-, and low-risk groups, respectively.

In summary, the short-term outcome of unstable angina can be predicted by a variety of methods (Table 41-5). Risk assessment should be updated during hospitalization as new information becomes available so that high-risk patients are not undertreated and low-risk patients are not overtreated. The most important predictors are the clinical presentation (Table 41-3), ST depression during attacks, elevated troponin levels, and continuing episodes in spite of medical therapy.

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Chapter 41: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

PROGNOSIS

Prognosis in patients with unstable angina can be viewed as a composite of the prognosis expected from the extent of coronary disease and left ventricular function overlaid with the short-term risk associated with the culprit lesion and the unstable state. The short-term risk is related almost entirely to myocardial infarction and its complications and to recurrences of unstable angina. Risk is highest in the hours, days, and first month after the onset of symptoms. The incremental risk associated with the unstable state dissipates completely by 1 year.[71,72] For example, 11 percent of unstable angina patients in one series experienced a myocardial infarction between hospital discharge and 1 year but the subsequent annual infarction rate was less than 2 percent.[124]

Published data on the prognosis in unstable angina are influenced by patient selection and treatment and can be quite misleading. The inclusion and exclusion criteria for clinical trials may bias the prognosis by eliminating low-risk or high-risk patients. If younger patients with atypical symptoms and no objective evidence of myocardial ischemia are included in large numbers, the prognosis of the cohort under study will tend to be better. By contrast, if ECG changes or elevated troponin levels are required, the prognosis will tend to be worse. The prognosis has improved dramatically over the past two decades with the introduction of increasingly more sophisticated medical therapy and revascularization techniques. As recently as the early 1980s, aspirin was not used routinely in the treatment of unstable angina. Results from that era are therefore below current expectations.

In a compilation of 10 representative series with a total of nearly 2000 unstable angina patients, excluding those with new-onset or postinfarction angina, the mortality was 4 percent in the hospital and 10 percent at 1 year.[125] Survival without infarction was 89 percent at 1 month and 79 percent at 1 year. Among 4488 unstable angina patients in GUSTO-IIb, the mortality rate was 2.4 percent at 30 days, 5 percent at 6 months, and 7 percent at 1 year.[126] The infarction rate was 4.8 percent at 30 days and 6.2 percent at 6 months. Recurrent ischemia had a major impact on these rates; for example, the 30-day infarction rate increased from 2.3 percent to 7.2 percent to 21.7 percent in patients with no ischemia, ischemia, and refractory ischemia, respectively. These outcomes are representative of the results of modern therapy in the late 1990s.

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Chapter 41: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

TREATMENT

The goals of treatment in unstable angina are to control symptoms and prevent myocardial infarction. Nitroglycerin, beta blockers, and to a lesser extent calcium channel blockers reduce the risk of recurrent ischemic attacks. Revascularization eliminates ischemia entirely in patients with favorable anatomy, and in some subgroups, coronary bypass surgery has been shown to prolong life. The risk of myocardial infarction is reduced by antiplatelet and antithrombotic therapy.

Nitroglycerin and Nitrate Therapy

In patients with unstable angina, sublingual nitroglycerin usually relieves attacks promptly, although it may be somewhat less efficacious than it is in stable angina patients. Patients with unstable angina often are treated with an infusion of intravenous nitroglycerin to prevent further attacks. A common starting dose is 10 μg/min. The dose can be increased in increments of 10 μg/min until symptoms are controlled or unwanted side effects develop. The most common adverse effects are headache, nausea, dizziness, hypotension, and reflex tachycardia.

The evidence that intravenous nitroglycerin prevents ischemic attacks in unstable angina patients is sparse (Table 41-6). In two studies of 35 and 40 patients, respectively, intravenous nitroglycerin reduced the number of angina episodes during treatment compared with a pretreatment period.[127,128] However, a placebo control group was not included in the design of either study. No studies of sufficient power have examined whether intravenous nitroglycerin or other nitrate preparations reduce the risk of infarction in unstable angina.

Table 41-6: Clinical Trials of Anti-Ischemic Therapy in Unstable Angina

Author[a]	Year	Active Treatment	Comparison Group	No. Patients	Duration of Study	End Point	Primary Results	Comments
Kaplan et al.[127]	1983	IV Nitroglycerin (NTG)	None	35	In hospital	Rest angina episodes	90% decrease in episodes	No control group
Curman et al.[128]	1983	IV NTG	Oral/topical nitrates	40	In hospital	Rest angina episodes	Fewer episodes in both groups	No difference between groups
Muller et al.[143]	1984	Nifedipine	Propranolol, oral nitrates	126	14 days	Angina relief	Equal angina relief in both groups	MI rate 9/63 in both groups
Gottlieb et al.[144]	1986	Propranolol	Placebo	82	4 weeks	Angina recurrence	Propranolol superior	Nitrates plus nifedipine in both groups

Théroux et al.[145]	1985	Diltiazem	Propranolol	100	5.1 months	Angina in hospital death/MI during follow-up (FU)	Equal angina relief in both groups	Equal rates of death/MI during FU
Andre-Fouet et al.[146]	1983	Diltiazem	Propranolol	70	In hospital	Angina	Equal angina relief in both groups	Diltiazem superior in variant angina patients
HINT[147]	1986	Nifedipine Metoprolol	Placebo	515	48 h	Recurrent angina death/MI	MI rate higher with nifedipine compared with meto-prolol	Angina relief when nifedipine added to meto-prolol
Gerstenblith et al.[150]	1982	Nifedipine	Placebo	138	4 months	Death/MI/coronary artery bypass grafting (CABG)	Nifedipine better than placebo	Nifedipine benefit in variant angina patients

[a]Several small studies are not included (see references [152,] [153,] [158,] and [159]).

Nitroglycerin acts through several mechanisms that could provide benefit in patients with unstable angina. As a venodilator at low doses and an arteriolar dilator at higher doses, it reduces preload and afterload and thus myocardial oxygen consumption. The drug directly dilates coronary stenoses and thus increases oxygen delivery to the ischemic region.[129] Nitroglycerin increases collateral flow and favorably redistributes regional coronary flow. Because of its preferential effect on capacitance vessels as opposed to resistance vessels, it does not have the potential to induce coronary steal, unlike other vasodilators.[130]

Nitroglycerin and longer-acting nitrates act by releasing nitric oxide in vascular smooth muscle through an enzymatic process.[130] Sulfhydryl-donating compounds are necessary for this activity, and their rapid depletion during chronic therapy with nitroglycerin or other nitrate preparations rapidly leads to tolerance to the hemodynamic effects of the drug.[131] In stable patients, intermittent nitrate therapy is recommended to circumvent nitrate tolerance; however, some studies have shown that a rebound increase in ischemic episodes occurs during nitrate-free intervals.[132] Rebound myocardial ischemia after abrupt interruption of intravenous nitroglycerin infusion also has been reported in unstable angina patients.[133]

A second strategy for avoiding nitrate tolerance involves the concomitant administration of a sulfhydryl donor such as captopril or *N*-acetylcysteine. Although this approach is not employed in patients with unstable angina, a randomized trial in 200 patients demonstrated that the combination of transdermal nitroglycerin and *N*-acetylcysteine reduced the incidence of death, myocardial infarction, and refractory angina requiring hospitalization over 4 months compared with placebo or transdermal nitroglycerin alone.[134] Combined therapy caused intolerable headache in one-third of patients, limiting its clinical utility.

Considerable data can be marshaled to support the argument that the antiplatelet effects of nitroglycerin explain that drug's efficacy in treating unstable angina. Early studies demonstrated that nitroglycerin inhibits platelet aggregation.[135] Nitroglycerin and other nitrates activate cyclic guanosine monophosphate (GMP) in platelets. Cyclic GMP modulates the availability of intracellular platelet calcium and thus influences the response of platelets to receptor-mediated activation.[135]

At therapeutic doses, nitroglycerin reduces platelet aggregability to adenosine diphosphate and thrombin in unstable angina patients.[136] The drug also has been shown to reduce platelet thrombin deposition in an

experimental model that simulates plaque rupture.[137] Platelet aggregation induced by thrombin and platelet thrombin deposition appear to be reduced by nitroglycerin even after tolerance to the hemodynamic effects of the drug has developed.[138] Intravenous nitroglycerin usually is replaced with transdermal nitroglycerin or an oral nitrate preparation after an angina-free interval of 1 or 2 days. In unstable angina patients who undergo coronary angiography and angioplasty, intravenous nitroglycerin usually is discontinued 12 to 24 h after the procedure. The doses of transdermal or oral nitrates that are prescribed for patients with unstable angina are similar to those used in stable angina patients. In most cases, they are lower than the doses found to be effective in preventing angina in clinical studies.

Beta Blockers

Ischemia occurs when myocardial oxygen demand exceeds the delivery of oxygenated blood to a territory of myocardium distal to the culprit lesion. The major determinants of myocardial oxygen consumption are heart rate, myocardial inotropic state, and left ventricular afterload. Treatment strategies to prevent episodes of unstable angina can be divided into those which increase regional blood flow and those which reduce myocardial oxygen demand.

Beta blockers are the most useful category of drug in reducing myocardial oxygen demand, primarily by slowing heart rate but also by decreasing myocardial contractility and afterload. Heart rate and arterial pressure often increase during episodes of rest angina.[139,140] This unwanted response can be limited by beta-adrenergic blockade.

Beta blockers attenuate the coronary vasodilating effect of beta-adrenergic stimulation and allow alpha-adrenergic vasoconstriction to predominate. In patients with Prinzmetal's variant angina, beta blockers may increase the frequency or duration of attacks,[141,142] presumably through this mechanism. However, in patients with unstable angina, the potentially harmful effect of beta blockers on coronary blood flow does not appear to be clinically relevant.

Although it is widely accepted that beta blockers are useful in controlling ischemic episodes in patients with unstable angina, the data to support this claim are mainly inferential or have been derived from small trials without placebo-treated controls (Table 41-6). These trials date from the early 1980s, an era when patients were not treated routinely with aspirin and heparin.

Muller and coworkers randomly allocated 126 patients with unstable angina to propranolol plus isosorbide dinitrate or to nifedipine for 14 days.[143] The principal end point-the absence of recurrent chest pain for at least 48 h-was attained with equal frequency in the two groups; however, the propranolol and nitrate combination was more effective in patients not previously taking a beta blocker, and nifedipine was more effective in patients who had been receiving beta blockers before admission. The incidence of myocardial infarction during the 14-day treatment period was 14 percent (9 of 63) in both groups. Four patients in the nifedipine group died, compared with none in the group treated with propranolol.

Gottlieb and associates randomized 81 unstable angina patients either to propranolol at a dose of at least 160 mg/day or to placebo.[144] Baseline therapy in all patients included long-acting nitrates and nifedipine 80 mg/day. The cumulative probability of experiencing recurrent angina was significantly lower in the propranolol group. Myocardial infarction during the 4 weeks of the trial occurred in 6 of 42 propranolol-treated patients and 3 of 39 controls, a difference that was not statistically significant.

Théroux and colleagues randomized 100 patients with unstable angina to propranolol 240 mg/day or diltiazem 360 mg/day.[145] Transient ST-segment changes during an episode of chest pain were a requirement for study entry, and patients with Prinzmetal's variant angina or those already being treated with a beta blocker were excluded. Both drugs significantly reduced the frequency of angina episodes during hospitalization, and their antianginal efficacy was approximately equivalent. After 5.1 months of follow-up, 2 of 50 patients in each treatment group had died; 4 propranolol-treated and 5 diltiazem-treated patients experienced myocardial infarction. Similar results were found with respect to angina relief in a randomized comparison of propranolol and diltiazem in 70 unstable angina patients.[146]

The largest trial of a beta blocker in unstable angina was the Holland Interuniversity Nifedipine/Metoprolol Trial (HINT).[147] The 338 patients not receiving a beta blocker on admission were randomized to nifedipine 60 mg/day, metoprolol 200 mg/day, both drugs, or double placebo therapy. The rate of recurrent ischemia or

myocardial infarction within 48 h, the main end point of HINT, was reached by 37 percent of placebo patients, 47 percent of nifedipine patients, 28 percent of metoprolol patients, and 30 percent of patients receiving combination therapy. Metoprolol was significantly better than nifedipine with respect to this end point. The trend in favor of metoprolol compared with placebo was not statistically significant.

Taken together, these trials indicate that beta blockers effectively reduce symptoms in unstable angina patients who are not already taking one of these drugs on admission. Whether or not a beta blocker also reduces the risk of myocardial infarction is uncertain. The trials in unstable angina are much too small to answer this question and are confounded by the use of nifedipine in the comparison groups. Five old randomized trials involving approximately 4700 patients with "threatened myocardial infarction" assessed the effect of acute intravenous beta blockade followed by oral treatment for 1 week.[148] Most patients in these studies had prolonged chest pain without ECG evidence of infarction on admission. A 13 percent reduction in the risk of infarction, from 32 percent to 29 percent, was reported in an overview of these trials, a difference of borderline statistical significance ($p < .04$). Neither antiplatelet nor antithrombotic therapy was used in these trials, and so their relevance to patients treated with current therapy is uncertain.

During chronic therapy, a long-acting beta blocker is preferable to a short-acting one because it can be given once per day. However, in the context of unstable angina, it is reasonable to try to achieve beta blockade within hours, not days. Therefore, beta blockade sometimes is initiated with intravenous boluses titrated to reduce heart rate. Early heart rate control is particularly important in high-risk patients and those with tachycardia or a high arterial pressure on admission. A reasonable target heart rate in unstable angina patients is 50 to 60 beats per minute at rest. The main contraindications to beta blockers in unstable angina are reactive airway disease, sinus node dysfunction or atrioventricular block, and severe heart failure. Most patients with chronic obstructive pulmonary disease will tolerate a beta blocker; a $beta_1$-selective agent (for example, metoprolol or atenolol) is theoretically less likely to provoke bronchoconstriction. In some patients with conduction system disease, permanent pacing may be indicated in part so that chronic beta blocker therapy can be given. Mild heart failure that is stable is not a contraindication to beta blockers in patients with unstable angina. Diltiazem or verapamil should be considered when a beta blocker cannot be used.

Calcium Channel Blockers

Calcium channel blockers increase coronary blood flow both globally and to the ischemic zone. Diltiazem and verapamil both slow heart rate, reduce afterload, and reduce myocardial contractility; they thus reduce myocardial oxygen demand. Most dihydropyridine calcium channel blockers induce a reflex increase in heart rate in the absence of beta blockade, a feature that is likely to mitigate any benefit in regard to myocardial ischemia. Dihydropyridine calcium channel blockers sometimes worsen myocardial ischemia and produce other "proischemic" complications in a minority of patients.[149]

The calcium channel blocker that has been used most often among the limited number of studies of unstable angina is the short-acting formulation of nifedipine. The rapid absorption and short half-life of this preparation produce frequent abrupt changes in arterial pressure and heart rate. Whether the poor results seen with nifedipine in trials of unstable angina and postinfarction patients would have been different with a long-acting formulation is open to debate.

As was noted above, in the study of Muller and colleagues[143] comparing propranolol and nifedipine in 126 unstable angina patients, nifedipine was more effective in controlling angina in patients who were already taking a beta blocker on admission but was less effective in other patients. The infarction rate during 14 days of treatment was 14 percent in both the propranolol and nifedipine treatment groups.

HINT was terminated prematurely because of a significantly higher rate of infarction in nifedipine-treated patients.[147] Among patients not already receiving a beta blocker on admission, recurrent ischemia or infarction within 48 h, the primary end point, occurred more often with nifedipine than it did with propranolol. However, among the 177 patients pretreated with a beta blocker, nifedipine was superior to placebo, with a relative risk for the primary end point of 0.68 (95 percent confidence interval of 0.47 to 0.97).

Gerstenblith and coinvestigators randomized 138 unstable angina patients taking propranolol and long-acting nitrates to nifedipine 80 mg/day or to placebo.[150] The primary end point of the trial-death, infarction, or coronary bypass surgery within 4 months-was reached by 43 of 70 placebo patients and 30 of 68 nifedipine-treated patients ($p = .03$). Nifedipine was particularly beneficial ($p = .02$) in the 52 patients with transient ST

elevation during attacks, who presumably had coronary spasm, with little difference seen between the groups for the remainder of the study patients.

The potential of nifedipine at a dose of 80 mg/day to prevent "threatened myocardial infarction" was assessed in a double-blind, placebo-controlled trial of 105 patients.[151] Entry criteria included chest pain lasting longer than 45 min and ECG ST-segment changes, and treatment was initiated a mean of 4.6 h after the onset of pain. The incidence of progression to infarction of 75 percent in both groups was not altered by nifedipine. A further 66 patients with documented infarction on admission also were randomized to the same treatments in another part of the trial. At the end of the 14-day treatment period, mortality among the entire 171 patients was higher in the nifedipine group: 7.9 percent versus 0 percent (p = .018).

Taken together, these trials provide fairly strong evidence that nifedipine is harmful when used in unstable angina patients who are not receiving beta blockers but that it may be helpful in controlling angina in patients with an adequate level of beta blockade. Even when the addition of nifedipine does control angina in patients whose unstable angina was previously refractory, the risk of infarction or death over the next few months in the absence of revascularization remains very high.[152] Long-acting formulations of nifedipine and newer dihydropyridines such as amlodipine have not been evaluated in unstable angina trials.

As was mentioned above, two trials compared diltiazem to propranolol in a total of 170 patients with unstable angina.[145,146] The two drugs were equally effective in controlling angina and were associated with equal rates of myocardial infarction. In two small series in which intravenous diltiazem was compared with an intravenous nitrate for the control of myocardial ischemic episodes, diltiazem was reported to be superior.[153,154]

Verapamil has not been studied in large numbers of patients with unstable angina. In two small, placebo-controlled trials, the frequency of ischemic episodes was reduced significantly.[155,156] Long-term follow-up of these patients showed continued control of symptoms but a high incidence of infarction and death.[157] Verapamil and propranolol were compared in two small clinical trials.[158,159] Both drugs reduced the frequency of ischemic episodes, with verapamil being somewhat superior to propranolol. Both diltiazem and verapamil are effective in preventing ischemic episodes caused by coronary spasm, a condition that was present in some of the patients in these trials.

Diltiazem and verapamil are reasonable choices for treating unstable angina patients for whom beta blockers are contraindicated. The scant evidence discussed above suggests that both drugs reduce the frequency of attacks in unstable angina, but there is no evidence that they prevent infarction. The combination of diltiazem or verapamil with a beta blocker is not commonly used in unstable angina because the effects of these calcium channel blockers on heart rate and myocardial contractility are additive to the effects of beta blockers.

Antianginal Therapy

An oral beta blocker at a dose that reduces heart rate and an intravenous nitroglycerin infusion are a reasonable treatment to control symptoms in a high-risk or intermediate-risk unstable angina patient. Low-risk and some intermediate-risk patients can be treated with oral or transdermal nitrates and beta blockers. A patient who develops unstable angina while taking two or three antianginal drugs should be treated with intravenous nitroglycerin, but the symptoms will be harder to control compared with an unstable angina patient who previously took no antianginal drugs.

In most patients hospitalized with unstable angina, symptoms do not recur after the institution of antianginal therapy. Patients with refractory unstable angina have a much higher risk of developing myocardial infarction than do patients whose angina is controlled with drugs. Patients who are labeled as refractory often become asymptomatic when medical therapy is intensified; for example, in one study an increase in medical therapy relieved symptoms in 83 percent of patients transferred because their unstable angina was refractory.[160] Intraaortic balloon counterpulsation prevents myocardial ischemia effectively in patients whose unstable angina is truly refractory.[161] This mechanical approach improves myocardial blood flow and reduces myocardial oxygen demand by collapsing the resistance to left ventricular ejection in early systole. Intraaortic balloon counterpulsation is needed for the control of symptoms in less than 1 percent of patients with unstable angina, but it also is used in high-risk patients at the time of coronary angioplasty to provide a margin of safety. Intraaortic balloon counterpulsation causes lower limb ischemia in approximately 10 percent of cases, but this complication almost always resolves after removal of the device.

Aspirin

Aspirin inhibits cyclooxygenase activity in all body cells. This inhibition is irreversible for the life span of a platelet, normally a median of 8 days. As a consequence, the platelet is unable to produce thromboxane A_2 , the platelet-specific prostaglandin that induces platelet aggregation. Aspirin also may influence the pathophysiology of unstable angina through other mechanisms. For example, aspirin inhibits prostacyclin production by the endothelium but also has been shown to block cyclooxygenase-dependent endothelium-derived vasoconstriction.[162]

Four trials have demonstrated conclusively that aspirin reduces the risk of myocardial infarction in patients with unstable angina (Table 41-7).[163-166] In the Veterans Administration study, 1338 men hospitalized with crescendo angina, prolonged pain, or pain at rest were randomized to aspirin 324 mg/day or placebo within 7 days.[163] The study duration was 12 weeks, and the primary end point was death or acute myocardial infarction. The principal outcome was reduced from 10.1 percent to 5.0 percent (p = .0005). In the Canadian multicenter trial, 555 unstable angina patients were randomized to aspirin 325 mg four times per day or placebo within 8 days of admission and were followed on therapy for a mean of 18 months.[164] The risk reduction for cardiac death or nonfatal myocardial infarction was identical to that in the Veterans Administration study at 51 percent, from 17.0 percent to 8.6 percent (p = .008). Sulfinpyrazone also was tested in this trial but showed no benefit.

Table 41-7: Clinical Trials of Aspirin in Unstable Angina

Author	Year	No. Patients	Dose	Duration of Follow-Up	Death/MI Rate in Aspirin Group, %	Death/MI Rate in Control Group, %	*p* value	Relative Risk	Comments
Lewis et al.[163]	1983	1266	324 mg/day	12 weeks	5.0	10.1	.0005	0.49	Men only
Cairns et al.[164]	1985	555	325 mg qid	18 months	8.6	17.0	.008	0.49	Not intention to treat
Théroux et al.[165]	1988	239	325 mg bid	6 days	3.3	11.9	.01	0.29	Treatment begun at 8 h
RISC[166]	1990	796	75 mg/day	3 months	6.5	17.1	.001	0.36	Men only, non-Q-wave MI included

Théroux and associates randomized 479 unstable angina patients to aspirin 325 mg twice daily or placebo at hospital admission, a mean of 8 h after the last episode of pain, with a mean follow-up of 6 days.[165] Patients also were randomized to intravenous heparin in a factorial design. Aspirin reduced the risk of death or myocardial infarction from 6.3 percent to 2.6 percent, a 63 percent decrease (p = .04). The Research Group on Instability in Coronary Artery Disease (RISC) randomized 796 men with unstable angina or non-Q-wave infarction within 4 weeks to aspirin 75 mg/day or placebo.[166] An additional 115 men were excluded per the protocol because their predischarge exercise tests revealed no evidence of myocardial ischemia. Aspirin reduced the risk of death and nonfatal infarction in both unstable angina and non-Q-wave infarction categories. At 5 days, the reduction was from 5.8 percent to 2.55 percent (p = .033), and at 30 days it was from 17.1 percent to 6.5 percent (p = .0001).

The results of these trials are remarkably consistent, and the risk reduction with aspirin for the prevention of death or nonfatal infarction is relatively large: from one-half to two-thirds. These findings attest to the central role platelets play in the pathophysiology of unstable angina. These studies show that the benefit from aspirin begins with the onset of unstable angina and extends for more than 1 year. Other trials have demonstrated that

aspirin reduces the risk of infarction in stable coronary patients, and so the drug should be continued for life after an episode of unstable angina. The dose of aspirin used in these trials ranged from 75 to 1300 mg/day. Gastrointestinal side effects increase with increasing dose levels. A dose of 325 mg acutely and a dose of 81 mg during chronic treatment are sufficient to inhibit the platelet cyclooxygenase pathway maximally.

Women were excluded from two of the four trials[163,166] and represented one-quarter to one-third of the patients in the other two studies.[164,165] However, it seems reasonable to assume that the benefit of aspirin extends to women with unstable angina, particularly since aspirin has been shown to reduce coronary events across the broad spectrum of patients with atherosclerosis.

The Antiplatelet Trialists' Collaboration meta-analysis of 145 trials with more than 100,000 patients randomized to antiplatelet therapy or placebo showed consistent benefit in cerebrovascular disease and stable and unstable coronary disease.[167] Almost all the antiplatelet therapy in these trials consisted of aspirin. Few treatments show a cost/benefit ratio that is superior to that of aspirin in the treatment of unstable angina.

Angiotensin-converting enzyme (ACE) inhibitors promote the release of prostaglandins, and inhibition of prostaglandin synthesis with aspirin or other nonsteroidal anti-inflammatory drugs attenuates the acute vasodilatory effect of ACE inhibition. In the SOLVED trial,[168] the CONSENSUS II trial,[169] and the GUSTO-1 trial,[170] a negative interaction between aspirin and ACE inhibitors was reported. However, in a data base of 11,576 patients with coronary disease, 5-year adjusted mortality was lower in ACE inhibitor-treated patients who also took aspirin than it was in those who did not in the presence or absence of heart failure.[171] On the basis of the information that is currently available, it appears reasonable not to withhold aspirin from coronary patients who are receiving ACE inhibitors in the absence of severe heart failure.

Ticlopidine and Clopidogrel

Ticlopidine and clopidogrel are thienopyridines, and their mechanism of action differs from that of aspirin (Fig. 41-7). Both drugs inhibit adenosine diphosphate (ADP)-mediated platelet activation.[172] Because they act independently of the arachidonic acid pathway, the antiplatelet activities of aspirin and either ticlopidine or clopidogrel are synergistic. Ticlopidine induces neutropenia in 1 to 3 percent of patients and also rarely causes severe adverse dermatologic effects. The drug also is limited by its slow onset of action: 3 to 4 days for the inhibition of platelet aggregation to exceed 50 percent and up to 2 weeks for the effect to plateau. The effect of ticlopidine also persists after treatment has been discontinued.

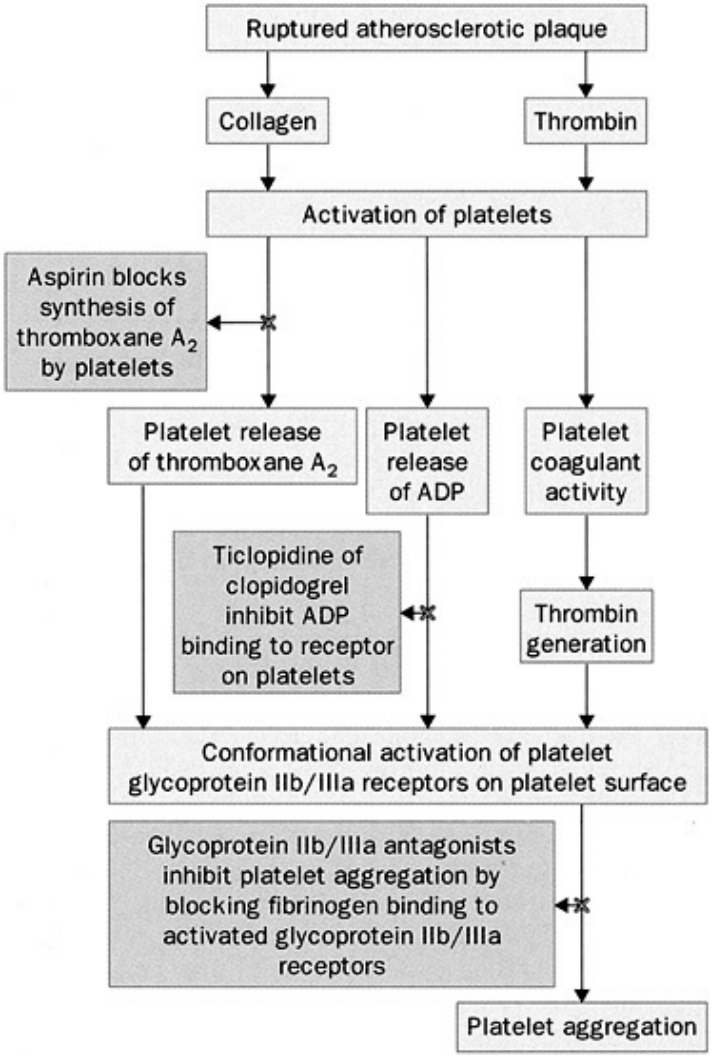

Figure 41-7: Sites of action of platelet inhibitors. (From Hirsh and Weitz,[219] with permission.)

Ticlopidine 250 mg twice per day was compared to conventional antianginal therapy without aspirin in a randomized but open-label trial in 652 unstable angina patients.[173] Over a 6-month follow-up period, the rate of fatal or nonfatal infarction was 7.3 percent in the ticlopidine group and 13.6 percent in controls, a 46 percent reduction (p = .009). However, the benefit of treatment developed only after 2 weeks; this is consistent with the known delayed onset of action of the drug. On the basis of this trial, ticlopidine has been considered as an alternative in unstable angina patients who cannot tolerate aspirin. Ticlopidine has been widely used with aspirin to prevent thrombotic complications in the weeks after coronary stenting, based on clinical trial evidence that it is superior to aspirin alone in this situation.[174] However, ticlopidine is rapidly being supplanted by clopidogrel for this indication because of the better safety profile of clopidogrel.

Clopidogrel is more potent than ticlopidine in inhibiting ADP-induced platelet aggregation in vitro and has a more rapid onset of action. Within 2 h of oral administration, antiplatelet activity can be detected, and the effect on platelet aggregation becomes maximal between 4 and 7 days. The usual dose is 75 mg once daily. The utility of clopidogrel in treating unstable angina is being assessed in a randomized clinical trial. In the *Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, clopidogrel reduced the combined end point of ischemic stroke, myocardial infarction, and vascular death by 8.7 percent (p = .043) for up to 3 years compared with aspirin in 19,185 patients with vascular disease.[175] Patients with peripheral arterial disease appeared to benefit more than did patients with previous infarction or stroke. The risk of gastrointestinal hemorrhage severe enough to stop the drug was higher with clopidogrel than it was with aspirin but was still less than 1 percent. Clopidogrel is not associated with the increased potential for neutropenia seen with ticlopidine. For these reasons, clopidogrel is preferred over ticlopidine in patients with unstable angina who do not tolerate aspirin.

Platelet Glycoprotein IIb/IIIa Receptor Inhibitors

Platelet membranes contain glycoprotein receptors, many of which are integrins.[176] Integrins are heterodimeric molecules composed of alpha and beta subunits. These subunits are combined in unique patterns to form receptors specific for various ligands. The $\alpha_{IIb}\beta_3$ integrin, or platelet IIb/IIIa receptor (Fig. 41-8), changes from its resting state to its active state when the platelet is activated by agonists or other platelets and serves as a receptor for fibrinogen and von Willebrand factor.[176] Fibrinogen binding is central to platelet aggregation and thrombus formation in the arterial circulation.

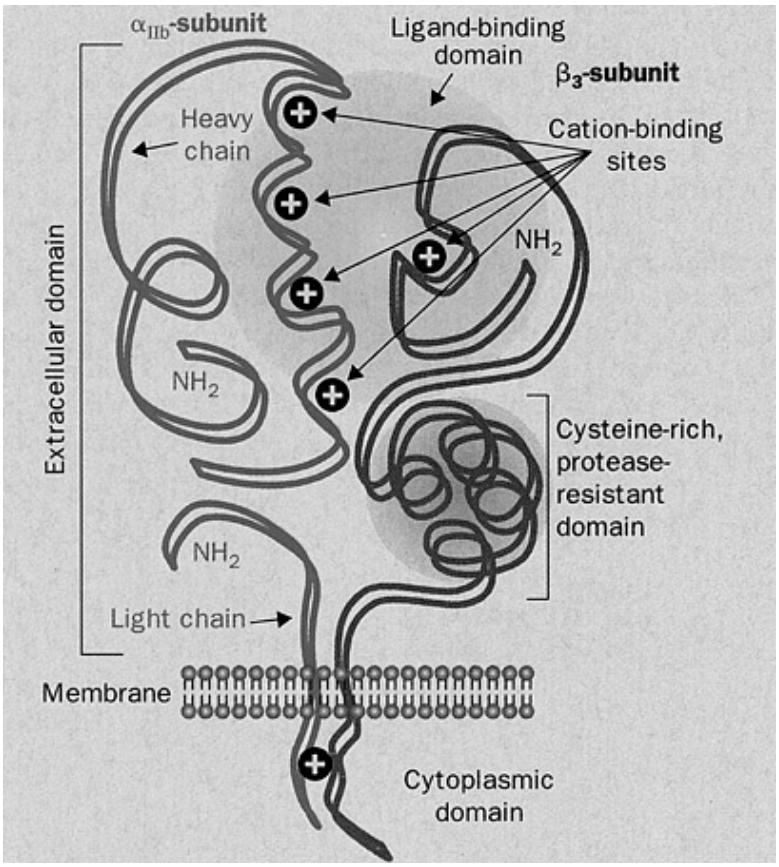

Figure 41-8: Schematic representation of the $\alpha_{IIb}\beta_3$ integrin, or the platelet IIb/IIIa receptor. (From Topol et al.,[176] with permission.)

Blockade of the platelet GP IIb/IIIa receptor is a theoretically attractive concept. Unlike aspirin and clopidogrel, which do not block thrombin-induced platelet aggregation, GP IIb/IIIa inhibitors block aggregation in response to all potential agonists (Fig. 41-7). Different receptors, GP Ib and GP IV, mediate platelet adhesion to the subendothelial matrix. Thus, hemorrhage should not be a major problem even with complete blockade of GP IIb/IIIa receptors.[176]

The first GP IIb/IIIa blocker to be approved and widely used clinically is abciximab, the Fab fragment of a monoclonal antibody to the $\alpha_{IIb}\beta_3$ integrin. Other GP IIb/IIIa inhibitors are either peptides or smaller molecules. Eptifibatide is the peptide GP IIb/IIIa inhibitor that has been approved for use in the United States. Tirofiban, lamifiban, fradafiban, xemilofiban, orbofiban, sibrafiban, roxifiban, lotrafiban, and lefradiban are all small-molecule GP IIb/IIIa inhibitors. Only tirofiban has been approved for use in the United States, but several of the other drugs are in the later stages of clinical development. All the currently approved drugs must be administered by parenteral infusion, but the last six compounds on the above list of small-molecule GP IIb/IIIa inhibitors will be for oral use.

Coronary Intervention Trials with GP IIb/IIIa Inhibitors

Platelet GP IIb/IIIa inhibitors have been evaluated mainly in patients with acute coronary syndromes (including

unstable angina and NSTEMI patients), patients undergoing coronary angioplasty, and patients in both categories (Fig. 41-9). The *Evaluation of c7E3 Fab for Prevention of Ischemic Complications (EPIC) trial enrolled 2099 patients considered at high risk for coronary angioplasty, including patients with unstable angina.[177] All these patients were treated with aspirin and heparin, and randomization was to placebo, a weight-adjusted abciximab bolus, or a bolus followed by an infusion of abciximab for 12 h. The primary end point was a composite of death, myocardial infarction, urgent repeat revascularization, or stent or balloon pump placement within 30 days after randomization. The event rate was 12.8 percent in the placebo group, 11.4 percent with bolus abciximab, and 8.3 percent in the bolus plus infusion group (p = .008 versus placebo). Benefit was most pronounced in unstable angina patients, with a 71 percent decrease in the primary end point and a 94 percent decrease in death or myocardial infarction (11.1 percent placebo versus 0.6 percent bolus plus infusion group, p < .0001). The benefit of abciximab in the EPIC patients persisted to 6 months[178] and 3 years.[179]

The Evaluation in PTCA to Improve Long-Term Outcome with abciximab GP IIb/IIIa blockade (EPILOG) trial compared a bolus plus 12-h infusion of abciximab to placebo in all but high-risk patients undergoing coronary angioplasty.[180] EPILOG is thus complementary to EPIC. Nearly half the EPILOG patients had unstable angina as their diagnosis, but patients with ECG changes within the 24 h preceding randomization were excluded. Randomization was to placebo plus standard-dose heparin and to abciximab with low-dose or standard-dose heparin. EPILOG was stopped after 2792 of the planned 4800 patients were enrolled because the composite end point of death, infarction, or urgent revascularization at 30 days was 11.7 percent in the placebo group and 5.2 percent and 5.4 percent in the abciximab groups (p < .0001). The clinical benefit of abciximab in EPILOG was maintained to 1 year.[181] Among unstable angina patients, the end point of death, myocardial infarction, or urgent intervention at 1 year was reached by 16.8 percent in the placebo group and 9.0 percent in the abciximab groups. Taken together, EPIC and EPILOG firmly established that abciximab reduces the rate of coronary events across a broad range of patients undergoing coronary angioplasty, including those with unstable angina.

The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial differed from EPIC and EPILOG in that it evaluated pretreatment with abciximab before coronary angioplasty among high-risk unstable angina patients.[182] To qualify, patients had to have chest pain with ischemic ECG changes within 48 h despite intravenous heparin and intravenous glyceryl trinitrate. All these patients also received aspirin and heparin. Placebo or abciximab bolus plus infusion was begun 18 to 24 h before angioplasty and continued until 1 h after the procedure. After the enrollment of 1265 patients, the trial was stopped prematurely. The primary end point-death, myocardial infarction, or urgent intervention within 30 days-was reached by 15.9 percent of placebo patients and 11.3 percent of abciximab patients (p =.012). Clinical benefit developed before the angioplasty procedure (Fig. 41-10): The infarction rate during this short interval was 2.6 percent among placebo-treated patients and 0.6 percent among abciximab-treated patients (p = .029). In contrast to the EPIC and EPILOG trials, the benefit of abciximab treatment in CAPTURE was attenuated by 6 months.

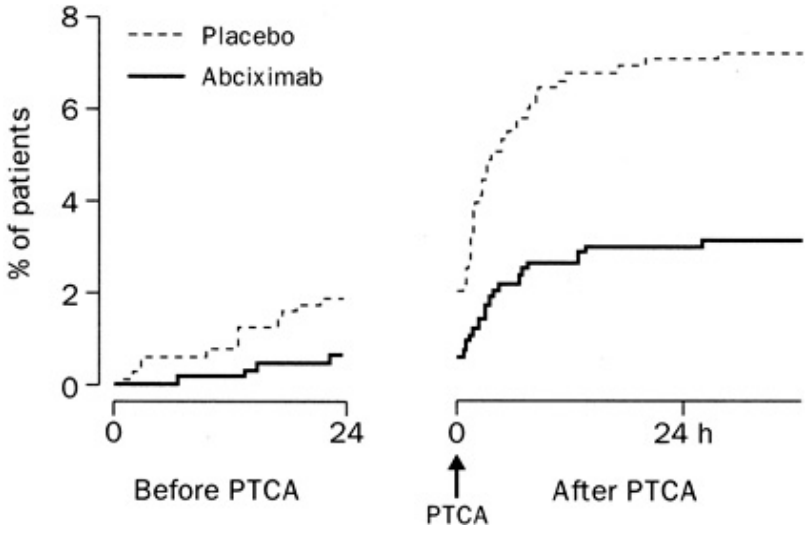

Figure 41-10: Reduction in the incidence of myocardial infarction with abciximab in the CAPTURE trial.[182] The benefit of abciximab was present both in the first 24 h before angioplasty (p = .029) and during and for the 24 h after angioplasty (p = .021). (From CAPTURE investigators,[182] with permission.)

Abciximab and coronary stenting were assessed in a wide spectrum of patients undergoing angioplasty in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial.[183] Slightly more than one-third of the 2399 EPISTENT patients had unstable angina within 48 h. Randomization was to stenting plus placebo, stenting plus abciximab (bolus plus 12-h infusion), or balloon angioplasty plus abciximab. The primary end point-a composite of death, myocardial infarction, or the need for urgent revascularization within 30 days-occurred at a rate of 10.8 percent in the stent/placebo group, 5.3 percent in the stent/abciximab group (odds ratio 0.48, 95 percent confidence interval 0.33 to 0.69), and 6.9 percent in the balloon/abciximab group (odds ratio 0.63, 95 percent confidence interval 0.45 to 0.88). By 6 months, death or myocardial infarction had occurred in 11.4 percent of the stent/placebo group, 5.6 percent of the stent/abciximab group (odds ratio 0.47, 95 percent confidence interval 0.33 to 0.68, $p < .001$), and 7.8 percent of the balloon/abciximab group (odds ratio 0.67, 95 percent confidence interval 0.49 to 0.92, $p = .01$).[184] EPISTENT demonstrated that the benefit of abciximab during angioplasty extends to patients who receive elective stents.

The Second Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT-II) trial evaluated eptifibatide in 4010 patients undergoing angioplasty.[185] Patients received aspirin and heparin and were randomized to placebo, a bolus of eptifibatide followed by a lower-dose infusion for 20 to 24 h, or a bolus plus a higher-dose infusion. In each treatment group, 38 percent of patients had unstable angina. The primary end point was the 30-day composite of death, myocardial infarction, unplanned revascularization, or stenting for abrupt closure. The primary end point occurred in 11.4 percent of placebo patients, 9.2 percent of lower-dose infusion patients (odds ratio 0.79, 95 percent confidence interval 0.61 to 1.01, $p = .063$), and 9.9 percent of higher-dose infusion patients (odds ratio 0.86, 95 percent confidence interval 0.67 to 1.10, $p = .22$). The benefit seen in IMPACT-II with eptifibatide was thus of borderline statistical significance and was less impressive than the results seen with abciximab in EPIC, EPILOG, CAPTURE, and EPISTENT (Fig. 41-9).

The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial evaluated the small-molecule GP IIb/IIIa inhibitor tirofiban in 2139 patients with acute coronary syndromes who were undergoing angioplasty.[186] Two-thirds of the patients had unstable angina. All were treated with aspirin and heparin. Tirofiban or placebo was begun after the lesion was crossed with the guidewire and was continued for 36 h, longer than in the other trials, because of the rapid reversibility of platelet inhibition with tirofiban. The primary end point was a composite similar but not identical to the preceding trials: death, infarction, repeat target lesion angioplasty, coronary bypass surgery, or coronary stenting by 30 days. Although a statistically significant reduction in events was seen with tirofiban at day 2 and day 5 after the procedure, by 30 days (the primary end point), the rate was 12.2 percent in the placebo group and 10.3 percent in the tirofiban group, a 16 percent relative reduction ($p = .16$).

Taken together, these trials indicate that platelet GP IIb/IIIa inhibition at the time of angioplasty reduces ischemic complications. The benefit with respect to the primary end point of the trials was less with eptifibatide and tirofiban (15 to 20 percent) than with abciximab (30 to 60 percent); however, the 95 percent confidence intervals overlap, and the drugs have not been compared directly in the same trial. If variability in efficacy does exist, potential explanations might be that abciximab gradually dissociates from the GP IIb/IIIa receptor over 36 h after the drug is discontinued, that abciximab also blocks the $\alpha_v\beta_3$ vitronectin receptor, or that the dose of eptifibatide selected for IMPACT-II was too low. The risk of hemorrhage during angioplasty with GP IIb/IIIa inhibitors can be reduced by early sheath removal, meticulous care of arterial puncture sites, and lower, weight-adjusted doses of heparin than were used traditionally.

Acute Coronary Syndrome Trials with GP IIb/IIIa Inhibitors

In addition to the six large trials discussed above in which GP IIb/IIIa inhibitors were tested during coronary angioplasty, four large trials have assessed the value of these drugs in patients with unstable angina or non-Q-wave myocardial infarction (also known as NSTEMI). Whereas abciximab was the drug used most frequently in the angioplasty trials, eptifibatide and the small-molecule GP IIb/IIIa inhibitors predominated in the acute coronary syndrome trials (Fig. 41-9).

The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study enrolled 3232 patients with an acute coronary syndrome including chest pain within 24 h.[187] One-quarter of these patients had non-Q-wave infarction, and the remainder had unstable angina with ECG abnormalities. With aspirin as baseline therapy, patients were randomized according to a double-blind protocol either to a weight-adjusted bolus plus infusion of tirofiban or to a bolus and infusion of heparin to maintain the activated partial thromboplastin time at twice the

control value. Treatment continued for 48 h, and the primary end point was a composite of death, myocardial infarction, or refractory ischemia during this period. The end point was reached by 5.6 percent of heparin-treated patients and 3.8 percent of tirofiban-treated patients (odds ratio 0.67, 95 percent confidence interval 0.48 to 0.92, $p = .01$). By 30 days, the primary end point with the addition of readmission for unstable angina was 17.1 percent in the heparin group and 15.9 percent in the tirofiban group, a difference that was not statistically significant. However, mortality at 30 days was lower in the tirofiban group at 2.3 percent compared with 3.6 percent ($p = .02$).

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study enrolled 1915 unstable angina and non-Q-wave infarction patients with prolonged or repetitive chest pains within 12 h and ECG changes.[188] Study treatment was continued for 72 h, and coronary angioplasty was done in 475 of the patients between 48 and 72 h. Randomization was to tirofiban, heparin, or tirofiban plus heparin, with all patients receiving aspirin unless it was contraindicated. The tirofiban bolus and infusion doses were one-third lower in patients treated with heparin than they were in those treated with tirofiban alone. The study was stopped prematurely for the group receiving tirofiban alone because of excess mortality at 7 days: 4.6 percent versus 1.1 percent among patients receiving heparin alone ($p = .012$). This early increase in mortality was explained by the investigators as most likely being due to chance, since no such increase was seen in PRISM. The frequency of the primary end point at 7 days-a composite of death, myocardial infarction, or refractory ischemia-was 17.9 percent in the heparin group and 12.9 percent in the heparin plus tirofiban group (odds ratio 0.68, 95 percent confidence interval 0.53 to 0.88, $p = .004$). This advantage persisted to 30 days and to 6 months. Death or myocardial infarction occurred within 7 days in 8.3 percent of the heparin-only patients and 4.9 percent of the heparin and tirofiban group ($p = .006$). This absolute difference of 3.6 percent narrowed slightly to 3.0 percent by 6 months, when the rates of death and infarction were 15.3 percent and 12.3 percent ($p = .06$). In the subset of patients who underwent angioplasty between 48 and 72 h, the risk of death, infarction, refractory ischemia, or rehospitalization for unstable angina over the next 30 days was reduced from 15.3 percent to 8.8 percent with combination therapy compared with heparin alone (odds ratio 0.55, 95 percent confidence interval 0.32 to 0.94). The benefit of combination therapy over heparin alone was of roughly equal magnitude in patients with unstable angina or non-Q-wave infarction.

The findings of PRISM and PRISM-PLUS are somewhat contradictory. PRISM indicates that tirofiban may be superior to heparin as acute therapy for unstable angina in patients taking aspirin. PRISM-PLUS suggests that the combination of aspirin, heparin, and tirofiban is superior to aspirin and heparin. The benefit of tirofiban added to aspirin and heparin among angioplasty patients in PRISM-PLUS was of greater magnitude and lasted longer than the benefit seen with this combination of treatment in RESTORE. However, the results of RESTORE are more credible because the number of patients was much larger: 2139 compared with 475 angioplasty patients in PRISM-PLUS. Pretreatment and selection biases might have influenced the angioplasty subgroup in PRISM-PLUS.

The Platelet glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy (PURSUIT) trial enrolled 10,948 patients with unstable angina or non-Q-wave infarction to eptifibatide or placebo.[189] Baseline therapy consisted of aspirin and heparin. Study drug treatment lasted for 3 days, with an additional day if coronary intervention was done near 72 h. The primary end point, a composite of death or nonfatal myocardial infarction at 30 days, was 15.7 percent in the placebo group and 14.2 percent in the eptifibatide group ($p = .04$). The treatment effect occurred consistently across most subgroups except for women, who had a statistically nonsignificant 10 percent higher event rate with eptifibatide. The absolute risk reduction of 1.5 percent was less than the 3.2 percent absolute risk reduction seen in PRISM-PLUS (Fig. 41-9). The Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON) trial tested lamifiban, a small-molecule GP IIb/IIIa inhibitor that has not yet been approved for use in the United States.[190] Low-dose lamifiban and high-dose lamifiban, with and without heparin, were compared to a placebo plus heparin group. All patients received aspirin. A total of 2282 patients with unstable angina and ECG changes were enrolled. The primary end point of death or myocardial infarction at 30 days occurred at a rate of 11.7 percent in the placebo group, 10.6 percent in the low-dose lamifiban group, and 12.0 percent in the high-dose lamifiban group. These differences were not statistically significant. At 6 months, the composite event rate was 13.7 percent for the low-dose lamifiban group compared with 17.9 percent for controls ($p = .027$). The high-dose lamifiban plus heparin group experienced more intermediate or major bleeding than did controls: 12.1 percent compared with 5.5 percent ($p = .002$).

The oral small-molecule GP IIb/IIIa inhibitors have failed to reduce coronary events in three large, recently completed trials.[191,192,192a] In the Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart

Events Post-acute Coronary Syndromes (SYMPHONY) study,[191] 9233 patients who had stabilized after an acute coronary syndrome were randomly assigned to aspirin, low-dose sibrafiban, or high-dose sibrafiban. The primary end point was a composite of death, nonfatal infarction, or severe recurrent ischemia at 90 days. Sibrafiban showed no additional benefit over aspirin, and was associated with more dose-related bleeding.

In the Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial,[192] 7232 patients were randomized to placebo or oral xemilofiban beginning just before coronary angioplasty and continuing for 182 days. This trial was not limited to patients with unstable angina. The primary end point (a composite of death, nonfatal infarction, or urgent revascularization) was not reduced by active treatment. The Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis in Myocardial Infarction 16 (OPUS-TIMI 16) trial[192a] enrolled 10,302 unstable angina patients to either of two doses of orbofiban or placebo. The trial was halted early because of excess mortality in one of the active treatment groups. The composite end point was not reduced by either dose of orbofiban at either 30 days or 10 months. The reason for the early increase in mortality is unclear, but may be related to intermittent platelet activation with the oral GP IIb/IIIa platelet inhibitors.

Guidelines for the Use of GP IIb/IIIa Inhibitors

Although GP IIb/IIIa inhibitors have firmly established their usefulness in a wide spectrum of patients undergoing coronary angioplasty, their value in unstable angina patients who are not undergoing intervention is incompletely defined. GP IIb/IIIa inhibitors have not been compared to clopidogrel or to low-molecular-weight heparins or studied in patients taking these drugs as background therapy.

The current high cost of these drugs makes it tempting to limit their use to high-risk patients. In a subgroup analysis from the CAPTURE study,[193] patients with troponin T elevations at study entry had a high event rate and derived a large benefit from abciximab therapy (odds ratio for death or myocardial infarction 0.32, 95 percent confidence interval 0.14 to 0.62, $p = .002$). Patients without elevated troponin T levels experienced a low event rate and did not benefit from abciximab.

Current guidelines recommend that eptifibatide or tirofiban be added to aspirin and heparin in the treatment of patients with some high-risk features or with refractory ischemia.[1] These drugs should be continued during coronary angioplasty and for 12 to 24 h after the procedure for tirofiban and for 24 to 72 h after the procedure for eptifibatide.[1] Abciximab also can be used in patients with unstable angina in whom angioplasty is planned within the following 24 h.[1] However, when abciximab is administered before diagnostic coronary angiography, the prolonged platelet inhibition it induces may force a delay in the urgent coronary bypass surgery that is needed for some patients. When aspirin and unfractionated heparin are used with GP IIb/IIIa inhibitors, the dose of heparin should be conservative during coronary procedures, and heparin should be discontinued after the procedure if it is uncomplicated.[1]

Heparin

Heparin binds with antithrombin to form a complex that inactivates thrombin and activated factors X, XII, XI, and IX.[194] The principal inhibitory effect of heparin on coagulation probably occurs through the inhibition of thrombin-induced activation of factor V and factor VIII. Fibrin binds thrombin and protects it from inactivation by the heparin-antithrombin complex. Platelets inhibit the anticoagulant effect of heparin by binding factor Xa and protecting it from inactivation.

The pharmacokinetics of heparin are complex, and the dose-response relationship is nonlinear. Heparin therapy is monitored to maintain the activated partial thromboplastin time (APTT) ratio within 1.5 to 2.5 times normal. The anticoagulant response to a standard dose of heparin varies widely among patients so that even when a weight-based nomogram is used in a clinical study, the APTT falls outside the therapeutic range more than one-third of the time.[195] Results in routine clinical practice are probably much worse. Pooled analyses of randomized trials have revealed an average incidence of major bleeding of 6.8 percent in continuous-infusion groups and 14.2 percent in intermittent-infusion groups (odds ratio 0.42, $p = .01$).[196]

Heparin was used to treat patients with unstable angina before that diagnostic term was used commonly,[2] but good clinical trial data in support of its use did not emerge until the 1980s (Table 41-8). In a randomized, double-blind, placebo-controlled trial of 214 patients with unstable angina, myocardial infarction developed

during 7 days of treatment in 9 (17 percent) of 54 patients taking placebo, 8 (13 percent) of 60 taking atenolol, 1 (2 percent) of 51 receiving heparin, and 2 (4 percent) of 49 on combined therapy.[197] The improved prognosis of heparin-treated patients was maintained during follow-up, and all five deaths occurred among patients who did not receive heparin. The impact of this trial was attenuated by a design problem in that 186 additional patients were withdrawn after randomization because of incorrect recruitment.

Théroux and colleagues randomized 479 patients with unstable angina to aspirin, heparin, combination therapy, or double placebo a mean of 8 h after the last episode of chest pain, with a mean follow-up of 6 days.[165] The results of this trial with respect to aspirin were discussed earlier in this chapter. The incidence of death or nonfatal myocardial infarction was reduced dramatically with heparin from 14 of 118 patients in the placebo group to 3 of 240 in the heparin groups (11.9 percent versus 1.25 percent, $p < .001$). Heparin also reduced the frequency of refractory angina 60 percent. The combination of heparin and aspirin was not superior to aspirin alone in the prevention of death or nonfatal infarction. In an extension of the trial, heparin and aspirin were compared directly in a total of 484 patients.[198] Death or myocardial infarction occurred in 3.7 percent of aspirin-treated patients and 0.8 percent of heparin-treated patients ($p = .035$).

Aspirin and heparin also were tested in a factorial design in the RISC trial.[166] RISC enrolled 796 men with unstable angina or non-Q-wave infarction. As was discussed above, aspirin exhibited a marked protective effect in this study. The effect of heparin on the event rate was not statistically significant, although a trend in its favor was seen during the 5 days in which it was administered. In two smaller trials comparing aspirin to aspirin plus heparin, no difference was seen between the treatment groups.[199,200] The Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial randomized 69 patients in a pilot study and 214 patients in the main trial to aspirin alone or to aspirin plus heparin followed by warfarin.[201,202] The composite end point of recurrent angina with ECG changes, myocardial infarction, or death within 12 weeks was reduced in the main trial by combination therapy from 27 percent to 10.5 percent ($p = .004$). A meta-analysis of these trials concluded that the addition of heparin to aspirin in the treatment of unstable angina reduces the rate of myocardial infarction approximately one-third.[203]

The way in which heparin is administered may influence its efficacy in treating unstable angina. In a trial of unstable angina patients who were refractory to medical therapy, heparin significantly decreased the frequency of angina attacks and the number of episodes of silent myocardial ischemia when it was administered as a bolus followed by an infusion but not when it was given as a bolus every 6 h.[204] In another study of refractory unstable angina patients done by the same investigators, both subcutaneous heparin and heparin given as a bolus and an infusion profoundly reduced the frequency of myocardial ischemic episodes.[205]

Discontinuation of heparin in unstable angina patients can results in a reactivation of refractory ischemic episodes within hours.[206] Aspirin or warfarin may block this phenomenon. Rebound has been described with other thrombin inhibitors, but the mechanism has not been defined. However, it has been shown that thrombin generation increases and tissue factor pathway inhibitor levels decrease within 24 h of heparin cessation.[207] Gradual weaning from heparin, as opposed to abrupt cessation, results in less thrombin generation.[207] Mild thrombocytopenia occurs in 10 to 20 percent of patients treated with unfractionated heparin.[208] In 2 to 10 percent of patients, a more severe form of thrombocytopenia develops. This antibody-mediated response occurs within 5 to 10 days after the initiation of treatment and is associated with thromboembolic sequelae in 30 to 80 percent of cases.[208] Other adverse effects of heparin include osteoporosis, skin necrosis, alopecia, hypersensitivity reactions, and hypoaldosteronism.[196]

Low-Molecular-Weight Heparins

Unfractionated heparin consists of a heterogeneous mixture of polysaccharide chains ranging in molecular weight from approximately 3000 to 30,000. Low-molecular-weight heparins (LMWHs) are fragments of unfractionated heparin produced by enzymatic or chemical depolymerization processes that yield chains with average molecular weights of approximately 5000.[209] The main difference between the two types of heparin is that unfractionated heparin has equivalent activity against factor Xa and thrombin while LMWHs have greater activity against factor Xa.[209] The reason for this difference is that long heparin chains such as those present predominantly in regular heparin are required to bind both antithrombin and thrombin(Fig. 41-11).

Both types of heparin interfere with thrombin-induced platelet activation by inhibiting the thrombin-glycoprotein Ib interaction, but standard heparin is more potent than LMWHs in this regard.[210] However, a

disadvantage of regular heparin is that it inhibits activation of the protein C anticoagulant pathway more than a LMWH does.[211]

Compared with unfractionated heparin, LMWHs produce a more predictable anticoagulant response because of their better bioavailability, longer half-life, and dose-independent clearance.[209] The plasma half-life of a LMWH after subcutaneous injection ranges from 3 to 6 h, and so once- or twice-daily administration is feasible. In contrast to unfractionated heparin, monitoring is not required with the use of LMWHs, with the possible exception of plasma antifactor Xa levels in patients with renal insufficiency.[209] LMWH caused less bleeding than unfractionated heparin did in laboratory animal experiments and in some clinical trials.[209] The main disadvantage of LMWHs is that they are far more expensive than unfractionated heparin.

LMWHs are somewhat more effective than standard heparin in preventing deep vein thrombosis after general or orthopedic surgery, according to meta-analyses of clinical trials.[195] Thrombus size by venography and a small trial in patients with established venous thrombosis showed better outcomes with LMWHs compared with unfractionated heparin.[195] In light of these encouraging findings and the obvious practical advantages of LMWHs, trials of LMWHs for unstable angina were anticipated with enthusiasm.

The first of these trials, a small open-label trial, showed that LMWHs plus aspirin reduced the risk of myocardial infarction better than did standard heparin plus aspirin or aspirin alone.[200] In a more definitive trial, the Fragmin during Instability in Coronary Artery Disease (FRISC) study, 1506 patients with unstable angina or non-Q-wave myocardial infarction were randomly assigned to a weight-adjusted dose of the LMWH dalteparin twice daily or to placebo.[212] After 6 days, the dose was changed to 7500 IU once daily and was continued for 35 to 45 days. All patients without contraindications took aspirin. The primary end point-the rate of death or myocardial infarction during the first 6 days-was reduced with dalteparin (odds ratio 0.37, 95 percent confidence interval 0.20 to 0.68). The benefit of treatment persisted to 40 days but was attenuated, mainly because of an increase in events among smokers in the active treatment group after the dose was reduced from twice daily to once daily. The results of FRISC demonstrated that LMWH is superior to placebo in aspirin-treated patients with unstable angina, but a more important issue is how LMWH compares with intravenous unfractionated heparin.

The Fragmin in Unstable Coronary Artery Disease (FRIC) study was the first trial to address this question. In the open-label, acute phase of FRIC, 1482 patients with unstable angina or non-Q-wave infarction were randomized to either dalteparin, administered as in FRISC, or doseadjusted intravenous standard heparin for 6 days.[213] All the patients received aspirin. The primary end point-a composite of death, myocardial infarction, or recurrence of angina-was 9.3 percent in the dalteparin group and 7.6 percent in the standard heparin group. Although this difference is not statistically significant, fewer deaths occurred in the unfractionated heparin group (3 versus 11, $p = .05$). After 6 days, most of the patients continued to the double-blind phase of the trial, in which they were treated from days 6 to 45 with dalteparin 7500 IU subcutaneously once daily or with placebo. During this period, the composite end point was 12.3 percent in both groups. The authors concluded that dalteparin at this dose during the month after hospital discharge provided no additional benefit over aspirin but speculated that twice-daily treatment might.

Thus, in the Fragmin and Fast Revascularisation during Instability in Coronary artery disease (FRISC II) trial, 2267 patients with unstable angina or non-Q-wave infarction were randomly assigned to subcutaneous dalteparin twice daily or to placebo for 3 months after at least 5 days of treatment with open-label dalteparin.[214] Half the patients had ST depression at study entry, and more than half had troponin T elevations. After 30 days, the rate of death or nonfatal infarction was 3.1 percent with dalteparin and 5.9 percent with placebo (odds ratio 0.53, 95 percent confidence interval 0.35 to 0.80). However, by 3 months this difference had shrunk to 6.7 percent versus 8.0 percent, which was not statistically significant. In the subgroup with elevated troponin T levels at baseline, dalteparin reduced the relative risk of death or infarction to 3 months by 30 percent and the absolute risk by 2.7 percent ($p = .07$). In troponin-negative patients, treatment beyond 5 days with dalteparin showed no benefit.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study randomly assigned 3171 patients with unstable angina or non-Q-wave infarction to enoxaparin 1 mg/kg subcutaneously twice daily or to continuous unfractionated heparin for a period of 2 to 8 days.[215] All the patients received aspirin. The primary end point-a composite or death, myocardial infarction, or recurrent angina at 14 days-was 16.6 percent with enoxaparin and 19.8 percent with regular heparin ($p = .019$). This difference

persisted to 30 days, and the need for revascularization to this point also was reduced significantly with enoxaparin. An economic substudy indicated that total medical costs to 1 month were lower in enoxaparin-treated patients because the added cost of the drug was more than compensated for by savings from reduced events.[216]

The Thrombolysis in Myocardial Infarction (TIMI) 11B trial randomly assigned 3910 patients with unstable angina or non-Q-wave infarction to enoxaparin or standard heparin for 3 to 8 days, with 60 percent of the population continuing treatment with enoxaparin or placebo for 43 days.[217] Enoxaparin reduced events compared with unfractionated heparin during the acute phase of the trial (odds ratio 0.83, 95 percent confidence interval 0.69 to 1.00, $p = .048$). No additional benefit or loss of benefit was seen with continued therapy. In another trial, 3468 patients with unstable coronary disease were allocated randomly to unfractionated heparin or to 6 days or 14 days of treatment with the LMWH nadroparin.[218] No benefit of the LMWH was seen in this study; in fact, at 3 months the composite end point of death, infarction, or refractory ischemia occurred in 22.2 percent of unfractionated heparin patients, 22.3 percent of those in the 6-day LMWH group, and 26.2 percent of those in the 14-day treatment group ($p = .03$).

In summary, trials of LMWH in unstable angina and non-Q-wave infarction have yielded conflicting results (Table 41-9). Two trials, ESSENCE and TIMI 11B, demonstrated that enoxaparin is superior to unfractionated heparin for the first few days of therapy. The only acute comparison between dalteparin and standard heparin, FRIC, had inadequate statistical power to detect a difference between treatments. Theoretically, enoxaparin may be superior to dalteparin because of its higher anti-factor Xa to anti-factor IIa ratio. The early benefit of LMWH treatment appears to dissipate over the ensuing months, and continuing therapy was not beneficial in most trials. However, in FRISC II, treatment from 5 days to 3 months with dalteparin produced an impressive reduction in death or infarction at 1 month, with gradual loss of that benefit thereafter.

Table 41-9: Major Clinical Trials of Low-Molecular-Weight Heparins (LMWH) in Patients with Unstable Angina or Non-Q-Wave Infarction

Trial	LMWH	No. Patients	Duration of Follow-Up	Death/MI Rate in LMWH Group, %	Death/MI Rate in Control Group[a], %	Relative Risk (RR) (95% Confidence Interval)	Comments
FRISC-I[212]	Dalteparin	1506	6 days	1.8	4.8	0.37 (0.20-0.68)	At 40 days, death/MI reduced from 10.7% to 8.0%; RR 0.75 (0.54-1.03)
FRIC[213]	Dalteparin	1482	6 days	3.9	3.6	1.07 (0.63-1.80)	From days 6-45, death/MI reduced from 4.7% to 4.3%; RR 0.92 (0.54-1.57)
FRISC-II[214]	Dalteparin	2267	3 months	6.7	8.0	0.81 (0.60-1.10)	At 30 days, death/MI reduced from 5.9% to 3.1%; RR 0.53 (0.35-0.80)
ESSENCE[215]	Enoxaparin	3171	14 days	4.9	6.1	0.80 ($p = .13$)	Death/MI/recurrent angina reduced from 19.8% to 16.6%; RR 0.80 (0.67-0.96)
TIMI-11B[217]	Enoxaparin	3910	8 days	4.6	5.9	0.77 (0.58-1.02)	Death/MI/urgent revascularization reduced from 14.5% to 12.4%; RR 0.83 (0.69-1.0)

FRAXIS[218]	Nadroparin	3468	90 days	8.8[b]	7.9[b]	1.10 (p = .46)	No benefit for any end point at any time point

[a]Control group treated with unfractionated heparin in all trials except FRISC-I.[b]Includes mortality only.

Heparin is recommended for the acute treatment of all unstable angina patients except those determined to be at low risk.[1] Unfractionated heparin should be started with an intravenous bolus of 60 to 70 units/kg followed by a constant infusion of approximately 16 units/kg per hour, adjusted to maintain the APTT at 1.5 to 2.5 times control, or to 50 to 70 s.[1] Subcutaneous administration of enoxaparin or dalteparin may be used instead of unfractionated heparin.[1] The dose of enoxaparin is 1 mg/kg twice daily, and the dose of dalteparin is 120 IU/kg (maximum of 10,000 IU) twice daily. Either standard heparin or an LMWH should be continued for 2 to 5 days, until the patient has been stabilized for 24 h, or until revascularization is performed.[1] The dose of unfractionated heparin should be conservative during coronary angioplasty when aspirin and GP IIb/IIIa inhibitors are being administered concomitantly, and heparin should be discontinued after an uncomplicated procedure.[1] Scant information is available on the combined use of LMWHs and GP IIb/IIIa inhibitors, particularly during coronary interventions; however, this combination is probably acceptable.[1]

Hirudin and Other Direct Thrombin Inhibitors

Hirudin is a 65-amino-acid polypeptide that was isolated from the salivary glands of the medicinal leech and now is produced through recombinant DNA technology.[219] Recombinant hirudin binds tightly to thrombin without requiring a cofactor, forming a slowly reversible complex. Hirudin has been shown to be more effective than heparin or LMWH in the prevention of venous thrombosis in patients undergoing total hip replacement[220] and has been approved for use in patients with heparin-induced thrombocytopenia.[219]

Hirudin and standard heparin were compared in 8011 patients with acute chest pain without ST elevation and in 4131 patients with ST elevation in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb study.[221] No differences in drug efficacy were seen between patients with and without ST elevation. A trend toward early benefit was seen with hirudin, with a 1.3 percent rate of death or myocardial infarction at 24 h compared with 2.1 percent in the heparin group (p = .001). However, by 30 days, the difference between the treatments for the primary end point of the trial was 8.9 percent versus 9.8 percent (p = .06).

The Organization to Assess Strategies for Ischemic Syndrome (OASIS-2) compared a slightly higher dose of hirudin to unfractionated heparin in 10,141 patients with unstable angina or suspected infarction without ST elevation.[222] Hirudin reduced the composite end point of cardiovascular death or myocardial infarction during the 3 days of treatment (odds ratio 0.76, 95 percent confidence interval 0.59 to 0.99), with statistically borderline benefit persisting to 7 days (p = .077). Major bleeding was more common with hirudin than it was with heparin.

Bivalirudin, a hirudin analog, was compared with heparin during coronary angioplasty in patients with unstable angina or postinfarction angina.[223] Bivalirudin caused less bleeding than heparin did and produced better results in the subgroup with postinfarction angina but did not significantly reduce the primary end point of the trial. Other direct thrombin inhibitors, such as argatroban and inogratran, have been investigated in acute coronary syndromes with disappointing results.[219] For example, inogratran was less effective than standard heparin in a trial involving 1209 patients with unstable coronary disease.[224]

Despite the encouraging early benefit compared with unfractionated heparin seen in GUSTO IIb and OASIS-2, hirudin is not currently recommended for use in patients with unstable angina.

Anticoagulation

Markers of ongoing thrombin generation remain elevated for months in some patients with unstable angina, and such markers have been correlated with increased risk.[108,225] In a small trial comparing aspirin to aspirin plus warfarin in unstable angina, the combination reduced progression of the culprit lesion compared with aspirin

alone.[226] Additionally, the combined-therapy group showed a trend toward fewer infarctions during the 10 weeks of the study. For these reasons, the combination of aspirin to block platelets and oral anticoagulants to suppress activation of the coagulation system has attracted interest for its potential to reduce events in the long term after an episode of unstable angina.

In the ATACS study, 214 unstable angina patients who were not previously taking aspirin were randomized to aspirin alone or to aspirin plus intravenous heparin followed by coumadin for 12 weeks.[202] The combination therapy significantly reduced ischemic events at 12 weeks, but most of the difference occurred early, during treatment with heparin, and the difference during coumadin therapy was not statistically significant.

The OASIS investigators conducted two pilot studies of anticoagulation in patients with unstable angina or non-Q-wave infarction.[227] In the first, aspirin plus a fixed low dose of warfarin, 3 mg/day, was compared with aspirin alone in 309 patients. The composite end point of death, infarction, or refractory angina during the 6 months of treatment was actually lower-3.9 percent versus 6.5 percent-in the group without warfarin, but the difference did not attain statistical significance. Major bleeding occurred in four warfarin plus aspirin and no aspirin-only patients, and minor bleeding was more common in warfarin patients. In the second phase of the pilot study, warfarin was given at a higher, adjusted dose to maintain the International Normalized Ratio (INR) between 2.0 and 2.5. Although only 197 patients were enrolled in this phase, the reduction in the composite rate of cardiovascular death, myocardial infarction, or refractory angina with warfarin was impressive (odds ratio 0.42) and approached statistical significance ($p = .08$). Long-term anticoagulation is being evaluated in a substudy of OASIS-2.

Thrombolytic Therapy

Myocardial infarction and unstable angina share a common pathophysiologic substrate: plaque rupture or erosion with overlying thrombosis. Thrombolysis effectively reopens occluded culprit arteries and reduces mortality in patients with acute infarction. It was therefore thought that thrombolytic therapy might prove useful in treating unstable angina.

A meta-analysis of nine small, randomized controlled clinical trials of thrombolysis in unstable angina, with heparin as background therapy, revealed an increased risk of myocardial infarction with active treatment (odds ratio 2.38, 95 percent confidence interval 1.15 to 4.94).[228] The failure of thrombolytic therapy for unstable angina and non-Q-wave infarction was confirmed in the TIMI-IIIB trial.[229] Among the 1473 patients randomized to intravenous tissue plasminogen activator or to placebo, the rate of fatal or nonfatal myocardial infarction at 6 weeks was 7.4 percent with thrombolysis and 4.9 percent with placebo ($p = .04$). In patients not receiving heparin initially, the event rate was 15.2 percent with TPA and 0 percent with placebo ($p = .01$). In another trial, urokinase was given at the time of coronary angioplasty in unstable angina patients to prevent ischemic events.[230] However, both acute closure and clinical end points were more common with the thrombolytic agent than with placebo.

The reason why thrombolytic therapy does not reduce events in unstable angina is not known. However, thrombolysis stimulates ongoing thrombin formation and also activates platelets.[228] These mechanisms are likely to be more important in patients with unstable angina than in patients with Q-wave-infarction. Thrombolytic therapy should be avoided in patients with unstable angina.

Coronary Revascularization

Coronary bypass surgery and coronary angioplasty frequently are performed in patients with unstable angina; however, the precise indications for revascularization, the choice of procedure, and its timing are controversial. Randomized trials comparing revascularization to medical therapy in patients with unstable angina were first performed more than 20 years ago. The results of all but the most recent trials are not applicable to current clinical decision making because major advances in medical and interventional practices have vastly improved the outcomes with both types of therapy. Randomized trials in this area are difficult to perform and interpret because of small sample sizes, frequent crossovers from medical to interventional treatment, and exclusion criteria that tend to eliminate the high-risk patients who might benefit the most from coronary revascularization.

An overview of the 10-year results from the clinical trials comparing coronary bypass surgery with medical treatment for stable angina indicate that patients with left main coronary artery stenosis or three-vessel disease obtain the greatest benefit from surgery.[121] In low-risk groups such as patients with single-vessel involvement,

no survival advantage can be demonstrated with bypass surgery. These conclusions also may be relevant to patients with unstable angina.

In the Veterans Administration Cooperative Study of Unstable Angina, 468 men age less than 70 years were randomized to medical or surgical therapy.[231-233] Those with left main coronary stenosis, previous bypass surgery, recent infarction, or ejection fractions less than 30 percent were excluded. Surgery consisted of saphenous venous bypasses only, a mean of 2.7 per patient, and 30-day surgical mortality was 4.1 percent.[231] By 2 years, one-third of the patients assigned to medical therapy had crossed over to surgery. Overall mortality at 5 years was 19 percent in medically assigned patients and 16 percent in bypass patients, a difference that was not statistically significant.[232] The rates of myocardial infarction also were not significantly different between the groups. High-risk subsets appeared to benefit from surgery; for example, 5-year mortality among patients with three-vessel disease was 11 percent in the bypass surgery group and 24 percent in the medical group (p = .02). For patients with three-vessel disease and left ventricular dysfunction, the mortality advantage for surgery is even greater: 29 percent compared with 9 percent ($p < .05$). Surgery appeared to nullify partially the increased risk associated with lower ejection fractions. By 10 years, mortality was 38 percent in the medical group and 39 percent in the surgical group.[233] The relationship between a low ejection fraction and a survival benefit from surgery persisted (Fig. 41-12).

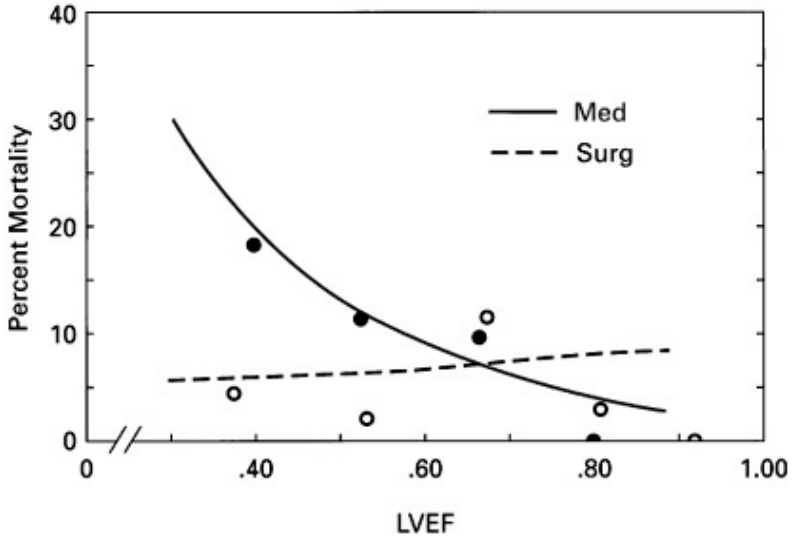

Figure 41-12: Mortality at 2 years according to baseline ejection fraction in the Veterans Administration Cooperative Study of Unstable Angina.[231] Although no overall mortality difference between the groups was seen, a relation between ejection fraction and outcome was evident. Survival was poor in medically treated patients with low ejection fractions. In surgically treated patients, survival was independent of ejection fraction. (From Luchi et al., [231] with permission.)

A common feature of the VA trial and trials in stable angina is that bypass surgery provides the greatest survival benefit to patients with the most advanced coronary disease and left ventricular dysfunction. Many patients with unstable angina are limited by exertional angina when they attempt to resume normal activities after the acute episode. Coronary bypass surgery effectively eliminates angina in 80 to 90 percent of cases. The long-term results of coronary bypass surgery for unstable angina have been good. In a compilation of more than 6000 patients from 14 reports from 1978 to 1988, operative mortality was less than 4 percent and 5-year survival was nearly 90 percent despite previous infarction in half the population, three-vessel disease in more than half, and left main stenosis in one-fifth.[234] Since that time, operative techniques have improved dramatically and the population of unstable angina patients undergoing bypass surgery has become older and sicker. These two factors have tended to cancel each other out, and so outcome statistics have remained relatively stable.

In its early phases of development, coronary angioplasty was applied to patients with unstable angina. The initial results were not as good as they were in patients with stable coronary disease. Advances in catheter technology have led to improved outcomes in all patient categories, with a narrowing of the gap between unstable and stable patients. The widespread use of coronary stents and GP IIb/IIIa inhibitors has further reduced the risk of coronary angioplasty in patients with unstable coronary disease.

Recent trials of coronary revascularization in unstable angina have compared an "aggressive" approach with a "conservative" approach. The aggressive approach involves early coronary angiography with revascularization by either coronary angioplasty or bypass surgery, depending on the coronary anatomy. Usually, patients with one or two severe narrowings are treated with angioplasty and those with more extensive disease undergo bypass surgery. The conservative approach limits coronary arteriography, usually to patients who require revascularization to control persistent symptoms and to those with very high-risk features.

In the TIMI IIIB trial, 1473 patients with unstable angina or non-Q-wave infarction were randomized within 24 h of chest pain to an early invasive or a conservative strategy.[229] The invasive group underwent coronary arteriography within 18 to 48 h after randomization, followed by a revascularization procedure when possible. Coronary arteriography was done in the conservative group for recurrent chest pain at rest with ischemic ECG changes, episodes of ST depression on ambulatory ECG monitoring, high-risk features on a stress test at the time of hospital discharge, severe angina after discharge, or hospitalization for a recurrence of unstable angina. Two-thirds of the patients had unstable angina, and the remainder had non-Q-wave infarction. Patients also were randomized in a factorial design to TPA or placebo, as was described above. The primary end point of the trial-death, myocardial infarction, or a failed symptom-limited exercise test within 6 weeks-occurred in 16.2 percent of patients randomized to the early invasive strategy and 18.1 percent of patients in the conservative group, a statistically nonsignificant difference. The rates of death (2.4 percent versus 2.5 percent) and nonfatal infarction (5.1 percent versus 5.7 percent) were almost identical with the two strategies. At 1 year, the cumulative rate of death or nonfatal infarction was 10.8 percent in the invasive group and 12.2 percent in the conservative group (p = not significant).[235] A major limitation of TIMI IIIB is that during the first 6 weeks, revascularization was performed in 63 percent of the invasive group and 50 percent of the conservative group. Such a small difference in the rates of revascularization is unlikely to produce a significant difference in end point events.

A major conclusion from TIMI IIIB was that rapid angiography and revascularization do not produce better outcomes than does a more leisurely approach that reserves angiography for patients who exhibit recurrent symptoms or high-risk features.

The Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial[236] included no patients with unstable angina, but its results may be relevant to all acute coronary syndromes. The 920 patients were assigned randomly to an invasive approach or a conservative approach. The composite end point of death or nonfatal infarction occurred more frequently in the invasive group during the first year: At hospital discharge, the difference was 7.8 percent versus 3.3 percent (p = .004); at 1 month, 10.4 percent versus 5.7 percent (p = .012); and at 1 year, 24 percent versus 18 percent (p = .05). By the end of the 23-month follow-up, the difference between the treatment groups had narrowed and was no longer statistically significant. VANQWISH has been criticized because revascularization was actually performed in only 44 percent of the patients assigned to the invasive strategy but in 33 percent of patients in the conservative group. Additionally, in the invasive patients who underwent bypass surgery, the mortality rate within 1 month of surgery was 11.6 percent, higher than the norm for this type of patient.

In the FRISC II study described above, 2457 patients with unstable coronary disease were randomized in a 2 by 2 factorial design to dalteparin or to placebo and to an invasive or noninvasive treatment strategy.[237] More than half the patients had elevated troponin T levels, and nearly half had ischemic ECG changes; one or the other of these criteria was necessary for entry into the trial. In the invasive arm, coronary angiography was performed within a few days of admission and revascularization was done shortly thereafter if feasible. An important difference between FRISC II and TIMI IIIB or VANQWISH is that most of the invasive patients underwent revascularization and most of the noninvasive patients did not, allowing a true comparison between the two approaches (Fig. 41-13). In the invasive group, the mean time from enrollment to angioplasty was 4 days and the mean time to bypass surgery was 7 days. By 10 days, 71 percent of the invasive patients and only 9 percent of the noninvasive patients had undergone revascularization. At 6 months, these rates were 77 percent and 37 percent, respectively. The mortality rate within 30 days among invasive patients who had bypass surgery was only 2.1 percent.

The primary end point of FRISC II-death or nonfatal infarction at 6 months-occurred in 9.4 percent of invasive patients and 12.1 percent of patients in the noninvasive group (odds ratio 0.78, 95 percent confidence interval 0.62 to 0.98, p = .031). During the first 2 weeks, the rate of death or infarction was higher in the invasive group than in the noninvasive group as a result of events associated with the procedures, but the curves crossed at 4 weeks (Fig. 41-14). Patients in the invasive group had a reduction in angina of about 50 percent compared with

the noninvasive group during the first 6 months of follow-up ($p < .001$) and also were significantly less likely to be readmitted to the hospital. Dalteparin was effective in reducing events in the entire study and in the noninvasive group but had little effect in the invasive group (9.1 percent dalteparin versus 9.7 percent placebo event rates). The event rate during the first 2 months was lowest in the dalteparin/noninvasive group. FRISC II clearly demonstrated that revascularization improves outcomes for unstable angina patients with ischemic ST changes or elevated troponin levels if the procedures can be done with a low rate of complications. With modern antiplatelet and antithrombotic therapy, revascularization does not need to be done urgently, within the first day or two after admission, but should be done within the first week or two. The early benefit seen with antiplatelet or antithrombotic drugs tended to dissipate within the first month or two in some of the clinical trials of these drugs.

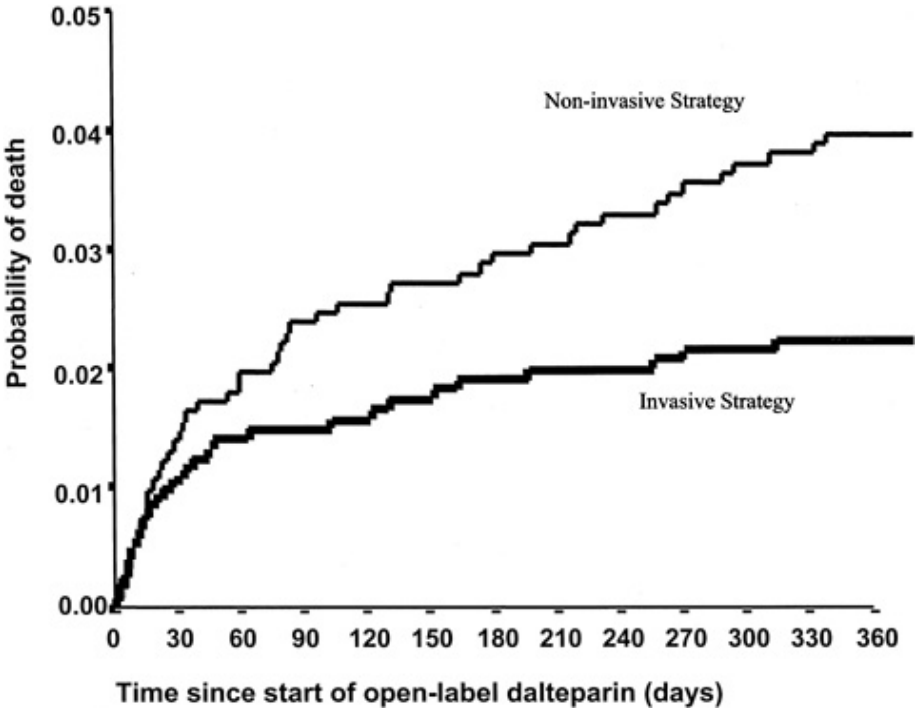

Figure 41-14: Incidence of death or myocardial infarction in patients randomized to the invasive and noninvasive strategies in the FRISC II trial.[237] At 6 months (the primary end point of the study), outcome was better in the invasive group ($p = .031$). This benefit persisted to 1 year. (Courtesy of Lars Wallentin, for the FRISC II investigators,[237] with permission.)

Survey data indicate that unstable angina patients who undergo revascularization outside clinical trial settings may not obtain benefit from the procedure. In the OASIS prospective registry of 8000 unstable angina patients treated in 95 hospitals in six countries, revascularization was performed in 49 percent of patients in the United States and Brazil, 34 percent of patients in Canada and Australia, and 17 percent of patients in Hungary and Poland.[238] The 6-month rates of death or myocardial infarction did not differ among patients in the three groups, although angina during follow-up was eliminated more effectively in countries with more intervention. Across the six countries, low-risk unstable angina patients benefited from being treated in a hospital with catheterization facilities, but the outcome of high-risk patients was significantly worse.

An Integrated Approach to Treatment

The treatment of unstable angina should be individualized to take into account the specific features of the disease and the particular circumstances of the patient. Nevertheless, the algorithms that have been developed recently provide a useful framework (Fig. 41-15). It should be remembered that unstable angina is an acute episode related to one active culprit lesion but that the patient has diffuse atherosclerosis. Coronary disease is a chronic condition that usually causes recurrent events that are spread out over many years. Thus, smoking cessation, cholesterol lowering, and control of hypertension and diabetes may be at least as important in the long term as are the specific treatment decisions related to the acute event. An episode of unstable angina may be viewed as an opportunity to improve the patient's profile with respect to secondary prevention.

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Chapter 41: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

VARIANT ANGINA

In 1959, Prinzmetal and associates described a syndrome characterized by angina at rest with transient ST-segment elevation.[239] Exercise tolerance usually was well preserved, and the attacks were cyclical in nature, often occurring in the early morning hours. The attacks did not last longer than ordinary anginal episodes, and the ST-segment elevation disappeared rapidly as the chest pain receded. Ventricular arrhythmias and atrioventricular block sometimes occurred at the height of an attack, and both myocardial infarction and sudden death were common complications (see also Chap. 40).

With the advent of coronary angiography, it soon became apparent that the syndrome was caused by coronary spasm, usually focal and often at the site of a coronary stenosis.[240] The underlying coronary lesion can vary from a subtotal occlusion to a very mild stenosis, and in some cases the coronary arteries are angiographically normal. Coronary spasm occurs in more than one artery in some patients,[241] and the site of spasm can fluctuate from one vessel to another.[242]

Pathophysiology

A large number of etiologic explanations for variant angina have been proposed or rejected. Evidence of parasympathetic nervous system overactivity[243] and reduced sympathetic activity[244] has been presented; however, coronary spasm has been demonstrated in the transplanted, denervated heart,[245] making central neural mechanism unlikely. The frequency of attacks of variant angina is not reduced by alpha-adrenergic blockade,[246] blockade of serotonin receptors,[247] inhibition of thromboxane A_2 production,[248] or the administration of prostacyclin.[249] Magnesium deficiency,[250] hyperinsulinemia,[251] and vitamin E deficiency[252] have been reported to be present in patients with variant angina. Vitamin C attenuates the abnormal coronary vasoconstriction in patients with variant angina, purportedly by inhibiting oxygen free radical generation[253] (see also Chap. 37).

Whether nitric oxide activity at sites of coronary spasm is normal or abnormal is controversial.[254,255] A mutation of the endothelial nitric oxide synthetase (eNOS) gene recently was reported to be significantly more common in patients with coronary spasm than in controls.[256] Depressed endothelial nitric oxide production could predispose patients with this defect to coronary spasm.

Coronary spasm usually is localized to the site of an atherosclerotic lesion. Even variant angina patients with no evident narrowing at angiography invariably will have atherosclerosis demonstrable by intracoronary ultrasound at the site of focal spasm.[257] Asian patients with variant angina appear to have generalized coronary artery hyperactivity, whereas in white patients the abnormality is focal.[258]

The pathophysiologic consequences of coronary spasm are well understood. Severe spasm rapidly induces transmural ischemia, resulting in segmental dyskinesis and ST-segment elevation. If the ischemic zone is large, cardiac output and systemic arterial pressure decrease. The risk of serious ventricular arrhythmias increases with the severity and extent of ischemia. Prolonged spasm can

induce intracoronary thrombosis, which may persist to cause myocardial infarction.[259]

Clinical Features

Variant angina is uncommon, and the presenting symptoms are usually not remarkable enough to be distinguished immediately from those of unstable angina. Angina at rest occurs with a cyclical pattern, often with attacks occurring in the early morning hours. Exertional angina coexists in slightly more than half these patients, but with an extremely variable ischemic threshold.[260] Variant angina can appear during the recovery phase of myocardial infarction[261] or soon after coronary bypass surgery[262] or angioplasty.[263]

Most patients with variant angina are heavy cigarette smokers, but their age, sex, and risk factor profiles are otherwise similar to those of other coronary patients.[264] Those with angiographically normal coronary arteries tend to be younger and more often are women. One-quarter of variant angina patients have a history of migraine headaches, and one-quarter have symptoms of Raynaud's phenomenon.[265] Thus, in some cases variant angina may be part of a more generalized vasospastic diathesis. Syncope, presumably caused by ischemia-induced ventricular arrhythmia or atrioventricular block, during rest angina is a useful clue to the diagnosis. Rare cases of life-threatening ventricular arrhythmias caused by silent myocardial ischemia resulting from coronary spasm have been reported.[266,267]

Cocaine causes coronary vasoconstriction and can precipitate coronary spasm, sometimes with myocardial infarction. This topic is discussed in Chap. 71.

Physical examination of variant angina patients between attacks reveals no abnormalities. Routine laboratory tests, including cardiac enzymes, are normal.

Diagnostic Procedures

Variant angina can be diagnosed most easily by recording an ECG during an episode of rest angina. The ST-segment elevation that occurs during an attack disappears promptly after the administration of nitroglycerin. Coronary spasm can induce ST elevation, ST depression, or pseudonormalization of abnormally negative T waves (Fig. 41-16). When variant angina is suspected, ambulatory ECG monitoring or an event monitor sometimes can be useful to confirm the diagnosis. Exercise testing will provoke angina with ST elevation in approximately one-third of variant angina patients during an active phase of the disease.[268] This response to an exercise test often leads to the diagnosis of variant angina when it was not previously suspected. Provocative testing has been used to confirm the diagnosis of variant angina when a spontaneous attack cannot be documented. The cold pressor response, exercise, and hyperventilation are physiologic stimuli for coronary spasm, but each has a sensitivity that is too low to be useful clinically.[268] The pharmacologic agents ergonovine and acetylcholine provoke coronary spasm with a sensitivity of approximately 90 percent in patients with variant angina.[268,269] Intracoronary acetylcholine is probably the preferred method, but a temporary pacemaker must be placed before right coronary (or dominant left coronary) injections are done because of the high incidence of bradyarrhythmias and conduction disturbances from cholinergic effects in the atrioventricular node.

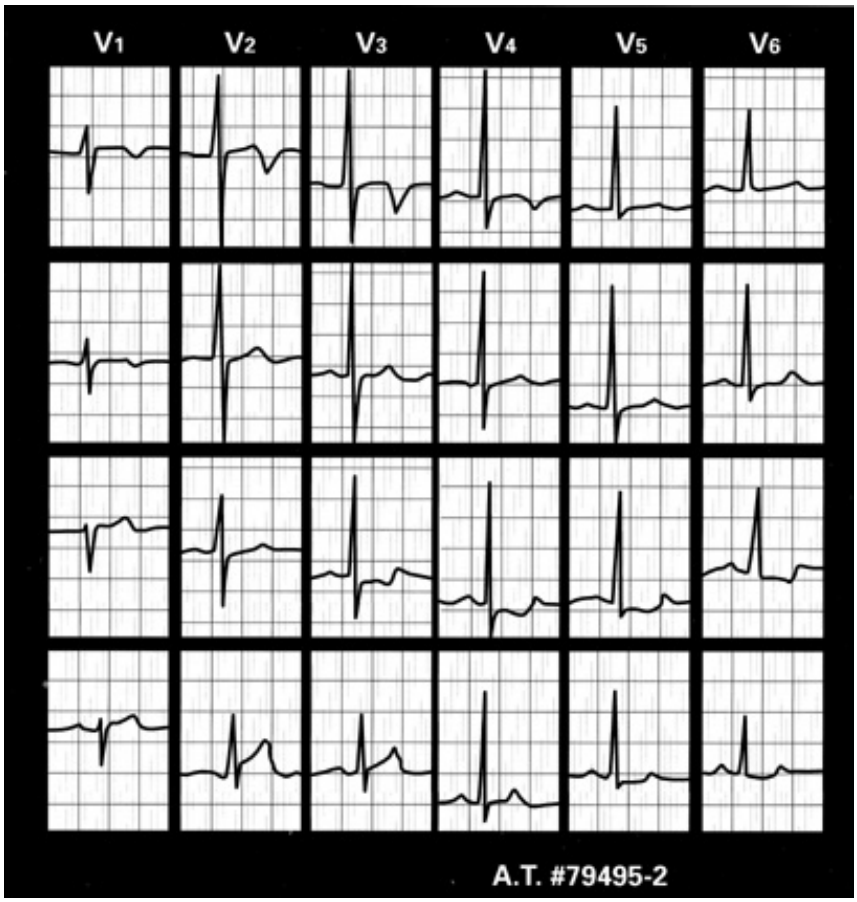

Figure 41-16: Electrocardiogram (leads V_1 to V_6) from a patient with active variant angina. Negative T waves are present in the control tracing (*top*). The other three tracings were recorded during separate episodes of rest angina and show pseudonormalization of T waves, ST depression, and ST elevation, respectively.

All patients with variant angina should undergo coronary angiography unless an absolute contraindication is present. Coronary angiography is the only certain method to distinguish between patients who have severe organic multivessel disease and those who have only mild narrowings or angiographically normal arteries.

Treatment

Variant angina is difficult to treat because attacks occur unpredictably and frequently without an obvious precipitating factor. For the patient's well-being, the goal of therapy therefore should be the elimination of all attacks. Spontaneous remission is a common outcome,[270] but myocardial infarction is a common complication within the first 3 months of diagnosis, particularly in patients with underlying multivessel disease.[271] Nitroglycerin relieves variant angina attacks within minutes and should be used promptly. Long-acting nitrates are effective in preventing variant angina attacks, but the development of nitrate tolerance limits their utility. Beta-adrenergic blockers should not be used in variant angina patients because of their propensity to increase the frequency and duration of attacks.[141,142]

Calcium channel blockers are very effective in preventing attacks of variant angina.[272-275] More than half the patients treated with one of these drugs become completely asymptomatic. The response is better at higher doses, for example, long-acting nifedipine 80 mg/day, diltiazem 360 mg/day, verapamil 480 mg/day, or amlodipine 20 mg/day. The efficacy of these drugs in preventing variant angina is roughly equal. Patients with an incomplete response to one drug often become angina-free on a combination of nifedipine and either diltiazem or verapamil. Evidence

from uncontrolled studies suggests that treatment with calcium channel blockers reduces the risk of myocardial infarction.[271,276]

Approximately 20 percent of variant angina patients will not respond to treatment with two calcium channel blockers plus a long-acting nitrate. Although not approved in the United States for this indication, amiodarone,[277] guanethidine,[278] and clonidine[278] have been reported to be effective in some of these refractory patients. Therapy for ventricular arrhythmias and conduction disturbances that complicate attacks in some cases should be directed toward the elimination of all episodes of spasm.[267] Patients with variant angina should be treated with low-dose aspirin, as are other patients with coronary disease, to reduce the risk of myocardial infarction, even though very high doses of aspirin have been reported to aggravate coronary spasm.[279]

Coronary bypass surgery should be considered in most patients with variant angina and multivessel atherosclerotic disease. Operative mortality and the perioperative infarction rate are higher than they are for comparable patients without variant angina.[280,281] However, surgery almost invariably eliminates variant angina, and the long-term outcome is excellent.[280] Bypass surgery will be successful when the anastomosis can be situated distal to the site of focal spasm but not when diffuse spasm involves the entire artery. Bypass surgery is not indicated for variant angina in the absence of significant organic stenoses.

Many patients with variant angina have coronary lesions that are ideal for angioplasty. When such patients are pretreated with calcium channel blockers and are given intracoronary nitroglycerin during the procedure, the primary success rate is high.[263,282] Coronary spasm may persist or recur after successful angioplasty, however, and calcium channel blockers therefore should be continued. The restenosis rate in variant angina patients is substantially higher than usual.[263,283] Whether coronary stenting improves outcomes for variant angina patients is not known. Coronary angioplasty is not indicated for patients with coronary spasm who have normal or nearly normal arteries on coronary angiography.

Prognosis

The long-term prognosis of variant angina has been reported for several large series of patients from different countries.[271276,280,284] The extent and severity of the underlying coronary disease appear to be the most important factors influencing the outcome (Fig. 41-17). Survival without infarction at 1 year in a consecutive series of 217 patients was 93 percent for those without stenoses of 70 percent or more, 86 percent for patients with single-vessel disease, and 65 percent for those with multivessel disease.[271] At 5 years, the corresponding figures were 83 percent, 74 percent, and 44 percent, respectively. Other variables that correlate with a poor outcome include the presence of abnormal left ventricular function, ventricular arrhythmias during attacks, multivessel spasm, and the absence of treatment with calcium channel blockers. The majority of these patients will become angina-free within months or years.[270] Variant angina will recur in rare cases after a long asymptomatic interval. More commonly, patients will develop other manifestations of coronary disease. Some evidence indicates that recurrent coronary spasm accelerates the progression of coronary atherosclerosis, with a histologic pattern of neointimal hyperplasia that resembles restenosis.[285,286]

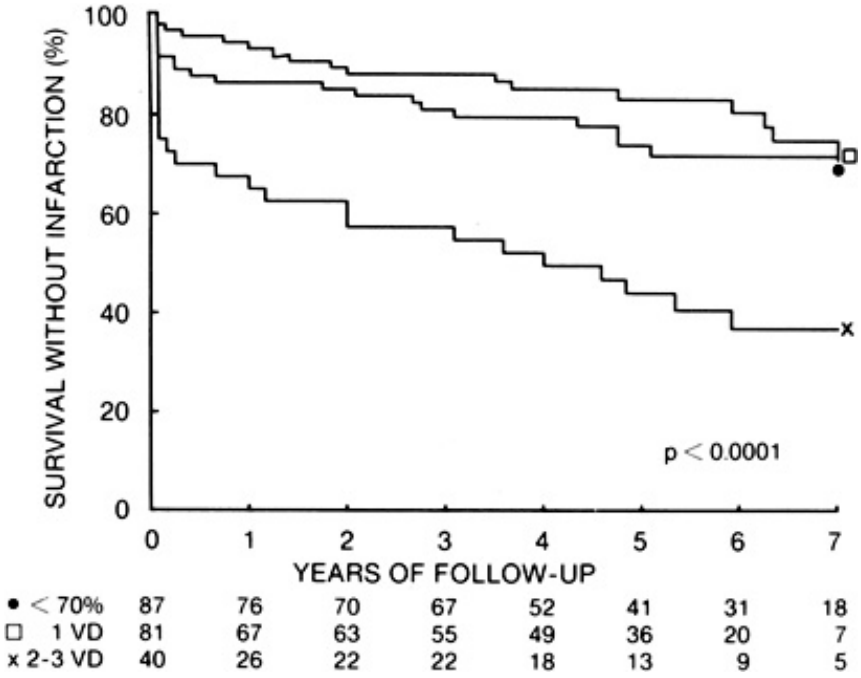

Figure 41-17: Survival without myocardial infarction in variant angina patients with no stenoses of 70 percent or more (▪), those with one-vessel disease (□), and those with multivessel disease (x). The outcome in the latter group of patients is much worse than that in the other two groups. Events are clustered in the early follow-up period. (From Walling et al.,[271] with permission.)

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Chapter 41: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

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Figure 41-11: Binding of unfractionated heparin (*top*) and low-molecular-weight heparin (*bottom*) to antithrombin. When bound to either form of heparin, antithrombin undergoes a conformational change that accelerates its interaction inactivating factor Xa. In contrast, formation of the heparin-antithrombin-thrombin complex (*top panel, bottom right*) requires the long saccharide chain of unfractionated heparin. (From Weitz,[209] with permission.)

Figure 41-12: Mortality at 2 years according to baseline ejection fraction in the Veterans Administration Cooperative Study of Unstable Angina.[231] Although no overall mortality difference between the groups was seen, a relation between ejection fraction and outcome was evident. Survival was poor in medically treated patients with low ejection fractions. In surgically treated patients, survival was independent of ejection fraction. (From Luchi et al., [231] with permission.)

Figure 41-13: Proportion of patients in the invasive and noninvasive treatment groups of TIMI IIIB,[229] VANQWISH,[236] and FRISC II[237] who underwent revascularization during the first year. The differences between invasive and noninvasive groups are small in TIMI IIIB and VANQWISH and large in FRISC II. This factor may partially explain why revascularization was shown to be beneficial in FRISC II but not in the other two trials. (Courtesy of Dr. Lars Wallentin, for the FRISC II investigators, with permission.)

Figure 41-14: Incidence of death or myocardial infarction in patients randomized to the invasive and noninvasive strategies in the FRISC II trial.[237] At 6 months (the primary end point of the study), outcome was better in the invasive group (p = .031). This benefit persisted to 1 year. (Courtesy of Lars Wallentin, for the FRISC II investigators,[237] with permission.)

Figure 41-15: Algorithm for managing patients with chest discomfort suggestive of unstable angina (*panel A*). The acute ischemic pathway (*panel B*) includes patients with documented unstable angina. This generalized guideline must be adapted to each patient's specific circumstances. (Adapted from the ACC/AHA guidelines for the management of patients with unstable angina,[1] with permission.)

Figure 41-16: Electrocardiogram (leads V_1 to V_6) from a patient with active variant angina. Negative T waves are present in the control tracing (*top*). The other three tracings were recorded during separate episodes of rest angina and show pseudonormalization of T waves, ST depression, and ST elevation, respectively.

Figure 41-17: Survival without myocardial infarction in variant angina patients with no stenoses of 70 percent or more (▪), those with one-vessel disease (□), and those with multivessel disease (x). The outcome in the latter group of patients is much worse than that in the other two groups. Events are clustered in the early follow-up period. (From Walling et al.,[271] with permission.)

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Part 6: CORONARY HEART DISEASE
Chapter 42:

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Authors: R. Wayne Alexander, Craig M. Pratt, Thomas J. Ryan, Robert Roberts

BACKGROUND AND INTRODUCTION*

Progress in the understanding of the pathogenesis of acute myocardial infarction (AMI) and of its treatment epitomizes scientific, evidence-based medicine at its best. Although myocardial infarction has long been a clinically recognized entity resulting from coronary artery atherosclerosis, its relative importance is a modern phenomenon. Its appearance as a modern epidemic reflects increasing longevity, permitting manifestation of chronic "degenerative" diseases such as atherosclerosis; the adoption of high-fat diets based on meats, permitted by increasing affluence; and decreased exercise, made possible by the increased mechanization of society. Osler devoted only a few pages in his textbook, published in 1892, to the discussion of AMI.[3]

The modern era can be said to have begun with the autopsy studies of Herrick, who concluded in 1912 that the clinical syndrome of myocardial infarction results from acute thrombotic occlusion of a coronary artery, with resulting downstream necrosis.[4] This conclusion was generally accepted for 60 years, and the term *coronary thrombosis* was not uncommonly used as the equivalent of *heart attack* or, more formally, *acute myocardial infarction.* The conventional wisdom was challenged in 1972, when it was suggested that coronary artery thrombus may be the result rather than the cause of acute infarction, since autopsy studies-which were frequently performed several days after the acute event-did not uniformly show thrombus.[5] In retrospect, these findings can be explained by spontaneous lysis of a thrombus that had been occlusive for a sufficient amount of time to cause tissue necrosis. Definitive proof of the central role of thrombus formation in the pathogenesis of myocardial infarction came from angiographic studies performed during the first hours of the acute event,[6,7] a diagnostic strategy that had previously been thought to be contraindicated.[8]

The unequivocal demonstration of the role of the thrombus in AMI quickly led to the systematic testing of thrombolytic strategies to abort myocardial infarctions.[9-11] Analysis of data from several small trials of thrombolytic therapy with streptokinase suggested improved mortality in treated patients as early as 1982.[12] These early efforts were followed by a large number of major multicenter clinical trials on the treatment of AMI; these demonstrated in a rigorous fashion the efficacy of beta-adrenergic receptor blockers,[13] streptokinase versus no thrombolytic therapy,[14] and recombinant tissue plasminogen activator versus streptokinase[15] in reducing mortality. These and other major trials are discussed in detail further on. The major point to be made here is that large, adequately powered, randomized studies in the treatment of myocardial infarction have helped set a new standard and approach to the goal of enhancing the evidence-based practice of medicine while moving away from one based on previous practice patterns and intuitive extrapolations from pathophysiologic principles. Key to the success of these very large trials has been the generalizability achieved mostly by the use of broad-entry criteria that facilitated the rapid enrollment of suitable patients and provided robust statistical power to the studies.

The availability of data from well-designed clinical trials has permitted the development, by panels of experts, of evidence-based practice guidelines for the treatment of myocardial infarction.[1,16] Furthermore, the confidence with which recommendations can be made for any particular diagnostic or therapeutic approach can be graded on the basis of judgments as to the strength of the supporting evidence. Thus, a committee convened by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines was charged with revising the ACC/AHA statement, "Guidelines for the Early Management of Patients with Acute Myocardial Infarction," published in 1990.[16] The results of the deliberations of this committee, "Guidelines for the Management of Patients with Acute Myocardial Infarction," were published in late 1996[2] and have been updated.[1] The evidence and expert opinion supporting use of a therapy, intervention, or diagnostic procedure were weighed and expressed in ACC/AHA format as follows:

- *Class I*: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- *Class II*: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- *Class IIa*: Weight of evidence/opinion is in favor of usefulness/efficacy.
- *Class IIb*: Usefulness/efficacy is less well established by evidence/opinion.
- *Class III*: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. In general, recommendations in this chapter are associated with a class I, II, or III designation to guide the reader in weighing diagnostic and therapeutic options.

The pathophysiologic bases and consequences of coronary artery disease and myocardial infarction are discussed elsewhere: natural history and prognosis (Chap. 1); pathogenesis of atherosclerosis (Chap. 35); pathology of coronary atherosclerosis (Chap. 36); risk factors and prevention (Chap. 38); nonatherosclerotic causes of coronary heart disease (spontaneous coronary artery dissection, aortic dissection, thrombosis associated with the use of birth-control pills, emboli, congenital coronary anomalies, metabolic abnormalities, blunt chest trauma, vasculitis, and drug abuse, especially cocaine) (Chap. 39); pathophysiology of myocardial ischemia (Chap. 37); pathophysiology of coronary artery disease as related to myocardial ischemic syndromes (Chap. 35); and thrombogenesis and antithrombotic therapy (Chap. 44).

The following are important general facts about myocardial infarction:

1. Approximately 800,000 people in the United States experience AMI annually; of these, about 213,000 die. Of those who die, approximately one-half do so within 1 h of the onset of symptoms, before reaching a hospital.[1,17,18]
2. The majority of early deaths are the result of ventricular arrhythmias that can be readily aborted by defibrillation, either during prehospital care or in coronary care units (CCU) in the hospital.
3. The major cause of myocardial infarction is atherosclerotic disease of the epicardial coronary arteries, as noted. Although luminal narrowing resulting in hemodynamically significant obstruction of blood flow is the major cause of symptoms of coronary ischemia (Chap. 40), the majority of myocardial infarctions occur as a result of the disruption of arterial lesions that are not hemodynamically significant (<60 percent). This breakdown of the structural integrity of the arterial intima occurs because of weakening induced by proteolytic degradation of matrix proteins by products released from inflammatory leukocytes[19] and results in the exposure of blood to thrombogenic intimal material, causing obstructive clot formation. Local vasospasm may contribute to the obstruction. *These observations have led to the concept that the biological state of atherosclerotic lesions and not the extent of stenosis is the major determinant of whether or not plaque rupture and*

myocardial infarction occur.

4. Myocardial infarction, or ischemia, is a segmental process limited to the distribution of the affected artery. Impaired contractility usually occurs within seconds of the cessation of blood flow. The process usually begins in the endocardium and spreads toward the epicardium. If flow is restored before cell death occurs, prolonged contractile impairment (stunning) may occur.
5. Episodes of ischemia preceding coronary occlusion enhance the survivability of myocardial cells (*ischemic preconditioning*).
6. Irreversible cardiac injury occurs if occlusion is complete for at least 15 to 20 min. Irreversible injury occurs maximally in the area at risk when occlusion is sustained for 4 to 6 h, but most of the damage occurs in the first 2 to 3 h. Thus, restoration of flow within the first 4 to 6 h is associated with salvage of the myocardium, but the salvage is exponentially greater if restoration occurs in 1 to 2 h.
7. Restoration of blood flow by thrombolysis results in myocardial salvage and improved mortality. The extent of the benefit is dependent upon restoration of near-normal blood flow *(open-artery hypothesis)* and is inversely related to the time between the onset of occlusion (symptoms) and the restoration of blood flow.
8. The percentage of tissue at risk that undergoes necrosis (infarct size) depends on existing collateral flow, which is highly variable and difficult to predict.
9. The major predictor of long-term outcome is infarct size, which is inversely related to the ejection fraction.
10. Q-wave infarction (usually presenting as ST-segment elevation) is a distinct clinical entity, as compared with non-Q-wave infarction (usually presenting with ST-segment depression). There are differential features in their clinical courses. (Q-wave infarction, untreated, has a relatively high in-hospital mortality rate that is favorably influenced by thrombolysis, whereas non-Q-wave infarction has a lower in-hospital mortality and complication rate with a prolonged vulnerability to reinfarction. Thrombolysis may worsen the clinical outcome.) Although there is no close anatomic correlation between the presence and absence of Q waves and transmural and nontransmural myocardial infarction, the distinct clinical outcomes of patients presenting with ST-segment elevation and ST-segment depression have made this electrocardiographic feature a major initial decision point in assigning therapeutic strategies to patients presenting with symptoms compatible with AMI.
11. Because of their salutary effects on thrombus formation and ventricular arrhythmias, aspirin and beta-adrenergic blockers, respectively, have proved to be effective for secondary prevention in patients who have had a myocardial infarction. Aspirin has also been shown to be modestly effective for primary prevention in middle-aged males.
12. Lipid lowering and smoking cessation have both been shown to be effective in the primary and secondary prevention of myocardial infarction. The enormous progress that has been made in understanding the pathogenesis and treatment of myocardial infarction has resulted in substantial improvements in outcomes in recent years. Indeed, the "natural history" of treated patients has improved dramatically. The mortality rate in the pre-CCU era has been estimated to have been about 30 percent.[20] The mortality rate dropped dramatically, to about 15 percent, in the CCU era, which embraced the use of hemodynamic monitoring, defibrillation, and the use of beta blockers. The increased use of thrombolytics, coronary interventions, aspirin, and angiotensin-converting enzyme inhibitors has decreased the mortality of patients treated for the conventional ST-elevated AMI to 6 to 7 percent.[15,21] This, of course, cannot be claimed for patients in the Medicare population where it is generally accepted that patients over the age of 70 have a mortality rate that approximates 20 percent when admitted for the management of AMI. The major challenge, however, is to bring the principles and lessons learned from the efforts of the past decade to everyday clinical practice.

* The ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction,

1996 version, have been updated in 1999. The 1999 update did not reprint the whole document. Reference to the Guidelines in this chapter will refer to the 1999 citation[1] but may also refer to data in the 1996 document.[2]

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Chapter 42: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

CLINICAL ASPECTS

Predisposing Characteristics and Circumstances

The standard risk factors for the development of coronary artery disease (dyslipidemia, family history, age, male gender, cigarette smoking, diabetes mellitus, and hypertension) are well established and are discussed in Chap. 38. *Careful consideration of the probabilities of the presence of coronary artery disease is centrally important in the initial assessment and evaluation of testing results of any patient with chest pain.* The experienced clinician will calibrate his or her responses even within the context of algorithmic approaches to the evaluation of chest pain. For example, the 35-year-old male with atypical chest pain whose father died of coronary disease at less than age 50 and whose mother had a coronary bypass at age 55 would be viewed with a higher index of suspicion than he would be if both his parents and grandparents were alive and well. This higher level of concern might translate into ordering diagnostic modalities with a higher level of sensitivity and specificity for detecting coronary artery disease in the former as opposed to the latter case.

As discussed in Chaps. 35, 36, and 38, atherosclerosis generally, and including the disease in the coronary arteries, is a chronic inflammation representing the response of the arterial wall to the stress imposed by various risk factors. AMI has commonly been shown to occur as a result of the disruption of a coronary artery plaque at a site of a high density of inflammatory cells.[21] Thus, AMI can be thought of as resulting from the acute exacerbation of a chronic inflammatory response. There is increasing clinical evidence supporting this view. Thus, unstable angina, a frequent antecedent of myocardial infarction,[22] has been shown to be associated with elevated plasma levels of the acute-phase reactant C-reactive protein.[23,24] Observations from the Physicians' Health Study, which showed that subjects with the highest levels of C-reactive protein have an increased long-term risk of cardiac events, is also supportive of the concept that inflammatory responses are important in the pathogenesis of AMI.[25] *Thus, events precipitating myocardial infarctions can be viewed as exacerbating the arterial inflammatory response and/or increasing the physical forces impinging on a coronary artery lesion weakened by inflammation, which leads to rupture.*

Precipitating Events

There is little direct, but intriguing indirect, evidence that external factors might exacerbate the arterial inflammatory response. An association has been noted between AMI and antecedent mild respiratory syndromes.[25] It is possible that an infection, by activating systemic responses, could stimulate or activate previously quiescent atherosclerotic lesions. A more specific relation between AMI and an infectious agent has been posited in the case of *Chlamydia pneumoniae*.[26-28] Increased antibody titers to *C. pneumoniae* in subsets of patients have been associated with increased risk for acute infarction, and acute infarction-associated increases in circulating immune complexes, followed by a subsequent increase in antibody titers, have been observed.[29] Evidence exists for the presence of chlamydiae in atherosclerotic coronary artery lesions.[30] Thus, it is possible that *C. pneumoniae* infection contributes to the inflammatory responses in atherosclerosis and that acute reinfection activates the inflammatory response, leading to myocardial infarction. This area requires further investigation.

There is considerable evidence associating AMI with emotional or environmental stresses. It is likely that the majority of these stresses involve activation of the sympathetic nervous system, with increases in locally released and circulating catecholamines. Increased sympathetic drive increases cardiac oxygen consumption by increasing contractility and rate. Sympathetic stimulation will also increase shear forces and stress on vascular atherosclerotic lesions by augmenting contraction and torque and elevating blood pressure. Superimposition of these forces on a vessel weakened by inflammation can lead to plaque rupture.

Enhanced circulating catecholamine levels can increase the propensity for thrombus formation by activating platelets. Such a scenario likely explains the association (in about 4 to 7 percent of patients) between acute increases in physical exertion and the development of myocardial infarction, especially among those who do not exercise regularly.[31,32] Similarly, episodes of anger increase the risk of precipitating myocardial infarction in susceptible persons.[33] Distressing or changing life events reportedly occur with increased frequency in the months preceding a myocardial infarction.[34-36] Another well-controlled study, however, found no correlation between the occurrence of acute infarction and the presence of unusual life events for up to 4 weeks prior to the event.[31]

It is apparent that any acute stressful event or intervention can precipitate AMI in a patient with "active," susceptible coronary atherosclerotic lesions. Anesthesia and surgery are well known to enhance the risk of myocardial infarction, and cardiac events are the leading cause of perioperative morbidity.[37] Perioperatively, stress can be induced by tachycardia and hypotension,[38] anemia,[39] and hypothermia.[40] A study of patients with coronary disease undergoing noncardiac surgery has shown that the usual perioperative hypothermia was associated with a relative risk of cardiac events of 2.2, as contrasted to a similar group in whom normothermia was maintained.[41] The salutary effects of maintaining normothermia were thought to be due to the prevention of cardiac stress imposed by activation of the sympathetic nervous system. By extension, many of the stressful events-such as pulmonary emboli, stroke, hypoxia, allergic responses, blood loss, etc.-that have been associated with the precipitation of AMI can likely be related to the effects of adrenergic stimulation by an excess of catecholamines.

Myocardial infarction can occur because of low perfusion pressure in shock of any etiology and can arise in severe aortic stenosis even in the absence of coronary artery disease because of excessive oxygen demands in a very hypertrophic ventricle with, for example, marked tachycardia. Other nonatherosclerotic causes of myocardial infarction, including trauma, embolism, and dissection, are discussed in Chap. 39. Vasospasm in the absence of angiographically demonstrable coronary artery disease has been reported to have caused AMI in several patients during general anesthesia.[42] Also, it is likely that vasospasm plays a central role in cocaine-induced myocardial infarction.[43]

Personality Types

It has been claimed that so-called coronary-prone individuals exhibit certain personality traits, such as being a compulsive hard worker, being deadline-driven, and being excessively competitive. Categorizing people with such traits as "type A" and thus as being at increased risk for myocardial infarction was formerly widely discussed.[44] This concept is not widely accepted now,[45] and the psychological contributions to heart disease are generally considered to be more complex (see Chap. 80).

Circadian and Seasonal Variation

Results of the Multicenter Investigation of Limitation of Infarct Size (MILIS) study showed a marked circadian periodicity in the occurrence of myocardial infarction, with a peak prevalence between 6 A.M. and noon. The circadian rhythm was present whether the onset of the infarction was marked subjectively by the appearance of pain or objectively by plasma MB-CK (creatine kinase) levels. There was a threefold increase in the frequency of infarction at peak (9 A.M.) periods as compared with trough (11 P.M.) periods.[46] As a corollary, sudden death attributed to ischemic heart disease has a similar circadian periodicity. Available data suggest that the rhythms both for the occurrence of myocardial infarction and for deaths from ischemic events are actually bimodal. These rhythms are characterized not only by the morning peak but also by a secondary, less pronounced late-afternoon or early-evening peak (6 to 8 P.M.).[47] The mechanisms underlying this temporal distribution of ischemic events are not completely understood but are probably related to diurnal variations in thrombotic tendencies and to sympathetic nervous system activity. There is both an enhanced platelet aggregability[48] and a trough in intrinsic fibrinolytic activity during the morning hours.[49] A similar circadian variation is observed for cerebral infarction,[50] which further implicates an increased propensity for thrombosis in the morning hours. The blunting of the morning peak of myocardial infarction by both aspirin and beta-adrenergic blockers emphasizes the contributions of both the sympathetic nervous system and the coagulation pathways to the circadian rhythm of cardiovascular events.[51]

Other endogenous daily rhythms may be causally related. Ambulatory ST-segment changes in patients with coronary artery disease have demonstrated a close correlation between basal heart rate (which is higher in the morning) and the frequency of ischemic ST-segment changes.[52] These observations may be mechanistically related to the morning increase in tone noted in coronary artery segments with dysfunctional endothelium-dependent dilation in patients with chronic stable angina (see Chaps. 6 and 40).[53] Circadian variations in blood pressure[54] and plasma catecholamine levels[55] that parallel those of ischemic events have been observed. The morning increase in sympathetic activity not only increases the metabolic demand but may also cause coronary vasoconstriction that is unopposed by normal endothelial vasodilator mechanisms, as implied earlier.

There also appear to be exogenous rhythms that influence the development of AMI. In a working population, there is an increased risk for infarction on Mondays.[56] Seasonal variations have also been commented upon, with increases in the winter months of January through March.[57]

Symptoms

Prodromal symptoms antedating AMI are common and occur in at least 60 percent of patients.[58] Since at least 8 to 10 percent of AMIs are painless (not necessarily silent) and many ischemic episodes are silent,[59] it is apparent that the great majority of patients capable of sensing cardiac pain during periods of unstable angina do so in the hours, days, or sometimes weeks prior to the acute event. Most of these symptoms are anginal or angina-like, especially when assessed retrospectively in the context of the character of the pain of the acute infarct. The antecedent symptoms may also be anginal equivalents, such as paroxysmal dyspnea (see Chap. 40). The clinical features of unstable angina are discussed in Chap. 41. If one considers the general feeling of malaise and fatigue that many patients report having experienced prior to acute infarction, it is apparent that it is relatively unusual for the episode to be totally unheralded-a conclusion that is consistent with general clinical experience.

The classic symptoms of AMI involve chest discomfort that is commonly retrosternal or precordial in location and is described as pressure, aching, burning, crushing, squeezing, heavy, swelling, or bursting in quality.[60,61] Typically it has all the features of prolonged angina pectoris that was so eloquently phrased by William Heberden in his original description to the assembly of the Royal College of Physicians in 1772;

> There is a disorder of the breast marked with strong and peculiar symptoms considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seed of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris. They who are afflicted with it, are seized while they are walking (more especially if it be uphill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes.

The location of chest pain is usually of little help in differentiating ischemia/infarction from other causes of chest pain,[62] but severe chest pain (as opposed to vague discomfort) and the presence of associated symptoms (dyspnea, nausea, diaphoresis, etc.) are more commonly associated with AMI.[63] The discomfort often radiates over the anterior chest and frequently into the left arm or both arms (particularly the medial aspect), and/or into the neck or jaw. In unusual instances, the pain may be in the back, particularly between the scapulae. There may be skip areas with retrosternal pain-associated with jaw, antecubital fossa, or wrist pain-or no pain between the two sites. Moreover, the pain may appear only in the referral area. The duration of the pain of infarction is prolonged, lasting conventionally longer than 15 min. While the intensity of the pain is usually steady following an initial crescendo, there is occasionally some waxing and waning. Sudden relief of pain may accompany reperfusion. Associated symptoms may include dyspnea, diaphoresis, nausea, and vomiting. Marked apprehension is common. Occasionally, presenting symptoms include syncope, acute confusion, agitation, stroke, or palpitations.

Approximately 23 percent of myocardial infarctions go unrecognized by patients because of the absence of symptoms or the lack of recognition of the significance of symptoms.[64] The common symptoms in this latter instance are nonclassic or atypical pain, dyspnea, nausea, vomiting, and/or epigastric pain. A

myocardial infarction may also masquerade as the development or worsening of congestive heart failure, the appearance of an arrhythmia, an overwhelming sense of apprehension, profound weakness, acute indigestion, pericarditis, embolic stroke, or peripheral embolus.[65] Presentation with painless myocardial infarction is more common in the elderly (age >65 years) than it is in the nonelderly, and this subgroup has an increased frequency of congestive heart failure as the initial presenting symptom.[66]

Physical Findings

GENERAL EXAMINATION

Features of the physical examination during AMI have been the subject of several reviews.[67,68] The patient is frequently sitting up because of a sense of suffocation or a feeling of shortness of breath. Most patients with cardiac pain or myocardial infarction have some sense of impending doom that is reflected in their facial expression. They may have a grayish appearance or one of panic or exhaustion. Diaphoresis is frequent. In severe cases, patients may be quite anxious, with an ashen or pale face beaded with perspiration. The patient should be examined in both the supine and left lateral decubitus position. The major findings pertaining to the heart appear on palpation of the precordium in the left lateral position. It is important to rapidly ascertain the vital signs and the nature, character, and rhythm of the arterial pulse; to observe the jugular venous pulse; to check the peripheral pulses; to palpate the precordium; and to auscultate the chest and precordium. Examination of the extremities should include subjective assessment of the temperature and color of the feet. The presence of very cool feet, especially with acrocyanosis in the setting of tachycardia, suggests low cardiac output.

The heart rate and rhythm are important indicators of cardiac function in the initial hours of myocardial infarction. *A normal rate usually indicates that the patient is not experiencing significant hemodynamic compromise.* In patients with inferior myocardial infarction, heart rates in the 50s and 60s are common in the initial hours. Up to 60 percent of these patients initially have bradycardia, but the rate gradually increases over the next few hours. The bradycardia, which may be associated with secondary hypotension, results from the stimulation of myocardial receptors with vagal afferents. *Persistent sinus tachycardia beyond the initial 12 to 24 h is predictive of a high mortality rate.* The pulse may be low in volume, reflecting decreased stroke volume. The blood pressure is usually normal but may be increased secondary to anxiety, or it may be decreased from cardiac failure. Blood pressure frequently normalizes temporarily with AMI in patients with hypertension. All peripheral pulses should be examined to observe their presence, and their status should be noted both to exclude current occlusion and to provide a baseline in case of future embolic events. The carotid pulse is most useful in assessing systolic upstroke time and stroke volume, which are decreased in the patient with a low output state.

The rhythm of the pulse is important because of the frequency of ectopic atrial and, in particular, ventricular beats in AMI. Observation of the jugular venous pulse is useful in determining whether ectopic beats are atrial or ventricular. A large A wave, indicating that the right atrium is contracting against a closed atrioventricular (AV) valve, suggests that the ectopic beat is ventricular. The respiratory rate is usually within the normal range. However, patients who are extremely anxious often exhibit hyperventilation, and those with pulmonary edema and cardiac failure have an increased respiratory rate associated with shallow inspirations. Abnormal breathing patterns, such as Cheyne-Stokes respirations, are rare unless the patient is in cardiogenic shock.

Examination of the jugular venous pulse is important with AMI, especially in patients with an inferior infarction, because insights can be gained into possible involvement of the right ventricle. The right ventricle is commonly involved with inferior infarction, but right-sided failure is seen only with major right ventricular involvement. It may be manifest by an elevated jugular venous pressure. In addition, in many patients with right ventricular infarction or ischemia, there is also a prominent A wave because of the decreased compliance of the right ventricle.[69] Kussmaul's sign, or an increase in the venous pressure on inspiration, may also be seen in right ventricular infarction/ischemia because of decreased right ventricular compliance. Generally, right ventricular failure commonly reflects left ventricular failure, with secondary elevation in pulmonary and right ventricular pressures. This circumstance usually occurs with large anterior or anterolateral infarction.

EXAMINATION OF THE LUNGS

Basilar rales are frequently detected in AMI. Cardiac failure diagnosed on the basis of mild signs of pulmonary congestion occurs in 30 to 40 percent of patients with otherwise uncomplicated myocardial infarction. A clinical classification proposed by Killip provides some uniformity in terms of describing cardiac failure and pulmonary congestion.[69a] Class I patients do not have any pulmonary rales or a third heart sound. Class II patients have rales of a mild-to-moderate degree, involving less than 50 percent of the lung fields, and may or may not have an S_3 gallop. Class III patients have rales more than halfway up the lung fields and an S_3 gallop. Class IV patients are those in cardiogenic shock.

CARDIAC EXAMINATION

Palpation of the precordium may reveal evidence of regional wall motion abnormalities. Palpation should be performed with the patient initially lying in the supine position; this is often adequate to ascertain whether there is a localized normal apical impulse and also permits assessment for dyskinetic impulses (see Chap. 10). Frequently, one may not feel any precordial impulse with the patient in the supine position because of the decreased intensity of contraction and/or body habitus. With the patient in the left lateral decubitus position, one may palpate a diffuse rather than a localized apical impulse, akinesis, or a paradoxical bulging during late systole; in some patients, there is a palpable atrial contraction corresponding to an audible S_4 gallop due to the decreased compliance of the left ventricle. One or more of these features of decreased contractility or lusitrophy and dysynergy are frequently present in the early hours of AMI, particularly with extensive damage.

The first and second heart sounds are often very soft because of decreased contractility. The first heart sound may also be diminished because of a prolonged PR interval. If there is tachycardia, a shortened PR interval may result in a somewhat accentuated first heart sound. The second heart sound is usually normal; however, with extensive damage, there may be a single second sound. Rarely, paradoxical splitting may reflect severe left ventricular dysfunction. A fourth heart sound is often audible in patients with AMI. A third heart sound is heard in probably only about 15 to 20 percent of AMI patients. A pericardial friction rub can be heard anytime between 24 to 72 h after the onset of myocardial infarction and, since its presence is often transient, frequently repeated auscultation is the best means of detection. The murmur of papillary muscle dysfunction is relatively common early in the course of infarction. This crescendo-decrescendo midsystolic murmur often reflects ischemia of the papillary muscles or the myocardial attachment rather than irreversible injury to these structures. This murmur usually disappears after the first 12 to 24 h if it is soft; however, if the murmur is moderate to loud in intensity, it may persist much longer, possibly throughout the patient's life. Mitral regurgitation is most commonly due to ischemia of the posteromedial papillary muscle (see also Chap. 10). Other findings on physical examination, such as the murmur of papillary muscle rupture or a ruptured ventricular septum, are described in appropriate sections under "Complications."

Diagnosis of Acute Myocardial Infarction

DIFFERENTIAL DIAGNOSIS

Myocardial infarction has typically been diagnosed on the basis of the triad of chest pain, electrocardiographic changes, and elevated plasma enzyme activity. Although AMI occurs without chest pain (20 to 25 percent of cases), chest pain remains the most common symptom and is usually responsible for the patient's seeking medical help. The differential diagnosis of prolonged chest pain is presented in Table 42-1. Chest pain, however, is not specific to cardiac disease, and it is often impossible on the basis of history alone to distinguish ischemia or infarction from other causes of chest pain. The differential diagnosis of chest pain is discussed in Chap. 40. Of patients presenting to the emergency department with chest pain, only about 14 percent are subsequently documented to have AMI.[70-73] Most patients at risk for myocardial infarction will be admitted to evaluate their chest pain unless definite noncardiac causes of chest pain-such as chest wall pain, hyperventilation, pleurisy, gastrointestinal pain, and so on-that are not imminently dangerous can be identified. In the CCU, only about 20 percent of patients admitted with chest pain have AMI.

Table 42-1: Differential Diagnosis of Prolonged Chest Pain

AMI
Aortic dissection
Pericarditis
Atypical anginal pain associated with hypertrophic cardiomyopathy
Esophageal, other upper gastrointestinal, or biliary tract disease
Pulmonary disease
Pleurisy: infectious, malignant, or immune disease-related
Embolus with or without infarction
Pneumothorax
Hyperventilation syndrome
Chest wall
Skeletal
Neuropathic
Psychogenic

ELECTROCARDIOGRAPHIC DIAGNOSIS

The electrocardiogram (ECG) is sensitive for detecting myocardial ischemia and infarction but is frequently not powerful enough for differentiating ischemia from necrosis (see Chap. 11).[70,71,74] Serial ECGs during AMI will show some evolutionary changes in the majority of patients.[75] An ECG obtained during cardiac ischemic pain frequently but not always exhibits changes in repolarization. The absence of electrocardiographic changes during pain provides evidence but not proof that the pain is not ischemic in nature. The early electrocardiographic changes of T-wave inversion or ST-segment depression may reflect ischemia or infarction. ST-segment elevation is more specific for AMI and reflects the epicardial injury-associated total occlusion of an epicardial coronary artery. The hallmark of AMI is the development of abnormal Q waves,[76,77] which appear on the average 8 to 12 h from the onset of symptoms but may not develop for 24 to 48 h. Abnormal Q waves usually reflect tissue death and the development of an electrical dead zone. Since abnormal Q waves do not develop immediately, they are not very helpful for initial diagnostic management and therapeutic triage except to signify the presence or absence of prior myocardial infarction. The diagnostic serial electrocardiographic changes consist of ST-segment elevation with the development of T-wave inversion and the evolution of abnormal Q waves (Fig. 42-1).[78] The appearance of abnormal Q waves is very specific to AMI; however, they are present in less than 50 percent of patients with documented AMI.[79] Most of the other patients who have AMI will have electrocardiographic changes restricted to T-wave inversion or ST-segment depression or no change at all. These patients represent the group with non-Q-wave infarction.[80]

The traditional concept that myocardial infarctions can be classified as transmural or nontransmural on the basis of the presence or absence of Q waves is misleading, since autopsy studies have demonstrated convincingly that pathologic Q waves may be associated with nontransmural infarction and may be absent with transmural infarction.[81-83] These misnomers have been replaced by the terms *Q-wave infarction* and *non-Q-wave infarction for transmural and nontransmural infarction*, respectively.[84] The evolution of a non-Q-wave infarction is characterized by a lack of development of an abnormal Q wave and by the appearance

of reversible ST-T-wave changes with ST depression that usually returns to normal over a few days, but is occasionally permanent. Differentiation between these two types of infarctions has become entrenched, since there are major differences in their pathogenesis, clinical manifestations, treatment, and prognosis (Table 42-2). The initiating events in the pathogenesis of Q-wave and non-Q-wave infarction are thought to be identical, namely, coronary occlusion induced by a thrombus superimposed on a plaque together with vasoconstriction (see Chap. 36). There is considerable evidence, however, to indicate that in non-Q-wave infarction, early spontaneous reperfusion occurs, the mechanism of which remains uncertain. In contrast, in Q-wave infarction, the coronary occlusion is sustained at least for a long enough period to result in extensive necrosis.

One explanation for early spontaneous reperfusion is the lack of sustained vasoconstriction, which may contribute to occlusion.[85] The evidence supporting the existence of early spontaneous reperfusion in non-Q-wave infarction is as follows:

1. Coronary angiographic studies performed in the early hours after onset show that only about 20 to 30 percent of patients have complete coronary occlusion of infarct-related vessels; however, for Q-wave infarction, it is about 80 to 90 percent.
2. Infarct size is routinely much less than observed with Q-wave infarction, which is consistent with salvage by early reperfusion.
3. Peak plasma CK levels are reached on an average of 12 to 13 h after onset of symptoms, indicating early washout of the enzyme, as opposed to about 27 h after Q-wave infarction.
4. Reperfusion-induced contraction necrosis is extremely common, as it is in patients who undergo early reperfusion induced by thrombolytic therapy.[86]
5. Acute mortality rates are around 2 to 3 percent, compared with 10 percent for Q-wave infarction.
6. The complications are minimal compared with those after a Q-wave infarction.
7. Finally, the long-term prognosis is characterized by recurrent episodes of reinfarction, so that after about 2 years, survival is the same as that after Q-wave infarction.[80,87-90]

Traditional teaching has held that AMI could not be diagnosed electrocardiographically in the presence of a left bundle branch block because of the unpredictability of the depolarization and repolarization patterns. It has been suggested that marked ST-segment deviation, beyond what could be anticipated from the conduction abnormality, could be useful in the diagnosis of AMI in the setting of a left bundle branch block.[91]

The resting ECG is insensitive for detecting the presence of atherosclerotic coronary heart disease; it is normal in 50 percent of patients with angiographically significant coronary obstruction.[92] Nevertheless, an abnormally wide Q wave on a resting ECG has been the standard criterion for the diagnosis of a myocardial infarction for over 60 years.[93]

The electrocardiographic criteria for the diagnosis of AMI as outlined in the MILIS study are the presence, in the setting of chest pain, of any one of the following: (1) new or presumably new Q waves (at least 30 ms wide and 0.20 mV deep) in at least two leads from any of the following: (a) leads II, III, or aV_F; (b) leads V_1 through V_6; or (c) leads I and aV_L; (2) new or presumably new ST-T- segment elevation or depression ($\geq$0.10 mV measured 0.02 s after the J point in two contiguous leads of the previously mentioned lead combination); or (3) a complete left bundle branch block in the appropriate clinical setting. An evaluation of these criteria in 1809 enzyme-confirmed infarctions found that 21 percent of the patients with an infarction had none of these changes.[94] Conversely, over 90 percent of patients who had ST-segment elevation of 0.1 mV, as described previously, were confirmed to have AMI. If the patients also had ST-segment depression in the so-called reciprocal leads, the infarction rate was 3 percent higher. Patients with a left branch bundle block or ST-segment depression without other abnormalities had a lower rate of infarction (46 and 52 to 56 percent, respectively) than those with ST-segment elevation. Furthermore, the presence of abnormal Q waves on the resting ECG accurately predicts the presence and location of left ventricular contraction abnormalities. In a study of 64 patients with abnormal Q waves on the ECG, all patients with abnormal Q waves in the anterior leads and 30 of 33 with abnormal Q waves in the inferior leads demonstrated contraction abnormalities in the corresponding left ventricular segments.[95] The evolution of a Q-wave myocardial infarction can be separated electrocardiographically into four phases: (1)

hyperacute, (2) acute, (3) subacute, and (4) chronic stabilized (Fig. 42-1; see Chap. 11).

In the hyperacute phase (Fig. 42-1), the earliest electrocardiographic manifestation of an acute infarction is usually a straightening of the normal upward concavity of the ST-T segment.[96] With further evolution, the straightened ST-T segment becomes elevated. The ST-T segment usually slopes upward, since the portion of the ST-T segment nearest the T wave is more elevated than the proximal portion. Also, the amplitude of the T wave is usually increased. Occasionally, the ST-T segment may be markedly elevated and yet retain its upward concavity. ST-T depressions in leads oriented toward the presumably noninfarcted myocardium were traditionally termed *reciprocal changes*. Studies have indicated that such ST-T depressions usually reflect more extensive infarction. In the subacute phase, the abnormal Q wave representing myocardial necrosis begins to appear, but the T-wave vector still points toward the infarct zone (Fig. 42-1). In the fully evolved phase, the ST-T segment begins to diminish in amplitude and becomes coved or convex upward. It blends into the now symmetrically inverted T waves (see Fig. 42-1). The abnormal Q waves (>0.03 s in duration and more than 25 percent of the R-wave amplitude) appear during this stage. During the chronic phase (Fig. 42-1), there is generally resolution of the ST- and T-wave changes, with the only residual change being an abnormal Q wave. Although the ST-T segments again become isoelectric, they are frequently horizontal, with a sharp-angled ST-T junction, rather than exhibiting the normal concavity. Occasionally, in small inferior infarctions, even the abnormal Q waves resolve.

Posterior myocardial infarction occurs in the posterior left ventricular wall. An isolated true posterior infarction is quite uncommon, since such an infarction is usually associated with an inferior or lateral infarction. Since there are no electrocardiographic leads oriented toward the posterior left ventricular wall, the electrocardiographic changes of a true posterior infarction are seen as mirror-image representations in leads V_1 to V_3. Schamroth described the criteria for a true posterior infarction as follows: R waves of 0.04 s in lead V_1 and in contiguous right precordial leads with upright T waves, and, in the acute phase, ST-segment depression and an R/S ratio $\geq$1 in leads V_1 and V_2.[96] Usually, there are associated changes of an inferior or lateral infarction. As the infarction evolves, the ST-segment depression decreases and the upright T-wave amplitude increases. It is helpful to turn the ECG upside down and look at it from the back while holding it to a strong light. The changes in leads V_1 and V_2, which might be overlooked on a direct glance, are seen as abnormal Q waves, ST-segment elevation, and T-wave inversion when viewed from this perspective.

Similarly, electrocardiographic diagnosis of right ventricular infarction offers special challenges. Since right ventricular infarction generally occurs in the presence of inferior left ventricular infarction, the resulting ST-segment elevation is usually overwhelmed in the conventional precordial leads overlying the right ventricle (V_2 and V_3) by the ST-segment elevation in the opposing left ventricular myocardium on the inferior surface. The right ventricular electrical forces might be manifest in this setting as a diminution of the usual reciprocal ST-segment depression seen in the right precordial leads in inferior infarction. If the injury to the inferior wall is minimal, ST-segment elevation will occasionally be seen in V_2 through V_4 in the presence of right ventricular infarction.[97] Otherwise, ST-segment elevation must be sought in the right chest leads, V_1, and V_{3R} through V_{6R}. ST-segment elevation in these leads provides reasonably strong evidence for the presence of right ventricular infarction.[98] A postmortem study has shown that a 25 percent or greater involvement of the right ventricle was necessary to produce ST-T-segment elevation.[99] Atrial infarction is usually reflected in PR-segment elevation or depression and P-wave abnormalities and is frequently associated with supraventricular arrhythmias, as discussed later.[100]

The phenomenon of "ischemia at a distance" reflects the occurrence, in AMI with ST-segment elevation, of ST-segment depression in other, frequently reciprocal leads. It remains uncertain whether these changes represent true reciprocal changes or subendocardial ischemia in the area, but the presence of the finding is associated with a less favorable prognosis than its absence.[101,102]

Criteria for electrocardiographic diagnosis of AMI in various areas of the heart are discussed more fully in Chap. 11. In view of a lack of sensitivity and specificity of the chest pain history or of the ECG, confirmation of the diagnosis of AMI is based on elevated plasma levels of cardiac-specific isoenzymes.

PLASMA DIAGNOSTIC MARKERS

Tissue Distribution of MB-CK, Troponin T, Troponin I, and Myoglobin

Myocardial necrosis is associated with the release of a variety of macromolecules, including enzymes, myoglobin, and contractile proteins that have been evaluated as potential diagnostic markers for AMI. The use of CK and MB-CK has become routine and is highly sensitive, specific, and cost-effective for diagnosing myocardial infarction.[103] The use of total CK alone without MB-CK yields a similar sensitivity, but specificity is markedly lower, in the range of 70 percent.[104] The use of total CK as a diagnostic marker for myocardial infarction is discouraged. CK consists of two monomers, each having a molecular weight of 43,000. The isoenzymes of CK are formed by the association of two M monomers (MM-CK), which predominate in muscle (hence the name); or of two B monomers (BB-CK), which predominate in the brain and internal visceral organs; and a hybrid form (MB-CK), found in the heart, composed of one M subunit and one B subunit. The isoenzymes MM, MB, and BB are located in the cytoplasm of the cell. There are separate genes for each of the monomers, which have been isolated, cloned, and sequenced.[105,106] About 5 percent of cellular MM-CK activity is associated with the M line of the sarcomere in both heart and skeletal muscle and a significant amount is in the Z line in heart muscle.

Fifteen percent of the CK in the myocardium is in the form of MB-CK, which provides for its sensitivity and specificity as a diagnostic marker of AMI. Several investigators have found small amounts of MB-CK in normal adult skeletal muscle,[107,108] whereas others have failed to detect any cytosolic CK other than MM-CK.[109,110] MB-CK is alleged to increase (1 to 5 percent) in skeletal muscle following injury such as chronic exercise,[111,112] inflammation,[113] trauma,[114] and electrical injury.[115] In hereditary muscle diseases, such as Duchenne muscular dystrophy (DMD), there is also increased MB-CK in the range of 1 to 5 percent. During the first 6 weeks of life in utero, only BB-CK is synthesized, while at about the eighth week, M-CK synthesis is induced and rapidly supplants the B-CK in skeletal and cardiac muscle, such that by about the twelfth week, MM-CK predominates.[116,117] It is believed that in DMD, the retained expression of the B-CK reflects the abnormal development of these muscles. It is postulated that in the case of the reaction to muscle injury, undifferentiated skeletal muscle cells differentiate to form mature skeletal myocytes and thus repeat the developmental program of fetal skeletal muscle, but the expression of B-CK is transient.[118] In the adult human heart, 15 percent of total CK activity is MB-CK and the remainder is MM-CK. Myoglobin, with a molecular weight of 17,000, is ubiquitously distributed throughout cardiac and skeletal muscles.[119]

Two new diagnostic cardiac markers have been introduced: troponin T and troponin I,[120] which are part of the sarcomere complex. Troponin T has a molecular weight of 38,000, and troponin I, 23,000. There are three genes for each of the troponins that encode for slow and fast skeletal and cardiac muscle.[121] Cardiac troponin I has 31 amino acids, which are not present in the skeletal forms. The recognition site of the antibody used in the assay is in the cardiac-specific region, which makes the test very specific as a marker for myocardial injury,[122] and since normal plasma levels of troponin I are near 0, it is also very sensitive. Furthermore, studies indicate that cardiac troponin I is not upregulated in skeletal muscle with hypertrophy or injury and the skeletal form is not upregulated in the heart with hypertrophy or injury.[123] Cardiac troponin T has 11 amino acids not present in the skeletal forms, which has permitted the development of a specific diagnostic test.[121] Troponin T has similar sensitivity to troponin I but the first generation assay had less specificity, while the second generation assay appears to have similar specificity to that of troponin I.[121]

Temporal Profiles of MB-CK, Myoglobin, Troponin I, and Troponin T Released into Plasma

Plasma MB-CK activity following myocardial infarction is significantly elevated, such that reliable diagnostic sensitivity (>90 percent) is reached within 12 to 16 h of the onset of symptoms. Maximal levels[124] of MB-CK are reached between 14 and 36 h, with a return to normal levels occurring after 48 to 72 h (Fig. 42-2). In patients with minimal cardiac injury, such as occurs in non-Q-wave infarction or following effective early reperfusion, plasma MB-CK activity reaches maximal activity at about 12 to 15 h. In contrast, after Q-wave infarction with reperfusion, it reaches maximal activity at an average of 28 h. The plasma temporal profiles of troponin I and troponin T are very similar to those of total CK and MB-CK. Troponin I and troponin T are released into the plasma so that reliable diagnostic sensitivity (>90 percent)

is reached by 12 to 16 h and maximal activity is reached by 24 to 36 h. The levels return to normal within 10 to 12 days.[124] Plasma myoglobin is increased within 2 h of the onset of symptoms and remains increased for at least 7 to 12 h.[119]

Early Diagnosis (6 to 10 h of Onset): MB-CK Subforms and Myoglobin

In the United States, over 5 million patients with chest pain go annually to the emergency department, but only about 10 percent with chest pain will subsequently be shown to have myocardial infarction.[124] About 50 percent of patients will have cardiac ischemia, 10 percent will have nonischemic cardiac pain, and about 30 percent will have pain of noncardiac origin.[124] It is important to have an early diagnosis to determine the initial therapeutic regimen and whether hospital admission is needed. In the United States, it is estimated that over $12 billion per year[125] is spent unnecessarily to exclude myocardial infarction in patients admitted to the hospital with chest pain without infarction. Thus, early, rapid diagnosis is required to triage patients, reduce costs, and select appropriate therapy in spite of the difficulty in distinguishing cardiac ischemia from infarction based on the patient's history, physical examination, and the ECG, as noted. This difficulty is emphasized by the observation that over 50 percent of AMI patients in the United States[126] have nonspecific ST-segment changes (non-Q-wave infarction) rather than ST-segment elevation (Q-wave infarction). The only specific electrocardiographic finding on admission for myocardial infarction is the recent development of ST-segment elevation or left bundle branch block. It is estimated that less than 50 percent of patients with AMI will have a diagnostic ECG, which represents only 5 percent of the total patients presenting with chest pain; thus, there is a need for an early objective marker (within 6 h of onset).[71] The ideal diagnostic test should have an assay performance time that is brief, and the marker must have a highly reliable negative predictive value, since only 10 percent of patients will have infarction, as noted. While a false-positive range of 5 to 10 percent is acceptable, a desirable false-negative range is 1 to 2 percent. Assessment of the plasma profile of the markers shows only two plausible candidates, namely, MB-CK subforms and myoglobin.

It was recognized for some time that MM and MB-CK, though present in tissue in single forms, exhibit different forms upon release into the circulation, as detected by electrophoresis.[127] In 1982, it was shown that upon release into the circulation, MM-CK is converted into three forms: MM-3, MM-2, and MM-1, and MB-CK is converted into MB-2 and MB-1, due to the proteolytic activity of carboxypeptidase-N, an enzyme present in the blood of all vertebrates.[128,129] Carboxypeptidase-N cleaves the terminal amino acid, lysine, from the M subunit of the MB-CK, which is positively charged, leaving the remaining molecule more negatively charged (MB-1). The more negative form (MB-1), upon electrophoresis, separates from the parent tissue form (MB-2), giving rise to the two forms of MB-CK in plasma. A new technique utilizing 1400 V, which provides separation of the MB subforms within about 6 min,[130] is coupled with automated densitometric quantification; this produces a value for MB-2 activity, the plasma ratio of MB-2 to MB-1, and total MB-CK activity.[131] The current assay for the MB-CK subforms is completely automated and requires about 25 min. In the plasma, the MB-CK subforms are in equilibrium, with a ratio of MB-2 to MB-1 of 1 to 1. Normally, the baseline plasma MB-CK activity is in the range of 2 to 4 IU/L, or a protein concentration of 3 to 5 ng/L. Thus, for a reliable diagnosis of myocardial infarction based on total MB-CK activity, one requires an increase above 9 IU/L, or, for protein, above 7 ng/L. When infarction occurs, MB-2, the tissue form, is initially released into the circulation in minute amounts so that total plasma MB-CK activity remains within the normal range, but the ratio of MB-2 to MB-1 changes markedly and provides the basis for an early diagnosis of myocardial infarction. In a large, blinded, prospective study involving 1110 patients presenting consecutively with chest pain, it was shown that MB-CK subforms reliably diagnosed myocardial infarction within 6 h of onset of symptoms.[131]

The introduction of troponins T and I necessitated the need to provide comparative diagnostic sensitivity and specificity for all of the markers. A large, multicenter, prospective, double-blind study, the Diagnostic Marker Cooperative Study (DMCS), was performed, comprising 1004 patients admitted consecutively with chest pain.[124] A serial analysis of all markers (MB-CK activity, MB-CK mass, MB-CK subforms, myoglobin, and cardiac troponin T and I) was performed on a sample taken on admission, at 1 h, every 2 h for up to 6 h from onset, and subsequently every 4 h for up to 24 h. Every effort was made to obtain the time of onset of symptoms. In keeping with previous observations, only 11 percent of the patients with chest pain were subsequently documented to have infarction (n = 118), of whom less than 47 percent had a diagnostic ECG (43 percent had ST-segment elevation and 4 percent had a left bundle branch block), with

the remainder having nonspecific ST-T changes (non-Q-wave infarction). Cardiac ischemia accounted for 51 percent and nonischemic cardiac pain for another 9 percent, while in 29 percent the pain was of noncardiac origin. The diagnostic sensitivity and specificity of each of the markers are indicated in Table 42-3. MB-CK subforms afforded a sensitivity and specificity of 91 percent for the diagnosis of infarction within 6 h of the onset of symptoms. Myoglobin had a sensitivity of 83 percent during the same interval. The negative predictive value of MB-CK subforms within the initial 6 h of onset was 97 percent and that of myoglobin was 95 percent. Thus, if a patient has a negative MB-CK subform test at 6 h after the onset of symptoms, one can reliably conclude that the patient does not have infarction. During the same interval of 6 h from onset, the total MB-CK (activity or mass assay) and troponins T and I afforded a sensitivity of only 65 percent. A major observation from this study-with significant diagnostic, therapeutic, and cost-saving implications-is the finding that MB-CK subforms correctly diagnosed 92 percent of the patients with myocardial infarction within 60 min of arriving in the emergency department. This was based on the results of the sample collected on admission to the emergency department and on a second sample collected 1 h later (Table 42-4). For the same two samples, however, myoglobin had a sensitivity of 83 percent. The mean time required to make the diagnosis of myocardial infarction using MB-CK subforms was 1.2 h ± 20 min from arrival in the emergency department, and a similar time was required to exclude those without infarction. It is evident from the data in Table 42-3 that total MB-CK, troponin T, and troponin I have high sensitivity and specificity for the diagnosis of myocardial infarction 12 to 16 h from the onset of symptoms. It is noteworthy that the sensitivity of myoglobin decreases after about 7 or 8 h because of rapid renal clearance and thus may not be reliable after 10 to 12 h, particularly in patients with minimal injury.

Table 42-4: Diagnostic Sensitivity of Myoglobin and MB-CK Subforms on Admission and 1 h Later

Markers	Sample on Admission (%)	Sample 1 h Later (%)
MB-CK subform	67	91
Myoglobin	63	78

Sampling Intervals and the Diagnosis of Infarction

In patients presenting within the first 10 h of the onset of myocardial infarction, the appropriate marker is either MB-CK subforms or myoglobin, since other markers lack the necessary sensitivity. It is recommended that a blood sample be taken immediately on admission, 1 h later, then every 2 h until 6 h from the onset of symptoms, and then, if positive, every 6 h for 24 to 48 h. The MB-CK subform assay provides a diagnosis based on the first two samples (initial and 1 h) in more than 90 percent of the patients with infarction. Once a sample is positive, one can sample every 6 h for 24 to 48 h. If the sample shows normal values for the MB-CK subforms, one must sample until 6 h from the onset of symptoms to reliably exclude infarction, at which time sampling can be discontinued. Sampling for 24 to 48 h in patients with positive MB-CK subforms is optional, but it is recommended for the following reasons: to obtain maximal total plasma MB-CK activity as a rough index of the extent of damage; to follow the decline in MB-CK subform activity as a baseline for subsequent procedures often performed, such as cardiac catheterization or percutaneous transluminal coronary angioplasty (PTCA); and to facilitate detection of early reinfarction, which accounts for 30 to 40 percent of in-hospital deaths in patients recovering from AMI. If the myoglobin is analyzed, a similar sampling algorithm is followed except that the interval required to exclude or include infarction with myoglobin may be longer, since with MB-CK subforms, 90 percent of patients with AMI are diagnosed within 60 min (two samples), whereas only 80 percent over the same interval will be diagnosed with myoglobin. Patients presenting 10 to 12 h or later after the onset of symptoms should have a sample taken on admission; if this is positive, it should be repeated every 6 h for 24 to 48 h. Total MB-CK, troponin T, or troponin I in this time frame will provide the desired diagnostic sensitivity and specificity. Normal total plasma MB-CK activity or protein concentrations at 12 to 16 h from the onset of symptoms excludes infarction with 95 to 100 percent reliability, as does a normal troponin T or I. Plasma myoglobin is not a reliable marker 8 to 10 h after the onset of symptoms. The upper level of normal for MB-2 is ≥2.6 IU/L, with a ratio of MB-2 to MB-1 of ≥1.7. The upper limit of normal for myoglobin is 85 ng/mL. The upper limit of total MB-CK activity is 9 IU/L, and for protein (mass) assays, 7 ng/mL. The upper limit of

normal for troponin T is 0.1 ng/mL and for troponin I 1.5 ng/mL. The following guidelines are suggested as enzymatic criteria for the diagnosis of myocardial infarction (Table 42-5).

Table 42-5: Enzymatic Criteria for Diagnosis ofMyocardial Infarction

Serial increase, then decrease of plasma MB-CK, with a change >25% between any two values
MB-CK >10-13 U/L or >5% total CK activity
Increase in MB-CK activity >50% between any two samples, separated by at least 4 h
If only a single sample available, MB-CK elevation > twofold
Beyond 72 h, an elevation of troponin T or I or LDH-1 > LDH-2

If there is a serial elevation in plasma MB-CK levels followed by a decrease to baseline, with a change of 25 percent or more between the two values or plasma MB-CK activity increases 50 percent or more between two samples separated by at least 4 h and not more than 12 h:

1. Preferably, the diagnosis is made on the basis of no fewer than two samples in a 24-h period, separated by at least 4 h.
2. If only a single sample is present, the diagnosis must be made on the basis of an elevation above normal by at least twofold.
3. In patients admitted beyond 72 h from the onset of infarction, troponin T or I is preferred, since MB-CK levels may have returned to normal. The preceding criteria for MB-CK have not been evaluated for troponin T or I but would probably serve as guidelines until further information is available. These principles are incorporated into the protocols for triaging patients in the emergency department, as illustrated in Fig. 42-3.

Limitations to Myoglobin, MB-CK, and Troponins I and T

Elevated plasma MB-CK as a diagnostic marker for myocardial infarction is associated with a very low incidence of false-negative results if samples are collected frequently and appropriately within 48 to 72 h of the onset of symptoms. However, false-positive results do occur, since trace amounts of MB-CK can be released from tissues other than the heart. Skeletal muscle injury may induce the synthesis of MB-CK and has been documented after crush injury,[114] electrical injury,[115] dermatomyositis and polymyositis,[113] and DMD,[132] as well as in professional athletes and marathon runners.[111,112] If one suspects that elevated plasma MB-CK activity is due to skeletal rather than cardiac muscle, the following should be considered:

1. The appropriate clinical setting, namely, skeletal muscle disease or trauma.
2. An atypical time course for the increase and decrease in plasma MB-CK activity, particularly if prolonged, as one might see in inflammatory disorders.
3. If MB-CK accounts for less than 5 percent of the total CK activity, then a skeletal muscle source should be suspected. Since tissues that contain MB-CK (other than the myocardium), such as skeletal muscle, contain only trace amounts (1 to 2 percent), elevated plasma MB-CK indicative of myocardial infarction should exceed 5 percent of total activity. At the time of peak plasma CK resulting from myocardial infarction, MB-CK levels usually make up 10 to 15 percent of the total activity.
4. A marked elevation of total CK activity of 20- to 30-fold suggests that the cause is more likely to be skeletal muscle injury. Hypothyroidism is associated with elevated levels of both total CK and MB-CK due to diminished clearance.[133] Occasionally, one sees what is referred to as macro CK-1, a complex of CK and macroglobulins, which migrates in the position of MB-CK upon electrophoresis[134,135] and results in a false-positive diagnosis of AMI. Macro CK-1 is common in elderly women and in patients who are chronically ill, with an overall stated incidence of 1.6 percent in hospitalized patients.[135] This is not a problem for assays utilizing MB-CK monoclonal antibody, as is currently the case for most MB-CK assays. Electrocardioversion causes a significant elevation

of total CK activity, but unless the procedure is repeated several times, it does not elevate plasma MB-CK. MB-CK is elevated in chronic renal failure;[136] however, it does not show any changes upon serial analysis and thus is not a significant diagnostic problem.

Troponin I has not been found to be elevated in patients with normal skeletal muscle, despite severe exercise or injury,[122] or in the blood of marathon runners.[137,138] Furthermore, in a study involving 100 patients undergoing noncardiac surgery with extensive skeletal muscle injury, only 1 patient had a slight elevation of cardiac troponin I.[139] Troponin I is not elevated in chronic renal failure.[122] *Troponin I is a more specific marker than MB-CK in patients with myocardial infarction and concomitant skeletal muscle injury, such as that following noncardiac surgery or severe muscle trauma.* An increase in troponin T has been reported in patients with polymyositis/dermatomyositis without cardiac involvement.[140] Wu et al.[141] reported that troponin T had lower specificity than MB-CK for myocardial damage. However, the antibody used in the assay for troponin T is reported to have a 3.6 percent cross-reactivity with skeletal troponin T,[142] which may account for this lack of specificity. A recent assay with a more specific monoclonal antibody shows similar specificity to that of troponin I.[121]

Rationale for Selecting a Diagnostic Marker

In view of the abundance of plasma markers and the increasing need to reliably triage patients with chest pain in a cost-effective manner, a careful choice must be made of which plasma marker or combination of markers will be utilized routinely. In selecting a marker for early diagnosis upon admission to the emergency department, there is essentially a choice between MB-CK subforms and myoglobin. MB-CK subforms, as compared with myoglobin, provide greater sensitivity as well as greater specificity overall for the early diagnosis of AMI. There has been extensive experience with the MB-CK subforms, while routine use of myoglobin for the diagnosis of infarction is minimal. Nevertheless, if patients with trauma are avoided, the specificity of myoglobin is quite acceptable, and it is the next best alternative for an early diagnosis, as indicated in Tables 42-3 and 42-4. Both assays are automated and simple to perform, requiring only about 25 min, and are identical in cost. For the diagnosis of patients presenting 10 h or later after the onset of symptoms, total MB-CK, which has been the standard for more than two decades, is extremely sensitive and specific. However, cardiac troponin I or cardiac troponin T, since they are not normally present in the blood and do not appear to be present in skeletal muscle, provide greater specificity than MB-CK in those clinical conditions in which there is concommitant skeletal muscle injury. It is also claimed that troponin I and T may provide increased sensitivity over that of MB-CK since they are not normally present in the blood; however, further studies are required before the claim of greater sensitivity can be accepted. The time required to assay each of these latter three markers is about 25 min, with identical costs. The choice of marker or markers used routinely may depend in part on the various tests with which the laboratory personnel are acquainted. However, there is no reason, based on diagnostic sensitivity and specificity, to assay all of these markers; in addition, the cost would be prohibitive. A single assay for both early and late diagnosis is the MB-CK subforms, which provide an early diagnosis and from which total MB-CK can be derived for the late diagnosis. Another is MB-CK subforms for early diagnosis, plus either troponin I or T for late diagnosis. Myoglobin provides an early diagnosis but is less specific and less sensitive than MB-CK subforms. In clinical situations where there is concommitant skeletal muscle involvement, MB-CK, if elevated, is less than 5 percent of total CK activity and is usually not a diagnostic problem. However, troponin I or T is more appropriate in those clinical conditions. The data from the DMCS indicate no advantage to simultaneously analyzing both MB-CK subforms and myoglobin for early diagnosis; similarly, for late diagnosis, there is no advantage to analyzing multiple markers.

Diagnosis of Acute Myocardial Infarction in Patients 48 h or more from the Onset of Symptoms

In patients admitted 48 to 72 h after the onset of symptoms, particularly when associated with minimal myocardial damage, plasma MB-CK may have returned to normal levels. In this situation, it has been traditional to utilize LDH isoenzymes, since LDH-1 activity peaks between 48 and 72 h and remains elevated for 10 to 14 days, but the preferred diagnostic marker is now troponin I or T. It is recommended that LDH, LDH isoenzymes, and SGOT (AST) be discontinued as diagnostic markers for AMI.

Diagnostic Assessment of Patients Undergoing Fibrinolytic Therapy or Angioplasty

Patients who receive fibrinolytic therapy or early angioplasty (within 4 to 6 h) for treatment of infarction should be assessed hourly for plasma MB-CK activity or one of the troponins for the first 4 to 6 h, then every 6 to 8 h for 36 h, with sampling reinitiated if chest pain or other features occur to suggest reinfarction. Following successful reperfusion, MB-CK is usually elevated within 30 to 60 min of the reperfusion and plasma activity reaches maximum levels within 10 to 15 h. Studies have shown that 15 to 20 percent of patients undergoing elective PTCA have elevated plasma MB-CK,[143-145] and these individuals have a worse prognosis over the subsequent 6 months.[146] It remains controversial whether routine sampling for MB-CK should be performed after elective PTCA, since changes in treatment based on increased MB-CK have not been assessed. In patients with triple-vessel disease or where complications are more likely, routine sampling with MB-CK subforms is recommended for 6 h; it should be discontinued if the results are normal. If they are positive, sampling should continue for at least 24 h, and the patient should be treated as having had myocardial damage. It is now recognized that increased plasma levels of MB-CK reflect cardiac cell death, and it is likely though not proven that cardiac troponin I and T do so also.

Diagnosis of Early Reinfarction

Diagnosis of early reinfarction (within 24 to 48 h) is difficult, since it represents an elevation superimposed on an already elevated plasma marker.[147,148] However, if MB-CK has returned to normal, then the diagnosis is relatively easy, since one sees a secondary increase in plasma MB-CK activity. Detection of early reinfarction with a secondary elevation in plasma MB-CK in patients who undergo successful thrombolysis is more appropriate, since MB-CK activity usually peaks within the first 10 to 15 h and returns to normal by 36 to 48 h. A secondary elevation of MB-CK activity 36 to 48 h after the onset of symptoms provides for a sensitive and specific diagnosis of reinfarction. In the latter situation, reinfarction is defined as an increase of 50 percent or more in the plasma MB-CK activity above the preceding baseline (mean of the two preceding samples) in at least two samples separated by a minimum of 4 h within a 24-h interval, with an absolute value of ±9 IU/L or 7 ng/L in at least one sample.[149] If the MB-CK activity is on the downslope from the antecedent infarction, a 25-percent increase is considered diagnostic; however, this is always less reliable than a secondary elevation after the return of MB-CK activity to baseline. These criteria were found to be reliable in three large clinical trials.[80,134,150] Confirmation of reinfarction occurring early, however, is more appropriately diagnosed using the MB-CK subforms. The MB-2 is near normal by 18 to 24 h and usually peaks at 10 to 12 h, so a well-defined downslope is apparent after 12 to 16 h. The other markers, cardiac troponin T and troponin I, since they remain elevated for 10 to 14 days, and, thus, because of the background, lack the necessary sensitivity. Myoglobin, since it returns to normal early after onset, is also a sensitive marker, but because of venipuncture or other minor skeletal muscle trauma commonly occurring in the hospital setting, makes it nonspecific.

Prognostic Role for Biochemical Markers in Assessment of Unstable Angina

Several studies have shown that patients presenting with the clinical diagnosis of unstable angina and minor elevations in MB-CK, troponin T, or troponin I have a more adverse outcome with respect to clinical events such as death, myocardial infarction, or the need for revascularization. In the GUSTO IIA trial,[151] of 835 patients with unstable angina, 36 percent had elevated troponin T and experienced increased mortality and other clinical events. Similarly, in the TIMI III trial,[152] of 1404 patients with non-Q-wave infarction and unstable angina, 41 percent had elevated troponin I and experienced increased mortality and other clinical events. In a study involving 593 patients with unstable angina, those with elevated MB-CK had increased mortality and other clinical events.[153]

It is now recommended that patients with unstable angina be assessed with one or more of these markers; however, treatment based on these indications and its long-term outcome have not been assessed. In the DMCS study,[154] there were 178 patients with unstable angina (rest pain of increased frequency or severity); the results of the various markers are shown in Fig. 42-4.[154] This is the only study in which the sensitivity of all of the markers has been compared. There is a dilemma with respect to the interpretation of elevated plasma markers in patients with unstable angina. Does this mean that these proteins are released due to ischemia (reversible injury) or that, in fact, limited infarction has occurred? Data[155] indicate release of CK reflects irreversible injury. In a series of conscious animal studies, it was shown that 20 min of coronary artery occlusion is consistently associated with increased plasma CK activity and, on light and electron microscopy, myocardial necrosis. In contrast, animals undergoing 10 min of coronary occlusion

who exhibited severe ischemia-as shown by ST-segment elevation, depletion of myocardial glycogen, and cell swelling-had no increase in plasma CK. In the group of animals undergoing 15 min of coronary occlusion, only 30 percent had increased plasma CK activity, and each of these also showed microinfarction of the myocardium as detected by light and electron microscopy.[155] This finding-coupled with the observation that patients with proven obstructive coronary disease during exercise-induced ischemia, as documented by thallium scintigraphy, exhibited no increase in plasma MB-CK or MB-CK subforms-provides the basis for interpreting elevated plasma MB-CK levels as reflective of irreversible injury.[156] Fibrinolytic therapy has been shown to be detrimental[157] in unstable angina; however, in non-Q-wave infarction, when given on an average of 9 h from onset, it showed no beneficial or detrimental effect. Early fibrinolytic, antithrombin, or antiplatelet therapy in patients with positive MB-CK subforms but ST-segment depression has yet to be evaluated. Similar studies have not been performed to determine whether increased troponin I or troponin T reflects cell death, although, since they are structural sarcomeric proteins, it is highly likely that their release does reflect cell necrosis. Since the molecular weight of troponin I is 23,000, however, and that of troponin T is 39,000, both of which are significantly less than that of MB-CK (82,000), leakage with myocardial ischemia will have to be excluded by appropriate studies.

Diagnosis of Myocardial Infarction after Surgery

Myocardial infarction after noncardiac surgery is also reliably determined from serial analysis of plasma MB-CK, MB-CK subforms, troponin T, or troponin I every 4 to 6 h.[104,158] There is a marked elevation of other enzymes due to tissue trauma, including total CK, but MB-CK, troponin T, and troponin I are highly specific to the myocardium. There is at least one study[139] showing that troponin I is more reliable than either total MB-CK or troponin T for the diagnosis of AMI in this setting. In the setting of cardiac surgery, however, MB-CK, like other cardiac markers, is almost always elevated due to manipulation and involvement of the myocardium and thus is not a reliable diagnostic index.[159,160] Nevertheless a severalfold elevation of MB-CK postoperatively is highly suggestive of periprocedural infarction, even in the absence of Q-waves, although it lacks specificity as a sole criterion. Multifold elevations of troponin T or troponin I probably have the same implications postoperatively.

Diagnosis of Previous Infarction

Determining whether a patient has had a remote infarction to account for the subsequent development of cardiac failure or other clinical conditions can be difficult. Until recently, the only reliable means of diagnosis was the presence of Q waves on the ECG. Since less than 50 percent of infarctions develop Q waves and since a significant percentage of these Q waves disappear with time, the ECG can be nonspecific and unreliable in diagnosing remote infarction.[161,162] Thallium-201 (^{201}Tl) perfusion scanning has been shown to be extremely reliable, sensitive, and specific in diagnosing remote infarction.[163]

Other Biochemical Alterations

The stress of myocardial infarction elicits numerous hormonal and metabolic responses. For example, both catecholamines and growth hormones are elevated. It is noteworthy, however, that serum cholesterol and lipoprotein fractions are relatively unchanged in the initial 1 to 2 days but decrease significantly over subsequent days and weeks. In establishing the baseline levels of these values for guiding future therapeutic interventions, measurements should be performed on admission or should be delayed for 6 to 8 weeks.[164,165] It should also be recognized that if myocardial infarction is occurring in individuals who have hypertension or for any reason are on medications such as diuretics, there may be significant electrolyte abnormalities that need to be treated, particularly in view of the increased propensity for arrhythmias, as with hypokalemia or alkalosis. The other abnormality seen on occasion is that of an increase in blood glucose following myocardial infarction, which, in some cases, particularly in patients with mild or moderate diabetes, may be associated with the development of significant ketoacidosis.[166,167] Not infrequently, it has also been shown that in the early days following myocardial infarction, the glucose tolerance curve is abnormal. It returns to normal after a few weeks. The white blood cell count is usually mildly to moderately elevated in 3 to 5 days.

Noninvasive Imaging in Acute Myocardial Infarction

CHEST ROENTGENOGRAM

The chest roentgenogram (x-ray) provides important information in the evaluation of chest pain and contributes to an integrative assessment of the clinical situation. Its usefulness in the early stages of evaluation of a patient with chest pain is frequently compromised by the fact that one is usually dealing with a portable study performed in the emergency department or in the CCU. Nonetheless, the chest film may assist in excluding causes of chest pain such as pneumothorax, pulmonary infarction with effusion, aortic dissection, skeletal fractures, and so on. In the patient with acute infarction, the chest film can be useful in establishing the presence of pulmonary edema, in assessing heart size to assist in determining whether or not cardiomegaly is present, and in deciding whether heart failure or myocardial or valvular disease is acute or chronic. It must be emphasized that severe left ventricular failure can be present without manifesting pulmonary edema on the chest x-ray and that, conversely, improvement in the x-ray appearance can lag behind hemodynamic resolution of pulmonary congestion (see Chap. 12).

ECHOCARDIOGRAPHY

Because of the quality of the images provided, their wide availability, and the portability of these modalities, two-dimensional and Doppler echocardiography have become very useful tools in the assessment of the patient with suspected AMI[168-170] (see also Chap. 13). Echocardiography is particularly valuable in assessing the patient with a nondiagnostic ECG. The presence of a regional wall motion abnormality provides strong supportive evidence of acute coronary ischemia and is generally present in transmural or Q-wave myocardial infarction.[171-174] Wall motion abnormalities are less common in non-Q-wave infarction but are still present in the majority of cases. Nonetheless, small infarctions can be missed, and a wall motion abnormality may not necessarily be acute.[175] Echocardiography also provides an assessment of ventricular function; it is useful in predicting the prognosis[176] and in diagnosing right ventricular infarction.[177] It can also provide information concerning alternative diagnoses such as aortic dissection and, coupled with Doppler, can provide information on such complications as ruptured chordae tendineae with mitral regurgitation and ventricular septal defect[178] (see Chap. 13). It is useful in detecting ventricular thrombus and pericardial fluid. Thus, echocardiography is extremely useful in the initial assessment of AMI. General guidelines on its clinical use, including those for myocardial infarction, have been published.[179]

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) offers great promise in assessing AMI (see Chap. 18A). Its major limitation is logistic, in that it requires transporting patients to the imaging facility-a major concern in the case of the acutely ill. It is potentially useful in the assessment of infarct size and viable myocardium and the extent of the ischemic insult as well as in estimating perfusion to ischemic and nonischemic areas.[180-182] Currently, MRI does not have a defined role in the routine management of AMI.

COMPUTED TOMOGRAPHY

Computed tomography (CT) is a powerful tool for cardiac imaging that gives high-resolution structural information (see Chap. 17). Ventricular thickness and dimensions can be assessed.[183] Also, CT is highly sensitive for detecting a left ventricular thrombus.[184] It has the same logistic limitations as MRI in the management of AMI. It does not have a routine role in the management of infarction. Whether electron-beam CT, with its very rapid acquisition times, can have a role in routine management requires further investigation (see Chap. 17).

RADIONUCLIDE SCINTIGRAPHY

The radionuclide techniques available for the diagnosis of AMI are discussed in detail in Chap. 16, and are summarized in Table 42-6.[185] Guidelines for the use of cardiac radionuclide scanning have been published and suggest that the indications for its use in the diagnosis of acute infarction are limited to the unusual case in which history, electrocardiographic changes, and plasma markers are unreliable or unavailable.[185] There

is no class I indication in the acute setting, and routine diagnostic use is not indicated (class III).[1,185] Radionuclide scintigraphy may have a diagnostic role in certain patients with right ventricular infarction by showing localized contractile abnormalities[186] or ^{99m}Tc pyrophosphate uptake (class IIa).[185]

Table 42-6: Uses of Radionuclide Testing in Acute Myocardial Infarction

DIAGNOSIS			RISK ASSESSMENT		
Indication	Test	Class	Indication	Test	Class
1. Right ventricular infarction	Rest RNA	IIa	1. Residual ischemia	Stress (exercise/pharmacological) thallium with redistribution	I
	^{99m}Tc pyrophosphate	IIa		Stress (exercise/pharmacological) sestamibi with redistribution	
2. Infarction not diagnosed by standard means - early presentation with successful reperfusion	Rest myocardial perfusion imaging	IIb	2. Myocardial infarct size	Tomographic thallium	IIa
	^{99m}Tc pyrophosphate	IIb		Tomographic sestamibi	IIa
3. Infarction not diagnosed by standard means - late presentation	^{99m}Tc pyrophosphate	IIa	3. Hibernating myocardium	Early, late thallium	IIa
4. Routine diagnosis	Any technique	III	4. Ventricular function	RNA	I

ABBREVIATIONS: RNA = radionuclide angiography; ^{99m}Tc = technetium 99m.
SOURCE: The ACC/AHA task force,[185] with permission.

ASSESSMENT OF INFARCT SIZE BY IMAGING

Infarct size can be assessed by echocardiography (see Chap. 13), computerized tomography (see Chap. 17), magnetic resonance imaging (see Chap. 18A), positron emission tomography (see Chap. 19), or radionuclide scintigraphy (Table 42-6[185]) (see Chap. 16). ^{99m}Tc sestamibi with tomographic imaging has been used to quantitate infarct size,[187,188] and shown to be inversely related to the patient's outcome.[189,190] Thallium 201 can also be used to measure infarct size.[185]

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Chapter 42: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PREHOSPITAL CARE

Recommendations[1]:

Class I

1. Availability of 911 access
2. Availability of an emergency medical services (EMS) system staffed by persons trained to treat cardiac arrest with defibrillation, if indicated, and to triage patients with ischemic-type chest discomfort

Class IIa

1. Availability of a first-responder defibrillation program in a tiered response system
2. Education from health care providers to patients/families about the signs and symptoms of AMI, about accessing EMS, and about medications

Class IIb

1. Use of 12-lead telemetry
2. Prehospital thrombolysis in special circumstances (e.g., transport time is greater than 90 min)

As mentioned previously, modern in-hospital care of the AMI patient has resulted in a substantial reduction in mortality. Some 40 to 65 percent of deaths from AMI, however, occur within an hour of the onset of symptoms and prior to arrival at a hospital.[191,192] Most of these deaths are attributable to ventricular fibrillation (VF).[193] To achieve a further substantial decrease in the mortality rate, it will be necessary to reduce the incidence of deaths outside the hospital.[194] Since, as noted, the earlier thrombolytic therapy can be initiated in eligible patients, the better the outcome, it is also essential to bring patients with chest pain into the medical care system as soon as possible because of the need to shorten the time between the onset of symptoms and the initiation of thrombolytic therapy. To that end, in the United States, the National Heart, Lung and Blood Institute of the National Institutes of Health has instituted the National Heart Attack Alert Program as a coordinated plan to extend the ACC/AHA guidelines promoting rapid identification and treatment of patients with AMI.[195,196]

Recognition and Management

A further reduction in the mortality rate will require the combined efforts of the patient, bystanders, minimally trained "first responders" who are capable of applying defibrillation therapy, and/or paramedics as well as the patient's physician. It has been established that a prolonged delay time in responding to a patient's symptoms is the rate-limiting step in defining the prehospital phase of myocardial infarction. Mean delay time in such response is almost 3 h.[197] Most of this time is consumed in decision making, while failing to recognize or acknowledge the seriousness of the problem.[198] Additional components of the delay between the onset of

symptoms and the initiation of definitive therapy involve prehospital evaluation, treatment, and transport time and the time involved with the diagnosis and initiation of treatment in the hospital. The National Registry of Myocardial Infarction found, in a review of 48,128 patients with confirmed AMI, that the average duration of the prehospital phase, defined as onset of chest pain to hospital presentation, was 5.1 h.

STRATEGIES TO REDUCE DELAY

Patient-specific issues for decreasing the delay in seeking assistance primarily involve education. The patient must perceive the symptoms, recognize their possible significance, and conclude that medical help is appropriate. For some patients, the decision time is prolonged because of a lack of knowledge. It is interesting, however, that the length of time patients take to get help is not dependent on educational level, occupation, socioeconomic class, or past history of cardiac disease. In fact, patients with a past history of myocardial infarction or angina have an unexpectedly long decision time,[199] a situation that must be viewed, at least in part, as a failure by physicians to educate patients with established coronary artery disease as to the appropriate response to a change in or reappearance of their symptoms. In other cases, the decision time is prolonged by denial or by "diagnostic trials" with household remedies, patent medications, or previously prescribed drugs. It has been noted that only 10 percent of patients arriving at the hospital within 1 h of the onset of pain utilized nonprescription medications, while 41 percent of those arriving after 12 h did so.[191] The remainder of the delay time is consumed by "human factors," including the time a patient takes to modify existing social obligations and to prepare for going to the hospital. There is evidence that public education can reduce the time required for decision making.[198] It follows that effective efforts by the physician and his or her staff in educating patients with coronary artery disease will have similar effects in inducing appropriate responses to ischemic coronary symptoms. Prodromal symptoms occur in about two-thirds of patients with AMI, as discussed previously, and patients must be taught to recognize them.[194] Patients and their families must be given a specific plan of action after the recognition of symptoms that includes medications to be taken (nitroglycerin and possibly aspirin), mode of transportation to the hospital, and the location of the nearest hospital that offers emergency cardiac care. It is desirable that coronary patients have a copy of their resting ECG with them. They should be instructed not to delay by attempting to contact their physician and should be shown how to use the EMS system and how to contact it (911 in the United States). As opposed to personal transportation, utilizing EMS is desirable, because it permits the earliest possible access to expertise in defibrillation and resuscitation and facilitates evaluation in the field to prepare the hospital to receive the patient, as discussed later. The use of the EMS usually decreases the delay in initiating definitive care.[195] Since the capabilities of the EMS vary by locale, the physician must be familiar with the system in the patient's home area.

Instructions concerning medications to be taken at the onset of symptoms should be individualized. In general, patients are instructed to take nitroglycerin immediately at the onset of angina or a recognized anginal equivalent. If pain is not relieved, another nitroglycerin dose is taken at 5 min and a third at 10 min. If there is no relief by the third dose of nitroglycerin, the patient should be transported to the appropriate emergency facility. The physician should decide whether to incorporate the chewing of an aspirin tablet into this regimen when the decision is made to proceed to the hospital.

Bystanders and family members can play an important role in both shortening patient delay time and responding to an arrest. It has been shown that a spouse's presence accelerated the hospital arrival time.[193] Furthermore, if basic life support is initiated by a bystander within 4 min of cardiac arrest and if defibrillation is accomplished within 8 min, 40 percent of patients will survive and be discharged from the hospital.[200]

EMERGENCY MEDICAL SERVICES

Many communities in the United States are served by a two-tier ambulance service consisting of basic and advanced life support units. Since these are usually more basic support units, the response time of these units is shorter and should ideally be less than 5 min.[1,201] The first responders may be any of a variety of public service employees who are trained in CPR and defibrillation and have been taught to have a sense of urgency in order to identify and treat the AMI patient rapidly. Automatic external defibrillators are safe and effective and can be used by even minimally trained first responders to analyze rhythms and deliver defibrillatory shocks to convert VF.[1,202-206] Incorporation of automatic external defibrillators into emergency medical systems is highly desirable.[1] Minimally, it has been recommended that every ambulance transporting victims of cardiac arrest be equipped with a conventional defibrillator.[204]

The goal of any emergency medical system should be to include individuals who are trained in advanced life support techniques-including the use of antiarrhythmics as well as the administration of intravenous fluids and analgesics-and who can reach the patient as soon as possible in a vehicle equipped as a CCU. Undirected EMS technicians can spend excessive amounts of time evaluating a patient with chest pain and actually delay the ultimate initiation of appropriate therapy.[1] The time elapsed between receiving a 911 call and the actual arrival in the hospital has been assessed, and, at over 46 min, was substantially longer than estimates (under 26 min) taken from the paramedics involved.[198] Most of this field time was consumed by the paramedic on-scene time, which was not prolonged by acquisition of a 12-lead ECG. It has been demonstrated that, by the use of a standardized protocol (Table 42-7[1]), evaluation of the patient with chest pain by experienced emergency medical technicians, acquisition of a 12-lead ECG, and initiation of therapy can be accomplished within 20 min.[1] The protocol should facilitate determination of the likelihood of AMI and the presence of comorbid conditions in which thrombolytic therapy would be dangerous. It should also identify those suspected AMI patients who are at high risk. Patients in this category include those with sinus tachycardia, hypotension, or pulmonary edema or those with signs of shock. It is ideal to be able to record 12-lead ECGs in the field to be transmitted to the hospital physician. The availability of these data facilitates establishing the diagnosis and allows for accelerating preparations to administer thrombolytic therapy.[207-209]

Table 42-7: Chest Pain Checklist for Use by EMT/Paramedic for Diagnosis of Acute Myocardial Infarction and Thrombolytic Therapy Screening

Check each finding below. If all [yes] boxes are checked and ECG indicates ST elevation or new BBB, reperfusion therapy with thrombolysis or primary PTCA may be indicated. Thrombolysis is generally not indicated unless all [No] boxes are checked and BP ≤180/110 mmHg.

	Yes	*No*
Ongoing chest discomfort (≥20 min and <12 h)	☐	—
Oriented, can cooperate	☐	—
Age >35 y (>40 if female)	☐	—
History of stroke or TIA	—	☐
Known bleeding disorder	—	☐
Active internal bleeding in past 2 weeks	—	☐
Surgery or trauma in past 2 weeks	—	☐
Terminal illness	—	☐
Jaundice, hepatitis, kidney failure	—	☐
Use of anticoagulants	—	☐

Systolic/diastolic blood pressure
Right arm: —/—
Left arm: —/—

	Yes	*No*
ECG done	☐	—

*High-risk profile**	*Yes*	*No*
Heart rate ≥100 bpm	☐	—
BP ≤100 mmHg	☐	—
Pulmonary edema (rales greater than one half-way up)	☐	—
Shock	☐	—

Pain began	—	AM/PM
Arrival time	—	AM/PM
Begin transport	—	AM/PM
Hospital arrival	—	AM/PM

*Transport to hospital capable of angiography and revascularization if needed.
ABBREVIATIONS: EMT = emergency medical technician; ECG = electrocardiogram; BBB = bundle branch block; PTCA = percutaneous transluminal coronary angioplasty; BP = blood pressure; TIA = transient ischemic attack. Adapted from the Seattle/King County EMS Medical Record.
SOURCE: Ryan et al.,[1] with permission.

PREHOSPITAL THROMBOLYSIS

As mentioned previously, there is unequivocal evidence that the earlier thrombolysis is administered to the AMI patient with ST-segment elevation, the more efficacious is the outcome;[14,210,211] in particular, the most favorable results are achieved when therapy is initiated within the first 1 to 2 h after the symptoms appear. It seems logical, therefore, that if thrombolysis could be initiated in appropriate patients during the prehospital phase by general practitioners or by EMS technicians guided by protocol, the 12-lead ECG, and communication with the emergency department physician, outcomes would be improved. Prehospital thrombolysis has been evaluated in several trials.[207,212-214] A meta-analysis of all of the trials showed a modest (17 percent) improvement in outcome, although none of the trials demonstrated significant improvement individually.[212] Prehospital thrombolysis, however, is fraught with a number of difficulties, beginning with the fact that only a small portion of chest pain patients (5 to 10 percent) have an AMI and are eligible to be treated with thrombolytics.[207,209,215,216] Thus, correctly selecting patients for thrombolytic therapy and avoiding its administration when not indicated or when contraindicated is difficult and has significant legal, medical, and economic implications. Because of these difficulties, prehospital thrombolysis should be emphasized

primarily in those circumstances in which it can be administered 60 to 90 min before reaching the hospital (because of a long transport time) or when a physician is in the ambulance.[1] Generally, emphasis should be placed on rapid screening and diagnosis in the field to facilitate hospital triage and thrombolytic administration within 30 min of the patient's arrival.

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Chapter 42: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

EVALUATION AND MANAGEMENT OF PATIENTS WITH CHEST PAIN IN THE EMERGENCY DEPARTMENT

Recommendation:[1]

Class I

1. Emergency department AMI protocol that yields a targeted clinical examination, a 12-lead ECG within 10 min, and administration of thrombolytic therapy, as appropriate, within 30 min.

Background

In general, the goals of the emergency department with respect to patients with chest pain are to rapidly identify those patients with AMI with both typical and atypical presentations so that appropriate therapy can be initiated; to recognize those patients with acute coronary syndromes (unstable angina) but without myocardial infarction and who, thus, are at high risk; and to assess accurately those patients at low risk who are candidates for noninvasive evaluation and early discharge.[217]

As mentioned previously, the earlier reperfusion therapy is initiated in the subset of patients with diagnostic ST-segment elevation, the more favorable the clinical results (Fig. 42-5).[210]

An important objective, obviously, should be a triage system that minimizes the number of patients at high risk (AMI or unstable angina) who are inadvertently discharged from the emergency department while also minimizing the admission to high-intensity CCUs of low-risk patients without myocardial infarction-a goal of increasing urgency in this era of intense pressures for cost containment. Of patients admitted to a CCU, for example, less than 20 percent will have AMI, as noted.[218,219] In contrast, even in the current era of an enhanced appreciation for atypical presentations, an increased potential for litigation, and a decreased threshold for admission to exclude myocardial infarction, the missed diagnosis rate has still been about 4 percent,[131] a percentage that appears not to have changed substantially since the 1980s.[220-222]

The reasons for misdiagnosis of acute coronary syndromes in the emergency department have been studied extensively and have been reviewed.[217] The misinterpretation of ECGs has been reported to occur in approximately 20 to 40 percent of missed AMIs.[222-224] Equally disturbing are the reports, which are indictments of training or focus, that patients are discharged even though the physician has recognized ischemic symptoms or electrocardiographic changes.[220,223,224] A major contributing problem is that even experienced clinicians are imprecise in their clinical judgment as to the presence or absence of myocardial infarction in a given patient. Sensitivities of 80 to 90 percent and specificities of approximately 70 to 80 percent in diagnostic precision in determining the presence or absence of AMI based on clinical impressions have been reported.[70,222,225] The diagnostic problem, however, is not limited to the diagnosis of myocardial infarction but also applies to whether unstable angina is present (see also Chap. 41). Patients who are admitted to the hospital with chest pain and only transient ST-segment changes and without aggressive therapy have a 22 percent incidence of death and myocardial infarction after a 28-month follow-up,[226] a figure not dissimilar to that for patients with an initial confirmed infarction. These similarities in outcome of unstable angina and myocardial infarction are not surprising, since the fundamental underlying pathophysiologic mechanisms-disruption of the atherosclerotic plaque and thrombus formation, with or without vasospasm-are likely to be identical, the major difference being the extent of luminal compromise by the thrombus. Thus, the clinical focus should not be simply to "rule out" AMI, but, taking a proactive approach, to "rule in" either acute infarction or unstable angina in an expeditious manner.[217] Once these

urgent conditions have been excluded or ascertained to be of low probability, the next level of concern is determining the presence of other acute cardiovascular or cardiopulmonary conditions, such as aortic dissection, pulmonary embolus, and pericarditis. The focus, subsequently, in a hierarchical fashion, is to establish whether or not stable coronary artery disease is present, to identify cardiovascular risk factors, and to consider noncardiac diagnoses, which, in nonurgent cases, can be evaluated further on an outpatient basis.

It has been suggested[217] that management of chest pain in the emergency department can be optimized by having the appropriate clinical focus, developing effective risk stratification approaches, and implementing systematic algorithmic protocols. There has been a great deal of interest in the development of actual or virtual chest pain units to facilitate the expeditious triage and management of patients with chest pain, as discussed later.

Initial Approach, Detection, and Assessment of Risk

Recommendations:[1]

Class I

1. Supplemental oxygen, intravenous access, and continuous electrocardiographic monitoring should be established in all patients with acute ischemic-type chest discomfort.
2. A 12-lead ECG should be obtained and interpreted within 10 min of arrival in the emergency department in all patients with suspected acute ischemic-type chest discomfort.

A major goal of the emergency department in dealing with patients with chest pain is the establishment of a routine approach that leads to a rapid (10 min) preliminary evaluation, acquisition of a 12-lead ECG, and establishment of intravenous access and continuous electrocardiographic monitoring (Fig. 42-3). The initial physical examination and assessment of the history are guided by the differential diagnosis of chest pain, with the goal of establishing whether or not myocardial ischemia is a likely or possible diagnosis. Blood is drawn for baseline cardiac marker levels, and if coronary ischemia is suspected and there are no contraindications, the patient is given aspirin of 160 to 325 mg to chew and swallow. Also, the patient with suspected coronary ischemia is given sublingual nitroglycerine unless the systolic blood pressure is less than 90 mmHg. This should be avoided with severe bradycardia or tachycardia. Because of the potentially catastrophic implications, the history of chest pain alone usually dictates entry into the system for evaluation. In general, the only patients with chest pain who are not systematically evaluated for myocardial ischemia would be those in whom a clear noncardiac cause, such as chest wall tenderness, can be demonstrated unequivocally to be the etiology of the presenting symptoms. Continuous ECG monitoring is essential because of the propensity for the development of sudden and potentially lethal ventricular arrhythmias in any patient with an acute coronary ischemic syndrome. Intravenous access is essential for therapeutic interventions under such circumstances as well as for more general purposes. Additionally, paroxysmal changes in the ST segment may be recognizable on the monitor. The differential diagnosis of chest pain and the clinical recognition of AMI were discussed previously. The causes of chest pain that are not the result of acute pathologic changes compromising the structural integrity of the large coronary arteries are listed in Table 42-8.

Table 42-8: Causes of Chest Pain Other Than Acute Coronary Artery Syndromes

Cardiovascular
Aortic dissection
Aortic stenosis
Pericarditis
Mitral valve prolapse
Microvascular angina
Hypertrophic cardiomyopathy
Syndrome X
Pulmonary embolus
Arrhythmia/palpitations
Noncardiovascular
Pleurisy
Pneumonia
Pneumothorax
Costochondritis
Gastrointestinal
Esophageal spasm/reflux
Acid peptic disease
Cholecystitis
Gastritis
Psychiatric
Panic attack
Cardiac neurosis
Depression
Malingering

As a general rule, and as previously mentioned, one should begin the evaluation of the patient with chest pain with the assumption that one is dealing with myocardial ischemia until proven otherwise. The three most serious and urgent alternative diagnoses that need to be considered specifically during the initial evaluation are aortic dissection, acute pulmonary embolus, and acute pneumothorax. Acute pericarditis and myopericarditis need to be considered as well.

Although relatively uncommon, aortic dissection must be considered and ruled in or out during the initial evaluation of the patient with chest pain, since specific intervention can decrease its high mortality. Furthermore, and not unexpectedly, administration of thrombolytic agents in the presence of aortic dissection is associated with high mortality.[227-229] Suspicion of dissection should be heightened especially

in hypertensive patients or in those with marfanoid habitus (see also Chaps. 62 and 88). Most patients with aortic dissection who have mistakenly received thrombolytic therapy did not meet the ECG criteria of ST-segment elevation that is usually required.[228] Aortic dissection is usually associated with sudden onset of a severe, tearing pain that may migrate and is frequently felt in the back at some point. Differential blood pressures in the arms may be noted, and pulse differences in the carotids or arms may be observed. An echocardiogram and, in particular, transesophageal echocardiography can be very efficacious in the diagnosis of aortic dissection (see Chaps. 13 and 88).

Pulmonary embolus can be life-threatening and should be suspected in anyone with a sudden onset of shortness of breath and chest pressure or pain, especially if there is a history of being sedentary or immobilized and/or of deep venous thrombosis. There may be a pleural rub, and the chest roentgenogram is usually normal, although arterial hypoxia may be present (see Chap. 53). Similarly, pneumothorax may be associated with persistent chest pain, hypoxemia, and evidence of hypoventilation on physical examination.

Acute pericarditis may mimic AMI in that the pain can be substernal and persistent. Frequently, however, there will be a positional component as well as characteristics of pleurisy, with accentuation by deep breathing. Furthermore, the diffuse ST-segment elevation may lead to a misdiagnosis of myocardial infarction. The key differentiating features in pericarditis include PR depression, the diffuse nature of ST-segment elevation in most leads, and the absence of reciprocal changes (see Chaps. 11 and 72). The presence of a pericardial rub is a key diagnostic finding. Echocardiography, by demonstrating a pericardial effusion in the case of pericarditis or a wall motion abnormality in the case of acute ischemia, can be helpful in making the appropriate diagnosis. Hemorrhagic pericardial effusions have been reported in patients given thrombolytic therapy in the setting of acute pericarditis.[227,228]

Although usually not urgent, it should be kept in mind that esophageal disorders, as assessed retrospectively by motility studies, are very common in patients presenting with chest pain in whom cardiac ischemia is ruled out[230-233] (see also Chap. 40). In fact, among all patients presenting with chest pain, gastroesophageal disease has been observed to be the most common etiology (42 percent), whereas ischemic heart disease was present in 31 percent and chest wall syndromes were responsible in 28 percent.[234] Because of the high frequency of gastrointestinal disease in patients with chest pain, "GI cocktails" or antacids have been used as a diagnostic tool to guide triage and disposition. Only 25 percent of patients with esophageal pain, however, have been reported to obtain pain relief with antacids.[235] Furthermore, coincidental, spontaneous relief of ischemic chest pain at the time of administration of the GI cocktail could be misleading. Similarly, administration of nitroglycerin as a diagnostic strategy for ischemic disease could be misleading, because it can relieve esophageal spasm. Moreover, it has been found that pain relief after nitroglycerin did not predict unstable angina or AMI in the chest pain patient.[236] The use of these "response-to-treatment" strategies as major decision points in the evaluation of chest pain has been discouraged.[217] This reservation, however, applies primarily to those patients without diagnostic ECG changes, and does not preclude giving sublingual nitroglycerin to patients with chest pain and ST-segment elevation as a test of vasospasm or Prinzmetal's angina.

DETECTION

The 12-Lead Electrocardiogram as a Guide to Management Strategy

The results of the 12-lead ECG guide the next level of decision making for the patient with chest pain thought to be compatible with myocardial ischemia (Fig. 42-3). The ECG interpretation is assigned to one of three categories: (1) ST- segment elevation in two or more leads or a presumptively new bundle branch block implicating acute coronary occlusion, usually thrombotic; (2) ST-segment depression and/or T-wave inversion implying subtotal occlusion or non-Q infarction; and (3) normal or nondiagnostic. The group with ST- segment elevation or a left bundle branch block is particularly important to define, as it is this group that has been shown to benefit from thrombolytic therapy. ST-segment elevation has a 46 percent sensitivity and a 91 percent specificity for the diagnosis of AMI.[94] There is no indication as yet of the benefit of thrombolytic therapy or primary angioplasty in those patients without ST-segment elevation or bundle branch block, however, appropriately focused randomized trials are lacking.

As discussed previously, the initial ECG is diagnostic in less than 50 percent of patients with AMI,[237,238] and the measurement of serum markers of myocardial damage plays a major role in diagnosis. Measurement of MB-CK is the benchmark laboratory test, and the specificity and sensitivity of samples taken 2 h apart during serial sampling have been reported to be 91 and 94 percent, respectively.[239] The limitations of conventional MB-CK measurements and the role of myoglobin and the troponins have been discussed. The rapid high-voltage method to separate MB-CK-1 and MB-CK-2 and to determine the ratio of the isoforms was described and may be particularly relevant to the initial evaluation in the emergency department, since it quickly provides information that not only facilitates establishing the appropriate diagnosis but also contributes to assigning a risk category to a patient.

RISK STRATIFICATION

Stratifying risk in the patient with AMI is an essential part of the management strategy during all phases of care. It permits not only the more precise calibration of treatment and diagnostic approaches with the level of risk but also, increasingly, facilitates the appropriate utilization of hospital resources. Traditional approaches to initial risk assessment have involved combinations of ECG changes and clinical manifestations. The ECG serves as a basis for initial risk assessment. ST-segment elevation or a new left bundle branch block in the patient with chest pain defines a high-risk group, and in those with elevated ST segments, the mortality correlates positively with the number of leads with the ST changes.[240] The presence of ST-segment depression or T-wave inversion also defines a high-risk group. In patients with unstable angina or non-Q-wave myocardial infarction, ST-segment depression on the initial ECG of at least 1 mm in two leads during pain predicted major clinical events in the subsequent 3 months.[241] A nondiagnostic or normal ECG is associated with low risk. For example, the incidence of myocardial infarction has been reported to be 10, 8, and 41 percent in patients who, at admission, had a normal, a nonspecific, or an abnormal ECG, respectively.[242] The incidence of complications paralleled the infarction rate-a predictable conclusion corroborated by other studies.[243,244] *High risk has been associated with age, ST-segment elevation or depression, T-wave inversions, and Q waves, as well as prolonged chest pain, especially if it radiates to cardiac referral areas.*[70,222,245-247]

Quantitative assessments of risk have been developed to guide the management of patients with chest pain in the emergency department.[244] *Predictors of an increased risk of complications included ECG evidence of ST-segment elevation or Q waves in two or more leads that are not known to have been present previously; ST-segment depression or T-wave inversions consistent with myocardial ischemia and not known to be present previously; pain worse than prior angina or the same as that experienced with prior myocardial infarction; systolic blood pressure of less than 100 mmHg; or rales bilaterally above the bases.* On the basis of these predictors, patients could be divided into four risk groups.[244] Furthermore, the risk could be updated if a complication occurred. This general approach can guide decisions concerning the level of intensity of the unit to which a patient is admitted and the length of observation required.

Blood levels of cardiac markers are prognostically important, as noted. In particular, increased levels of any of the markers-CKMB or the subforms or troponins (I and T), but not myoglobin (×1)-at presentation appear to be strong predictors of risk in patients with acute ischemic syndromes[151,152] (see Chap. 41).

INITIAL MANAGEMENT

As discussed, one frequently does not have a definitive diagnosis of AMI in the patient with chest pain in the emergency department, although this situation may ultimately be improved by the wider availability of the very rapid assays of blood cardiac markers, as discussed earlier. Nevertheless, the initial general treatment of the acute coronary syndromes is the same.

Routine General Measures

OXYGEN ADMINISTRATION

Recommendations for oxygen administration:[1]

Class I

1. Overt pulmonary congestion
2. Arterial oxygen desaturation (Sa_{O_2} less than 90 percent)

Class IIa

1. Routine administration of oxygen to all patients with uncomplicated myocardial infarction during the first 2 to 3 h

Class IIb

2. Routine administration of supplemental oxygen to patients with uncomplicated myocardial infarction beyond 3 to 6 h

Hypoxemia is not uncommon in patients with AMI, even with an uncomplicated course, and presumably because of ventilation-perfusion mismatch.[248] Oxygen administration has been reported to decrease ST-segment elevation in anterior myocardial infarction.[249] Thus, oxygen administration for up to several days has previously been routine. There is concern with this practice, however, since oxygen may increase vascular resistance, and there may not necessarily be increased delivery to tissues. Because of these concerns and because of the expense of prolonged oxygen administration, there appears to be little justification for extending its use in uncomplicated myocardial infarction with an (Sa_{O_2} of greater than 90 percent beyond 2 to 3 h.[1] Justification of its use in uncomplicated infarction can be based on its potential for limiting of ischemic injury and on the fact that nitroglycerin can induce ventilation-perfusion abnormalities due to its pulmonary vasodilator activity, thus contributing to hypoxia.

Oxygen administration should be continued in patients with pulmonary congestion and desaturation. In patients with complicated myocardial infarction, nasal oxygen or oxygen by face mask may be insufficient to maintain saturation, and positive-pressure breathing or intubation and mechanical ventilation may have to be considered. If necessary, they should be initiated promptly.

ANALGESIA

The alleviation of pain and anxiety remains an essential element in the care of the patient with AMI. The pain and accompanying anxiety contribute to excessive activity of the autonomic nervous system and to restlessness. These factors, in turn, increase the metabolic demands of the myocardium. Physician reassurance from the beginning is an essential part of treatment and should be provided with compassion, patience, and confidence. Optimal care of the patient with AMI requires a team of experienced individuals who can help alleviate anxiety by their air of competence and caring.

It is a common clinical observation that reperfusion in AMI is associated with rapid relief of pain, suggesting that the pain is due to ongoing ischemia of the viable myocardium rather than to the effects of tissue necrosis. Thus, the approach to pain consists of the dual strategy of relieving ischemia and attacking the pain directly. Anti-ischemic therapy consists of reperfusion, beta blockers (if appropriate), nitrates, and oxygen administration, as discussed. Narcotics not only relieve pain directly but also indirectly by diminishing the sympathetic nervous system's drive and catecholamine secretion, which will increase blood pressure and drive cardiac chronotrophic and inotrophic responses to increase oxygen consumption and ischemia. The increased sympathetic drive will also enhance the propensity for serious ventricular arrhythmias. Morphine, in most instances, is the drug of choice, since it is well tolerated and offers analgesia without significant cardiac depression.[250] It also relieves anxiety and the feeling of doom commonly described. Morphine sulfate can be given at doses of 2 to 4 mg every 15 min until adequate relief has been obtained, which, in some patients, may require 25 to 30 mg.[251] The peak effect of intravenous morphine occurs within 15 to 20 min, thus requiring titration. Morphine has frequently been given in inadequate doses because of fear of respiratory depression or hypotension. Respiratory depression is less common in patients with myocardial infarction than it is in patients generally, because of the anxiety and respiratory drive from hypoxia, and can be treated with intravenous naloxone should it occur.[1]

Hypotension related to morphine is usually orthostatic and volume-dependent and is less common in supine patients.[252] In patients with severe ongoing pain, it may be prudent to avoid concomitant administration of substantial doses of morphine and vasodilators, such as nitroglycerin. In patients with an acute inferior myocardial infarction with bradycardia with or without hypotension, the vagolytic narcotic meperidine may be substituted for the parasympathomimetic morphine. If the patient's anxiety is not controlled by the administration of narcotics, mild sedation with a benzodiazepine is appropriate. Diazepam in doses of 5 mg orally every 8 to 12 h or alprazolam in doses of 0.25 mg every 8 h are most often used.

NITROGLYCERIN

Recommendations for intravenous nitroglycerin[1]:

Class I

1. For the first 24 to 48 h in patients with AMI and congestive heart failure, large anterior infarction, persistent ischemia, or hypertension
2. Continued use (beyond 48 h) in patients with recurrent angina or persistent pulmonary congestion

Class IIa

1. None

Class IIb

1. For the first 24 to 48 h in all patients with AMI who do not have hypotension, bradycardia, or tachycardia
2. Continued use (beyond 48 h), perhaps in an oral or topical form, in patients with large or complicated infarction

Class III

1. Patients with systolic pressure less than 90 mmHg or severe bradycardia (less than 50 beats per minute)

Nitroglycerin has become very widely used in the treatment of AMI. It is an anti-ischemic agent not only by virtue of its actions to decrease preload and afterload, and thus to decrease oxygen demand, but also because of its vasodilator actions on epicardial coronary arteries and coronary collaterals. Consequently, and especially in patients with good collaterals, nitroglycerin is likely to increase flow into the ischemic regions.[253,254] Apart from relieving ischemia and pain, intravenous nitroglycerin, in early studies, appeared to reduce the likelihood of developing cardiac failure, infarct extension, or cardiac death. Both clinical data[255,256] and animal studies suggest that the early administration of nitroglycerin limits the extent of myocardial damage and favorably affects survival.[257] Long-term nitrates after reperfusion in animals favorably affect ventricular remodeling.[258]

Small, early trials before the widespread use of reperfusion suggested that the early administration of intravenous nitroglycerin was associated with improved morbidity and mortality. A meta-analysis of these trials suggested that the use of nitrates reduced the odds of mortality after AMI by greater than 30 percent.[259] The efficacy of nitrates in improving short-term mortality after AMI was tested prospectively in the GISSI-3 trial.[260] At 6 weeks, there was no significant difference between the nitrate and control groups. The power to distinguish between the two, however, was diminished, because about one-half of the control group received nitrates during the first 2 days at the discretion of the attending physician. The angiotensin-converting enzyme (ACE) inhibitor lisinopril was tested in a similar fashion in GISSI-3. Mortality was decreased slightly at 6 weeks. The combined use of nitrates and lisinopril was associated with decreased mortality at both 6 weeks and 6 months compared with the no-nitrate group or with the group that received lisinopril alone. There was no significant difference noted at 35 days in comparison with the control group in another large trial, International Study of Infarct Survival (ISIS-4), which evaluated the effects of nitrates

on mortality after myocardial infarction.[261] This trial was also compromised by the high frequency of discretionary nitrate use in the control group. A meta-analysis of all randomized, controlled trials involving the use of nitrates in AMI show a small, statistically significant reduction in mortality (about 5 percent).

The weight of the evidence does not justify the routine, long-term use of nitrates in uncomplicated AMI. The use of intravenous nitroglycerin early after acute infarction is justified because of its ease of titration, rapid onset, and ability to be quickly withdrawn in case of complications. Long-term use of nitrates is appropriate in the case of recurrent ischemia, large infarction, congestive heart failure, or hypertension.

COMPLICATIONS AND LIMITATIONS

The most serious complication of nitroglycerin is hypotension. The fall in blood pressure may cause reflex tachycardia, and, together with decreased perfusion pressure, may cause or worsen angina. Thus, nitroglycerin should be avoided with a systolic pressure of less than 90 mmHg. Caution should be exercised in the case of inferior wall infarction because of the possibility of right ventricular involvement. Nitroglycerin should be used only with extreme caution if at all in right ventricular infarction, because the right ventricle in this circumstance becomes extremely dependent upon preload, which can be diminished by the venodilating properties of the drug.[262] Similarly, nitroglycerin should be avoided in patients with severe bradycardia (heart rate less than 50 beats per minute), as hypotension may result.[263] If hypotension and bradycardia develop, nitroglycerin should be stopped, legs elevated, fluid administered, and atropine given if needed. Headache is a common side effect of nitrate administration.

Nitrate tolerance is common (see Chap. 81). With intravenous nitroglycerin, this may be recognized only as a diminution of clinical effect after 24 to 48 h. An increase in dose may be required.

DOSAGE OF NITROGLYCERIN

Long-acting nitrates should generally not be used as initial therapy in AMI. Intravenous nitroglycerin is preferable, as noted, because of rapidity of onset, ease of titration, and ease of removal in case of complications. Dose titration can be assessed by frequent determinations of blood pressure and heart rate. Invasive monitoring is not essential but is probably prudent if high doses are required or if there is hemodynamic instability or uncertainty about the adequacy of ventricular preload.

Treatment should be initiated with a bolus injection of 12.5 to 25 μg and should be followed by infusion by pump of 10 to 20 μg/min, with increases of 5 to 10 μg every 5 to 10 min while assessing hemodynamic and clinical responses.[1] Control of symptoms is a major end point; in the case of high left ventricular filling pressure, a decrease of 10 to 30 percent in pulmonary artery wedge pressure is the objective. Limitations of nitroglycerin dosing are a decrease in mean arterial pressure of 10 percent in normotensive patients or a decrease of 30 percent in hypertensive patients, but not below a systolic pressure of 90 mmHg, or an increase in heart rate of 10 beats per minute not to exceed 110 beats per minute.

Doses of nitroglycerin greater than 200 μg/min are associated with an increased risk of hypotension. The development of such high requirements may indicate tolerance, and alternative drugs such as ACE inhibitors or nitroprusside should be considered. If tolerance is the issue, responsiveness should return after a 12- to 18-h period off of nitroglycerin.

ASPIRIN

Recommendations for aspirin therapy[1]:

Class I

1. A dose of 160 to 325 mg should be given on day 1 of AMI and continued indefinitely on a daily basis thereafter.

Class IIb

1. Other antiplatelet agents such as dipyridamol, ticlopidine, or clopidogrel may be instituted if a true aspirin allergy is present or if the patient is unresponsive to aspirin.

Aspirin has become a standard part of the armamentarium for treating not only AMI but also atherosclerotic vascular disease generally. A 23 percent reduction in mortality at 35 days in patients treated with aspirin during the early stages of AMI was observed in the Second International Study of Infarct Survival (ISIS-2).[211] The reduction in mortality due to aspirin in combination with streptokinase was 42 percent. In a summary of a large number of clinical trials, aspirin has been shown to reduce the incidence of vascular events in patients with AMI at 1 month; a prior history of MI (2 years); a history of transient cerebral ischemia or stroke; and unstable angina.[264]

Aspirin irreversibly inhibits platelet cyclooxygenase, an enzyme that causes formation of thromboxane A_2, a mediator of platelet aggregation.[265] Its antithrombotic and side effects are discussed in detail in Chap. 44. Aspirin should be avoided in cases of true hypersensitivity. In the case of a history of bleeding from acid peptic disease, aspirin rectal suppositories can be used. Ticlopidine or clopidogrel, which are antiplatelet drugs acting as adenosine diphosphate receptor antagonists and can be used in acute infarction in patients in whom aspirin is contraindicated. Their actions do not develop immediately. They are discussed in Chap. 44. Clopidogrel is safer than ticlopidine and was shown to be more effective than aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.[266]

Aspirin is an effective antithrombotic at doses as low as 80 mg, but the rapid, acute effect probably requires 160 mg, which is absorbed and is thus clinically effective more quickly if the tablet is chewed rather than swallowed whole. *Thus the patient suspected of having a coronary ischemic syndrome should receive, early in the course, 160 to 325 mg of non-enteric-coated aspirin, which is chewed.*

Management after Triage into Electrocardiographic Subgroups

As discussed earlier, the initial ECG, as a first approximation, permits the assignment of patients with chest pain into subgroups that are distinguishable in terms of therapeutic responsiveness and risk. Thus, those with either ST-segment elevation and presumptively new bundle branch block or those with ST-segment depression and/or T-wave inversion are in high-risk groups, whereas those with either normal ECGs or nonspecific changes are in a low risk category. Furthermore, the high-risk groups can be subdivided into those (ST-segment elevation or new bundle branch block) who have a favorable therapeutic response to thrombolytics and those who do not (ST-segment depression and/or T-wave inversion). *It must be kept in mind that these initial categorizations do not necessarily define ultimate outcome. Thus, patients with no ST-segment elevation at presentation may, in fact, have unstable angina and ultimately have no infarction or may progress to have either a Q-wave or a non-Q-wave infarction. Similarly, those presenting with ST-segment elevation may have a non-Q-wave infarction, although the majority of these will develop Q waves.* This potential for variable outcomes provides the underlying rationale for close monitoring and continuous reassessment of clinical course, risk, and therapeutic strategies during the period of observation and for monitoring both in the emergency department and subsequently in other hospital units.

APPROACH TO THE PATIENT WITH ST-SEGMENT ELEVATION

The approach to the patient with chest pain and ST-segment elevation is guided heavily by the evidence that this subgroup has a high frequency of epicardial coronary artery occlusion by a thrombus that can be halted by prompt reperfusion.[267,268] Furthermore, multiple clinical trials of thrombolytic therapy have shown clinical benefit, but only in those with ST-segment elevation (Fig. 42-5).[210] This efficacy, however, has been shown in men, women, and diabetics and is manifest regardless of any history of previous myocardial infarction, existing heart rate, or recorded blood pressure (if less than 175 mmHg).[210] The greatest benefit is seen in patients with anterior myocardial infarction (and inferior infarction with right ventricular involvement), those with signs of a large infarction (systolic blood pressure less 100 mmHg or heart rate greater than 100 beats per minute), and in those with diabetes. Thus, the evaluation and management of the patient with ischemic chest pain and ST-segment elevation is focused on the rapid assessment of suitability for and delivery of reperfusion therapy. The approach to these patients is summarized in Fig. 42-6.[1]

During the initial evaluation, the patient will have had aspirin given, blood drawn, intravenous access established, a 12-lead ECG showing ST-segment elevation in at least two adjacent leads, nasal oxygen administered, appropriate analgesia, and continuous electrocardiographic monitoring initiated. The appropriate next steps are to administer a beta-adrenergic blocker, if not contraindicated, and to initiate evaluation for reperfusion therapy. Based on the data from nine major clinical trials of thrombolytic therapy summarized by the Fibrinolytic Therapy Trialists Collaborative Group, thrombolytic therapy is efficacious in AMI (although linearly decreasing with the passage of time) for up to 12 h after the onset of symptoms.[210] There was a statistically uncertain benefit from 13 to 18 h. Thus, the 12-h point was chosen as defining the time frame in which the risk-benefit ratio is clearly favorable for administering thrombolytic therapy (Fig. 42-5).

Beta-Adrenergic Receptor Blockers

Recommendations for early therapy[1]:

Class I

1. Patients without a contraindication to beta-adrenoceptor blocker therapy who can be treated within 12 h of onset of infarction, irrespective of administration of concomitant thrombolytic therapy or performance of primary angioplasty
2. Patients with continuing or recurrent ischemic pain
3. Patients with tachyarrhythmias, such as atrial fibrillation with a rapid ventricular response
4. Non-ST elevation myocardial infarction

Class IIb

1. Patients with moderate left ventricular failure (the presence of bibasilar rales without evidence of low cardiac output) or other relative contraindications to beta-adrenoceptor blocker therapy, provided they can be monitored closely

Class III

1. Patients with severe left ventricular failure

Beta-adrenergic receptor blockers interfere with the positive inotropic and chronotropic effects of catecholamines, thus reducing afterload (blood pressure) and therefore myocardial oxygen consumption. In the myocardial ischemic syndromes, these drugs should decrease ischemia and catecholamine-induced arrhythmias and should potentially reduce infarct size, in part by prolonging diastole and by improving subendocardial perfusion. Most of these theoretical advantages have, in fact, been borne out in clinical trials. The pharmacology of beta-adrenergic blockers is discussed in Chap. 81.

Many studies have demonstrated the clinical efficacy of beta blockers in the treatment of AMI. Analysis of pooled data from 28 trials revealed an average reduction of mortality of 28 percent at 1 week, and the majority of the benefit was seen in the first 48 h.[269] The Beta-Blocker Heart Attack Trial demonstrated that the benefits on mortality persisted and were about 20 percent after 2.5 years.[13] In the First International Study of Infarct Survival, patients were enrolled within the first 12 h from the onset of symptoms and atenolol, 5 to 10 mg, was immediately given intravenously and followed by oral atenolol, 100 mg daily.[13] Seven-day mortality was reduced by 14 percent. In the Metoprolol in Acute Myocardial Infarction (MIAMI) trial, metoprolol, 15 mg, was given intravenously in three divided doses early in the course and followed by 50 mg orally every 6 h for 48 h and then by 100 mg twice daily.[270] Mortality relative to placebo was reduced 12 percent at 15 days. In both of these trials, benefit was seen after 1 day and was sustained. Beta blockers have also enhanced therapeutic efficacy when given adjunctively with thrombolytic therapy. In the Thrombolysis in Myocardial Infarction phase II (TIMI-II) trial of conservative versus invasive strategies after treatment with recombinant tissue-type plasminogen activator (rt-PA), a subgroup was selected to receive either early intravenous followed by daily oral metoprolol or to begin oral metoprolol on day 6 after AMI.[271] The beta-blocker regimen was metoprolol, 15 mg, intravenously,

followed by 50 mg orally twice daily for 1 day and 100 mg twice daily subsequently. The alternative protocol involved beginning the oral metoprolol regimen on day 6. The immediate intravenous metoprolol regimen was associated with a 45 percent reduction in nonfatal reinfarction and a 27 percent reduction in recurrent ischemic events in comparison with the group beginning beta-blocker therapy on day 6. Thus, available data strongly support the use of beta blockers early in the course of acute Q-wave myocardial infarction in the absence of contraindications. As discussed later, the data supporting the use of beta blockers in non-Q-wave myocardial infarction are less compelling. The effects of beta blockers in Q-wave MI are summarized in Table 42-9. While metoprolol and atenolol are the only beta blockers approved for use by the Federal Drug Administration in the United States in AMI, it is generally thought that therapeutic efficacy is a class effect of beta blockers lacking intrinsic sympathomimetic activity.

Table 42-9: Effects of Beta Blockade in Q-Wave AMI

Reduces ventricular ectopy, atrial fibrillation, and nonfatal cardiac arrest
Reduces frequency of progression of threatened infarction to completed infarction
Reduces recurrent ischemia and infarction during first 6 weeks after initial event

The relative contraindications to beta-blocker therapy are as follows:[1] (1) heart rate less than 60 beats per minute; (2) systolic blood pressure less than 100 mmHg; (3) moderate or severe left ventricular failure; (4) signs of peripheral hypoperfusion; (5) PR interval greater than 240 ms; (6) second- or third-degree AV block; (7) severe chronic pulmonary disease; (8) history of asthma; (9) severe peripheral vascular disease; and (10) insulin-dependent diabetes mellitus. Since these contraindications are relative and not absolute, the clinician has the option of assessing the effects of beta blockade with the short-acting intravenous beta blocker esmolol, which has an onset of action within 5 to 10 min and a half-life of about 30 min. If the beta blockade is tolerated by the patient, long-acting oral beta-blocking drugs can then be used with increased confidence.

Thrombolysis

Recommendations[1]:

Class I

1. ST elevation (greater than 0.1 mV in two or more contiguous leads at any time during the observation period); time to therapy 12 h or less since the onset of continuous chest pain discomfort, causing hospital presentation; and age less than 75 years
2. Bundle branch block (obscuring ST-segment analysis and history suggesting AMI)

Comment

Treatment benefit is present regardless of gender, presence of diabetes, blood pressure (if <180 mmHg systolic), heart rate or history of previous myocardial infarction.[210] *Benefit is greater in the setting of anterior myocardial infarction, diabetes, low blood pressure (<100 mmHg systolic) or high heart rate (>100 beats per minute). The earlier therapy begins, the better the outcome with the greatest benefit decidedly occurring when therapy is given within the first 3 h; proven benefit occurs, however, up to at least within 12 h of onset of symptoms. Benefit is less with inferior AMI, except for the subgroup with associated right ventricular infarction (ST-elevation in V_{4R}) or anterior-segment depression indicative of a posterior current of injury as often occurs with occlusion of a large circumflex coronary artery.*

Class IIa

1. ST elevation (as earlier), age 75 years or older

Comment

Persons above age 75 benefit from thrombolytic therapy, but because of the high overall mortality rate, the relative benefit is reduced.[210]

Class IIb

1. ST elevation (as earlier), time to therapy (as previously) greater than 12 to 24 h
2. Blood pressure on presentation >180 mmHg systolic and/or >110 mmHg diastolic associated with a high-risk myocardial infarction

The potential for a therapeutic benefit of thrombolysis when the blood pressure is markedly elevated must be carefully considered against the increased risk of intracranial hemorrhage under these circumstances. Lowering the blood pressure pharmacologically before administering thrombolytics has been recommended but is of unproven benefit. If available, coronary artery bypass grafting or primary PTCA should be considered.[1]

Class III

1. ST-segment elevation, time to therapy >24 h, ischemic pain resolved
2. ST-segment depression only

Comment

In the absence of ST elevation, there is no evidence for benefit in patients with normal electrocardiographic or nonspecific changes. Using current thrombolytic regimens, there is some suggestion of harm (including increased bleeding risk) for patients with ST-segment depression only.[157,210] *When marked ST-segment depression is confined to leads V1-V4, there is a likelihood that this reflects a posterior current of injury and suggests a circumflex artery occlusion for which thrombolytic therapy would be considered appropriate. The prospective analysis of the late assessment of thrombolytic efficacy (LATE) trial*[272] *also casts some uncertainties about withholding thrombolytic therapy from this heterogenous group of patients.*

INDICATIONS FOR THROMBOLYTIC THERAPY

Reperfusion therapy should be given immediate consideration in all patients presenting with AMI. Patients with ST-segment elevation in two or more contiguous leads or a bundle branch block masking ST-segment changes occurring within 12 h of symptoms are candidates for thrombolytic therapy.[210,273] In the ISIS-2 trial,[274] patients with bundle branch block had a mortality of 28 percent when treated with a placebo versus 19.8 percent when treated with streptokinase and aspirin. A similar beneficial effect was noted in ISIS-3.[275] Patients of unknown age with bundle branch block and with the clinical features of AMI are candidates for thrombolytic therapy.[273] *Patients with ongoing symptoms suggestive of myocardial ischemia should be repeatedly evaluated by 12-lead ECGs as frequently as every 10 to 15 min in order to identify ST-segment elevation as soon as possible*. Conversely, ST-segment elevation in the absence of suggestive symptoms should raise such possibilities as early repolarization, pericarditis, and previous infarction with aneurysm formation. Elderly patients should not be excluded from thrombolytic therapy primarily because of their age or because of the increased risk of bleeding. In patients over 75 years of age enrolled in the GISSI-2 trial, there were 4.2 fewer deaths per 100 patients in those treated with streptokinase than there were in the control group;[276] while in ISIS-2, there were 3.3 fewer deaths per 100 patients in those patients over 70 years of age who were treated.[211] The results of ISIS-3,[275] GUSTO-I,[15] and GUSTO-III[277] showed benefit regardless of age or site of infarction.

Large, placebo-controlled clinical trials have consistently demonstrated reduced mortality in patients receiving thrombolytic therapy within 6 h of the onset of an AMI.[278] In comparison with conventional medical therapy, thrombolytic therapy reduces the 35-day mortality by 21 percent. It is estimated that 34 lives per 1000 patients treated are saved when thrombolysis is used within the first hour of symptom onset, compared to 16 lives saved per 1000 treated when thrombolytics are given 7 to 12 h after the onset of

symptoms.[1] The true benefit of thrombolytic therapy between 6 and 12 h has been somewhat unresolved; however, the ACC/AHA guidelines[1] have indicated acceptance that there may be a definite benefit between 6 and 12 h and have, therefore, recommended that the time limit for therapy be up to 12 h from the onset of symptoms. The EMERAS trial[279] showed an insignificant (14 percent) improvement in survival using streptokinase between 6 and 12 h after an infarction, while the LATE trial[280] observed a significant improvement (22 percent) in patients treated with rt-PA up to 12 h after infarction. Results of pooling the data from the LATE, EMERAS, and ISIS trials indicate a statistically significant improvement in survival with the use of thrombolytics up to 12 h after the onset of symptoms. Thus, the benefit of thrombolytics given between 6 and 12 h postinfarction is greater in patients classified with high-risk infarction, such as those with severe heart failure. In patients with anterior infarction, left bundle branch block, or severe hypotension, thrombolytic therapy should be given even if the precise time of onset of symptoms is unknown. Conversely, the young patient with inferior infarction having ST-T-segment elevation might not benefit greatly from thrombolytic therapy after 6 h from the onset of symptoms.

In contrast, patients with ST-segment depression, T-wave inversion, or no ECG changes have not been shown to benefit from thrombolytic therapy, as noted earlier.[281] A major problem in patients with nonspecific ST depresson or T-wave inversion is that less than 20 percent will have infarction as opposed to ST-segment elevation, in which case 90 to 95 percent will have infarction. To properly assess thrombolytic therapy in this group of patients without ST-segment elevation, one would need to have some objective marker other than the ECG to triage for infarction upon admission, which, until recently, was not possible (see previous discussion of MB-CK subforms). In the TIMI-III trial, the importance of differentiating non-Q-wave infarction from unstable angina was demonstrated, in that patients with unstable angina receiving rt-PA experienced an increased incidence of reinfarction and death compared with conventional therapy, and the trial had to be discontinued.[157] However, the mean time of initiating thrombolytic therapy in patients with non-Q-wave infarction was 9 h from the onset of symptoms and was probably too late to have a significant beneficial effect (see "Management of Non-Q-Wave Myocardial Infarction" later). An appropriate trial in which non-Q-wave infarction is diagnosed upon presentation to the emergency department within 20 to 30 min, as with MB-CK subforms or myoglobin, and is followed by thrombolytic therapy or PTCA is yet to be performed. This would be an important trial, since about 50 percent of infarctions in the United States are now non-Q-wave infarctions.[126]

CONTRAINDICATIONS TO THROMBOLYTIC THERAPY

The major contraindication to thrombolytic therapy is a cerebrovascular accident (CVA) within the preceding 3 months. A hemorrhagic CVA in the past is an absolute contraindication, whereas a nonhemorrhagic CVA in the more distant past with complete or nearly complete recovery is only a relative contraindication.[282] Patients who have undergone recent (within 2 weeks) major surgery or vaginal delivery are not candidates for thrombolytic therapy, and neither are those with active internal bleeding or bleeding from a peptic ulcer. Puncture of a noncompressible vessel within the previous 10 days makes thrombolytic therapy inadvisable. Other absolute contraindications to thrombolytic therapy include suspected aortic dissection, recent head trauma or known intracranial neoplasm, and pregnancy. Previous exposure to streptokinase or anistreplase (APSAC) requires the use of rt-PA in subsequent attempts at thrombolysis. Systemic arterial hypertension and cardiopulmonary resuscitation should no longer be regarded as absolute contraindications to thrombolytic therapy. The ISIS-2 trial found that, among patients with a systolic blood pressure greater than 175 mmHg, the mortality rate was lower in those receiving streptokinase than it was in control subjects (5.7 versus 8.7 percent).[274] Some practitioners consider a recorded blood pressure greater than 200/120 an absolute contraindication. A history of severe chronic hypertension with diastolic blood pressure greater than 100 mmHg, with or without drug therapy, is a relative contraindication. Most clinicians proceed with thrombolytic therapy in a high-risk patient if elevated blood pressure normalizes promptly, with the easing of pain and anxiety through the use of narcotics and more direct therapy, including nitroglycerin and beta blockers. Califf et al. noted that patients who had brief (<10 min), nontraumatic cardiopulmonary resuscitation had no evidence of tamponade or hemothorax with thrombolytic therapy.[283] Prior administration of cardiopulmonary resuscitation should be considered a relative contraindication, since the risk of further bleeding in the chest may not outweigh the benefit. Other relative contraindications include trauma or surgery less than 2 weeks previously, active peptic ulcer disease, and bleeding diathesis or current use of anticoagulants. The absolute and relative contraindications for thrombolytic therapy are summarized in Table 42-10.

Table 42-10: Absolute and Relative Contraindications to Thrombolytic Therapy

Absolute Contraindications	Relative Contraindications
Active internal bleeding	History of nonhemorrhagic cerebrovascular accident in distant past with complete recovery
Intracranial neoplasm or recent head trauma	Prolonged, traumatic CPR
Suspected aortic dissection	Recent trauma or surgery >2 weeks previously
Pregnancy	Active peptic ulcer disease
History of hemorrhagic cerebrovascular accident or recent nonhemorrhagic cerebrovascular accident	History of severe hypertension with diastolic blood pressure >100
Recorded blood pressure >200/120	Bleeding diathesis or concurrent use of anticoagulants
Trauma or surgery that is a potential bleeding source within previous 2 weeks	Previous treatment with SK or APSAC if being considered (does not apply to rt-PA)
Allergy to SK or APSAC if being considered	

ABBREVIATIONS: CPR = cardiopulmonary resuscitation; SK = streptokinase; APSAC = anistreplase; rt-PA = recombinant tissue plasminogen activator.

CHOICE OF THROMBOLYTIC AGENT

Four thrombolytic agents have been approved in the United States: streptokinase (SK), rt-PA, APSAC, and reteplase (r-PA). Each has been shown to limit infarct size, preserve ventricular function, and improve survival rates. These drugs and their pharmacologic properties are discussed in detail in Chap. 44.

In angiographic studies,[284,285] rt-PA and r-PA recanalized the coronary artery at 90 min in about 70 to 75 percent of patients, compared with 55 to 60 percent of those receiving SK or APSAC. Patency determined at 24 to 36 h is essentially the same for all four agents. The time course for this "catch-up" phenomenon in vessel patency, as defined by the GUSTO angiographic substudy, occurs within the first 3 h after administration of the lytic agent.[15] The ISIS-3 trial reported a 30-day mortality rate, which was the same for all three agents (10.5 percent for SK, 10.6 percent for APSAC, and 10.3 percent for rt-PA).[275] Conversely, the GUSTO trial found a 30-day mortality rate of 6.3 percent for the accelerated rt-PA regimen, which was significantly less than the 7.2 percent mortality with SK and subcutaneous heparin and less than the 7.4 percent mortality with SK and intravenous heparin[286] (Table 42-11). This absolute reduction of 1 percent reflects a 14 percent reduction in the risk of death, compared with that of SK or APSAC. A major difference why GUSTO I demonstrated an advantage for rt-PA and GISSI-2 or ISIS-3 did not was the manner in which heparin was used in GUSTO I. In GUSTO III,[277] rt-PA and r-PA exhibited similar beneficial results and a similar incidence of side effects. The 1-year follow-up on the GUSTO-I patients[287] showed that the 1 percent lower mortality rate compared with SK was maintained, which provided further evidence that rt-PA is more effective than SK.

Table 42-11: 30-Day Mortality Rates from the GUSTO Trial

Regimen	Mortality, %
SK and subcutaneous heparin	7.2
SK and intravenous heparin	7.4
Accelerated rt-PA and intravenous heparin	6.3[a]
Combination rt-PA and SK with intravenous heparin	7.0

[a]14% reduction in mortality rate was achieved with the accelerated rt-PA regimen versus the SK strategies ($p = 0.001$).
ABBREVIATIONS: SK = streptokinase; rt-PA = recombinant tissue plasminogen activator.

r-PA is a modified recombinant form of rt-PA with a longer half-life (15 min) and can be given as 2 boluses 30 min apart (see Chap. 44). In the initial open-phase trials (Reteplase Angiographic Phase II International Dose-Finding Trial: RAPID I and RAPID II),[288,289] patency was compared to that of rt-PA. In RAPID I, 60-min patency with r-PA was 78 percent, versus 66 percent for rt-PA, and TIMI-III flow was 51 percent, versus 33 percent for rt-PA. At 90 min after administration, patency was 85 percent for r-PA and 77 percent for rt-PA, with TIMI-III flow being 63 percent for r-PA and 49 percent for rt-PA. These results suggested slightly better patency rates with r-PA than with rt-PA. In the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial of 6000 patients, r-PA was compared with SK.[290] The mortality and the incidence of complications for r-PA was identical to SK. This was followed by the GUSTO-III trial,[291] which compared r-PA with rt-PA, and showed that mortality and bleeding complications were similar. At 30 days, the mortality rate in the r-PA group was 7.43 percent; with rt-PA, it was 7.22 percent. The rate of hemorrhagic strokes was very similar: 0.91 percent for r-PA, versus 0.88 percent for rt-PA. The overall stroke rate was 1.67 for r-PA versus 1.83 for rt-PA. The rate of bleeding events was virtually identical between the two treatments. There remains some lack of clarity, since there were 10,000 patients in the r-PA limb and 5000 in the rt-PA limb, and the confidence limits were somewhat wide, leaving the interpretation open to some extent. Utilizing 95 percent confidence intervals, interpretation may be that rt-PA is 1.1 percent better than r-PA or that r-PA is 0.7 percent better than rt-PA. For this reason, there is still some uncertainty as to whether these drugs are truly equivalent.[291] Nevertheless, the generally accepted conclusion is that the two drugs have similar efficacy and safety.

Bolus administration of a thrombolytic agent, in addition to being more convenient, can be given with the assurance that the patient has received the full dose of the thrombolytic agent, which is not always the case in an infusion that will require 3 h or longer. Two new agents that can be given by bolus have reported results showing similar efficacy to alteplase: one is lanatoplase and the other TNK-tpa. Both agents were found to have comparable rates of intracranial hemorrhage in preliminary trials (0.9-1.1 percent) and are awaiting approval for use by the FDA.

The selection of a thrombolytic agent must be based on its adverse effects as well as upon its efficacy. The major risk with any thrombolytic agent is its propensity for causing bleeding, with the most devastating bleeding being a hemorrhagic stroke. In the GUSTO trial, the frequency of hemorrhagic stroke was 0.49 percent for SK and subcutaneous heparin, 0.54 percent for SK and intravenous heparin, 0.72 percent for rt-PA, and 0.94 percent for combined SK and rt-PA. There was a small but significant excess of hemorrhagic strokes for rt-PA and for the combined rt-PA and SK strategy ($p < 0.001$) compared with the SK arms. The combined end point of death or nonfatal hemorrhagic stroke was, however, significantly reduced in the rt-PA group, compared with the SK groups (6.6 versus 7.5 percent; $p = 0.004$).[286] One reason to choose rt-PA over SK is the 14 percent decreased risk of mortality. Nevertheless, a 10-fold greater cost of rt-PA must be considered. Choosing between rt-PA and r-PA, since both are equally effective and cost the same, may depend on choosing between monitoring an intrave-nous infusion of rt-PA versus 2 bolus injections of r-PA separated by 30 min.

Another thrombolytic agent, TNK-tPA, is in the process of clinical evaluation (see Chap. 44). It has a short half-life of about 17 min and can be given as a single bolus. It is highly fibrin-specific and somewhat

resistant to plasminogen activator inhibitor.[292] The phase II trial Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-1)[293,294] was performed on 3235 patients, and the results were comparable to that of rt-PA in GUSTO-I and III. In the ASSENT-2 trial[293] the 30-day mortality was 6.17 versus 6.15 percent for rt-PA, and the bleeding rates were also similar. Another thrombolytic agent undergoing clinical trials is that of lanoteplase (see Chap. 44). Preliminary results showed no difference in 30-day mortality, which was 6.6 percent and 6.7 percent with alteplase and lanoteplase, respectively.[295]

DOSE AND ADMINISTRATION OF THROMBOLYTIC AGENTS

Streptokinase is given in a dose of 1.5 million U intravenously over 30 to 60 min. Since antibodies develop and may persist for several years, a subsequent need for thrombolytic therapy, as for early or late reocclusion, would require the use of rt-PA or r-PA. If the patient has had a streptococcal infection within 3 to 6 months, the use of rt-PA is preferable. Although APSAC is identical to SK as a thrombolytic agent, it can be given as a rapid infusion of 30 U over 5 to 10 min. Its therapeutic half-life is similar to that of SK, which is about 90 min. In contrast, the half-life of rt-PA is about 5 min. The FDA-approved dose of rt-PA is an initial bolus of 15 mg, followed by an infusion of 50 mg or 0.75 mg per kilogram of body weight over the next 30 min, and an infusion of 35 mg or 0.50 mg per kilogram of body weight over the subsequent 60 min, for a total of up to 100 mg given over 90 min. Reteplase is given as an initial bolus of 15 megaunits (MU), followed by a second bolus of 15 MU in 30 min.

OVERALL STRATEGY FOR REPERFUSION OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

The criteria for initiating thrombolytic therapy are as follows (Table 42-12):

Table 42-12: Criteria for Initiating Thrombolytic Therapy

Chest pain consistent with angina
ECG changes
ST ↑ ≥ 1 mm, ≥2 contiguous limb leads
ST ↑ ≥ 2 mm, ≥2 contiguous precordial leads
New left bundle branch block
Absence of contraindications

1. Patients presenting with chest pain suggestive of myocardial ischemia, having ST-T-segment elevation greater than 1 mm in two contiguous limb leads or greater than 2 mm in two contiguous precordial leads or new left bundle branch block and who are within 6 h of the onset of symptoms should receive thrombolytic therapy if there are no contraindications. In patients presenting between 6 and 12 h of the onset of symptoms, one must weigh more heavily the risk versus the benefit. Patients presenting after 12 h are no longer routinely considered for thrombolytic therapy.
2. Contraindications for thrombolytic therapy are absolute or relative, as discussed earlier (Table 42-10).
3. In patients receiving rt-PA or r-PA, it is recommended that heparin be given as a bolus at the initiation of infusion (60 U/kg) and then an additional maintenance dose of 12 U/kg/h (with a maximum of 4000 U bolus and a 1000 U/h infusion for patients weighing >70 kg), adjusted to maintain a partial thromboplastin time (PTT) at 1.5 to 2.0 times control (50 to 70 s) for 48 h. Continuation of heparin infusion beyond 48 h should be considered in patients at high risk for systemic or venous thromboembolism. In patients treated with nonselective thrombolytic agents (streptokinase, anistreplase, or urokinase), heparin should be given intravenously for those who are at high risk for systemic emboli (large or anterior myocardial infarction, atrial fibrillation, previous embolus or known left ventricular thrombus). It is recommended that heparin be withheld for 6 h

and that aPPT testing begin at that time. Heparin should be started when aPPT returns to 2 times control (approximately 70 s), then infused to keep aPPT 1.5 to 2.0 times control (initial infusion rate approximately 1000 U/h). After 48 h, a change to subcutaneous heparin or warfarin or aspirin alone should be considered.

4. Patients allergic to SK or APSAC who require thrombolytic therapy should receive rt-PA or r-PA. Patients who received SK or APSAC and who again require thrombolytic therapy should receive rt-PA or r-PA.
5. Patients presenting with ST-T-segment depression and chest pain are not candidates for thrombolytic therapy. These patients need to be triaged, as indicated in Fig. 42-3, as to whether their pain is of cardiac or noncardiac origin. If the former, those with either unstable angina (see Chap. 41) or non-ST-elevated infarction should be treated with intravenous unfractionated heparin or low-molecular-weight heparin subcutaneously. In all patients not treated with thrombolytic therapy who do not have a contraindication to heparin, subcutaneous unfractionated heparin (e.g., 7500 U bid) or low-molecular-weight heparin (e.g., Enoxoparin) 1 mg/kg bid should be used. In patients who are at high risk for systemic emboli, intravenous heparin is preferred.
6. As discussed subsequently and in detail in Chapter 46, PTCA as a primary procedure is an alternative to thrombolytic therapy only if performed in a timely fashion by individuals skilled in the procedure and supported by experienced personnel in high volume centers (class I). The individual must perform 75 such PTCA procedures per year, and the center a minimum of 200 PTCAs per year. PTCA is indicated in patients with a contraindication to thrombolytic therapy because of a severe bleeding diathesis or in those who are in cardiogenic shock (class IIa).
7. Elective angioplasty should be reserved for patients who develop ischemia or reinfarction or in whom thrombolytic therapy appears ineffective. In patients in whom angioplasty cannot be performed and who develop recurrent ischemia with possible infarction, the possibility of readministering a thrombolytic agent should be considered; rt-PA may be given in a full dose if the patient has not received it for 24 to 48 h.

Percutaneous Transluminal Coronary Angioplasty as a Primary Therapy for Acute Myocardial Infarction

Recommendations[1]:

Class I

1. "As an alternative to thrombolytic therapy in patients with AMI and ST segment elevation or new or presumed new LBBB who can undergo angioplasty of the infarct artery within 12 hours of onset of symptoms or >12 hours if ischemic symptoms persist, if performed in a *timely fashion* by persons skilled in the procedure** and supported by experienced personnel in an appropriate laboratory environment*."***[1]
2. "In patients who are within 36 hours of an acute ST-elevation/Q-wave or new LBBB MI who develop cardiogenic shock, are <75 years of age, and revascularization can be performed within 18 hours of onset of shock."[1]

Class IIa

1. "As a reperfusion strategy in candidates for reperfusion who have a contraindication to thrombolytic therapy."[1]

Class IIb

1. "In patients with AMI who do not present with ST elevation but who have reduced [less than Thrombolysis in Myocardial Infarction (TIMI) grade 2] flow of the infarct-related artery and when angioplasty can be performed within 12 hours of onset of symptoms."[1]

Class III

"This category applies to patients with AMI who

1. Undergo elective angioplasty of a non-infarct related artery at the time of AMI
2. Are beyond 12 hours after onset of symptoms and have no evidence of myocardial ischemia
3. Have received fibrinolytic therapy and have no symptoms of myocardial ischemia"[1]

Comment

There is serious concern that a routine policy of primary PTCA for patients with AMI will result in unacceptable delays in achieving reperfusion in a substantial number of cases and less than optimal outcomes if performed by less experienced operators. Strict performance criteria must be mandated for primary angioplasty programs so that such delay in revascularization and performance by low-volume operators and centers do not occur. Interventional cardiologists and centers must operate within a specified "corridor of outcomes" to include (1) balloon dilatation within 90 (±30) min of admission and diagnosis of AMI; (2) a documented clinical success rate with TIMI-2 through 3 flow attained in >90 percent of patients without emergency coronary artery bypass graft, stroke, or death; (3) emergency coronary artery bypass graft rate <5 percent among all patients undergoing the procedure; (4) actual performance of angioplasty in a high percentage of patients (85 percent) brought to the laboratory; and (5) mortality rate <10 percent. Otherwise, the focus of treatment should be the early use of thrombolytic therapy.

ANGIOPLASTY AS PRIMARY OR ADJUNCTIVE THERAPY TO THROMBOLYSIS

Detailed discussions of PTCA and its indications appear in Chap. 45. Comprehensive discussions of PTCA in the treatment of acute MI are presented in Chapter 46. Direct angioplasty has been compared with thrombolytic therapy in a meta-analysis of 10 randomized trials involving 2606 patients.[297] In 1290 patients treated with primary PTCA, the mortality rate at 30 days was 4.4 percent compared to 6.5 percent in 1316 patients treated with thrombolytic therapy. Pooled rates of nonfatal reinfarction or death were also lower in the PTCA as opposed to the thrombolysis groups. The incidence of stroke was also lower with PTCA than it was with thrombolysis. These authors concluded that "primary PTCA appears to be superior to thrombolytic therapy for treatment of patients with AMI, with the proviso that success rates for PTCA are as good as those achieved in these trials. Data evaluating longer-term outcome, operator expertise, and time delays before treatment are needed before primary PTCA can be recommended universally as the preferred treatment."[297] Registry data (Second National Registry of Myocardial Infarction) of 4939 patients with acute AMI (ST-segment elevation) who received primary PTCA and 24,705 who received alteplase showed similar in-hospital mortality (5.2 percent and 5.4 percent, respectively) in the absence of shock.[298] These results also add some caution against the general embracement of primary PTCA over thrombolysis in the treatment of ST-segment elevation myocardial infarction.

In the case of cardiogenic shock in AMI (ST-segment elevation/new left bundle branch block) primary angioplasty, if rapidly available, offers benefit over thrombolysis as part of a strategy of emergency revascularization.[299] In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) Trial, a strategy of emergency revascularization was compared with initial medical stabilization and delayed revascularization based on clinical indicators. The 30-day mortality showed a favorable but not significant ($p = 0.11$) trend for emergency revascularization over initial medical restabilization in the case of mortality at 30 days (46.7 versus 56.0 percent, respectively). The mortality at 6 months, however, was significantly lower ($p = 0.027$) for the emergently revascularized group (53.5 percent) compared to the initially medical stabilized group (65.7 percent). Patients <75 years old had a more favorable outcome with emergency revascularization than did older patients (>75) with a 15.4 percent reduction in 30-day mortality (56.8 versus 41.4 percent, $p < 0.01$). Patients in the emergency revascularization group who were >75 years old fared worse than they did in the medical stabilization group. PTCA was the revascularization procedure in 60 percent, and coronary artery bypass grafting was used in 40 percent of patients with similar outcomes.

Thus, there is increasing evidence of the efficacy of PTCA as an alternative to thrombolysis in the treatment of ST-segment elevation/new left bundle branch block myocardial infarction. It is the method of choice in cardiogenic shock and in the presence of contraindications for thrombolytic therapy. There is increasing concensus that, in high-volume centers with skilled, experienced operators, PTCA is the procedure of

choice if it can be performed in a timely manner (generally within the first 2 h). Indeed a report showed a 53 percent reduction in 30-day mortality in patients having PTCA within the first 2 h of pain in comparison to those more than 2 h into their pain.[1,300] Because of the logistic issues involved (including transfer from a community hospital to an interventional center) in obtaining PTCA within an appropriate time frame, the approach of combining a low-dose thrombolytic (to obtain early patency) with PTCA outside of the 2-h time is being explored.[1] These and other issues including the use of stents are discussed in detail in Chapter 45.

Several caveats must be considered before embracing PTCA as the therapy of choice for AMI generally. Only about 20 percent of hospitals in the United States have cardiac catheterization laboratories and relatively few can perform PTCA on an emergency basis. In many cases the time delay involved in transferring a patient to a hospital capable of performing emergency PTCA may outweigh any benefit.[1] *The excellent results for emergency PTCA described earlier were achieved by highly experienced and enthusiastic investigators in hospitals that have devoted extraordinary support and personnel to achieving opening of the coronary artery within 60 to 90 min of arrival.*[1,301,302] Available data suggesting that emergency PTCA may be comparable to thrombolysis in many community settings were alluded to previously.

Heparin as Conjunctive or Adjunctive Therapy

Recommendations for heparin administration post-MI[1]:

Class I

1. Patients undergoing percutaneous revascularization.

Class IIa

1. Administer intravenously in patients undergoing reperfusion therapy with rt-PA (alteplase) or r-PA (reteplase).
2. Administer subcutaneously unfractionated heparin (7500 U BID) or low-molecular-weight heparin (enoxaparin 1 mg/kg bid) in all patients not treated with thrombolytic therapy who do not have a contraindication to heparin. Intravenous heparin is acceptable as an alternative and is preferred in patients who have a large or anterior myocardial infarction, atrial fibrillation, a known left ventricular thrombus, or a previous embolus and thus are at high risk for systemic emboli.
3. Administer intravenously in patients treated with nonselective thrombolytic agents (streptokinase or anistreplase) who are at high risk for systemic emboli (anterior or large infarction, history of embolus, atrial fibrillation, or demonstrable left ventricular thrombus).

It is recommended that heparin not be started immediately but that an activated partial thromboplastin time (aPTT) be drawn at 4 h and that heparin be started when the aPTT returns to less than twice control (about 70 s).

Lysis of a thrombus by any thrombolytic agent induces a surface that is perhaps the most thrombogenic known.[285,303] Furthermore, lysis with either rt-PA or SK has been shown to be associated with marked elevation of plasma levels of thrombin, which return to normal after 24 h.[304] Since aspirin has no effect on thrombin-induced platelet aggregation,[305] the use of heparin during the initial 24 to 48 h was assumed to be critical to prevent rethrombosis and reocclusion.

The necessity of heparin for maintaining coronary patency induced by rt-PA was established in the HART trial.[284] In this trial, 208 patients received rt-PA within 4 h of the onset of their infarction. Simultaneously, 50 percent of these patients received heparin administered as a bolus, followed by an intravenous infusion, while the remainder received only oral aspirin in a dose of 81 mg/day. Coronary angiographic studies performed at 18 to 81 h showed a patency of 82 percent in the group receiving heparin and 52 percent in the group receiving aspirin (Fig. 42-7). Stratifying the group on the basis of PTT established an excellent correlation between patency and PTT (Fig. 42-8). In patients with aPTT of <45 s, the patency was only 45

percent; patency was 83 percent or greater in patients with aPTT >45 s.[306] The findings of HART were confirmed by Bleich et al.,[307] who showed that rt-PA given with heparin had a patency of >90 percent; without heparin, the patency rate was 44 percent (Fig. 42-7). In the National Heart Foundation of Australia Study,[308] all patients received rt-PA, followed by intravenous heparin for 24 h. They were then randomized to continue heparin for 72 h or were switched to antiplatelet agents. The study found the patency rate at 72 h to be the same for both groups.

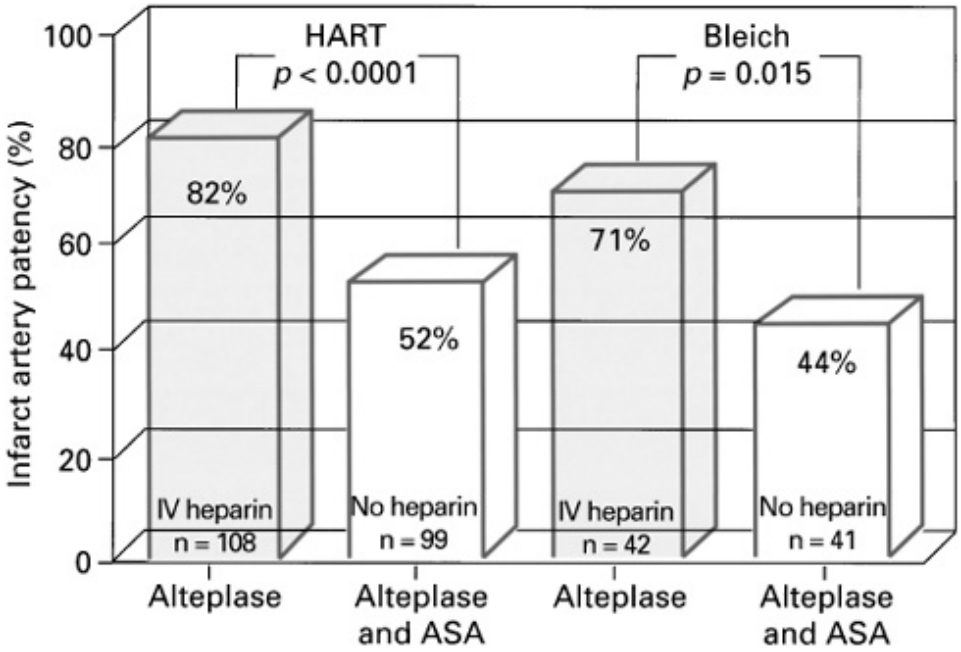

Figure 42-7: Influence of effective anticoagulation on early patency rates with rt-PA. Patency assessed angiographically at an average of 18 to 81 h is significantly greater in patients treated with intravenous heparin.

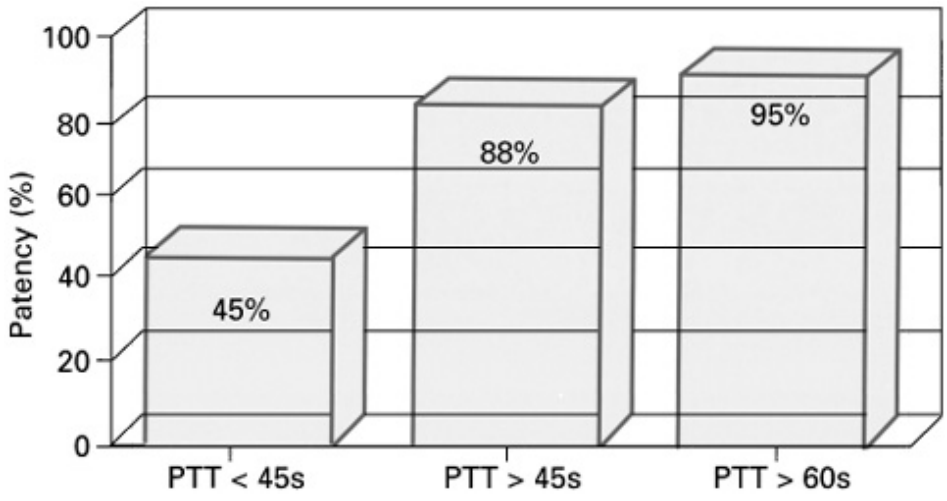

Figure 42-8: Retrospective analysis of the HART trial showing the relationship between increased PTT and coronary artery patency (*n* = 94). This illustrates the importance of heparin.

Heparin appears to act by preventing early reocclusion, at least after rt-PA.[309,310] The adjunctive heparin therapy in both GISSI-2 and ISIS-3 was administered by the subcutaneous route (12 h after thrombolytic therapy in GISSI-2 and 4 h afterward in ISIS-3). Such a heparin regimen seems to be suboptimal adjunctive

therapy for rt-PA and is believed to be the main reason why rt-PA was not shown to be superior over SK in GISSI-2 and ISIS-3. A subcutaneous heparin dose of 12,500 U twice a day used in the megatrials failed to provide therapeutic anticoagulation for at least 24 h in various cohort analytic studies.[311,312] The administration of SK without adjunctive heparin has not been properly tested. However, the ISIS data raise the possibility that it may not be necessary in the early hours, since the marked increase, after SK administration, in plasma levels of fibrinogen breakdown products, which inhibit platelet aggregation, may prevent rethrombosis and reocclusion.[273] In contrast, these platelet-inhibiting breakdown products are not present in high concentrations with the fibrin-selective agents, rt-PA and r-PA. The results of the SCATI trial argue for the existence of a beneficial effect of heparin even in patients treated with SK.[313] In the SCATI trial, patients receiving SK with subcutaneous heparin had a mortality rate of 4.5 percent, while those receiving SK without heparin had a mortality rate of 8.8 percent.[313] The combined data from these studies suggest that heparin is not necessary to achieve reperfusion but is essential in the first 24 h to maintain patency rates with rt-PA. While heparin may be beneficial when SK is used, subcutaneous administration of heparin appears adequate in this circumstance.[273] At present, heparin is recommended in a bolus of 5000 U intravenously followed by an infusion of 1000 to 1200 U/h to keep the PTT at 1.5 to 2.0 times normal. It is recommended that the PTT not be measured until 4 h after heparin therapy is initiated, because it has not yet reached a steady state. If the PTT has increased more than twofold over normal, the same dose of heparin should be continued; if PTT exhibits less than a twofold increase, the infusion rate of heparin should be increased. Initiation of heparin is recommended either during or following completion of thrombolytic therapy, as discussed earlier, and should be maintained in uncomplicated cases for 24 to 48 h.

The use of heparin has also been recommended conjunctively in patients with AMI who are not being treated with the drug for other reasons, i.e., postthrombolysis or postprimary PTCA. Currently, the American Association of Chest Physicians' guidelines recommend heparin 7500 U twice daily subcutaneously as prophylaxis against deep venous thrombosis.[264] Given the enhanced risk of stroke after AMI in patients with atrial arrhythmias, those with large and especially anterior and apical infarction, and those with history of previous stroke,[314] the ACC/AHA guidelines have incorporated this recommendation for broader prophylaxis against systemic embolization.[1] In high-risk patients, the intravenous route is probably preferable. Heparin therapy should be continued for 48 h and judgment should be made at that point about continuation based on individual patient characteristics. Heparin therapy, including precautions concerning the monitoring of platelet counts because of the risk of heparin-induced thrombocytopenia, is discussed in Chap. 44.

Low-molecular-weight heparins are cleavage products of heparin with a mean molecular weight of ~5000 which have higher anti-Xa activity and less antithrombin activity. Low-molecular-weight heparin preparations are widely used in non-ST-segment elevation acute coronary syndromes (unstable angina, non-Q-wave myocardial infarction) as discussed subsequently in Chapter 41. Low-molecular-weight heparins are being evaluated as adjunctive therapy for thrombolysis.[1] Their use has a class IIa recommendation in all patients with ST-segment elevation AMI who have not been treated with thrombolytics and who do not have a contraindication to heparin.[1] High-risk patients for systemic embolization should be treated with heparin, as noted.

Early Coronary Angiography in Patients with ST-Segment Elevation Not Undergoing Primary Percutaneous Transluminal Coronary Angioplasty

Recommendations[1]:

Class I

1. None

Class IIa

1. In the presence of cardiogenic shock or persistent hemodynamic instability

Class IIb

1. In the presence of evolving large or anterior infarction and evidence that thrombolysis has not resulted in arterial patency and if adjuvant PTCA is planned

Class III

1. Routine use of angiography and subsequent PTCA within 24 h of administration of thrombolytic agents

Routine immediate or delayed angioplasty is not recommended as a standard mode of therapy following thrombolysis. The TIMI-IIA and TIMI-IIB trials,[315] the TAMI study,[310] The European Cooperative Study Group trial,[316] and the SWIFT trial[317] all showed no reduction in the incidence of coronary reocclusion or hospital mortality rates and no evidence of improved ventricular function with routine immediate or delayed angioplasty compared with elective angioplasty in the case of manifest ischemia following thrombolytic therapy. The TIMI-II trial found that angioplasty either performed routinely at 18 to 48 h when anatomically appropriate or in response to induced or spontaneous ischemia did not improve survival or reduce the reinfarction rate at either 6 weeks or 1 year,[318] and neither did it reduce the need for surgery (Fig. 42-9). At present, the most widely accepted recommendation is to perform cardiac catheterization for possible angioplasty or bypass surgery in patients who develop angina or manifest evidence of myocardial ischemia during submaximal exercise testing or who develop hemodynamic or ischemic instability. Thus, if intervening with PTCA generally offers no demonstrable benefit after thrombolysis, there is little apparent reason to perform early coronary angiography routinely.

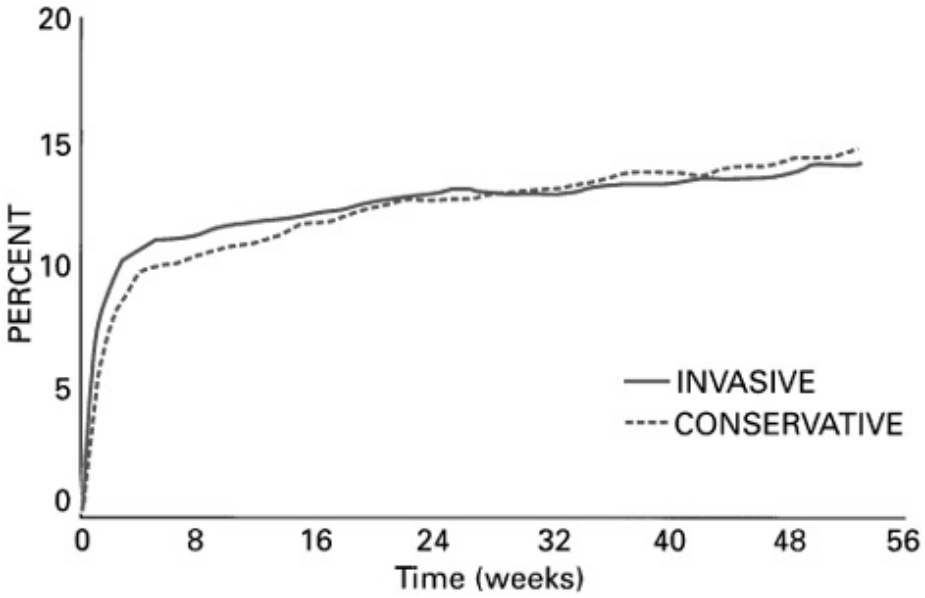

Figure 42-9: Kaplan Meier curves for death and infarction in patients assigned to the invasive or conservative strategies in TIMI-2. Routine cardiac catheterization after thrombolytic therapy and revascularization with PTCA or bypass grafting (when anatomically appropriate) was not a superior strategy to catheterization and revascularization when there is development of spontaneous ischemia or ischemia induced by exercise testing. (Reproduced with permission. Williams DO, Braunwald E, Knatterud G, et al.: One-year results of the thrombolysis in myocardial infarction investigation (TIMI) phase II trial. *Circulation* 1992; 85:533-542.[318] Copyright 1992 American Heart Association.)

Rescue angioplasty to open occluded arteries after presumptive failed thrombolysis has been advocated and, in fact, studies indicate that TIMI grade 3 flow can be achieved in a high percentage of these patients.[319] In the reported TIMI-IV trial, however, it was found that although a strategy of rescue angioplasty could restore flow that is superior to that of thrombolysis alone, the incidence of adverse events for the strategy as a whole was the same as for not undertaking PTCA (35 percent adverse event rate whether or not PTCA

was performed for an occluded artery). Both rates tended to be higher than the incidence in patients with patent arteries (23 percent, $p = 0.07$).[320] *Thus, rescue angioplasty as a routine strategy for failed or presumptively failed thrombolysis cannot be recommended.* This issue is discussed further in Chapter 46.

Patients with cardiogenic shock have a very high mortality (>70 percent) with or without thrombolysis. As noted previously, the results of the reported SHOCK Trial now provide data to suggest that emergency revascularization results in a 41.4 percent survival rate at 30 days.[299] All of these patients received intraaortic balloon assist whether they received revascularization urgently or whether they had initial medical stabilization. These data suggest that other means of metabolically manipulating the myocardial cell may be required for further advances in the management of this lethal complication of AMI.

Emergency or Urgent Coronary Artery Bypass Surgery

Recommendations[1]:

Class I

1. Failed PTCA with hemodynamic instability or persistent pain in patients with coronary anatomy suitable for surgery
2. AMI with medically refractory recurrent or persistent ischemia in patients who are not candidates for PTCA but who have coronary anatomy suitable for surgery
3. After myocardial infarction, at the time of surgical repair of mitral insufficiency or ventricular septal defect

Class IIa

1. Postinfarction cardiogenic shock with coronary anatomy suitable for surgery

Class IIb

1. Failed PTCA and a relatively small mass of myocardium at risk and if hemodynamically stable

Class III

1. When the anticipated operative mortality rate exceeds or equals the mortality rate associated with appropriate medical therapy coronary artery bypass grafting in cardiogenic shock in patients in whom other strategies have failed or where they have not been indicated has been associated with mortality rates from about 10 to 40 percent.[321-323] These results are generally better than those associated with PTCA. Thus, AMI patients with multivessel coronary artery disease or cardiogenic shock who have had unsuccessful thrombolysis and/or PTCA and are within 4 to 6 h of the onset of symptoms should be considered for emergency coronary artery bypass grafting.[1]

Arrhythmias Early in the Course of Acute Myocardial Infarction

BRADYCARDIA

Bradyarrhythmias are relatively common (30 to 40 percent) early in the course of AMI, especially in inferior infarction, or after reperfusion of the right coronary artery, because of the activation of vagal afferents that ultimately result in enhanced parasympathetic tone.[1] Atropine, because of its anticholinergic effects, can be very useful in this situation, since it enhances the discharge rate of the sinus node and facilitates AV conduction,[324] as well as reversing the peripheral effects of excessive cholinergic activity such as vasodilation with associated hypotension. Parasympathomimetic effects with bradycardia, hypotension, and nausea and vomiting are also produced by morphine and can be reversed by atropine. Atropine should be used sparingly and appropriately in AMI, however, because of the protective effect of vagal stimulation against VF.[325]

THE USE OF ATROPINE

Recommendations[1]:

Class I

1. Sinus bradycardia with evidence of low cardiac output and hypoperfusion peripherally or frequent ventricular premature complexes at the onset of symptoms of AMI
2. Acute inferior infarction with type I second- or third-degree AV block associated with symptoms of hypotension, ischemic discomfort, or ventricular arrhythmias
3. Sustained bradycardia and hypotension after administration of nitroglycerin
4. Morphine-induced nausea and vomiting
5. Ventricular asystole

Class IIa

1. In patients with inferior infarction and type I second- or third-degree block at the AV-nodal level (narrow QRS complex or known preexisting bundle branch block) who are symptomatic from the low output and/or vagal predominance

Class IIb

1. Vagal symptoms and sinus bradycardia associated with the administration of morphine
2. Patients with inferior infarction who are asymptomatic with type I second-degree heart block or third-degree block at the AV node
3. Second- or third-degree AV block of uncertain mechanism and unavailability of pacing

Class III

1. Asymptomatic sinus bradycardia and a rate of greater than 40 beats per minute with no signs of hypoperfusion or frequent ventricular premature contractions
2. Type II and third-degree AV block and third-degree AV block with new, wide QRS complex (i.e., block below the AV junction)

SINUS BRADYCARDIA, ATRIOVENTRICULAR BLOCK, OR VENTRICULAR ASYSTOLE

Atropine is indicated for the treatment of type I second-degree AV block, especially with complicating inferior myocardial infarction, and is useful at times in third-degree AV block at the AV node in restoring AV conduction or for increasing the junctional response rate.[1] By increasing the sinus node rate or by improving AV conduction, atropine may improve signs or symptoms of congestive heart failure, hypotension, or frequent, complex ventricular arrhythmias associated with AV block or sinus bradycardia; thus, pacemaker insertion may be avoided.[1] Treatment of sinus bradycardia or first- or second-degree AV block is generally not indicated in the absence of hemodynamic compromise,[1] and atropine should seldom be used in the treatment of type II AV block (location of block below the AV node). Symptomatic bradycardia that is unresponsive to atropine should be treated with pacing.

Atropine should be administered intravenously at a dosage of 0.5 to 1.0 mg and repeated as necessary to achieve an adequate heart rate every 3 to 5 min, up to a total maximum dose of 2.5 mg, which gives complete vagal blockade.[1] Atropine may also be efficacious in ventricular asystole and should be given intravenously at a dosage of 1.0 mg every 3 to 5 min during cardiopulmonary resuscitation up to a maximum of 2.5 mg if asystole persists.

At doses of 0.5 mg or less, atropine may produce, paradoxically, bradycardia and suppression of AV nodal conduction due to a central or peripheral parasympathomimetic effect.[326] Atropine dosage should be titrated carefully, because tachycardia can be induced and ischemia can be worsened. Thus, atropine should

be given in 0.5-mg increments, as noted, to achieve an adequate heart rate of 50 to 60 beats per minute.

HEART BLOCK

Heart block develops in about 10 percent of patients with AMI and is associated with an increased mortality during hospitalization, but it does not predict long-term mortality in those who survive to be discharged.[327-329] Intraventricular conduction delay or bundle branch block is also associated with increased in-hospital mortality.[210] The increase in mortality associated with heart block reflects the extent of myocardial damage, not heart block per se. Thus, a heart block in the setting of anterior myocardial infarction reflects extensive infarction and concomitant destruction of the conduction system and is associated with relatively high mortality. In contrast, heart block with inferior myocardial infarction may primarily reflect ischemia of the AV node rather than extensive tissue damage and is associated with a more favorable prognosis. Because of the overwhelming effect of the extent of myocardial damage on prognosis, pacing has not been shown to lessen mortality associated with AV block or bundle branch block.[328,330] It is likely, however, that pacing will benefit subgroups of these patients with severe slowing of ventricular rates but without extensive myocardial damage[330,331] by preventing hypotension, ischemia, and ventricular escape arrhythmias associated with the appearance of a heart block. In AMI, the risk of developing heart block is augmented by the presence of any evidence of conduction system abnormality including first-degree AV block, Mobitz type I or II AV block, left anterior or posterior hemiblock, or a left or right bundle branch block.[1]

TEMPORARY PACING EARLY IN THE COURSE OF ACUTE MYOCARDIAL INFARCTION

The "Guidelines for the Management of Patients with Acute Myocardial Infarction"[1] place increased emphasis on transcutaneous pacing in view of the availability of new systems that provide standby status for pacing in AMI patients who do not necessitate immediate pacing and are at intermediate risk for developing heart block. These systems use a single pair of multifunctional electrodes, permitting electrocardiographic monitoring, transcutaneous pacing, and defibrillation.[332] Transcutaneous pacing does not entail the risk and complications of transvenous pacing and, because invasive procedures may thus be avoided or delayed, is well suited for use in the patient who has undergone thrombolysis. Percutaneous pacing is painful; if prolonged pacing is required, the patient should be switched to transvenous systems.

Placement* of Transcutaneous Patches and Active (Demand)† Transcutaneous Pacing Recommendations[1,333]:

Class I

1. Sinus bradycardia (rate less than 50 beats per minute) with symptoms of hypotension (systolic blood pressure less than 80 mmHg) unresponsive to drug therapy†
2. Mobitz type II second-degree AV block†
3. Third-degree heart block†
4. Bilateral bundle branch block (alternating left and right bundle branch block or right bundle branch block with alternating left anterior and posterior fascicular block-irrespective of time of onset)*
5. Newly acquired or age-indeterminant left bundle branch block, right bundle branch block, and anterior or posterior fascicular block*
6. Right bundle branch block or left bundle branch block and first-degree AV block*

Class IIa

1. Stable bradycardia (systolic blood pressure greater than 90 mmHg, no hemodynamic compromise, or compromise responsive to initial drug therapy)*
2. Newly acquired or age-indeterminant right bundle branch block*

Class IIb

1. Newly acquired or age-indeterminant first-degree AV block*

Class III

1. Uncomplicated AMI without evidence of conduction system disease

As noted, transcutaneous pacing is intended to be temporary; if prolonged pacing is required, transvenous pacing should be instituted (discussed later). In addition, patients with a high probability of requiring pacing should have it instituted early on.[1] Technical aspects of transcutaneous pacing have been reviewed.[334]

VENTRICULAR ECTOPY, TACHYCARDIA, AND FIBRILLATION

Recommendations[1]:

Class I

1. Ventricular fibrillation should be treated with an unsynchronized electric shock starting with an energy of 200 J. If the initial shock is unsuccessful, a second shock of 200 to 300 J should be administered, and, if required, a third shock of 360 J should be given.
2. Polymorphic ventricular tachycardia (VT) lasting more than 30 s or causing hemodynamic collapse should be treated with an unsynchronized shock, initially of 200 J, and, if necessary, with a second shock of 200 to 300 J, to be followed by a shock of 360 J if the arrhythmia persists.
3. Sustained monomorphic VT associated with hypotension, with blood pressure of less than 90 mmHg, pulmonary edema, or angina should be treated with a synchronized electric shock of 100 J initially, to be followed by high-energy shocks if required.
4. Monomorphic VT that is sustained but not associated with hypotension, angina, or pulmonary edema should be treated with one of the regimens as follows:

   Lidocaine bolus from 1.0 to 1.5 mg/kg intravenously with supplemental boluses of 0.5 to 0.75 mg/kg every 5 to 10 min, up to a maximum loading dose of 3 mg/kg as needed. This loading regimen is followed by an infusion of 2 to 4 mg/min (30 to 50 mg/kg/min).

   Procainamide at a loading infusion rate of 20 to 30 mg/min to a maximum of 12 to 17 mg/kg total, which may be followed by infusion of 1 to 4 mg/min.

   Amiodarone infused initially at 150 mg over 10 min, followed by a constant infusion of 1.0 mg/min for 6 h, and then at a rate of 0.5 mg/min.

   Synchronized electrical cardioversion with an initial starting level of 50 J after anesthesia is induced briefly.

Note that drug metabolism can vary depending upon age, body size, and liver and renal function, and that doses may need to be adjusted accordingly.

Class IIa

1. Antiarrhythmic drug infusions may be utilized after an episode of ventricular tachycardia or fibrillation but should be discontinued after 6 to 24 h, when the need for further management of the arrhythmia is reassessed.
2. Metabolic abnormalities of electrolytes and acid-base balances should be corrected as prophylaxis against recurrence when the initial ventricular arrhythmia has been treated.

Class IIb

1. Polymorphic VT, which is refractory to drug treatment, should be managed by focusing on relieving

the presumptive underlying ischemia with beta blockers, intraaortic balloon pumping, and/or emergency revascularization. Amiodarone infusion, as noted earlier, may also be useful.

Class III

1. Treatment of isolated ventricular premature beats, couplets, runs of accelerated idioventricular rhythm, and nonsustained VT.
2. Use of antiarrhythmic drugs prophylactically during administration of thrombolytic agents.

Ventricular rhythm abnormalities are common during the early phases of AMI, with an incidence of VF within the first 4 h, so-called primary VF, of 3 to 5 percent, which declines rapidly thereafter.[335] Primary VF is thought to be the result of micro reentry mechanisms in the infarct zone.[1] Postulated triggering mechanisms include hypokalemia, hypomagnesemia, enhanced adrenergic tone, acidosis, increased intracellular calcium, increased free fatty acids, and reperfusion-induced production of free radicals.[336-338] Although the relative contribution of each of these factors to early VT/VF and the effects of their specific treatment are not known,[1] epidemiologic evidence suggests that there has been a decrease in the incidence of primary VF,[339] which may be related generally to more aggressive treatment strategies, including the use of beta blockers. Primary VF is associated with increased in-hospital mortality but not with increased long-term mortality for patients who survive and are discharged.[340]

Post-AMI VT occurs in about 15 percent of patients and is also most commonly manifest during the relatively early period.[335] Ventricular tachycardia is classified according to its electrocardiographic morphology (monomorphic or polymorphic) and by its duration and consequences: sustained (lasting more than 30 s and/or causing hemodynamic compromise earlier, which requires intervention) and nonsustained (not resulting in hemodynamic compromise and lasting less than 30 s).[1] Short runs (5 beats or less) of nonsustained VT are common in the early post-myocardial infarction period and do not require specific treatment.

Because primary VF is one of the major contributors to mortality in the first 24 to 48 h after AMI, a great deal of attention has been paid to attempting to define characteristics of ventricular premature beats that predict VT/VF in order to provide prophylaxis. The hierarchical classification of ventricular arrhythmias according to propensity to cause VT/VF-for example, early coupled R-on-T premature beats as opposed to late-cycle, coupled beats-has fallen out of favor because of the realization that the late-cycle premature beats were equally likely to induce VT/VF.[341]

Accelerated idioventricular rhythm normally occurs frequently during the first hours of AMI,[1] and occurs after thrombolysis as a reperfusion arrhythmia. In neither case is it a premonitory rhythm for VT/VF.[342-344] *Accelerated idioventricular rhythm should ordinarily be observed and not treated specifically.*[1] It has been suggested, however, that if accelerated idioventricular rhythm speeds up to a rate of about 120 beats per minute, it should be considered an automatic rhythm for which suppression with lidocaine should be considered.[341]

Formerly, it was common practice, in order to prevent VT/VF, to treat prophylactically with lidocaine either all patients with AMI or, selectively, those with patterns of premature ventricular contractions thought to predict VT/VF. This approach is no longer common practice, because meta-analysis of trials of lidocaine prophylaxis, although confirming a substantial reduction in primary VF, showed evidence of increased mortality, probably because of episodes of profound bradycardia and asystole.[345] Thus, *routine use of prophylactic lidocaine in AMI in the presence or absence of thrombolysis is not recommended.*

Two prophylactic approaches to the prevention of VT/VF, however, are recommended.[1] Routine administration of beta blockers, as described previously, has been shown to reduce the incidence of VT/VF. Also, since evidence suggests that hypokalemia is a risk factor for VT/VF,[337,338] it is recommended that serum potassium levels be kept above 4.0 meq/L by supplementation as necessary. Although the supporting evidence is less compelling, it is also considered to be good clinical practice to maintain serum magnesium

levels above 2.0 meq/L in AMI patients.[1]

TREATMENT OF VENTRICULAR TACHYCARDIA/FIBRILLATION

Electrical cardioversion of VT that is hemodynamically compromising should be performed immediately.[335] Rapid polymorphic VT should be considered the equivalent of VF and cardioverted with an unsynchronized shock of 200 J; monomorphic VT at a rate of greater than 150 beats per minute can be treated initially with a synchronized discharge of 100 J.[1,333] Urgent cardioversion for VT with rates of under 150 beats per minute is usually not needed. Ventricular tachycardia that is tolerated hemodynamically can be approached initially with trials of lidocaine, procainamide, or amiodarone, as outlined earlier, with attention being paid to need for dose modifications based on age and renal and hepatic function.

Ventricular fibrillation should initially be treated with an unsynchronized shock of 200 J, then incrementally with 200 to 300 J, and finally with 360 J as needed.[333] There are no definitive data concerning appropriate adjunctive therapy for fibrillation that is difficult to cardiovert.[1] The Advanced Cardiac Life Support (ACLS) protocol recommends the following hierarchical approach, as needed, to adjunctive therapy of resistant VF:[333] (1) epinephrine (1 mg intravenously); (2) lidocaine (1.5 mg/kg intravenously); and (3) bretylium (5 to 10 mg/kg intravenously). Intravenous amiodarone (150 mg intravenously bolus) may also be used.[1] In the case of resistant or recurrent VT/VF, electrolyte imbalances should be sought and corrected and ongoing ischemia suspected. Beta-adrenergic blockers should be used in recurrent VT or primary VF to decrease both sympathetic input to the heart and ischemia.[1] Intravenous amiodarone should be used in these life-threatening ventricular tachyarrhythmias.[346] *If ongoing ischemia is involved, intraaortic balloon pumping or emergency revascularization should be considered.*

APPROACH TO THE PATIENT WITH ISCHEMIC-TYPE CHEST PAIN AND WITHOUT ST-SEGMENT ELEVATION

As discussed previously, the initial criterion differentiating patients with symptoms compatible with AMI for therapeutic purposes is the presence or absence of ST-segment elevation. This distinction is important, because in the absence of ST-segment elevation, there is no therapeutic benefit to thrombolysis in the AMI patient (Fig. 42-5). Patients without ST-segment elevation are less likely to develop Q waves on the ECG, although about one-half of those who present with ST-segment elevation as well will not develop Q waves, especially if thrombolysis is utilized.[347,348] AMI in which Q waves do not develop is categorized as non-Q-wave myocardial infarction (NQWMI), and most patients (90 percent) present with ST-segment depression.[80,131] NQWMI currently accounts for about 50 percent of all AMIs.[87,126]

An important development over the last several years has been the understanding and acknowledgment that the coronary ischemic syndromes (unstable angina, NQWMI, ST-elevation myocardial infarction) represent a continuum that has come to be referred to as *acute coronary syndrome*. ST-segment elevation AMI is clinically distinct, as described. It is apparent that at the time of initial presentation, the clinician does not know whether the patient with chest pain that is compatible with coronary ischemia and with either ST-segment depression and/or T-wave changes or no ECG changes has unstable angina, NQWMI, or another condition. In the case of ST-segment depression and a compatible history, the initial approach in the emergency department is unchanged but the treatment and, especially, the use of drugs interferring with thrombus formation has changed dramatically.

NQWMI, like infarction with Q-waves, is precipitated by plaque disruption.[349,350] Total coronary occlusion demonstrated angiographically is much less common than in Q-wave myocardial infarction.[349] When total occlusion is present, it probably occurs in a well-collateralized vessel.[349,351] These observations-considered together with early data showing that NQWMIs involved loss of a smaller mass of myocardium than did Q-wave myocardial infarctions[352,353]-are consistent with the concept that either NQWMI is associated with less than total compromise of blood flow to a region of myocardium or that early reperfusion occurs. The evidence that early reperfusion is relatively common in NQWMI was reviewed previously. Because of the residual noninfarcted myocardium at risk distal to a disrupted plaque, moreover,

patients with NQWMI have a high propensity for recurrent ischemia, infarction, and death[89] and present an opportunity for secondary prevention (Fig. 42-10). Nondiagnostic ECGs (ST-segment depression, T-wave inversion) on admission and NQWMI are more common in the elderly and in those with a history of prior AMI.[208,351] Generally, the incidence of NQWMI may be increasing in concert with the aging population and with the increased use of thrombolytic therapy, beta blockers, and aspirin.[1]

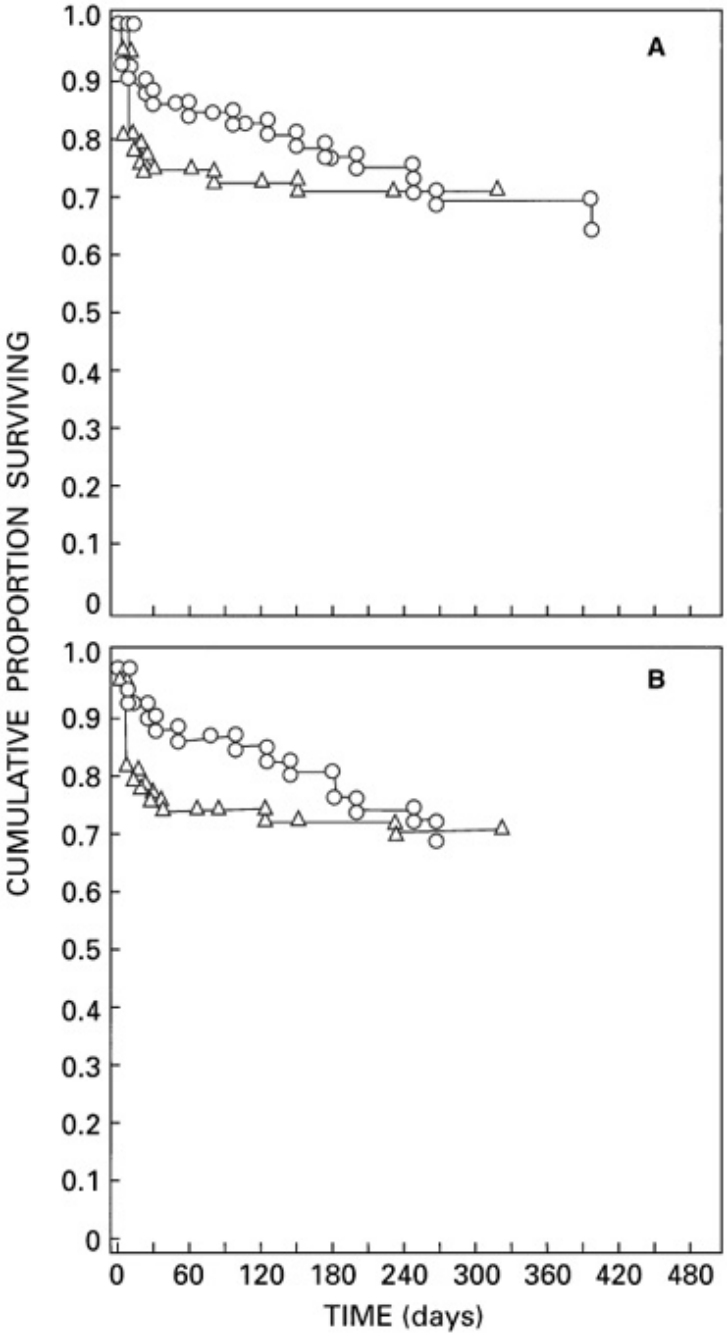

Figure 42-10: Comparison of the survival of patients with Q-wave infarction (triangles) to that of patients with non-Q-wave infarction with (circles). Early mortality was higher after Q-wave infarction than it was after non-Q-wave infarction and no recurrence (*A*), but survival was identical for patients with Q-wave infarction and those with non-Q-wave infarction and an early recurrent infarction (*B*). Long-term mortality rates are similar in Q-wave infarction and non-Q-wave infarction with or without early recurrence.

No therapeutic benefit of thrombolytic therapy was detected in patients with ST-segment depression in the first GISSI study and, in fact, mortality was slightly higher in the SK-treated group.[14] Patients with less

strikingly abnormal ECGs had a lower mortality rate (8 percent) than the control group with ST-segment depression (16.2 percent) but, similarly, there was no benefit to thrombolytic therapy. The ISIS-2 trial illustrated the same principles.[211] ST-segment depression was associated with relatively high mortality and was not decreased by thrombolytic therapy. The mortality rate was relatively low in patients with only T-wave abnormalities (5 percent) and normal ECGs (1 to 2 percent). In the TIMI-IIIB trial of rt-PA in NQWMI and unstable angina, no benefit was observed with thrombolysis as compared with aspirin and heparin.[157] Data from this trial do indicate that patients with NWQMI or unstable angina who have elevated troponin I on admission have an increased risk of nonfatal myocardial infarction or death in the ensuing 6 weeks. Two important conclusions can be derived from the available data: *(1) thrombolysis cannot be recommended in AMI patients without ST-segment elevation, and (2) in the NQWMI group and based on the admission ECG, there is a graded, decremental spectrum of risk ranging from ST-segment depression to T-wave inversion to normal*. The latter data are consistent with increasingly compelling evidence that the presenting ECG permits risk stratification across the range of the acute coronary syndromes increasing from normal ECG (lowest risk) in ascending order as: T-wave inversion; ST-segment depression; ST-segment elevation; ST-segment elevation and depression.[354]

Management of Non-Q-Wave Myocardial Infarction

MEDICAL MANAGEMENT

Recommendations[1]:

Glycoprotein IIb/IIIa Inhibitors

Class IIa

1. For non-ST-segment elevation myocardial infarction patients with high-risk features and/or recurrent, difficult to control ischemia and who do not have contraindications of risk of bleeding

Beta-Adrenergic Blockers

Class I

1. Non-ST-segment elevation myocardial infarction

Heparin

Class IIa

1. Low-molecular-weight heparin subcutaneously or intravenous unfractionated heparin in NQWMI

Early Coronary Angiography and/or Interventional Therapy

Class I

1. In cases of recurrent (stuttering) or persistent symptoms of ischemia, whether spontaneous or induced, in presence or absence of associated ECG changes

Calcium Channel Blockers

Class I

1. None

Class IIa

1. Verapamil or diltiazem may be given to patients in whom beta-adrenergic blockers are ineffective or contraindicated (i.e., bronchospastic disease) for relief of ongoing ischemia or control of a rapid ventricular response with atrial fibrillation after AMI in the absence of congestive heart failure, left ventricular dysfunction, or AV block.

Class IIb

1. In infarction without ST-segment elevation, diltiazem may be given to patients without left ventricular dysfunction, pulmonary congestion, or congestive heart failure. They may be added to standard therapy after the first 24 h and continued for 1 year.

Class III

1. Nifedipine (short-acting) is generally contraindicated in the routine treatment of AMI because of its negative inotropic effects and the reflex sympathetic activation, tachycardia, and hypotension associated with its use.
2. Diltiazem and verapamil are contraindicated in AMI with associated left ventricular dysfunction or congestive heart failure.

Although the situation may change with the increasing availability of very rapid assays for CK isoforms, it is important to remember that, at present, during the initial evaluation in the emergency department, the NQWMI patient-who by definition does not have diagnostic ST-segment elevation-cannot be distinguished from the patient with unstable angina and no myocardial necrosis. Thus, patients are admitted to the CCU or, if judged to be at relatively low risk, to a unit with continuous electrocardiographic monitoring but of less intensity, and *the initial pharmacologic approach, other than avoiding thrombolytic therapy, is identical* (Fig. 42-3). Serial ECGs and cardiac marker measurements should be performed and, in the case of recurrent pain with the development of ST-segment elevation, thrombolysis or primary PTCA should be performed. If the patient has recurrent, stuttering symptoms, angiography should be performed.

ANTITHROMBOTIC THERAPY Drugs Blocking the Glycoprotein IIb/IIIa Receptor

The glycoprotein IIb/IIIa receptor is found in the membrane of platelets.[355] When platelets are activated by a variety of stimuli, including thrombin, collagen, adenosine diphosphate, and epinephrine, the glycoprotein IIb/IIIa receptor changes confirmation to be receptive to one end of the fibrinogen dimer. Occupancy of a glycoprotein IIb/IIIa receptor by the other end of the dimer provides the basis for platelet aggregation. Thus, the glycoprotein IIb/IIIa receptor is considered the final common pathway of platelet aggregation.[356] Multiple therapeutic agents have now been developed to block the receptor.

1. Abciximab is a chimeric Fab fragment of a monoclonal antibody to the glycoprotein IIb/IIIa receptor. Although multiple clinical trials have documented the reduction in the composite of death and nonfatal myocardial infarction with abciximab in the setting of percutaneous interventions,[357-360] only one trial has been completed in the setting of non-ST elevation acute coronary syndrome.[357]
2. Eptifibatide is a cyclical heptapeptide, which binds to the receptor with a short half-life.[361]
3. Tirofiban is a small nonpeptide compound that also has a short half-life. It has been evaluated in over 5000 patients in 2 randomized trials of non-ST elevation acute coronary syndrome.[362-363]

The role of antiplatelet therapy in patients with non-Q-wave infarction is evolving. More than 30,000 patients with an acute coronary syndrome without ST-segment elevation (unstable angina and NQWMI) (see Chap 41) have now been randomly assigned into trials comparing glycoprotein IIb/IIIa inhibitors with a placebo in addition to treatment with aspirin and heparin. A direct comparison of the various IIb/IIIa inhibitors is not available and, thus, no specific choice of agent can be made at this time. The three agents available for clinical practice are described earlier. Only one trial[357] has been performed in patients with unstable angina and non-Q-wave infarction using abciximab. Eptifibatide[361] has been evaluated in a trial of 11,000 patients with non-ST elevation, 45 percent of whom had enzymes positive for myocardial necrosis. Tirofiban has been evaluated in 5147 patients in 2 randomized trials[362,363] of non-ST elevation. Again, about 45 percent of the patients in these trials had positive enzymes for infarction. An overview of these

trials shows a reduction in the composite end point of death and myocardial infarction and the need for revascularization and procedures.[364] There was no reduction in mortality and, when treatment was discontinued, no further beneficial or detrimental effects were observed. Thus, intravenous glycoprotein IIb/IIIa inhibitors are being accepted increasingly as treatment in NQWMI to stabilize the patients in the acute phase and have a IIa recommendation for patients at high risk and with refractory ischemia.[1] Unfortunately, none of the trials have assessed the effect of this therapy in NQWMI alone. It remains to be determined whether these agents will be effective for *routine* use in patients with NQWMI. Since these agents can only be given intravenously, they can only be given for stabilization of the acute phase.

Low-Molecular-Weight Heparin Low molecular weight heparins are antithrombotics that have higher anti-X_a activity than antithrombin (II_a) activity (see Chap 44). Clinically, there is usually only modest prolongation of the activated partial thromboplastin time (aPTT). The role of low-molecular-weight heparin has been extensively explored in patients with acute coronary syndrome, which include a significant proportion of patients with NQWMI (see also Chap. 41). In the FRISC trial of NQWMI and unstable angina, 746 patients received 7500 IU daily of dalteparin versus 760 patients who received a placebo which included aspirin.[364a] At the six-day evaluation there was a 63 percent reduction in death and nonfatal MI in the dalteparin group, but this difference had disappeared by 40 days. In the FRIC Study, dalteparin was given subcutaneously twice a day and was compared with intravenous heparin in patients with unstable angina and NQWMI, during the acute phase of the first 6 days and thereafter.[365] There was no difference in the composite end points either at 6 days or at 45 days. In the ESSENCE trial (Efficacy and Safety of Subcutaneous Exoxiparin in Non-Q-wave Coronary Events),[365a] the study compared the effectiveness of exoxiparin in unstable angina and NQWMI with that of dalteparin. This was a large multicenter double-blind trial where 3171 patients received either twice daily subcutaneous injections of enoxiparin (1 mg/kg) or continuous intravenous infusions of unfractionated heparin (UFH) during the acute period of 2 to 8 days after hospitalization. The primary end point was a composite of death or myocardial infarction or recurrent angina 14 days after hospitalization. In the enoxiparin group, the end point rate was 16.6 versus 19.8 percent for the UFH group. Patients treated with enoxiparin required less revascularization procedures which continued up until 30 days. A cost-effectiveness analysis showed that, despite a small increase in drug cost ($75 per patient), the lower rate of cardiac catheterization and revascularization procedures led to a savings of $1072 per patient if enoxiparin was used instead of UFH. There is considerable difference among the low-molecular-weight heparins, and enoxiparin is claimed to have a high antifactor X_a ratio than that of dalteparin. In another trial,[366] two different doses of enoxiparin were compared in patients with unstable angina and non-Q-wave infarction and the dose of 1 mg/kg every 12 h had a hemorrhage incidence of only 1.9 percent compared to 6.5 percent in doses of 1.25 mg/kg. TIMI 11B[367] enrolled 4020 patients with unstable angina and NQWMI and compared two strategies, UFH or enoxiparin. The analysis showed that at 48 h there were significantly fewer events in the enoxiparin group with a 24 percent reduction in relative risk compared to the group receiving UFH. This beneficial effect was maintained through day 43. Thus, it was concluded that enoxiparin is superior to UFH in the treatment of patients with unstable angina and NQWMI. One concern with all of these studies is there is no separation between NQWMI and unstable angina. *Nevertheless, there does appear to be a role for low-molecular-weight heparin in non-Q-wave infarction, and at the present time studies suggest that enoxiparin is superior to that of other preparations.*

There has been no prospective trial assessing aspirin in NQWMI, but retrospective analysis showed significant benefit.[368] It seems prudent to recommend aspirin (160 to 325 mg/day) for NQWMI (Class I).

BETA BLOCKERS IN NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

No prospective studies of beta blockers have been performed solely in patients with NQWMI, but retrospective analyses of trials performed prospectively, involving both Q-wave infarction and NQWMI, generally show no effect of beta blockers on the reinfarction rate in patients recovering from NQWMI.[89,369,370] Beta blockers may be given to relieve pain or arrhythmia, as discussed previously for Q-wave myocardial infarction. The general benefit of beta blockers in the acute coronary syndromes has led to their being recommended (Class I) for use in NQWMI.[1]

CALCIUM CHANNEL BLOCKERS

The calcium channel blocker diltiazem (immediate-release form) has been shown to be effective in reducing reinfarction in the Diltiazem Reinfarction Study (DRS) (NQWMI)[80] and in the Multicenter Diltiazem Postinfarction Trial (MDIPIT) (Q-wave myocardial infarction and NQWMI)[371] in patients with preserved left ventricular function and with no evidence of congestive heart failure. The DRS study was performed during hospitalization only (14 days); diltiazem was given in the initial 24 to 48 h after NQWMI and was shown to reduce the reinfarction rate by 47 percent, as compared with conventional therapy over a 2-week period. In the long-term prospective, randomized, blinded MDIPIT study, no overall benefit of diltiazem over conventional therapy was observed. In MDIPIT, 20 percent of patients upon entry had pulmonary congestion or clinical cardiac failure, and diltiazem was associated with increased mortality in this subgroup. In the remaining 80 percent of patients, there was a 27 percent reduction in reinfarction and death in the group receiving diltiazem. Most of this benefit was in the prospective NQWMI substudy of 640 patients in whom diltiazem reduced reinfarction and death by 40 percent at the end of 1 year and 34 percent at the end of 4.5 years in patients without evidence of pulmonary congestion.[372] Analysis in the NQWMI subgroup for either end point alone (reinfarction or death) did not show a statistically significant benefit of diltiazem over the placebo. A meta-analysis of the heart-rate-lowering calcium channel blockers (diltiazem and verapamil) in 3 randomized, blinded clinical trials involving 5670 patients, with a mean follow-up of 550 days, showed a clinical event rate of 20 percent in the placebo group and 18 percent in the calcium channel blocker group ($p < 0.01$).[373] Verapamil has been studied somewhat less extensively than has diltiazem in the treatment of AMI; but when it is used within 2 weeks, a 16.7 percent reduction in death or myocardial infarction has been observed.[374] Verapamil has adverse effects on patients with heart failure or bradyarrhythmias when used within the first 24 to 48 h after AMI.[375,376] Most of the data on the use of calcium channel blockers in AMI were collected before the widespread use of aspirin, low-molecular-weight heparin, and platelet GIIb/IIIa inhibitors, and their precise role in the current management of AMI is somewhat ill defined. Currently in the treatment of non-ST-segment elevation AMI, diltiazem has a Class IIa recommendation only in patients in whom beta blockers are ineffective or contraindicated for relief of ongoing ischemia or control of a rapid ventricular response in atrial fibrillation.[1] The role of sustained-release diltiazem and aspirin is being studied in AMI after thrombolysis in the Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis (INTERCEPT).[377]

EARLY INVASIVE/INTERVENTIONAL STRATEGY: EARLY CORONARY ANGIOGRAPHY AND/OR INTERVENTIONAL THERAPY

Recommendations[1]:

Class I

1. Patients with recurrent (stuttering) epidoses of spontaneous or induced ischemia or evidence of shock, pulmonary congestion, or left ventricular dysfunction and hypotension

A prospective observational trial (VANQUISH) was performed comparing PTCA with conventional therapy in patients with NQWMI. The mortality was less in patients receiving medical therapy. A contrary view was presented by FRISC II.[378] In addition to the randomization to low-molecular-weight heparins, patients were assigned within 48 h to invasive or noninvasive early management. The invasive strategy consisted of early coronary angiography within 2 to 7 days, whereas the noninvasive strategy consisted of exercise testing with referrals to coronary angiography if the test was positive. At 6 months, the rate of death or myocardial infarction in the invasive group was 9.5 versus 12 percent in the noninvasive group ($p = 0.045$). In this study, men particularly benefited with a difference of 9.1 versus 13.9 percent for the conservative strategy. Further studies will have to be performed to determine whether the invasive strategy is preferred over conservative therapy. This must also be considered in light of the new medical therapy of glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparins being evaluated. Currently, early angiography and/or interventional therapy is indicated (Class I) in non-ST segment elevation myocardial infarction only with spontaneous or induced ischemia.[1]

* Performance standard: balloon inflation within 90 (±30) min of admission.

** Persons who perform >75 PTCA procedures per year.[296]

*** Centers that perform >200 PTCA procedures per year and have cardiac surgical capability.[296]

* Put pacing system in place.

† Activate system.

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Chapter 42: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOLS, CLINICAL PATHWAYS, AND CHEST PAIN EVALUATION UNITS

There are increasing pressures, driven by both economic and clinical imperatives, to improve the management of patients with chest pain. The goal of controlling costs has contributed to the need to triage patients with chest pain accurately to levels of care that are appropriate to need and to facilitate evaluation and treatment in the shortest time that is commensurate with good medical care. For example, low-risk patients with normal ECGs frequently do not have to be admitted to the hospital, much less to the intensive care unit (ICU), and can have a total time in the health care facility of hours rather than of days. The medical necessity of achieving rapid, accurate diagnoses has been discussed earlier. These two driving forces have led to the development of predictive algorithms to guide triage decisions.[70,225] For example, one analysis provided evidence that patients with chest pain with ECG changes of ischemia or infarction were, depending on age, the only subgroup with a probability of AMI high enough (21 percent or moderate) to justify admission to the CCU as opposed to an intermediate care unit of reduced intensity.[379] While these algorithms have been shown to be effective in, for instance, reducing ICU admissions without compromising clinical care,[225,245] they have not been widely adopted for a variety of reasons, including the fact that most experienced clinicians are comfortable with their decision making in triaging patients with chest pain.[217]

The continuing need to improve the process of chest pain management has led to the development of clinical pathways, protocols, and practice guidelines that differ from predictive instruments in that they provide structure to the decision-making process rather than influence decision making.[217,380] A chest pain evaluation unit, which may either be a defined area, frequently near the emergency department, or a virtual entity embracing a team approach to chest pain evaluation and management, is frequently central to the strategy to systematize the approach to the patient with chest pain.

In general, the approach is to triage the patient to evaluation and management pathways according to risk based on electrocardiographic findings, history, and symptoms. For example, and at the opposite end of the clinical spectrum, the patient with ST-segment elevation would receive thrombolytic therapy within 30 min of arrival and be rapidly admitted to the CCU, whereas the low-risk patient with a normal ECG would be evaluated in a unit of low intensity and acuity and would be discharged within a matter of hours. There is a great deal of interest in the use of imaging modalities such as nuclear scanning with sestamibi or stress echocardiography to guide decision making in cases of intermediate or low probability for AMI during the initial evaluation period.[217] While the results using the systematized approach of a chest pain evaluation unit appear promising, further assessment is needed in large-scale trials to test both clinical value and cost-effectiveness before a specific strategy can be recommended. The general strategy of systematizing the approach to the patient with chest pain, however, is strongly encouraged.

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MANAGEMENT AFTER HOSPITAL ADMISSION

General Approach

Recommendations[1]:

Class I

1. Selection of electrocardiographic monitoring leads based on infarct location and rhythm to maximize diagnostic utility
2. Bed rest with bedside commode privileges for initial 12 h in hemodynamically stable patients who are free of ischemic-type chest discomfort
3. Avoidance of the Valsalva maneuver and straining
4. Optimization of pain relief

Class IIb

1. Routine use of anxiolytics

Class III

1. Prolonged bed rest (more than 12 to 24 h) in stable patients without complications

The general issues involved in the management of the patient with suspected or manifest AMI in the intensive or moderate care unit are to provide for adequate monitoring for the detection of arrhythmia, ischemia, and hemodynamic instability; to provide the patient with a calm, supportive, and reassuring environment; to control the level of activity; to begin the education process for a lifetime of living with coronary heart disease; to control pain and inappropriate anxiety; and to treat adverse events promptly. It is assumed, as previously discussed, that oxygen therapy, beta-adrenergic blockers, aspirin, thrombolytics, unfactionated heparin, low-molecular-weight heparin, and nitroglycerin have been begun or given as appropriate in the emergency department. Also, it is assumed that a decision has been made about the appropriateness of adding glycoprotein IIb/IIIa inhibitors.

MONITORING

The patient must have continuous electrocardiographic monitoring and frequent hemodynamic evaluation by the assessment of blood pressure and heart rate. Electrocardiographic monitoring leads should be selected to maximize the ability of the CCU staff to detect and diagnose arrhythmias and recurrent ischemic ST-segment changes. Thus, the lead selected should ideally permit identification of the P wave as well as providing a QRS complex of adequate size. Furthermore, the lead should be selected to interrogate the area of known infarction or ischemia.[1] Blood pressure and pulse rate should be monitored with a frequency to be determined by the perceived level of acuity, but generally every one-half hour until stable and then every 4 h. Pulse oximetry is becoming standard. Precise orders should be given to notify the physician of, for example, systolic pressures >150 and <90 mmHg, heart rates >110 or <60 beats per minute, respiratory rate of >22 or <8 per minute, or significant decreases in blood oxygen saturation.[1]

ACTIVITY

Minimizing physical exertion is an important approach, in addition to minimizing sympathetic nervous

system drive by administering beta-adrenergic blockers and by controlling pain and excessive anxiety, so as to decrease myocardial oxygen demand and thus decrease myocardial ischemia and necrosis. *Prolonged bed rest and a severe limitation of activities such as self-feeding are no longer recommended except in the case of continuing ischemic pain and/or hemodynamic instability because of evidence that cardiovascular deconditioning and unfavorable shifts in intravascular volume develop very rapidly in immmobilized patients in the supine position*.[381] Losses of plasma volume occur that decrease preload and stimulate compensatory reflexes, enhancing sympathetic activity. These fluid shifts may be the major cause of cardiovascular dysfunction with prolonged bed rest.[382] It is prudent to prescribe about 12 h of bed rest and a bedside commode for the patient with uncomplicated AMI.[1] Subsequently, low-level activities such as routine self-care, assisted bathing, and brief ambulation should be permitted to prevent deconditioning.

The major coronary precaution that should be strictly adhered to is the avoidance of the Valsalva maneuver, which increases cardiac wall stress because of increases in systolic blood pressure and heart rate.[1] These changes in wall stress may cause localized repolarization abnormalities in the infarct zone that may precipitate ventricular arrhythmias.[383,384] Constipation should be avoided and stool softeners routinely prescribed. A bedside commode is preferable to a bedpan in all but the most unstable patients.

ANALGESICS AND ANXIOLYTICS

The importance of controlling chest pain and excessive anxiety and the use of morphine and diazepam were discussed previously (see "Evaluation and Management of the Patient with Chest Pain in the Emergency Department"). Morphine is sometimes used in inadequate doses because of fear of side effects, and anxiolytics may be overused. Ischemic chest pain, heart rate, blood pressure, and perceived anxiety level have not been found to be different in patients treated with diazepam or with a placebo.[385] Conversely, strong psychological support in hospitals has prolonged effects to prevent anxiety and depression after AMI.[386] Anxiolytics may be useful in treating symptoms of nicotine withdrawal in smokers during hospitalization. Psychosis manifesting as delirium and agitation is not uncommon, particularly in the elderly, during prolonged stays in the ICU ("ICU psychosis"). Intravenous haloperidol can be useful and safe in this setting. Drug-induced psychosis or delirium caused by lidocaine, for example, should be considered.

EDUCATION

Education of the AMI patient by both the CCU staff and the physician are essential components of medical management and should be begun early during hospitalization. Presenting the patient with information about the management of symptoms and prevention of a recurrence gives a sense of empowerment associated with changes in behavior[387] and decreased anxiety.[388] Information should be presented in a direct fashion at a relatively simple level and should emphasize issues relevant to patient behavior, such as control of chest pain, diet, smoking, and exercise, rather than the pathophysiology of the disease. Family members, and, in particular, the spouse should participate in the education process. Because of the substantial risk of cardiac arrest in the 18 months after AMI, family members should be taught cardiopulmonary resuscitation.[389,390] Ideally, educational materials can be presented in a permanent printed form so that the self-education process can continue after discharge and can supplement that given by health care professionals during cardiac rehabilitation and physician visits.

Adjunctive Therapy during the Early In-Hospital Period

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Recommendations[1]:

Class I

1. Patients within the first 24 h of a suspected AMI with ST-segment elevation in two or more anterior precordial leads or with clinical heart failure in the absence of significant hypotension or known contraindications to the use of ACE inhibitors

2. Patients with AMI and a left ventricular ejection fraction (LVEF) <40 percent or patients with clinical heart failure on the basis of systolic pump dysfunction during and after convalescence from AMI

Class IIa

1. All other patients within the first 24 h of a suspected or established AMI provided that significant hypotension or other clear-cut contraindications are absent
2. Asymptomatic patients with mildly impaired left ventricular function (ejection fraction of 40 to 50 percent and a history of old myocardial infarction)

Class IIb

1. Patients who have recently recovered from myocardial infarction but have normal or mildly abnormal global left ventricular function.

A number of clinical trials have shown that ACE inhibitors reduce left ventricular dysfunction and dilatation and slow the progression to congestive heart failure in patients with left ventricular dysfunction after AMI.[391-393]

The ACE inhibitors have also been shown, with few exceptions, to reduce mortality after AMI. Meta-analysis of 4 major and 11 minor trials involving, collectively, more than 100,000 patients showed an odds reduction in the ACE-inhibitor group of 6.5 percent ($2p = 0.006$).[394] Originally, there was some doubt about the timing of initiation of the ACE inhibitor after AMI because of the results of the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) II.[395] In this randomized study, patients were assigned to intravenous placebo or enalapril during the first day of AMI and were subsequently given an oral placebo or enalapril. The trial was stopped in its early stages by the Safety Monitoring Committee because it was unlikely to show a positive effect and because of hypotension in elderly patients. The issue of timing of the initiation of ACE inhibitor therapy has been clarified subsequently. In GISSI-3, patients with either ST-segment elevation or depression were given oral lisinopril or were assigned to an open control group starting on the first day of AMI.[260] There was a significant reduction in mortality at 6 weeks (odds ratio 0.88), and the majority (60 percent) of lives saved were in the first 5 days. In ISIS-4, patients were assigned to an oral placebo or to captopril within the first 24 h, and a 7 percent mortality reduction was seen at 5 weeks in the captopril group.[261] The majority of the decrease in deaths was seen in the first 2 days. There was no increase in adverse events in the elderly in ISIS-4 or in GISSI-3. Thus, the hypotension in CONSENSUS II may be attributed to the use of intravenous enalapril.

Initiation of ACE-inhibitor therapy within the first few days after AMI in patients with left ventricular dysfunction and continuation of therapy over the long term was associated with a decrease in mortality and in fatal and severe nonfatal cardiovascular events in three other trials: Survival and Ventricular Enlargement (SAVE), captopril[392]; Acute Infarction Ramipril Efficacy (AIRE2), ramipril[396]; and Trandolapril Cardiac Evaluation (TRACE), trandolapril.[397]

Thus, trials of ACE inhibitors have shown clear evidence of benefit in AMI from their use early in the course of AMI. Efficacy may be greatest in those at highest risk, that is, patients with prior MI, anterior MI, tachycardia, or CHF. Therapy should begin within the first 24 h after hemodynamic stabilization, whether or not thrombolytic therapy has been administered. Intravenous forms should be avoided, and therapy should be started with low doses. The ACE inhibitors should not be given if systolic blood pressure is below 100 mmHg or if there are contraindications-that is, bilateral renal artery stenosis, renal failure, history of severe cough, or angioedema with previous treatment.[1] In the presence of significant left ventricular dysfunction, therapy should probably be continued indefinitely. Evidence from the Heart Outcomes Prevention Evaluation (HOPE) trial using the ACE inhibitor ramipril has shown significant decreases in cardiovascular events in high-risk individuals including, but not limited to, those with prior AMI.[398] These data, which will be discussed in more detail subsequently, provide support for the strategy of using ACE inhibitors in most patients indefinitely after acute MI.

MAGNESIUM

Recommendations[1]:

Class I

1. None.

Class IIa

1. Correction of documented magnesium (and/or potassium) deficits, especially in patients receiving diuretics before the onset of infarction.
2. Episodes of VT-torsades de pointes type-associated with a prolonged QT interval should be treated with 1 to 2 g of magnesium administered as a bolus over 5 min.

Class IIb

1. Magnesium bolus and infusion in high-risk patients such as the elderly and/or those for whom reperfusion therapy is not suitable.

The available data are conflicting but suggest that early (<6 h) administration of magnesium in high-risk patients may be associated with mortality reduction.

Magnesium has a number of potential cardioprotective effects, including vasodilatation,[399] inhibition of platelet function,[400] stabilization of cell membranes,[401] and protection against the cardiotoxic effects of catecholamines.[402]

Meta-analysis of 7 early randomized trials of the effects of magnesium in AMI was consistent with a significant benefit in mortality (odds ratio 0.44).[403,404] The Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) was consistent with this interpretation in that the magnesium-treated patients in comparison with those not receiving magnesium had a 24 percent reduction in overall mortality ($p < 0.04$), a 25 percent decrease in the incidence of congestive heart failure in the CCU, and a 21 percent lower rate of coronary artery disease mortality at 4 years.[405,406] The large ISIS-4 trial, however, was negative and even raised the possibility of some harm.[261] Incorporation of the ISIS-4 data with that of the previous randomized trials and performance of meta-analysis resulted in the loss of the benefit that was previously apparent. It has been speculated that the lack of benefit in ISIS-4 was due to the relatively late administration of magnesium,[407] since the time to randomization in ISIS-4 was 8 h, as contrasted with 3 h in LIMIT-2. It may also have been a consequence of the low control-group mortality in ISIS-4 (7.2 percent) and the statistical inability to detect a treatment effect at this level.[408] That only 36 percent of patients in LIMIT-2 received thrombolytic therapy as opposed to 70 percent in ISIS-4 complicates interpretation further. Analysis of subgroups in ISIS-4 in which magnesium was administered within 6 h of the onset of symptoms or within 2 h of thrombolytic therapy also failed to demonstrate a therapeutic effect. Another randomized trial of intravenous magnesium in AMI patients who were not candidates for thrombolysis demonstrated a significant reduction of mortality in the treated group (4.2 versus 17.3 percent, $p < 0.01$), due primarily to a decrease in cardiogenic shock and congestive heart failure.[409]

The conflicting data that are available do not permit a recommendation that magnesium be used as standard general therapy in AMI. Magnesium should be used in situations where it would otherwise be recommended, as in the presence of magnesium deficiency or VT of the torsades de pointes type with a prolonged QT interval. Intravenous magnesium can be considered in high-risk patients, such as the elderly and in those for whom reperfusion is not suitable. Ongoing clinical trials are investigating the question further.

Management of the Low-Risk Patient

As discussed previously, there are increasing pressures to minimize resource utilization while not compromising safety in the patient with ischemic-type chest discomfort. As a practical matter, this means matching patient acuity and risk appropriately with the hospital facilities required to deal with their situation and to appropriately control time spent in these units. For example, the patient who is at low risk for AMI may be evaluated in the emergency department or in a chest pain evaluation unit, and if AMI or unstable angina are excluded, may be discharged within a matter of hours without having been formally admitted to the hospital. The patient with AMI who has an uncomplicated initial course and is at low risk for development of complications is a candidate for transfer out of the CCU within 24 to 36 h.[410-413] *Such a low-risk patient does not have a history of prior AMI and has not had recurrent ischemic pain, hypotension, congestive heart failure, persistent sinus tachycardia, heart block, or sustained VT. This patient may be a candidate for early discharge at 3 to 4 days.*

Patients who have been treated with thrombolytics are frequently candidates for early discharge from the CCU.[414-417] In this setting, the *absence* of early sustained VT or VF, as well as the absence of early sustained hypotension or shock, and the *presence* of a LVEF > 40 percent and of only one- or two-vessel coronary artery disease are independent predictors of freedom from late complications.[416]

Approaches to risk stratification and noninvasive testing, to guide management decisions in the post-AMI patient, are discussed subsequently (see "Noninvasive Risk Stratification in Patients Surviving Acute Myocardial Infarction"). Excessive diagnostic testing in all post-AMI patients, especially those at low risk, should be discouraged. The variability in practice in this regard, without demonstrable correlative changes in outcomes, suggests the need for more rigorous adherence to guidelines and protocols.[1]

As discussed previously, AMI can be diagnosed rapidly using serum cardiac markers. If AMI is effectively ruled out and the patient is at low risk (i.e., normal ECG and absence of the characteristics noted earlier, especially the absence of prolonged initial pain or the recurrence of pain), then noninvasive testing can establish the safety of early discharge (3 to 12 h) from the emergency department, chest pain evaluation unit, or CCU, for further evaluation as an outpatient.[217] In general, such patients do not necessarily need to be admitted to the CCU unless noninvasive testing is positive for ischemic heart disease. Patients with ischemic-type chest discomfort and intermediate probabilities of AMI-that is, duration of chest pain >20 to 30 min and nondiagnostic ECG changes (without significant ST-segment elevation or depression, T-wave inversion, or bundle branch block), without known coronary artery disease-should be admitted to an observation unit or to the CCU if an intermediate unit is unavailable. They should be placed on a fast track to rule in AMI or unstable angina, as previously outlined. If the clinical course is unrevealing and if early imaging is negative, then stress testing and further evaluation can be planned. Clinical decisions can usually be made within 12 h in this setting.[217]

Management of the High-Risk Patient with Acute Myocardial Infarction

The AMI patient at low risk is defined in the previous section by the absence of certain characteristics. By contrast, the *high-risk AMI patient is defined by the presence of one or more of these clinical features, which include recurrent chest pain; congestive heart failure and low cardiac output; arrhythmias and, in particular, recurrent or sustained VT or VF; mechanical cardiac complications of AMI such as ruptured papillary muscle or intraventricular septum; and/or inducible ischemia and extensive coronary artery disease.*

RECURRENT CHEST PAIN

The most common causes of recurrent chest pain after AMI are coronary ischemia and pericarditis.

Recommendations for diagnosis and treatment of recurrent chest discomfort[1]:

Class I

1. Aspirin for pericarditis

2. Beta-adrenergic blocking drugs (continue or initiate) intravenously, then orally for ischemic-type chest discomfort
3. for patients with recurrent ST-segment elevation
4. Coronary arteriography for ischemic-type chest discomfort recurring after hours to days after initial therapy and associated with objective evidence of ischemia in patients who are candidates for revascularization

Class IIa

1. Nitroglycerin intravenously for 24 h, then topically or orally for ischemic-type chest discomfort

Class IIb

1. Corticosteroids for pericarditis
2. Indomethacin for pericarditis

Recurrent Ischemia

Recurrence of chest pain in the patient who has had an AMI is a serious development and requires immediate attention to establish the correct diagnosis and initiate treatment, especially if the pain represents recurrent ischemia, which is a more serious development than if the pain is a manifestation of pericarditis. Early postinfarction angina is an important predictor of the severity of coronary artery disease and has an overall incidence of about 18 percent.[418] Postinfarction angina is defined as chest pain that is frequently similar to the original discomfort, occurring at rest or with limited activity during hospitalization 24 h or more after onset of the AMI. The pain may or may not be associated with ST-segment elevation or depression or with pseudonormalization of inverted T waves on the postmyocardial ischemia ECG.[419] The pain is usually a result of ischemia in the territory of the myocardium supplied by the vessel that precipitated the initial myocardial ischemia. At least three categories of patients are at high risk for postinfarction angina: (1) patients with NQWMI; (2) patients who have received thrombolysis; and (3) patients with multiple risk factors.[420-422] The incidence of postinfarction angina is almost twice as high after NQWMI (25 to 35 percent) than after Q-wave myocardial infarction. Thrombolytic therapy for AMI created a new high-risk group for postinfarction angina (35 to 45 percent incidence), with a 12 to 15 percent incidence of reinfarction during the early experience with lytic therapy for reperfusion.[423] Regardless of whether postinfarction angina occurs after Q-wave myocardial infarction, NQWMI, or thrombolytic therapy, it is more likely to occur in patients with two- or three-vessel disease than in patients with single-vessel disease.[418] Postinfarction angina is important because it is associated with a twofold increase in the incidence of reinfarction. The 1-year mortality rate and acute risk of reinfarction is two- to fourfold greater in patients with postinfarction angina associated with ECG changes than in patients without chest pain or in patients with chest pain but without associated ST-T changes.[424,425]

The incidence of reinfarction following NQWMI has previously been reported to be as high as 40 percent within the first month following the event,[426] but with current treatments with glycoprotein IIb/IIIa inhibitors and fractionated heparins and possibly diltiazem, the incidence is less than 10 percent, as discussed previously. The incidence of reinfarction following thrombolytic therapy has been reduced from 12 to 15 percent to 5 to 7 percent with the use of adjunctive therapy, including heparin, aspirin, nitroglycerin, and beta blockers, as discussed previously. Nevertheless, reinfarction, despite the use of heparin and aspirin, still accounts for one-quarter of all deaths that occur following thrombolytic therapy and thus remains a major concern.[427] Patients with Q-wave myocardial infarction who do not receive thrombolytic therapy were previously likely to have an incidence of postinfarction angina of only about 12 to 15 percent and a reinfarction rate of about 5 to 7 percent, although these absolute rates have probably decreased with the more widespread use of adjunctive therapy with beta blockers, aspirin, and ACE inhibitors. Death, ventricular arrhythmias, and severe congestive heart failure are early sequelae of reinfarction, and there is an increased rate of sudden death and cardiogenic shock.[110,113]

Diagnosis of reinfarction within 18 h after thrombolytic therapy is based upon the recurrence of ischemic-type chest pain, as noted, lasting at least 30 min, which may be associated with ST-T-wave changes. There

is a reelevation of MB-CK, and the diagnostic criteria were discussed previously. Adequate beta-adrenergic blockade should be achieved. Sublingual nitroglycerin should be administered, and restarting of intravenous infusion should be considered. Pain should be controlled. Coronary arteriography generally should be performed early after the redevelopment of ischemic chest pain, and it is common that a high-grade stenosis is found. If the lesion is suitable, PTCA should be performed, or additional thrombolysis should be administered if mechanical reperfusion is not feasible or available. With appropriate ECG changes-that is, ST-segment elevation-thrombolysis should be considered if cardiac catheterization and PTCA are not immediately available. If either APSAC or SK was used originally, it should not be readministered and rt-PA or r-PA should be utilized. These latter agents can be readministered. If multiple high-grade stenoses are found, coronary artery bypass grafting should be considered.

Pericarditis

Pericardial involvement associated with AMI assumes one of two forms. By far the most common type is pericardial inflammation overlying the necrotic segment of a transmural myocardial infarction. This particular pericarditis is usually an incidental finding in the course of a more significant illness. The less frequent form of postinfarction pericarditis is generally a delayed complication, which may represent an immunologic or autoimmune reaction. This pericarditis, a component of Dressler's syndrome, generally represents a major complication that often outlasts the basic illness (see also Chap. 72).

EARLY POSTINFARCTION PERICARDITIS

The prevalence of early postinfarction pericarditis, as reflected by the presence of typical symptoms and a friction rub, is 6 to 11 percent.[428,429] However, the general consensus among cardiologists is that this entity occurs far more frequently than is clinically recognized. This suspicion is supported by postmortem studies finding evidence of postinfarction pericarditis when it was not recognized clinically.[430] The pericarditis usually becomes evident between the second and fourth day following the AMI, but it may occur up to several weeks later. In comparison to post-AMI patients without pericarditis, those who develop the condition have larger infarcts, a lower ejection fraction, and a higher incidence of congestive heart failure.[431,432]

The most common manifestation of pericarditis other than the chest pain is a scratchy two- or three-component friction rub along the left sternal border. The friction rub may have only a single component and may be dismissed erroneously as a systolic murmur. The rub is evanescent, generally lasting 1 to 6 days. The pain of pericarditis is generally perceived by the patient to be different from that of the AMI. The location of the pain may be the same, but any radiation is usually to the neck, shoulder, or scapula rather than to the arms or jaw. Characteristically, the pain is aggravated by inspiration, swallowing, coughing, or recumbency. Fever, usually less than 39°C, frequently accompanies the pericardial inflammation and typically lasts longer than 3 days, unlike the fever in an uncomplicated myocardial infarction.[433] The ECG is frequently not helpful in these patients, partially because it is usually distorted by the infarction and perhaps because of the localized nature of the inflammation. The cardiac rhythm is generally sinus, but there is an increased prevalence of atrial fibrillation.[434] Since significant effusion is unusual with this form of pericarditis, the echocardiogram is of limited diagnostic value.

The treatment of choice is aspirin (160 to 325 mg daily), although higher doses (650 mg every 4 to 6 h) may be required.[1,435,436] Indomethacin is effective in relieving symptoms,[1] but experimentally causes thinning of scar formation.[437] Corticosteroids and ibuprofen provide pain relief but also have been associated with thinning of scar formation as well as with cardiac rupture.[438,439] The use of anticoagulants is relatively contraindicated in AMI complicated by pericarditis. Situations ordinarily calling for anticoagulation, such as mural thrombosis seen on echocardiography, require excellent clinical judgment in assessing the risk-benefit ratio if pericarditis is also present.

POSTMYOCARDIAL INFARCTION SYNDROME (DRESSLER'S SYNDROME)

The clinical features of this syndrome are fever, chest pain, evidence of polyserositis, and a tendency to recur.[435] The reported frequency is 1 to 3 percent of AMIs.[434,435] The incidence, however, has appeared to

diminish dramatically in the reperfusion era.[440] While there is usually a latency period of at least 1 week before its appearance, the pleuropericarditis may develop within the first week following the AMI.[441] The syndrome can occur in association with NQWMI, and it is usually associated with fever in the range of 38 to 39°C and occasionally up to 40°C. The chest pain is the most sensitive index of this syndrome and often precedes the fever. Aggravation of the pain by deep inspiration and turning is its most distinctive feature. The pericarditis is manifest by a friction rub, usually occurring between the second and eleventh week after the infarction and lasting from 3 days to 3 weeks. Pericardial effusion is common. While pericarditis is the dominant feature, as many as two-thirds of patients have pleural effusions. These effusions are usually small and are frequently bilateral but may be large and hemorrhagic. About one-quarter of patients have linear or patchy infiltrates in the lung bases.

The clinical features, pathologic findings, and prompt response to steroids all suggest an immunologic or autoimmune reaction. The presence of antimyocardial antibodies has been demonstrated in the majority of patients tested with the syndrome.

Treatment is similar to that of early postinfarction pericarditis but is more likely to require a course of oral corticosteroids. Recurrences are common for several months and require the reinstitution of corticosteroids with a more gradual tapering. Anticoagulants should generally be discontinued in the presence of postmyocardial infarction syndrome.[442]

HEART FAILURE IN ACUTE MYOCARDIAL INFARCTION

Pathophysiology and Hemodynamics

The immediate hemodynamic consequences of myocardial infarction include both systolic and diastolic dysfunction. Systolic dysfunction is secondary to a loss of contractile function of the infarcted and ischemic myocardium.[443] Experimentally, over a period of 1 to 3 min, the regional disturbance of contraction progresses from dyssynchrony (disturbed temporal sequence of contraction) through hypokinesis (diminished motion) and akinesis (total lack of motion) to dyskinesia (paradoxical systolic expansion).[444] This loss of contractile function results in a decreased systolic ejection, increased end-systolic volume, increased end-diastolic volume, and a secondary increase in diastolic filling pressure caused by the increase in ventricular volume. The diastolic impairment often precedes the systolic dysfunction, which is characterized immediately by a transient increase in left ventricular diastolic distensibility,[445,446] followed by decreased distensibility due in part to adenosine triphosphate depletion and restraint by the pericardium and perhaps ultimately by the infiltration of inflammatory fluid and cells. The hemodynamic consequence of the reduced distensibility is increased diastolic pressure. The systolic stress on the ischemic segment, which contributes to "cell stretch" and "cell slippage," results in expansion of the infarcted segment[447] and provides the stimulus for volume overload hypertrophy, characterized by sarcomere replication, fiber elongation, and chamber enlargement. The chamber enlargement accommodates the increased volume and allows the diastolic pressure to return toward normal.[444]

Cardiac failure develops when left ventricular function is reduced to 30 percent or more of normal and usually occurs within minutes or hours of the onset of a large infarction. Since even with sustained coronary occlusion only 60 to 70 percent of the ischemic region undergoes necrosis, compromise of cardiac function associated with AMI is transient (24 to 72 h) in perhaps more than two-thirds of the cases. *Unlike the situation with chronic heart failure, the circulatory volume is normal or decreased in acute ventricular dysfunction associated with myocardial infarction.* The usual clinical scenario is one of left ventricular dysfunction with pulmonary congestion and without hypoperfusion. There is sometimes biventricular failure, and in about 5 to 10 percent of cases there is predominantly right ventricular failure, as discussed later. The severity of the failure, its duration, and whether or not it is reversible are predominantly dependent on infarct size.[448,449] If more than 40 percent of the myocardium is destroyed, decompensation occurs, resulting in shock.[450-452] In a few patients, failure develops later as a consequence of expansion of the infarcted segment, reinfarction, or ischemia.[445] Less commonly, failure is precipitated by papillary muscle dysfunction or ventricular septal rupture. The compromised heart will also be negatively affected by supraventricular or ventricular arrhythmias, conduction disturbances, drugs with negative inotropic effects, fever, and hypovolemia.

Left ventricular dysfunction with the clinical signs of failure is said to occur in 30 to 40 percent of patients and usually develops when the abnormally contracting segment exceeds 30 percent of the left ventricular circumference.[453] Another factor contributing to cardiac failure is residual scarring from previous episodes of infarction, which limits the extent of compensation. After myocardial infarction, adjacent normal myocardium increases its contractility because of increased stimulation by catecholamines and also utilizes the Starling mechanism in an attempt to maintain cardiac output. The pathophysiology of heart failure is discussed in Chap. 20. That intravascular volume may be normal or decreased in acute heart failure in AMI is important in considering the therapeutic approach to low cardiac output and pulmonary congestion in acute infarction.

Right Ventricular Infarction

Until about 15 to 20 years ago, right ventricular infarction was recognized infrequently and was usually thought not to be of great consequence. Subsequently, it was shown that the majority of patients with acute inferior infarction had abnormal regional function of the right ventricle,[454-456] although typical hemodynamic abnormalities are seen in only 10 to 15 percent of patients.[457,458] Right ventricular function returns to normal in most of these patients, suggesting that substantial stunning, rather than massive infarction, has occurred[1] (see also Chap. 37).

Inferior myocardial infarction associated with right ventricular infarction defines a high-risk subset with a mortality rate of 25 to 30 percent, as opposed to an overall mortality of about 6 percent in inferior myocardial infarction.[457] This group should be approached aggressively with consideration for reperfusion therapy. *Right ventricular involvement should always be considered and should be specifically sought out in inferior myocardial infarction with clinical evidence of low cardiac output because the therapeutic approaches are quite different in the presence of right ventricular involvement from those for predominantly left ventricular failure.*

PATHOPHYSIOLOGY OF RIGHT VENTRICULAR INFARCTION

Right ventricular infarction is unusual in the absence of inferior infarction because occlusion of the right coronary artery proximal to the right ventricular branches usually also causes infarction in the inferior left ventricle, which is supplied by the distal distribution of the vessel.[459] The infarction usually involves the posterior septum and posterior wall rather than the right ventricular free wall. The relative sparing of the free wall results from the high degree of collateralization of the right ventricular arterial blood supply, from the blood flow derived from thebesian vessels, and from diffusion of oxygen from the ventricular cavity as well as from the fact that it is thin and has comparatively low oxygen demands because of its mass and low workload.[460-463]

The hemodynamic consequences of right ventricular ischemia or infarction share features previously described for the left ventricle. Thus, there is impairment of contractility and diastolic dysfunction related to dilatation and pericardial restraint. In a low-pressure volume pump, such as the right ventricle, this combination has even more deleterious effects than in the left ventricle and causes substantial increases in diastolic pressure and decreases in systolic pressure. If the right ventricular afterload is also increased because of left ventricular dysfunction, then right-sided output can decrease dramatically and the driving force becomes essentially the right atrial pressure. Under these circumstances, right atrial transport essentially becomes critical, and anything decreasing it, such as diminished volume and filling pressure or loss of AV synchrony, may cause severe decreases of right and, secondarily, left ventricular output.[422,464,465]

DIAGNOSIS OF RIGHT VENTRICULAR INFARCTION

As noted, right ventricular infarction should be considered in all cases of acute inferior myocardial infarction, especially in the setting of low cardiac output. A typical presentation would include inferior myocardial infarction, clear lung fields, and jugular venous distention. Jugular venous distention that is enhanced by inspiration (Kussmaul's sign) in the setting of inferior myocardial infarction is highly suggestive of right ventricular involvement but may not be manifest with volume depletion and might only become apparent with repletion.[466] A right atrial pressure >10 mmHg that is >80 percent of the pulmonary

wedge pressure is a sensitive and specific sign of right ventricular infarction.[467]

The differential diagnosis of heart failure or low cardiac output in inferior infarction includes (1) arrhythmia, such as atrial fibrillation, sustained ventricular arrhythmia, or high-degree AV block; (2) ongoing ischemia, such as ischemia at a distance if the occluded artery to the inferior wall was also supplying, through collaterals, the anterior wall; (3) previous infarction at another location; (4) a mechanical complication such as papillary muscle dysfunction or, less commonly, a ventricular septal defect; or (5) right ventricular infarction.[468] This differential diagnosis of causes of congestive heart failure in inferior AMI is summarized in Table 42-13.

Table 42-13: Differential Diagnosis of Congestive Heart Failure in Inferior AMI

Arrhythmia: high-degree AV block, atrial fibrillation, or sustained ventricular tachycardia
Ischemia at a distance, with the occluded artery to the inferior wall supplying the anterior wall via collaterals
Previous infarction at another location
Mechanical complication, such as papillary muscle dysfunction
Right ventricular infarction

ST-segment elevation in lead V_{4R} is the single most powerful predictor of right ventricular involvement in inferior infarction and identifies a patient subset with a markedly increased in-hospital mortality.[457] All patients with inferior infarction should be screened by recording ECG lead V_{4R}. Echocardiography can also be useful as an adjunctive diagnostic approach[179] and can be particularly valuable in detecting right-to-left shunting of blood through the foramen ovale, which can occur because of the high right atrial pressures in right ventricular ischemia. Such shunting can be a cause of hypoxemia unresponsive to oxygen administration in this setting.[469]

TREATMENT OF RIGHT VENTRICULAR ISCHEMIA AND INFARCTION

The major objectives in treating right ventricular infarction are to maintain right ventricular preload, provide inotropic support, reduce afterload of the right ventricle, and achieve early reperfusion.[262] The recommendations are summarized in Table 42-14.[1] Venodilators such as nitrates should be avoided, and diuretics should be used with caution. Volume loading with 1 to 2 L of saline will frequently restore cardiac output and correct hypotension; this should be the initial step. Excessive volume loading, however, may dilate the ventricle and decrease output. Inotropic support should be initiated if saline administration does not restore output and correct hypotension.[1] Dobutamine is an ideal initial choice.

The critical role of atrial transport in maintaining output in right ventricular infarction and the need to maintain AV synchrony have been discussed. High-degree AV block occurs in about 50 percent of patients in this setting, and AV sequential pacing can restore cardiac output.[470,471] Atrial fibrillation occurs in up to one-third of these patients, in whom prompt cardioversion should be considered if there is any evidence of hemodynamic compromise.[472] If there is significant left ventricular dysfunction, which may further compromise right ventricular function, as noted, afterload reduction by nitroprusside infusion or intraaortic balloon pumping is indicated.[1]

Reperfusion with thrombolytic therapy or primary PTCA improves right ventricular ejection fraction and hemodynamic status[473] and decreases the incidence of complete heart block.[473-475] Coronary artery bypass grafting should be considered if multivessel disease is found.

MANAGEMENT OF CONGESTIVE HEART FAILURE IN ACUTE MYOCARDIAL INFARCTION: GENERAL ISSUES

Hemodynamic Monitoring

Recommendations for balloon flotation right side of the heart catheter monitoring[1]:

Class I

1. Severe or progressive congestive heart failure or pulmonary edema
2. Cardiogenic shock or progressive hypotension
3. Suspected mechanical complications of acute infarction, i.e., ventricular septal defect, papillary muscle rupture, or pericardial tamponade

Class IIa

1. Hypotension that does not respond promptly to fluid administration in a patient without pulmonary congestion

Class III

1. Patients with acute infarction without evidence of cardiac or pulmonary complications

The balloon flotation (Swan-Ganz) catheter fundamentally permits one, in the setting of low cardiac output, to distinguish between inadequate ventricular filling pressures and inadequate systolic function. The former is treated with volume expansion and the latter with inotropic support and frequently afterload reduction. The catheter, even when used correctly, is not totally benign and during manipulation may precipitate VT and pulmonary hemorrhage or infarction. To minimize the risk of infection, the catheter should not be left in place longer than 5 days.[1]

INTRAARTERIAL PRESSURE MONITORING

Recommendations[1]:

Class I

1. Patients with severe hypotension (systolic arterial pressure less than 80 mmHg) and/or cardiogenic shock
2. Patients receiving vasopressor agents

Class IIa

1. Patients receiving intravenous sodium nitroprusside or other potent vasodilators

Class IIb

1. Hemodynamically stable patients receiving intravenous nitroglycerin for myocardial ischemia
2. Patients receiving intravenous inotropic agents

Class III

1. Patients with acute infarction who are hemodynamically stable. Arterial monitoring in AMI is useful in all hypotensive patients but especially in those who are in shock. The radial artery is the preferred site, although the brachial and femoral arteries can be used. Intraarterial catheters should not be left in place longer than 72 h because of the risk of thrombosis and infection.[1]

Intraortic Balloon Counterpulsation

Recommendations[1]:

Class I

1. Cardiogenic shock not quickly reversed with pharmacologic therapy as a stabilizing measure for angiography and prompt revascularization
2. Acute mitral regurgitation or ventricular septal defect complicating myocardial infarction as a stabilizing therapy for angiography and repair and revascularization
3. Recurrent intractable ventricular arrhythmias with hemodynamic instability
4. Refractory postmyocardial infarction angina as a bridge to angiography and revascularization

Class IIa

1. Signs of hemodynamic instability, poor left ventricular function, or persistent ischemia in patients with large areas of the myocardium at risk

Class IIb

1. In patients with successful PTCA after failed thrombolysis or those with three-vessel coronary disease, to prevent reocclusion
2. In patients known to have large areas of myocardium at risk, with or without active ischemia

By inflating in the aorta during diastole and by deflating during systole, the intraaortic balloon pump reduces afterload during ventricular systole and increases coronary perfusion during diastole. The decrease in afterload and increased coronary perfusion account for its efficacy in cardiogenic shock and ischemia. It is particularly useful as a stabilizing bridge to facilitate diagnostic angiography and revascularization and repair of mechanical complications of AMI. The use of the intraaortic baloon pump after AMI postthrombolysis or post-PTCA has not been uniformly successful in improving clinical outcome, including reocclusion rate or global or regional left ventricular function.[476] Thus, the routine use of the intraaortic baloon pump after either drug or mechanical reperfusion cannot be recommended.[1]

Diuretics and Positive Inotropic Agents

DIURETICS AND CARDIAC FAILURE IN ACUTE MYOCARDIAL INFARCTION

As previously mentioned, patients with failure due to AMI have normal total body water, and the transudation of fluid into the lungs may induce hypovolemia. As ventricular compliance is decreased, an increased left ventricular end-diastolic pressure is necessary to maintain cardiac output, since the heart operates on the steep portion of the ascending limb of Starling's curve.[477,478] The administration of a diuretic in this setting may be associated with a decrease in cardiac output.[479-481] Thus, diuretics should not be the drugs used initially in the treatment of pulmonary congestion in AMI. Their use early in the course should usually be guided by hemodynamic measurements from a Swan-Ganz catheter. Diuretic therapy may become appropriate later if salt and water retention occur and left ventricular filling pressures become excessively high->18 to 20 mmHg, for example.

INOTROPIC AGENTS IN CONGESTIVE HEART FAILURE ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION

Digoxin is a relatively weak inotropic agent and is not the drug of choice in acute heart failure in myocardial infarction. In a direct comparison, dobutamine was shown to increase cardiac output by 40 percent and to decrease left ventricular filling pressure, whereas digoxin increased cardiac output by only 10 percent and did not decrease filling pressure.[482] Since endogenous catecholamine levels can be quite elevated, digoxin may contribute little. The primary use of digoxin in AMI is to control heart rate in atrial fibrillation.

Dobutamine has favorable pharmacologic properties for use in heart failure in myocardial infarction (see

Chap. 21). It has a rapid onset of action and increases cardiac output because of its positive inotropic properties. It is a vasodilator and increases coronary flow. It decreases filling pressure, as noted. Dopamine has a tendency to increase heart rate more than dobutamine. With higher doses, dopamine may increase peripheral resistance and filling pressures, offsetting some of the positive inotropic effects. The phosphodiesterase inhibitor amrinone increases contractility and is a vasodilator that has been used in patients with heart failure due to AMI. There is concern that positive inotropic agents may increase infarct size. Evaluation of dobutamine in AMI showed that, as long as heart rate was not increased more than 10 percent above baseline, there was no increase in infarct size or in the incidence of reinfarction or arrhythmia.[483]

Management of Uncomplicated Cardiac Failure after Acute Myocardial Infarction

The major determinant of left ventricular dysfunction is the extent of myocardial injury.[448,449,484] The loss of contractile function in the initial minutes or hours (1 to 4) is potentially reversible and accounts in part for the transient nature of cardiac failure in the setting of uncomplicated AMI, as noted above. The presence of cardiac failure and its severity depend not only on the extent of damage but also upon the extent of injury from previous episodes.

Since the introduction of the Swan-Ganz catheter, considerable data have accumulated correlating hemodynamics with clinical features. In 1967, prior to invasive monitoring, Killip and Kimball[485] devised a clinical classification based on physical findings present on admission that provided a prognostic guide. That guide was followed by the classification of Forrester and colleagues,[486,487] based on extensive data obtained from invasive monitoring of patients with acute MI (Table 42-15). The latter classification combined the presence or absence of pulmonary congestion with the presence or absence of systemic hypoperfusion. They added the underlying hemodynamics to this classification based on the pulmonary arterial occlusive (wedge) pressure and the cardiac index. These classifications also provide important diagnostic and therapeutic guidelines, despite the observation that patients frequently cross over from one class to the other and are seldom restricted to one particular hemodynamic subset. Each classification illustrated that with increasing severity of ventricular dysfunction, there is an increased risk of mortality. Nevertheless, there is imprecision in predicting mortality rates from hemodynamics. Rackley and coworkers[488] observed that patients with a ventricular filling pressure >29 mmHg had a 100 percent mortality rate; those with a filling pressure >15 mmHg and a cardiac index <2 L/min per square meter of body surface had a mortality rate of 93 percent; while those with a ventricular filling pressure <15 and a cardiac index <2 L/min per square meter of body surface had a mortality rate of 63 percent.

In patients with uncomplicated AMI, there is no need to perform invasive monitoring if careful clinical observations are made. There should be repeated assessment of the heart and lungs; examination of the skin and mucous membranes; monitoring of the systemic arterial pressure, cardiac rhythm, and heart rate; and routine laboratory examinations, including chest x-ray and determinations of urine output and arterial blood-gas values. If there are clinical indications of pulmonary congestion and/or decreased peripheral perfusion, invasive monitoring includes the insertion of a Swan-Ganz catheter in order to monitor right ventricular hemodynamics and pulmonary artery occlusive pressure (which will reflect ventricular end-diastolic pressure) and to obtain serial determinations of the cardiac output. Occasionally, it may be necessary to insert an arterial catheter to measure the arterial pressure; however, one can usually follow the pressure adequately with the use of a sphygmomanometer or an automatic blood pressure monitoring device. Frequently, it is also essential to insert a Foley catheter to follow the urine output, particularly in patients with sustained hypotension or cardiogenic shock.

In most patients in whom cardiac failure is not complicated by mechanical factors-such as mitral valve rupture, ventricular septal rupture, pulmonary embolus, or tamponade-the failure is transient and of mild-to-moderate severity. If the cardiac output is normal, aggressive treatment is often not recommended.[149] In patients with rales at the base of the lungs with only minimal increase in heart rate and no other signs of hypoxemia (Killip class III), conventional therapy with morphine; nasal oxygen; intravenous, oral, or transdermal nitrates; and bed rest is adequate without any specific therapy for failure. In patients with extensive pulmonary edema who are normotensive and exhibit hypoxia and dyspnea (Forrester class II), the treatment of choice is nitroglycerin given intravenously at 0.1 μg/kg per minute and increased in increments of 5 to 10 μg/min, stopping at a dose that does not decrease the systolic blood pressure below 100 mmHg.

On the average, nitroglycerin in a dose of 0.5 μg/kg per minute is required in patients with evolving acute infarction and failure. Another vasodilator that has been used extensively in the past in AMI is sodium nitroprusside, which is initiated at 0.5 μg/kg per minute and increased by 10- to 20-μg/min increments every 10 to 15 min until the desired therapeutic point or a maximum of 10 μg/kg per minute is reached. Nevertheless, nitroglycerin is the preferred agent, since it has been shown to offer some cardioprotection when given in the early phase of myocardial infarction and to be both reliable and safe. In contrast, in experimental infarction in the dog, it has been shown that nitroprusside is more likely to redirect coronary flow away from the ischemic area to normal areas and to induce coronary steal.[253] The effect of nitroprusside on cardioprotection has been inconsistent and in one large study was shown to be detrimental.[489] In view of the data showing ACE inhibitors to be effective in cardiac failure, these agents are being used more generally in this setting. It is preferable that hemodynamics be monitored invasively (by Swan-Ganz catheter) when one gives a vasodilator to reduce the ventricular filling pressure to 15 to 17 mmHg while maintaining adequate cardiac output and coronary perfusion. Whether or not one monitors hemodynamics invasively will depend in part on the confidence that clinical features reflect the volume status. Mitral valve regurgitation due to papillary muscle dysfunction is commonly an aggravating factor even in mild-to-moderate cardiac failure and responds well to a vasodilator, as does systemic hypertension. Usually a vasodilator is not adequate, in which case an intravenous inotropic agent should be added. The inotropic agents are generally those of sympathomimetic drugs, including dobutamine, dopamine, and norepinephrine (see Chaps. 21 and 49). Dobutamine, a synthetic direct-acting agent, is preferred, as noted, and has actions that include vasodilatation, increased cardiac output, decreased ventricular filling pressure, and increased coronary flow.[490] The infusion should be initiated at 2 to 5 mg/kg per minute and should be increased such that adequate systemic pressure is maintained and the heart rate does not increase by more than 10 to 15 percent. Dobutamine is preferably titrated to cardiac output and ventricular filling pressure. The ventricular filling pressure should be decreased to a range of 14 to 18 mmHg while maintaining adequate cardiac output and blood pressure. In general, the objective is to maintain adequate cardiac output and blood pressure without inducing tachycardia while maintaining a filling pressure that is normal or minimally increased.

In patients with inferior infarction and low cardiac output, right ventricular infarction should be suspected, as discussed. If it is present, a Swan-Ganz catheter should be inserted to determine the filling pressure. Therapy with a positive inotropic agent, such as dobutamine, should be used after assuring that there is appropriate intravascular volume to facilitate right ventricular filling.[491,492]

In patients with borderline blood pressure and evidence of peripheral hypoperfusion, therapy should be initiated with an inotropic agent and not a vasodilator. Similarly, in patients with left ventricular failure and frank hypotension (<95 mmHg), a vasodilator must be avoided and initial therapy should be with a positive inotropic agent. Dopamine would frequently be the choice under these circumstances, since it exerts cardiovascular effects similar to those of dobutamine, but it also possesses an $alpha_1$-adrenergic activity and releases endogenous norepinephrine from sympathetic nerve endings. Low doses of dopamine (2 to 7 mg/kg per minute) are associated with increased stroke volume, cardiac output, and renal blood flow and moderate effects to increase peripheral resistance. High doses of dopamine induce significant vasoconstriction and may increase the left ventricular filling pressure due to increased afterload, which further exacerbates pulmonary congestion. Dopamine also has a more positive chronotropic effect than does dobutamine, which can be a disadvantage in AMI. Norepinephrine, which produces potent arteriolar and venous constriction, is used for hypotension in other settings but is otherwise relatively contraindicated in AMI. It is seldom used unless patients are hypotensive and do not respond to dopamine, amrinone or milrinone, or dobutamine. It is used in cardiogenic shock after dopamine has failed, since it is the major alternative that can be used for maintaining adequate perfusion pressure.

As indicated earlier, diuretics should be used with more caution in acute heart failure associated with AMI than in chronic heart failure, since volume expansion is usually not the primary problem. If high filling pressure (>18 to 20 mmHg) persists after adequate output is achieved with positive inotropic agents and/or vasodilators, diuretics may be added. However, this effect can be achieved by vasodilator therapy, which avoids the hypovolemia and hypotension that may occur secondary to the subsequent diuresis (1 to 2 h). The preferred diuretics are intravenous furosemide or ethacrynic acid.[493] These drugs also provide some acute venodilation.

Complicated Heart Failure after Myocardial Infarction

Some AMI patients present with acute, fulminating pulmonary edema (with severe respiratory distress; generalized inspiratory crackles and wheezing; expectoration of pink, frothy sputum; cool, clammy, diaphoretic skin; and cyanosis) and require much more aggressive therapy than do patients with uncomplicated AMI. The condition is usually associated with pulmonary artery wedge pressure exceeding 25 mmHg and an in-hospital mortality rate of at least 15 to 20 percent.[494] The systolic blood pressure is usually either low normal or borderline normal (95 to 105 mmHg). The maintenance of adequate oxygenation must be the primary concern. Administration of high concentrations (60 to 100 percent) of oxygen via a face mask is essential. If the patient appears moribund, endotracheal intubation should be performed. While an assessment of arterial blood gases is appropriate, the speed with which clinical events change in these emergent situations may demand that decisions be made without benefit of these values. After the institution of mechanical ventilation, positive end-expiratory pressure may be needed to maintain adequate oxygenation while keeping the inspired oxygen concentration within safe levels (FI_{O_2} < 60 percent). Positive end-expiratory pressure should be applied only with an awareness of its risks of pneumothorax and reduction in cardiac output secondary to decreased left ventricular preload.[494] Invasive hemodynamic monitoring is particularly useful in these patients. Therapeutic interventions, however, should not be delayed until the monitoring is established. The therapy for severe pulmonary edema should include intravenous morphine unless the patient is known to have chronic CO_2 retention. From 5 to 10 mg of morphine sulfate should be given slowly with careful observation for evidence of respiratory depression. If the systolic blood pressure is adequate (≥100 mmHg), nitroglycerin is administered intravenously. In the patient with severe pulmonary edema, the improvement in left ventricular pump performance afforded by the prompt reduction in systemic vascular resistance by nitroprusside[495] may be essential for the rapid reversal of this life-threatening situation (particularly if systemic hypertension had been present). Either nitroglycerin or nitroprusside will provide a reduction in preload. If the systolic blood pressure is 100 mmHg or less, treatment with a positive inotropic agent should probably be initiated, with the subsequent addition of a vasodilator or an agent to improve cardiac output. The adjunctive use of intravenous diuretics is the same as outlined for mild degrees of heart failure.

PERIPHERAL HYPOPERFUSION WITHOUT PULMONARY CONGESTION

Patients with clinical hypoperfusion without pulmonary congestion (with cool, cyanotic extremities, somnolence or confusion, and decreased urine flow) usually have a cardiac index <2.2 L/min. The mortality rate in these patients is four times greater than that in patients without hypoperfusion.[494] Invasive hemodynamic monitoring of the pulmonary capillary wedge pressure is essential. Volume augmentation is the initial therapeutic step in patients with a pulmonary capillary wedge pressure <15 mmHg. If possible, this pressure should be maintained below the level of pulmonary congestion (>20 mmHg). Vasodilators are usually not indicated at least until adequate filling pressures have been achieved and cardiac output is augmented with positive inotropic agents. This situation is commonly seen with severe biventricular infarction and thus should be suspected with inferior and right ventricular infarction. In this case, bradycardia should be treated with atropine if it is thought to be contributing to the systemic hypoperfusion. Excessive treatment with nitroglycerin and volume contraction from previous diuretic therapy can also contribute to systemic hypotension.

HYPOTENSION AND CARDIOGENIC SHOCK

Cardiogenic shock may occur when 40 percent or more of the left ventricle is destroyed.[450,451,496] It is the most common cause of in-hospital death with myocardial infarction. The incidence of cardiogenic shock was about 15 percent in the early 1970s, but it has now decreased to approximately 5 to 7 percent.[494] The mortality rate is frequently over 80 percent.[497] The most effective therapy in the treatment of cardiogenic shock is prevention, since its major determinant is infarct size.[448,498] Cardiogenic shock usually occurs within hours of the onset of infarction due to massive ischemia and necrosis.[498] In other cases, a relatively small infarction that is superimposed on extensive previous damage may precipitate cardiogenic shock. Less commonly, cardiogenic shock may develop days after the initial event. This occurrence is almost always due to development of new necrosis (extension or early reinfarction) in the area of the preceding infarction. The decrease in the incidence of cardiogenic shock is believed to be in part due to better treatment of angina and ischemia, together with the widespread use of thrombolytic therapy and other

cardioprotective agents. Cardiogenic shock by definition represents a more severe form of cardiac failure, resulting in decreased organ perfusion in addition to the conventional features of pulmonary congestion and left ventricular dysfunction. Cardiac failure with hypoperfusion and that regarded as cardiogenic shock may differ only in the severity of decreased perfusion. Clearly, every effort must be made to treat hypoperfusion whether or not it satisfies the strict criteria of cardiogenic shock. Characteristics of cardiogenic shock are (Table 42-16) (1) evidence of organ hypoperfusion with cold, clammy skin, especially on the feet and hands, that may be associated with peripheral cyanosis of the nail beds; (2) oliguria, disordered mentation, and systolic blood pressure <80 to 90 mmHg; (3) left ventricular end-diastolic pressure or, more commonly, pulmonary capillary wedge pressure >18 mmHg; (4) evidence of a primary cardiac abnormality; and (5) a cardiac index *not* >1.8 L/min per square meter of body surface. Hypotension or shock due to a primary abnormality of cardiac rhythm or conduction is not considered cardiogenic shock.

Table 42-16: Characteristics of Cardiogenic Shock

Evidence of hypoperfusion: cold clammy skin, especially of feet and hands; impaired mentation; and oliguria
Systolic blood pressure <80-90 mmHg
LVED pressure (or PCW pressure) ≥18mmHg
Evidence of primary cardiac abnormality
Cardiac index ≤1.8 L/m/m^2

ABBREVIATIONS: LVED = left ventricular end-diastolic; PCW = pulmonary capillary wedge.

The advantage of early revascularization in reducing mortality in the acute setting (SHOCK trial)[299] was discussed earlier. Since the prognosis is extremely poor for patients with cardiogenic shock due primarily to loss of muscle mass, reversible causes associated with a better prognosis must be excluded. Potentially reversible causes include mitral valve rupture, ventricular septal rupture, right ventricular infarction, pulmonary embolus, and cardiac tamponade. While the mortality associated with surgical correction of infarct-associated mitral rupture or ventricular septal defect is still high, it is far less than that associated with cardiogenic shock due solely to myocardial injury. The details of management of these mechanical causes of shock are discussed later. Hypotension may be due to inadequate fluid administration, to vasodilatation induced by such drugs as morphine and vasodilators, and occasionally to depressed contractility due to antiarrhythmic therapy. Inadequate filling pressure is a very important cause of hypotension and should be corrected immediately. It is particularly common in patients with inferior infarction, as noted. A Swan-Ganz catheter should be inserted to determine the circulatory status and assess the response to therapy.

Therapeutic objectives are to establish and maintain a systemic arterial pressure adequate for perfusing the vital organs and for reducing pulmonary congestion. The approaches to pulmonary congestion include the judicious use of morphine, and the maintenance of adequate oxygenation, together with endotracheal intubation and mechanical ventilation if necessary. In addition to instituting hemodynamic monitoring, one should assess urinary output using an indwelling catheter. If the pulmonary artery wedge pressure is <15 mmHg, prompt volume expansion to raise the capillary pressure to 18 to 20 mmHg should be initiated. The cornerstones of therapy are inotropic and vasopressor agents. If the systemic arterial pressure is below 80 to 90 mmHg, a pressor agent such as dopamine should be infused.[499] At relatively low doses of 2 to 5 mg/kg per minute, increases in stroke volume and cardiac output are mediated by beta-adrenergic stimulation and increases in renal blood flow are mediated by the dopaminergic-specific receptors. The alpha-adrenergic vasoconstrictor effects are manifest progressively at doses above 5 mg/kg per minute. The use of intravenous dopamine requires careful titration, beginning with a low dose and gradually increasing until an adequate (90 to 100 mmHg) systemic pressure is achieved. If high doses of dopamine are necessary to maintain adequate perfusion, a change to norepinephrine infusion should be considered. This drug is a potent arteriolar and venous constrictor that is mediated through alpha-adrenergic stimulation. It demonstrates relatively modest beta-adrenergic stimulation. It is, therefore, a very potent pressor agent with

less chronotropic or arrhythmogenic effects than dopamine.[267] The drug should be started at low doses of 1 to 4 mg/min. Extravasation should be avoided, since it will produce tissue sloughing.

When the systemic blood pressure is 90 mmHg or more, dobutamine is frequently the preferred agent. By increasing cardiac output, dobutamine may produce a rise in systemic blood pressure, but this increase would not be expected to be >10 to 15 mmHg.[500,501] Dobutamine will not support arterial pressure except by its effect on cardiac output. As the cardiac output rises, the left ventricular filling pressure should decline. Dobutamine therapy should begin with a dose of 2 to 5 mg/kg per minute with increases every 5 to 10 min. Inappropriate increases in heart rate are unlikely to occur with doses <15 to 20 mg/kg per minute.[483]

On occasion, the severity of cardiac pump dysfunction will require the use of two divergent therapeutic modalities in order to facilitate left ventricular emptying.[502] The most commonly utilized of these combined therapies is nitroprusside and dopamine. The principal advantage offered by nitroprusside in this combination is a reduction in left ventricular preload. The cardiac output is not appreciably increased by the addition of nitroprusside to dopamine therapy. The advantage offered by dopamine in this combination is an augmentation of cardiac output and the maintenance of systemic arterial pressure.[503] A less frequently used combination, dobutamine and nitroprusside, has been shown to result in higher cardiac output and lower pulmonary capillary wedge pressures than has resulted with either drug alone.[502] Stabilization of the patient with cardiogenic shock may be achieved by mechanical circulatory assist devices, such as the intraaortic balloon as demonstrated in the completed SHOCK Trial.[299] Aortic balloon counterpulsation reduces afterload while simultaneously improving coronary perfusion by increasing diastolic aortic pressure, as discussed. It is the only intervention that will increase diastolic aortic pressure without increasing myocardial oxygen demand. Aortic counterpulsation is often helpful for patients in cardiogenic shock due to a potentially reversible condition or in whom cardiac transplantation is being considered. Such conditions include an acute but still evolving MI or AMI with a severe mechanical complication (e.g., mitral regurgitation or ventricular septal defect). In such cases, aortic counterpulsation should be used to stabilize the patient's condition in preparation for salvage of the jeopardized but still viable myocardium or correction of the mechanical defect.[267] Intraaortic counterpulsation in patients without a reversible defect is now being used with greater frequency, especially in patients <75 years of age based on the compelling data emerging from the long-term follow-up of the SHOCK Trial patients.[299]

Restoration of coronary blood flow is the most effective therapy in salvaging patients with cardiogenic shock who are unresponsive to fluid and pharmacologic management in the early hours after a myocardial infarction. If angioplasty and/or coronary artery bypass grafting are not readily available, thrombolytic therapy should be tried if it has not already been utilized-although it has not been shown to improve survival in this setting.[504,505] These patients should be transferred quickly to a tertiary care center. Blood pressure should be stabilized with an intraaortic balloon pump, and cardiac catheterization should be performed as soon as possible. Assessment of correctable mechanical lesions, such as ruptured papillary muscles, can be made together with evaluation of coronary anatomy. Depending upon this anatomy, a judgment can be made as to whether to attempt PTCA or to proceed to coronary artery bypass surgery. Mechanical revascularization appears to improve survival in cardiogenic shock complicating AMI.[299,506]

MECHANICAL DYSFUNCTION CONTRIBUTING TO CARDIAC FAILURE

PAPILLARY MUSCLE RUPTURE

Rupture of the left ventricular papillary muscle occurs in approximately 1 percent of myocardial infarctions and accounts for 0.4 to 5.0 percent of infarct-related deaths.[507] It occurs slightly less frequently than ventricular septal rupture. The posteromedial papillary muscle is involved 6 to 12 times more frequently than is the anterolateral muscle.[508] Thus, papillary muscle rupture with an acute anterior myocardial infarction is uncommon. The rupture may occur distally and may involve one or several of the smaller heads of the muscle or, less commonly, may occur proximally and produce complete dehiscence of the papillary muscle.

Papillary muscle rupture is manifest by the sudden appearance of pulmonary edema, usually 2 to 7 days after the infarction. The abruptness of onset and severity of pulmonary edema are usually greater than seen

with ventricular septal rupture. A mid- or holosystolic murmur with wide radiation is usually audible. Although the murmur is generally loud, a thrill is rarely present, and the murmur may seem inconsequential. The diagnosis can be established by Doppler echocardiographic studies (see Chap. 13). The two-dimensional echocardiogram will generally show a flail mitral leaflet and may reveal a portion of the papillary muscle visualized as a mass attached to the chordae. Even when the flail leaflet is not observed, documentation of relatively intact ventricular systolic function in the postinfarction patient with pulmonary edema should suggest the diagnosis. The Doppler study will establish the presence and severity of the mitral regurgitation. Bedside right side of the heart catheterization can be used to exclude an oxygen step-up from the right atrium to the right ventricle, indicative of ventricular septal rupture, and to confirm elevated pulmonary capillary wedge pressures with tall V (regurgitant) waves characteristic of acute mitral regurgitation.

Studies in the presurgical era demonstrated a poor prognosis for these patients, with a 50 percent mortality rate in the first 24 h and a 6 percent survival rate for longer than 2 months.[442] Thus, immediate recognition and treatment are essential. Intraaortic counterpulsation alone or with vasodilator and inotropic therapy may frequently be required for temporary stabilization. During this period, the patient should undergo cardiac catheterization to define coronary anatomy and should be transferred to surgery for mitral valve replacement or repair.

PAPILLARY MUSCLE DYSFUNCTION

The sudden development of an apical systolic murmur after a myocardial infarction is much more often secondary to papillary muscle dysfunction than it is to rupture. Twenty percent of patients who die from infarction have histologic evidence of papillary muscle necrosis, usually without rupture.[509] Papillary muscle dysfunction is frequently compatible with long-term survival.

The posteromedial papillary muscle is involved with ischemia or infarction more commonly than the anterolateral muscle because the latter receives blood from two arteries (left anterior descending and circumflex), whereas the posteromedial muscle is supplied predominantly from the circumflex.[510] Dysfunction may be transient during ischemia. Papillary muscle ischemia is usually accompanied by ischemia of the contiguous ventricular wall.[511] Involvement of the contiguous ventricular wall is a key factor in the development of significant mitral regurgitation, since isolated papillary muscle ischemia or even infarction is usually not sufficient to cause important mitral regurgitation.[512]

Papillary muscle dysfunction typically presents with an apical systolic murmur. The murmur may be holosystolic, late systolic, or even early systolic. Echocardiography coupled with Doppler flow studies will confirm the presence of mitral regurgitation, grade its severity, and permit assessment of left ventricular function. There is generally no hemodynamic deterioration associated with the appearance of the murmur. It is the unusual patient who develops pulmonary edema, and these patients usually have concomitant significant left ventricular dysfunction. The ordinary patient with papillary muscle dysfunction will require no specific therapy for the regurgitation, while the unusual patient with severe regurgitation should be treated as in the case of papillary muscle rupture. In intermediate cases with moderate to moderately severe regurgitation where cardiac surgery is not contemplated, afterload reduction with ACE inhibitors should be considered.

VENTRICULAR SEPTAL RUPTURE

Rupture of the interventricular septum is estimated to occur in 1 to 3 percent of AMIs and accounts for approximately 5 percent of all infarct-related deaths.[513] Ventricular septal rupture occurs with an approximately equal frequency between anterior and inferior infarctions. There is a higher prevalence in first infarctions and the majority occur within the first week. Some 20 to 30 percent may develop as early as the first 24 h after the infarction.[514,515] Septal rupture rarely occurs after 2 weeks. Ventricular septal rupture is usually manifest by the appearance of a new harsh, holosystolic murmur along the left sternal border (often associated with a thrill) and sudden clinical deterioration with hypotension and pulmonary congestion. Right ventricular volume overload secondary to the shunt may produce signs of systemic venous congestion out of proportion to those of pulmonary venous congestion. Often the event is heralded by a recurrence of chest pain.

The diagnosis can be established by two-dimensional and Doppler echocardiographic studies that will demonstrate the site and approximate size of the rupture as well as the left-to-right shunt. Right-sided heart catheterization is useful in confirming the diagnosis (an increase in O_2 saturation of >5 percent from right atrium to right ventricle) and is an aid in managing the patient. The primary diagnostic concern is to exclude rupture of the papillary muscle. The presence of a thrill or an anterior infarction would be unusual with papillary muscle rupture, and results of the Doppler echocardiographic studies and/or the oxygen step-up on right side of the heart catheterization would confirm the presence of septal rupture.

When medical therapy alone is used, most patients with ventricular septal rupture deteriorate rapidly and virtually all patients die, many within 24 h after rupture. Except for the rare case in which there is no clinical or hemodynamic deterioration, medical therapy can be expected to be ineffective. *It is now axiomatic, that upon discovery of rupture of the ventricular septum, prompt surgical repair should take place, even for those patients who are clinically stable*. Inotropic and vasopressor agents may be required to sustain arterial blood pressure but can increase the left-to-right shunt. Prompt but temporary stabilization can be achieved with intraaortic balloon counterpulsation alone or in conjunction with vasodilator and inotropic drug therapy. Cardiac catheterization should be performed in an expeditious manner to define cardiac anatomy, left ventricular function, and mitral valve competence. An aggressive approach of immediate operative repair of these patients results in a short-term survival rate of 42 to 75 percent.[516-518] The 5-year actuarial survival rate for the operative survivors has been reported to be as high as 88 percent.[519] Surgical results are worse when ventricular septal rupture complicates inferior infarction and when there is combined right ventricular and septal dysfunction.[518]

CARDIAC RUPTURE

Cardiorrhexis, or rupture of the heart, occurs in up to 24 percent of fatal AMIs. After cardiogenic shock and arrhythmias, it is the most common cause of death. The free wall of the ventricle is the most common site of rupture.[520]

Rupture of the free wall generally occurs within the first 2 weeks of the infarction and may occur within the first 24 h.[514,515] Rupture occurring after this interval usually represents extension of the infarction or rupture through a false aneurysm.[521]

The rupture occurs primarily in the left ventricle, with a fairly even distribution between the anterior, inferior, and lateral walls. Given the relatively smaller number of lateral infarctions, the incidence of rupture with lateral wall infarctions would presumably be relatively smaller than at other sites.[522] Free wall rupture is more likely to occur with the initial myocardial infarction, in women, in the sixth decade of life or later, and in patients with systemic arterial hypertension, particularly if there is no associated ventricular hypertrophy.[514] The prolonged use of corticosteroids might predispose a patient to cardiac rupture.

Cardiac rupture generally presents as sudden, unanticipated death. Symptoms such as pain, agitation, sinus tachycardia, or vagally mediated bradycardia seldom precede death by more than minutes. Occasionally, intermittent chest pain and/or transient hypotension may precede and portend the final catastrophic event. Cardiac rupture is diagnosed terminally by the development of electromechanical disassociation in the setting of recurrent chest pain. Few cases, and only those with immediate recognition, can be salvaged. Even these few cases require heroic measures, such as immediate pericardiocentesis, emergency thoracotomy, and surgical repair.

OTHER COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

Pulmonary Embolism

The prevalence of deep venous thrombosis in AMI is reported to be between 12 and 38 percent. Patients with large infarctions in any location, anterior infarctions, evidence of congestive heart failure, and complicated infarctions have a greater frequency of deep venous thrombosis.[523,524] Reduced cardiac output and immobilization are additional predisposing factors for deep venous thrombosis (see Chap. 90).

Venous thrombosis is usually a minor and frequently unrecognized complication of infarction but is potentially life-threatening. A prevalence of pulmonary embolism of 10 to 15 percent and a prevalence of fatal embolism in 3 to 6 percent of cases has been reported in the past.[525] More recently, pulmonary embolism has been reported to account for less than 1 percent of deaths in myocardial infarction, probably because of earlier ambulation and better therapy of low output.[521]

Early mobilization combined with therapy directed toward improving cardiac output, when appropriate, is probably the most effective means of preventing pulmonary emboli. Prophylactic anticoagulant therapy is not routinely recommended for all patients after a myocardial infarction but is advisable for patients with increased risk factors for deep venous thrombosis and pulmonary embolism.

Systemic Emboli

Emboli to the cerebrovascular, renal, mesenteric, iliofemoral, or other arterial systems may complicate the AMI. The reported prevalence of clinically apparent systemic emboli in patients with myocardial infarction varies from 0.6 to 6.4 percent.[526,527] These emboli result from dislodgement of left ventricular thrombi, which are found in 20 to 40 percent of anterior myocardial infarctions. A ventricular thrombus is unusual in patients with an inferior infarction.[527,528] The predilection of the apical wall for thrombus development appears to be related to a combination of stagnant blood flow and poor wall contractility. Severe depression of left ventricular function is not a prerequisite for thrombus formation. The development of a mural thrombus in a small infarction (CK < 1000 U), however, is unusual.[529,530] Thrombus morphology and mobility would seem to correlate with systemic embolization.[526,531,532] Pedunculated and freely mobile thrombi have been thought to have a greater chance of embolization. At least two studies, however, could not correlate risk of embolization to any particular thrombus morphology.[527,530]

Left ventricular thrombosis usually occurs within the first 3 days after a myocardial infarction,[530,533] but may occur at any time during the hospital course. Early mural thrombosis occurs in large infarctions that have an unfavorable prognosis.[530] Systemic embolization occurs an average of 14 days after AMI and is unlikely to occur after more than 4 to 6 weeks.[534] Anticoagulation appears to reduce the incidence of mural thrombus formation[535] and the prevalence of systemic embolization.[526,528,529] All patients with an anterior myocardial infarction should have two-dimensional echocardiography performed within 24 to 72 h following the infarction, with particular emphasis on the two- and four-chamber apical views. Those with a severe apical wall contraction abnormality (akinesis or dyskinesis) should receive heparin for several days, followed by warfarin (INR 2 to 3) for 1 to 3 months. In patients with a left ventricular thrombus demonstrated by echocardiographic studies, chronic warfarin therapy (Chap. 44) is continued for approximately 3 months. Warfarin administration should be maintained indefinitely for atrial fibrillation.

Two-dimensional echocardiography has a sensitivity of 83 to 95 percent and a specificity of 86 to 90 percent in diagnosing a mural thrombus.[527,529,531,536] Angiography has a sensitivity of 20 to 63 percent and a specificity of 67 to 75 percent.[526,537] Occasionally, a technically unsatisfactory echocardiogram may require the use of alternative noninvasive imaging modalities. Both computed tomography and magnetic resonance imaging offer a similar sensitivity and perhaps superior specificity to echocardiography in this setting.[537]

Ventricular Aneurysm

The true prevalence of ventricular aneurysm after myocardial infarction is not well defined. Probably the best approximation comes from postmortem studies estimating a 3 to 15 percent prevalence.[533,538] The CASS registry documented angiographically defined left ventricular aneurysms in 7.6 percent of patients with coronary artery disease. The location of the aneurysm is usually anterior, anteroapical, or apical. True posterior ventricular aneurysms located in the diaphragmatic wall between the septum and insertion of the posterior papillary muscle have been observed but are quite uncommon.[539]

Pathologically, the aneurysmal area is characterized by a thinned-out transmural scar that has completely lost its trabecular pattern. The scar, which may eventually calcify, is clearly delineated from surrounding ventricular muscle. Aneurysms characteristically have a wide base (the diameter of the mouth is equal to or

larger than its greatest internal diameter), and one-half are lined by a laminated thrombus.[540]

As many as 80 percent of chronic ventricular aneurysms can be diagnosed clinically by the presence of an abnormal precordial impulse, most often located in the third left intercostal space at the midclavicular line; a typical bulge on the left ventricular border on chest x-ray, frequently with calcification around the apex; and ECG evidence of a large anterior infarction with ST-segment elevation persisting beyond 2 weeks following the infarction. Two-dimensional echocardiographic studies can confirm the diagnosis.[527] Left ventricular aneurysms are associated with a reduced survival rate. The prognosis for these patients, however, is primarily related to the left ventricular dysfunction and not to the presence of the aneurysm. True ventricular aneurysms rarely rupture. In fact, the survival rate for patients with an aneurysm is no different than that for patients without an aneurysm but with a similar degree of left ventricular dysfunction. Moreover, the incidence of sudden death is no different. Whether or not clinical recognition of the presence of a ventricular aneurysm is important in the management of the patient after an AMI remains to be answered.[536]

Most patients with ventricular aneurysms should be treated the same as any other postinfarction patient with a similar degree of left ventricular dysfunction. Vasodilators, digoxin, anticoagulants, and antiarrhythmics should be used, based not on the presence of the aneurysm but as dictated by presence of heart failure, mural thrombi, and life-threatening arrhythmias. Occasionally, surgical resection of the aneurysm is justified in order to correct refractory heart failure, recurrent life-threatening arrhythmias, or multiple systemic emboli. The aneurysm resection should usually be combined with coronary bypass grafting and, in cases of ventricular arrhythmias, should be guided by electrophysiologic mapping.

Pseudoaneurysm

A pseudoaneurysm is a rare complication of myocardial infarction, the prevalence of which is not known. The probable sequence of events in the development of a pseudoaneurysm is as follows: occurrence of a transmural infarction with localized pericarditis arising at the site of infarction; development of adhesions between the visceral and parietal pericardium; rupture of the infarcted myocardium, with the extravasated blood confined by the adherent pericardium; progressive enlargement of the aneurysmal sac; and development of thrombus within the sac.[521]

Unlike a true ventricular aneurysm, a pseudoaneurysm has a narrow base (site of rupture). The wall is composed only of a thrombus and pericardium, and the risk of rupture is high.[541] While the neck is small (its diameter is <50 percent of the diameter of the fundus), the pseudoaneurysm may progressively enlarge to become larger than the left ventricle. The pseudoaneurysm may be clinically silent or may present as progressively worsening heart failure, an abnormal bulge on the cardiac border, persistent ST-segment elevation in the area overlying the infarction, or systolic murmurs.[542]

The diagnosis can be established by two-dimensional echocardiographic studies, ventriculographic radionuclide studies, MRI, or left ventriculographic contrast studies.[541] Surgical resection is always indicated.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES COMPLICATING ACUTE MYOCARDIAL INFARCTION

Arrhythmias and conduction disturbances that are likely to be significant problems during the early phases of AMI and their management have been discussed earlier, under "Evaluation and Management of the Patients with Chest Pain in the Emergency Department." The arrhythmias and conduction abnormalities discussed include sinus bradycardia, AV block, idioventricular rhythm, VT, and VF. In general, the acute management of these rhythm disturbances is the same in the early and in the late phases of AMI. Sustained VT and VF are exceptions, however, in that their occurrence after the first 24 h has more ominous implications for long-term electrical instability and sudden cardiac death. Other rhythm and conduction abnormalities that may be manifest throughout the course of AMI and are not characteristically associated with the early phases, are discussed here.

Ventricular Ectopy, Ventricular Tachycardia, and Ventricular Fibrillation

The management of VT and VF after the first 24 h of hospitalization for AMI is similar to that discussed for the early phase. The occurrence of symptomatic, sustained VT or VF in the later phases of the hospital course, however, suggests that a chronic arrhythmogenic focus may be developing in the damaged ventricle. These ventricular arrhythmias are classified as secondary and indicate increased risk for subsequent sudden cardiac death.

Sinus Tachycardia or Atrial Premature Beats

Sinus tachycardia following AMI is common and is frequently an unfavorable prognostic sign. The increased heart rate enhances myocardial oxygen demand, while the decreased diastolic time decreases diastolic coronary flow. Patients with a large area of infarcted myocardium may have sinus tachycardia on the basis of left ventricular dysfunction, which causes reflex sympathetic nervous system activation. Other obvious causes of sinus tachycardia-such as fever, anxiety, pain, pulmonary embolism, anemia, hypovolemia, or hypoxemia-must be evaluated and treated. Sinus tachycardia may occur as a result of the effects of drugs, such as dobutamine, dopamine, theophylline, and atropine.[543] In the absence of precipitating causes, a persistent sinus tachycardia most likely reflects progressive left ventricular dysfunction, which should be evaluated and managed accordingly.

Frequent atrial premature complexes are relatively common in AMI and are caused by atrial ischemia or infarction and pericarditis.[543-547] No specific therapy is indicated; rather, attention should be given to the underlying disease process.

Paroxysmal Supraventricular Tachycardia

Episodes of paroxysmal supraventricular tachycardia occur rather commonly in AMI and are usually transient.[544] Underlying causes are similar to those of atrial premature complexes. For reasons discussed, the tachycardia may worsen ischemia. Rate control is essential, and the therapeutic approaches-which may include carotid sinus massage, adenosine, digoxin, verapamil, or diltiazem-are discussed in Chaps. 23 and 24.

Atrial Flutter and Atrial Fibrillation

Atrial flutter is relatively uncommon in AMI, whereas atrial fibrillation has an incidence of 10 to 15 percent.[544,545] Atrial fibrillation is associated with an increased in-hospital mortality rate, probably because it is associated with large infarcts and is seen relatively more commonly in older patients and those with cardiac failure, complex ventricular arrhythmias, advanced AV block, atrial infarction, and pericarditis.[548] The pathophysiologic implications are similar to those for paroxysmal supraventricular tachycardia in that a rapid ventricular response can worsen ischemia and infarction by increasing oxygen consumption. Furthermore, the loss of atrial transport can worsen cardiac output and lead to hemodynamic instability.

Atrial fibrillation increases in incidence with age; it occurs in less than 5 percent of patients with AMI under the age of 60 and in about 16 percent of those over age 70.[1] The incidence of atrial fibrillation has been reported to be lower in patients receiving thrombolytic therapy than in control patients.[549]

Systemic embolization occurs more commonly in AMI in the presence of atrial fibrillation (1.7 percent) than in its absence (0.6 percent). Fifty percent of these emboli occur during the first hospital day and 90 percent have occurred by the fourth day.[550] Thus, heparin therapy is indicated in patients not already receiving it, despite that the rhythm is usually transient.

If the patient experiences new or worsening pain, ischemic ST changes, or hemodynamic instability during atrial fibrillation with a rapid ventricular response rate, immediate electrical cardioversion is indicated. In the conscious patient, brief anesthesia is indicated (see Chaps. 24 and 29).

If the clinical situation is less urgent, the ventricular rate can be reduced with drugs. Rapid digitalization with intravenous digoxin is effective but will not result in an immediate response, which may take 1 to 2 h.

In the absence of contraindications such as congestive heart failure or bronchospastic pulmonary disease, intravenously administered beta-blocking drugs are highly effective in slowing the ventricular rate. Intravenous administration of the calcium channel blockers, verapamil or diltiazem, can also be effective in slowing the ventricular response, but these are not considered to be first-line drugs (except possibly in the setting of NQWMI).

Firm recommendations have not been made about the use of class I and III antiarrhythmics to prevent the recurrence of atrial fibrillation in AMI.[1] Since recurrence is associated with a worse prognosis, however, it seems prudent to consider amiodarone or sotalol or, alternatively, quinidine or procainamide. Neither anticoagulation nor antiarrhythmic therapy should be continued for the long term. With stable sinus rhythm, either or both, as the case may be, should be stopped after 6 weeks.

Junctional Rhythm

An escape AV junctional rhythm at a rate of 40 to 60 beats per minute in patients with inferior myocardial infarction and high-degree heart block is not uncommon.[544] Therapy usually is not required. Accelerated junctional rhythms are occasionally seen in AMI, more likely at rates of 70 to 130 beats per minute,[551] but are rarely seen at considerably higher rates. Treatment generally focuses on the underlying conditions, such as ischemia or digitalis toxicity.

Heart Block

First-, second-, and third-degree AV blocks have been discussed briefly. First-degree block is frequently seen in AMI, and especially in inferior myocardial infarction. This is attributable to ischemia or enhanced vagal activity. It can be worsened by drugs such as beta blockers. Treatment is seldom required.

Second-degree AV block is also relatively common, especially Mobitz type I or Wenckebach block. This block, characterized by progressive lengthening of the PR interval before the atrial beat, is not conducted and may occur in as many as 10 percent of AMI patients.[552] It is associated with a narrow QRS and frequently is the result of AV node ischemia in inferior myocardial infarction. It is usually transient, and its presence does not affect the prognosis. Mobitz type II block is uncommon but is associated with more serious complications and a worse prognosis. It usually occurs with anterior myocardial infarction and reflects trifascicular block. It is characterized by a wide QRS and a nonvarying PR interval before a nonconducted atrial beat. Heart block may develop suddenly and is an ominous sign, with a mortality of about 80 percent. It is usually permanent.

Third-degree AV block, or complete heart block, occurs in about 5 percent of patients with AMI and is most commonly seen with inferior infarction, usually with block at the AV node. As indicated, complete heart block in inferior myocardial infarction is usually transient and may occur early or late in the hospital course with the same implications for prognosis. There is some increase in in-hospital mortality rates in this setting, but complete heart block in inferior myocardial infarction is not an independent predictor of poor long-term prognosis.[328] In contrast, patients with anterior infarction who develop third-degree AV block have a mortality rate of 80 percent.[553] Implications for temporary and permanent pacing are discussed subsequently.

Intraventricular Conduction Disturbances

The development of bundle branch block during AMI usually signifies an extensive infarct. In one multicenter trial, the presence of bundle branch block was associated with a twofold increase in the in-hospital mortality rate (28 versus 14 percent), compared with the absence of bundle branch block.[331,554] Data indicate that the presence of bundle branch block identifies patients who (1) are more likely to develop congestive heart failure, (2) are more likely to develop high-degree heart block, (3) are more likely to have an episode of ventricular fibrillation, and (4) have a higher mortality rate.[554]

Indications for Temporary Transvenous Pacing

Recommendations[1]:

Class I

1. Asystole
2. Symptomatic bradycardia (including sinus bradycardia with hypotension and type I second-degree AV block with hypotension not responsive to atropine)
3. Bilateral bundle branch block (alternating or right bundle branch block with alternating left anterior fascicular/posterior fascicular block; any age)
4. New or indeterminate-age bifascicular block (right bundle branch block with left anterior or posterior fascicular block) with first-degree AV block
5. Mobitz type II second-degree AV block

Class IIa

1. Right bundle branch block and left anterior or left posterior fascicular block (new or indeterminate)
2. Right bundle branch block with first-degree AV block
3. Left bundle branch block, new or indeterminate
4. Incessant VT, for atrial or ventricular overdrive pacing
5. Recurrent sinus pauses (greater than 3 s) not responsive to atropine

Class IIb

1. Bifascicular block of indeterminate age
2. New or age-indeterminant isolated right bundle branch block

Class III

1. First-degree heart block
2. Type I second-degree AV block with normal hemodynamics
3. Accelerated idioventricular rhythm
4. Bundle branch block or fascicular block known to exist before acute myocardial infarction

Cardiac pacing is discussed in Chap. 31. The indications generally agreed on for temporary pacemaker insertion in AMI include asystole, complete heart block in the setting of anterior myocardial infarction, new onset of right or left bundle branch block with persistent Mobitz II second-degree AV block in the setting of anterior myocardial infarction, or other symptomatic bradycardias unresponsive to atropine.[200]

Bundle branch block in the setting of AMI, as noted, identifies a population at risk for both electrical and mechanical complications. Such patients must be monitored for evidence of transient high-degree heart block. Prolonged intermediate care with telemetry monitoring and repeat assessments of heart failure status are important.

Permanent Pacing

Recommendations[1]:

Class I

1. Persistent second-degree AV block in the His-Purkinje system with bilateral bundle branch block or complete heart block after AMI
2. Transient advanced (second- or third-degree) AV block and associated bundle branch block
3. Symptomatic AV block at any level

Class IIb

1. Persistent advanced (second- or third-degree) block at the level of the AV node

Class III

1. Transient AV conduction disturbances in the absence of intraventricular conduction defects
2. Transient AV block in the presence of isolated left anterior fascicular block
3. Acquired left anterior fascicular block in the absence of AV block
4. Persistent first-degree AV block in the presence of bundle branch block that is old or age-indeterminate

The use of permanent pacemakers is discussed in detail in Chap. 31. The subject is reviewed extensively in the ACC/AHA guidelines for pacemaker implantation.[555] That temporary pacing may have been required in the course of AMI does not necessarily indicate a need for permanent pacing. Patients who have had permanent pacemakers inserted after AMI usually have a relatively unfavorable prognosis primarily related to the extensiveness of the underlying disease and myocardial damage.[1] Thus, these patients are at increased risk for death from progressive congestive heart failure and VTs. The generally accepted indications for insertion of a permanent pacemaker after AMI are summarized in the previous recommendations.

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Chapter 42: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

DISCHARGE FROM THE CORONARY CARE UNIT

The length of stay in the CCU should be based on the risk of developing VT and VF. The risk of developing primary VF after AMI decreases exponentially, with the majority of arrhythmic deaths occurring within the first 24 h. After the third day, the episodes of life-threatening arrhythmias are fairly evenly distributed over the remainder of the hospitalization.[556] Thus, a patient with an uncomplicated infarction can be transferred from the CCU on the third day. Since 31 to 34 percent of in-hospital deaths from AMI occur after discharge from the CCU and half of them are sudden and unexpected, certain patients need more prolonged cardiac monitoring.[557,558] Those patients who are prime candidates for late-hospital sudden deaths manifest, while in the CCU, one or more of the following: (1) the arrhythmias of pump failure (sinus tachycardia, atrial flutter, or atrial fibrillation); (2) the arrhythmias of electrical instability (VT or VF); (3) acute interventricular conduction disturbances; (4) evidence of circulatory failure (congestive heart failure, pulmonary edema, or significant hypotension); or (5) large anterior infarction. The effectiveness of prolonged monitoring of this select group of patients in an intermediate care unit following CCU discharge is evident in a doubling of the rate of successful resuscitations.[559,560] Patients who do not fit into these high-risk subgroups can be discharged from the CCU to a medical unit without continuous monitoring. The wide availability of continuous monitoring in many hospitals in nonacute care units, however, permits easy further monitoring even on lower-risk patients and is preferable if available.

The activity permitted the patient with uncomplicated infarction has changed immensely during the last two decades. In an uncomplicated myocardial infarction, the patient does not need to be confined to the bed for longer than 24 h. In fact, the patient may use a bedside commode from the time of admission. The safety and benefits of chair rest were initially promoted by Samuel Levine and Bernard Lown in 1951.[561] Upon transfer from a CCU, the patient should be started on a program of progressive ambulation. The speed with which the patient progresses from one stage to the next depends on the severity of the infarction, the presence or absence of complications, the patient's age, and the presence of comorbid conditions. The length of hospitalization following an AMI should likewise depend on these same factors. If the patient has not manifested the arrhythmias of pump failure or electrical instability, evidence of circulatory failure, or advanced AV block during the first 4 days of hospitalization, he or she is very unlikely to do so at any later time.[562] This patient could probably be discharged after 7 or fewer days in the hospital.[563] The last 2 to 3 days of the hospitalization are generally necessary to resolve the questions pertaining to residual ventricular function, the presence or absence of ventricular ectopy, and the adequacy of the remainder of the coronary circulation. In addition, time is needed for instruction in risk-factor modification (see Chap. 50). As discussed previously, time in the hospital is being shortened, especially after successful thrombolysis.

Noninvasive Risk Stratification in Patients Surviving Acute Myocardial Infarction

The purpose of risk stratification of patients surviving AMI assumes that the information provided will enhance decision making, resulting in improved long-term outcome. While numerous tests provide prognostic information, only some have resulted in a treatment strategy that improves outcome. No single noninvasive cardiac test better exemplifies this potential "benefit gap" than ventricular premature beats after AMI which are associated with an increased risk of death; however, no antiarrhythmic intervention has been demonstrated to reduce mortality; some have even paradoxically increased the mortality rate.

Survivors of AMI have a substantial risk of incurring subsequent cardiovascular events. Noninvasive risk assessment provides useful information to individualize the extent of further workup and therapy by: (1) targeting specific long-term therapies that are established to alter mortality and morbidity; (2) identifying high-risk patients requiring aggressive diagnostic tests and therapies; (3) identifying low-risk groups as

targets for a conservative approach emphasizing established long-term prophylactic therapies; (4) providing information that facilitates counseling the patient on prognosis; (5) provide data to recommend an exercise program; and (6) provide information used in planning and prioritizing modifications of lifestyle.

Three interrelated prognostic factors are the focus of predischarge assessment: (1) assessment of left ventricular function, (2) detection of residual myocardial ischemia (jeopardized myocardium), and (3) assessment of the risk of arrhythmic (sudden cardiac) death. Most proposed algorithms of noninvasive test selection focus on these three important clinical areas.[564,565] High-risk patients can be clinically identified, as previously discussed, without such noninvasive assessments because of evidence of one or more of the following: decompensated congestive heart failure, angina associated with electrocardiographic changes, in-hospital cardiac arrest, spontaneous sustained VT, or the development of a high-degree heart block.[566-569] In contrast to these high-risk groups, the majority of postinfarct patients have a relatively benign hospital course. In these patients, noninvasive testing can accurately identify a group at very low risk whose annual mortality is 1 to 3 percent.[416,417,570,571] The practical consequences of identifying a low-risk group is that emphasis is focused on early discharge, lifestyle modification and targeted prophylactic medical therapy rather than expensive, invasive diagnostic testing.

As discussed previously, there is general agreement that early coronary angiography and aggressive interventional therapy are indicated for patients with recurrent episodes of spontaneous angina or ischemia, in patients with evidence of persistent decompensated congestive heart failure or cardiogenic shock. In the following sections, the emphasis is on the noninvasive evaluation of asymptomatic patients.

ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND LEFT VENTRICULAR EJECTION FRACTION

Many clinical features are associated with an increased risk for the development of congestive heart failure, including anterior and anterolateral infarction, papillary muscle dysfunction, and recurrent AMI as well as the development of transient episodes of high-degree heart block. Congestive heart failure in the setting of inferior AMI associated with right ventricular infarction is also a prognostically important category, necessitating an aggressive management strategy, as discussed. Measurement of LVEF is mandatory in such patients but also useful in patients without such obvious left ventricular dysfunction. Left ventricular ejection fraction can be assessed by either echocardiographic, radionuclide, or angiographic techniques.[572,573] Left ventricular ejection fraction is an important determinant of survival after AMI regardless of reperfusion status. In-hospital mortality is directly related to the severity of left ventricular dysfunction. In the absence of significant ischemia or ventricular arrhythmias, patients with a LVEF ≥40 percent have mortality rates in the range of 5 percent over 1 to 2 years, whereas a LVEF of 30 to 39 percent or <30 percent have mortality rates that increase to 10 to 15 percent compared to 20 to 25 percent, respectively.[564,572,573] Although measured much less frequently, the end-systolic volume index is also an accurate predictor of survival following AMI.[573,574]

Clinical reflections of the degree of left ventricular systolic dysfunction include the patient's exercise capacity as judged by exercise testing and/or the New York Heart Association clinical classification, which is an independent predictor of outcome. Patients with good exercise capacity, even in the presence of a reduced ejection fraction, have a superior long-term outcome in comparison with those who cannot perform mild-to-moderate exercise.[575]

ASSESSMENT OF MYOCARDIAL ISCHEMIA

Exercise Testing: Timing and Protocol Selection

During hospitalization, in patients recovering from AMI, a practical and safe approach to exercise testing has been to utilize a submaximal treadmill exercise protocol (modified Naughton or modified Bruce protocol) rather than the standard Bruce protocol.[576] The target for completing the test is often symptom-limited exercise to a specific heart rate goal (e.g., 70 to 75 percent age-predicted) or to a peak work level (e.g., 5 metabolic equivalents, or METs) unless other factors (≥2 mm ST depression, chest pain, ventricular arrhythmia, or hypotension) arise first (see Chap. 14). The exercise ECG most accurately reflects the risk of

subsequent ischemic events when baseline ECG is normal.

Exercise testing is also useful in planning the exercise prescription for a cardiac rehabilitation program (see Chap. 50). For safety, patients should be angina-free and free of cardiac failure before exercise testing. Patients selected in this fashion under the supervision of a physician are at minimal risk for complications.[570,571,577,578] One caveat is that in most of these studies, patients exercised 1 to 2 weeks after AMI, a time frame incompatible with managed care early discharge strategies.[577,578]

CLINICAL SIGNIFICANCE OF PREDISCHARGE SUBMAXIMAL EXERCISE TESTING

Numerous studies have analyzed the predictive value of predischarge exercise testing during a 6- to 12-month follow-up after AMI.[570,571] Exercise variables of prognostic significance are exercise-induced ST-segment depression, ST-segment elevation, development of angina during exercise, inadequate blood pressure response to exercise, or exercise of short duration. From the practical standpoint, it is important to consider all of these exercise variables rather than to focus solely on the presence or absence of ST-segment depression. Done appropriately, submaximal exercise testing consistently identifies a high-risk group for recurrent cardiac events (AMI, unstable angina) or mortality in the first year after the AMI. However, the relative risk for mortality or cardiac events associated with a "positive exercise test" varies greatly between studies (twofold to more than 15-fold versus a "negative test"). A normal submaximal exercise test identifies a very low risk group (1 to 3 percent mortality rate for the first year).[570,571,578] Thus, a negative test result is adequately reassuring to encourage early discharge as well as discourage an aggressive diagnostic approach. The ACC/AHA guidelines support the widespread use of submaximal exercise testing in uncomplicated patients before discharge.[1]

For patients with a normal exercise test before discharge, symptom-limited maximal exercise testing can be repeated 2 to 6 weeks after AMI. The maximal exercise test can be used to identify additional high-risk patients.[579,580] The magnitude of this additional ischemia detection, however, as compared to a submaximal exercise test prior to hospital discharge, appears to be modest. Since many cardiovascular events can occur in the first 4 to 6 weeks, predischarge assessment of ischemia is preferred. Evidence of exercise-induced ischemia generally mandates cardiac catheterization to define the coronary anatomy and the consideration of revascularization (see algorithm in Fig. 42-11).[1] The consensus opinion of the ACC/AHA guidelines management group is that exercise testing is still useful in the risk stratification of patients who have received thrombolytic therapy, and it retains a class I indication in uncomplicated patients postinfarction.[1,581,582]

The clinical inference is that the detection of ischemia should lead to coronary arteriography. A randomized trial supports the performance of coronary arteriography in post-myocardial infarction patients with evidence of inducible ischemia before hospital discharge. In the DANAMI trials of 503 patients that survived AMI who were randomized to receive thrombolytic therapy, those patients with evidence of inducible ischemia prior to discharge had a nearly twofold higher cardiac event rate than did a group receiving early invasive intervention.[583] These study results are supportive of the usefulness of coronary arteriography in asymptomatic AMI patients with inducible ischemia.

Ambulatory Electrocardiographic Detection of Myocardial Ischemia

A number of studies have assessed the presence of silent myocardial ischemia (usually defined as ≥1-mm ST-segment depression for ≥30 s) using 24-h ambulatory electrocardiographic monitoring in patients who have survived AMI. Some of the episodes of transient ST-segment depression on ambulatory ECGs are associated with chest pain and typical angina symptoms, but the majority of these ischemic episodes are silent. Many of these episodes of "silent ischemia" occur during levels of low activity and/or mental stress.[584-587] As with other modalities to measure ischemia, the detection of ambulatory electrocardiographic ischemia has been predictive of a poor outcome in long-term follow-up trials in patients surviving AMI. The correlations among exercise testing, ambulatory ECGs, and ischemia detected by thallium appear to overlap but are not identical.[588] No studies show that the reduction in episodes of silent ischemia result in an improved outcome. Thus, routine ambulatory electrocardiographic assessment of ischemia is not recommended.[1]

Alternatives for Evaluating Myocardial Ischemia

THALLIUM-201 SCINTIGRAPHY

There are several alternatives to standard exercise testing. One well-studied technique is exercise thallium-201 scintigraphy, as discussed previously (see Chap. 16). Exercise thallium-201 scintigraphy has a number of potential advantages over routine exercise testing: (1) it can be used when the 12-lead ECG is uninterpretable for ischemic ST-segment shifts because of baseline changes such as a left bundle branch block where it has a class I indication; (2) it allows assessment of reversible and irreversible perfusion defects, both within and outside the vascular region involved in the AMI; (3) the technique of single-photon emission computed tomography (SPECT) thallium scintigraphy provides a semiquantitative evaluation of ischemia; (4) exercise thallium-201 scintigraphy offers superior sensitivity and specificity for the detection of multivessel disease when compared with standard exercise testing; and (5) if pharmacologic adenosine stress is used, it can be safely performed on day 3 or 4 after myocardial infarction.[589,590]

High-risk patients are identified if (1) perfusion defects exist in more than one discrete vascular zone; (2) there is distinct evidence of redistribution; or (3) there was evidence of increased lung uptake. Low-risk patients are defined by thallium scintigraphy showing involvement of a single vascular region without redistribution, with no evidence of increased lung uptake. A high-risk thallium-201 scintigram is correlated with multivessel coronary disease. Thallium scintigraphy has been shown to be excellent at identifying high-grade stenoses of 90 percent or greater, especially high-grade lesions of the left anterior descending coronary artery.[590]

As in routine exercise testing, a limited number of studies have evaluated the value of pharmacologic stress thallium tomography in patients with thrombolytic therapy, with some conflicting results. Provocative pharmacologic studies using thallium-201 tomography also predicted risk of subsequent ischemic events after AMI.[589] Adenosine tomography also offers the advantage of allowing the safe assessment of ischemia as early as 3 to 4 days following AMI. In the era of cost containment and pressure for early hospital discharge, this approach, although not proven, may be beneficial in identifying patients who can safely be discharged early.[589]

Since adenosine single photon emission computed tomography (SPECT) can safely be performed early in asymptomatic post-myocardial infarction patients,[591] it may gain more general acceptance as the preferred test for post-myocardial infarction ischemia. At present ACC/AHA guidelines only give a class I indication to performing this test when the 12-lead ECG is abnormal (uninterpretable). Adenosine SPECT imaging can identify high-risk patients and also can track the relation between therapeutic changes and subsequent changes in risk of cardiac events by tracking changes in perfusion defect size. In a preliminary trial, cardiac event-free survival was 96 percent at 1 year for patients in whom the ischemic burden could be reduced to ≤9 percent by pharmacologic and/or invasive therapy.[591]

Other radionuclide techniques are useful in the evaluation of patients after AMI, but the focus here has been on thallium scintigraphy, which provides prognostic information by the detection of myocardial ischemia. Other techniques include the use of radionuclide angiography for the assessment of ventricular function, including the evaluation of right ventricular infarction, and the use of technetium pyrophosphate to estimate myocardial infarct size and hibernating myocardium. These are summarized in Table 42-6.[185] Only exercise and pharmacologic thallium studies have a class I indication for the evaluation of ischemia.[1] The choice between stress thallium and standard exercise testing depends on ECG interpretability, availability, cost, and clinical experience.[591]

EXERCISE ECHOCARDIOGRAPHY

Exercise two-dimensional echocardiography is an alternative technique for identifying postinfarction ischemia. A reversible segmental wall motion defect is felt to represent an area of significant ischemia. Studies from specialized centers with expertise in echocardiography have shown that exercise or pharmacologic stress echocardiographic studies have a high sensitivity and specificity in identifying

patients with multivessel coronary disease (see Chap. 13).[592-594]

The definition of high risk on dobutamine stress echocardiograms includes (1) the presence of four or more akinetic or diskinetic segments in the infarct territory during low-dose dobutamine (an index of infarct size); (2) the presence of two or more coronary artery territories demonstrating abnormal wall motion at rest or during peak-dose dobutamine; and (3) a lack of improvement in wall thickening (i.e., lack of viability) within the infarct region during low-dose dobutamine infusion.[592,593] As with thallium scintigraphy, the findings of dobutamine stress echocardiograms may provide comparable or superior risk stratification to that of coronary angiography. The procedure is predictive of cardiac events in patients treated with thrombolytic agents as well as in those who did not receive thrombolytic therapy.[594]

Prospective studies to identify the incremental value of exercise echocardiograms compared to routine exercise testing after AMI have not been performed. In general, negative tests with exercise, dipyridamole, or dobutamine echocardiography are associated with a low rate of cardiac events.[592-595] Variation among institutions in expertise in the quality of echocardiographic study and interpretation are limitations to a widespread recommendation for the preferred use of echocardiography.

A multinational study provides long-term verification for the use of pharmacologic stress echocardiography in post-myocardial infarction patients with single-vessel coronary artery disease.[596] Either persantine or dobutamine stress resulted in useful long-term prognostic information, with stress echocardiographic "ischemia" detection associated with high 4-year rates of myocardial infarction. The investigators emphasized that stress echocardiography provided effective risk stratification at a relatively low cost.[596]

META-ANALYSIS OF VARIOUS METHODOLOGIES OF EXERCISE TESTING POST-MYOCARDIAL INFARCTION

In their comprehensive meta-analysis of alternative methodologies of post-myocardial infarction exercise testing by Peterson and colleagues, a few general patterns are apparent (Table 42-17). All exercise testing modalities share a high negative predictive value. However, all testing modalities have a rather dismal positive predictive value. None of the more sophisticated technologies appear to have a positive predictive value for subsequent cardiac events that substantially exceed simple stress echocardiography. The prognostic value of the testing modalities appear equally valid in patients with thrombolytic therapy.[597]

Exercise Testing in Uncomplicated Patients

Recommendations[1]:

Class I

a. Stress electrocardiography
b. Before discharge, for prognostic assessment or functional capacity (submaximal at 4 to 6 days or symptom-limited at 10 to 14 days)
c. Early after discharge for prognostic assessment and functional capacity (14 to 21 days)
d. Late after discharge (3 to 6 weeks) for functional capacity and prognosis if early stress was submaximal
e. Exercise, vasodilator stress nuclear scintigraphy, or exercise stress echocardiography when baseline abnormalities of the ECG compromise interpretation

Class IIa

1. Dipyridamole or adenosine stress perfusion nuclear scintigraphy or dobutamine echocardiography before discharge, for prognostic assessment in patients judged to be unable to exercise
2. Exercise two-dimensional echocardiography or nuclear scintigraphy (before or early after discharge for prognostic assessment)

Class III

1. Stress testing within 2 to 3 days of AMI.
2. Either exercise or pharmacologic stress testing at any time to evaluate patients with unstable postinfarction angina pectoris.
3. At any time, to evaluate patients with AMI, who have uncompensated congestive heart failure, cardiac arrhythmia, or noncardiac conditions that severely limit their ability to exercise.
4. Before discharge, to evaluate patients who have been selected for cardiac catheterization. In this situation, the exercise test may be useful after catheterization to evaluate function or identify ischemia in a distribution to correlate with coronary stenoses judged to be of borderline severity.

Suggested Algorithm for the Evaluation of Myocardial Ischemia after Myocardial Infarction

Based on all of the evaluable data, the task force on practice guidelines for the management of AMI created a strategy for the evaluation of myocardial ischemia after AMI in low-risk patients, presented in Fig. 42-11.[1] If there are clinical indications of a high-risk patient, as detailed earlier, such patients are considered for early cardiac catheterization and coronary angiography (strategy I).[1] The evaluation of myocardial ischemia in low-risk patients is alternatively presented for strategies II and III. Strategy III favors using a submaximal exercise test or alternative imaging study prior to hospital discharge. Strategy II alternatively suggests that a symptom-limited exercise test be performed soon after hospital discharge. Regardless of whether exercise testing or a more sophisticated exercise imaging study is ordered in the hospital, a negative test does not preclude the repeat evaluation for myocardial ischemia once the patient is fully ambulatory, after 3 to 6 weeks.

ASSESSMENT OF THE RISK OF ARRHYTHMIC (SUDDEN CARDIAC) DEATH: OVERVIEW

Although the technology to assess the risk of arrhythmic death in patients after AMI has improved in sophistication, antiarrhythmic therapies to reduce risk have thus far proved disappointing. For comparison, there is consensus that the identification of postinfarction patients with a LVEF of ≤40 percent mandates the use of ACE inhibitors.[392,393,598] Likewise, the identification of asymptomatic postinfarction patients with ischemia indicates the need for early performance of coronary angiography to assess the potential for PTCA or coronary artery bypass surgery.[1] Unfortunately, the identification of asymptomatic but high-risk patients for arrhythmic death after AMI is not similarly associated with a successful treatment strategy. This section addresses AMI patients who are asymptomatic and have not had sustained VT or VF-identifiers that all agree require aggressive management, most commonly the placement of an implantable cardioverter defibrillator (ICD).

The preponderance of evidence is that the majority of asymptomatic AMI patients who experienced arrhythmic (sudden cardiac) death have had sustained VT and/or VF.[599] A review of selected clinical trials of antiarrhythmic therapy focusing on patients after AMI is presented in Table 42-18[392,393,598,600,605] for the purpose of demonstrating the total deaths attributable to arrhythmic or sudden cardiac death, which vary widely in the placebo groups of these trials. The Cardiac Arrhythmia Suppression (CAST) trials[600,601] and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[604] identified high-risk patients after AMI using the criteria of ventricular arrhythmia on ambulatory ECGs. In the placebo groups, the range of death attributable to arrhythmia varied from 48 to 66 percent. The Survival and Ventricular Enlargement (SAVE) trial,[392] the European Myocardial Infarction Amiodarone Trial (EMIAT),[603] and the Survival With Oral d-sotalol (SWORD)[602] trial identified patients after AMI using an ejection fraction cutoff. The range of deaths attributable to arrhythmia in the placebo group was 45 to 67 percent. Patients in trials with a mixture of etiologies of left ventricular dysfunction including old AMI, such as the Studies of Left Ventricular Dysfunction (SOLVD) prevention and SOLVD treatment trials, have a lower percentage of deaths attributable to arrhythmia.[393,598] The wide discrepancy in arrhythmic death rates and the variety of screening tests used to identify "high-risk" patients highlight a significant deficit in current arrhythmic death classification.[605]

Table 42-18: Review of Representative Clinical Trials: Placebo Cause-Specific Mortality

Trial (No. of Placebo Patients), Entrance Criteria	Mean Follow-up (months)	Annualized Mortality, %	Arrhythmia/SCD, %
CAST I[600] (743), VPC ≥6/VT/AMI	10	4.2	62
CAST II[601] (574), VPC ≥6/VT/AMI/EF ≤40%	18	6.4	66
SAVE[392] (1116), EF ≤40%/AMI 3-16 d	42	7.1	45
SOLVD PREV[598] (2117), No CHF/EF ≤35%	37	5.3	31
SOLVD Rx[393] (1294), CHF (II/III) + EF ≤35%	41	11.7	22
SWORD[602] (1572), MI, EF ≤40%	5	1.5	67
EMIAT[603] (743), MI + <40%	21	7.8	49
CAMIAT[604] (596), MI + VPC ≥10 or VT	20	4.7	48

ABBREVIATIONS: SCD = sudden cardiac death; CAST = Cardiac Arrhythmia Suppression Trial; VPC = ventricular premature complexes; VT = ventricular tachycardia; AMI = acute myocardial infarction; EF = ejection fraction; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction; PREV = prevention; CHF = congestive heart failure; Rx = treatment; SWORD = Survival With Oral d-Sotalol; EMIAT = European Myocardial Infarction Amiodarone Trial; CAMIAT = Canadian Amiodarone Myocardial Infarction Arrhythmia Trial.
SOURCE: Adapted from Pratt et al.,[605] with permission.

The changing proportion of deaths attributable to arrhythmia and other causes after AMI is conceptually depicted in Fig. 42-12. Sustained VT and VF occur most frequently in the first year following AMI.[564] As ischemic cardiomyopathy develops over many years, deaths attributable to VT/VF decrease and proportionately more "sudden deaths" are attributable to asystole, electromechanical dissociation, or a high-degree heart block.[606] Also, noncardiac conditions emulate the circumstances of VT or VF (for instance, massive pulmonary embolism, ruptured abdominal or thoracic aortic aneurysm, or massive stroke).[605] Thus, the temporal influence on cause-specific mortality after AMI is an important consideration. Risk stratification for arrhythmic death is clearly more relevant immediately following myocardial infarction (Fig. 42-12).

This discussion is limited to tests available for evaluating asymptomatic patients. The preponderance of evidence does not support a class I or even a class IIa indication for any of the modalities to be discussed: ambulatory ECG, heart rate variability, signal averaged ECG, or electrophysiologic testing. What is lacking in each is the absence of compelling data that the identification of "arrhythmic death risk" is coupled with a strategy to improve outcome.[1]

Ambulatory Electrocardiographic Recordings: Ventricular Arrhythmias

Asymptomatic spontaneous ventricular arrhythmias detected on ambulatory ECGs are predictive of an increased risk of arrhythmic (sudden) death in the first 1 to 2 years following AMI.[564,607] The mechanism responsible for the majority of arrhythmic deaths in post-myocardial infarction patients is, as noted, sustained VT or VF.[599] Vulnerability for arrhythmic death appears to be highest in the first year after AMI,

probably accounting for one-half of the first-year mortality.[564,607] Thus, it appears that arrhythmic death risk should be assessed prior to hospital discharge. The use of ambulatory electrocardiographic recording to identify a "high-risk" group, however, has a poor positive predictive value.[600,608] As seen in Table 42-19, postinfarction patients with no baseline ventricular arrhythmia on ambulatory electrocardiographic recording uniformly have a low risk for arrhythmic death.[564,608] Frequent premature ventricular complexes and nonsustained VT are generally associated with a two- and threefold increased risk, respectively.[13,564,607,608] As can be deduced from the data in Table 42-19, for every 100 patients identified with "warning arrhythmias," only 4 to 7 will have arrhythmic death in the following 1 to 2 years. Thus, a treatment strategy that would include routine prophylactic administration of an antiarrhythmic drug would necessitate a superb safety profile, since approximately 95 percent of the patients cannot benefit but all would be exposed to potentially lethal proarrhythmic risk. Such hazards have been documented in prophylactic antiarrhythmic drug trials.[600-602] Thus, ambulatory ECG has an adequate negative predictive value, but a poor positive predictive value, consistent with its class IIb rating.

Ambulatory Electrocardiogram Recordings: Heart Rate Variability

Heart rate variability, measured by the standard deviation of the RR interval on monitored electrocardiographic leads, is an indirect assessment of proportional autonomic tone. Extensive variability in the heart rate connotes a preponderance of parasympathetic activity, whereas less variability in the heart rate is consistent with proportionately more sympathetic activity.[609-611] In animal models, enhanced sympathetic activity increases the vulnerability of the ischemic myocardium to the development of VF.[612]

Clinical trials have assessed the relation of heart rate variability to mortality rate in patients surviving AMI. Depressed heart rate variability is associated with an increased risk of death. Multivariate analysis has identified reduced heart rate variability as an independent predictor of arrhythmic death.[609-611,613] In one study, patients selected for depressed heart rate variability and ventricular arrhythmias, excluding patients with the lowest ejection fractions, identified a patient population in whom 75 percent of the deaths were presumed arrhythmic.[614] Heart rate variability measured after thrombolytic therapy still has clinical relevance, and an improvement in heart rate variability correlated with TIMI grade 3 flow.[615]

Practical approaches to minimizing cost, while focusing noninvasive testing on a targeted group, are under evaluation. In a study of 729 survivors of AMI prior to hospital discharge from St. George's Hospital in London, a 24-h heart rate variability index was compared to a 5-min analysis of an ectopic-free segment of the Holter recording, measuring the standard deviation of normal-to-normal RR intervals (SDNN).[616] The 5-min analysis of SDNN measurement was a useful and inexpensive tool to select patients for more extensive 24-h heart rate variability index evaluation.[4]

At present, while heart rate variability is a very promising method of evaluating parasympathetic and sympathetic effects in the heart, it cannot be recommended as a standard clinical test in AMI patients, unless and until trials demonstrate clinical benefits of a treatment strategy based upon the knowledge of this marker of sudden cardiac death.[1,617]

Baroreflex Sensitivity

Baroreflex sensitivity is another autonomic marker that is a measure of the change in heart rate (anticipated reduction) to an increase in blood pressure. In this respect, it provides an index of the ability to reflexly increase cardiac vagal activity. Heart rate variability, in contrast, is a marker of vagal tone.[618]

The importance of these two autonomic markers is demonstrated by the results of the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) trial, a study of 1284 patients with a recent (≤28 days) myocardial infarction.[619] One-year mortality was increased in patients with a reduced baroreflex sensitivity as well as a low heart rate variability (see Table 42-20).[618] There was an additive value to the measurement of the two markers: If both are low there is a 15-fold increased risk of death than if both markers are normal (15 versus 1 percent; $p < 0.0001$). The interaction of LVEF and these autonomic markers is also apparent from Table 42-20, each being associated with a twofold greater risk of death in patients with LVEF <35

percent than it is in those with better preserved left ventricular systolic function. It is reasonable to conclude that both baroreflex sensitivity and heart rate variability have independent prognostic value for stratifying the risk of death after myocardial infarction.[74]

Table 42-20: Multivariate Analysis of Influence of Baroreceptor Sensitivity and Heart Rate Variability on Relative One-Year Mortality Risk after AMI

Variable Examined	Variable in Analysis	Groups	RR	95% CI	P
Baroreflex sensitivity	LVEF	35-50%	2.1	0.90-4.69	0.08
		<35%	4.7	2.04-10.9	0.0003
	BRS (ms/mmHg)	3.0-6.1	1.7	0.81-3.69	0.15
		<3.0	2.8	1.24-6.16	0.01
	VPCs per h	≥10	1.8	0.94-3.46	0.07
Heart rate variability	LVEF (%)	35-50%	1.9	0.87-4.49	0.10
		<35%	3.9	1.69-9.25	0.001
	SDNN	70-105	1.9	0.86-4.04	0.11
		<70	3.2	1.42-7.36	0.005
	VPCs per h	≥10	1.8	0.97-3.50	0.06

ABBREVIATIONS: RR = relative rate; CI = confidence interval; LVEF = left ventricular ejection fraction; BRS = baroreflex sensitivity; VPC = ventricular premature complex; SDNN = standard deviation of all normal beats.
SOURCE: Schwartz,[618] with permission.

Signal-Average Electrocardiogram

Time-domain analysis of the signal-averaged ECG can be used to detect low-amplitude, high-frequency potentials at the end of the QRS complex, termed *ventricular late potentials*. The presence of late potentials identifies patients likely to have inducible sustained monomorphic VT during programmed electrical stimulation and is associated with an increased risk of subsequent arrhythmic events.[609,620,621] The predictive value of late potentials is best established in patients with AMI and is of less established value in other patient populations.

In some studies, the presence of an abnormal signal-averaged ECG, of frequent ventricular premature complexes on the ambulatory electrocardiographic recording, and left ventricular aneurysm were independent predictors of VT, regardless of whether or not a patient had received thrombolytic therapy.[621] If results of the signal-averaged ECG are negative-that is, there are no afterdepolarizations-the negative predictive value in this population is good and the likelihood of subsequent arrhythmic death is low. As with the evaluation of heart rate variability, the interpretation of the signal-averaged ECG can be improved by combining it with other variables, especially the LVEF. Even when multiple tests are combined for assessing the risk of sudden cardiac death, the strength is in their negative predictive value rather than their positive predictive value, which usually falls below 50 percent.[620,621] There is an adverse prognostic consequence of a positive signal-averaged ECG and an occluded infarct-related artery.[622] The routine use of signal-averaged ECGs in AMI is not at present recommended.[1]

Invasive Electrophysiologic Testing (Programmed Electrical Stimulation)

Invasive electrophysiologic assessment has been evaluated in two distinct populations who survived AMI. The first and relatively small group had a cardiac arrest or an episode of sustained VT following an AMI. In such patients, the risk of recurrent cardiac arrest or arrhythmic events is high, and electrophysiologic studies are an alternative for assisting in therapy selection.[623]

The much larger patient population are those with an increased risk of arrhythmic death based upon the results of one or more noninvasive tests, as discussed previously. Performing electrophysiologic studies on all asymptomatic "high-risk" patients is not justified.[1] Reports on the utility of electrophysiologic studies have been inconsistent in predicting total mortality and are only slightly more consistent in identifying patients likely to have subsequent arrhythmic events.[624,625]

Results from the Multicenter Automatic Defibrillation Implantation Trial (MADIT) are somewhat relevant to this issue.[626] Patients in MADIT had had a prior Q-wave infarction with a LVEF of <35 percent and were selected if programmed electrical stimulation induced sustained VT that was nonsuppressible with intravenous procainamide. Patients were randomized to an implantable cardioverter-defibrillator group and/or conventional arrhythmic therapy. Although total mortality was less in the cardioverter-defibrillator group, the relevant point is that this invasive screening appeared to identify a high-risk group for subsequent arrhythmic death.[626] This study alone is not sufficient, however, to support the wider use of electrophysiologic testing in asymptomatic postinfarction patients for at least two reasons: (1) imbalances in the use of beta blockers between the two treatment strategies cloud the results, and (2) these patients were many years from their index infarction. Therefore, the relevance to predischarge risk assessment of AMI is tenuous.

Assessing Arrhythmic Death: Conclusions

In the ACC/AHA guidelines, none of the noninvasive techniques is generally agreed upon to be beneficial, useful, and effective, either unequivocally (class I) or based upon the weight of evidence or opinion (class IIa) for predicting arrhythmic death. These techniques have class IIb indications, meaning that their usefulness and efficacy are not well established by either scientific evidence and/or general opinion.[1] In addition to their poor positive predictive value, no clinical trial has demonstrated that the use of any one or a combination of these modalities of testing identifies a high-risk population in whom an intervention strategy results in clinical benefit. Unless and until such studies are carried out to show that targeting a high-risk population and using the data to direct subsequent prophylactic therapy result in patient benefit, these modalities of risk assessment remain interesting tools for investigational studies and for use on selected individual patients. Other assessments of risk for sudden death, such as QT dispersion, are in an even earlier investigational stage, and at present, there is little supporting evidence that they are useful and effective in improving the management and outcome of AMI patients.[1,627]

Coronary Angiography and Percutaneous Transluminal Coronary Angioplasty

Recommendations[1]:

Class I

1. Patients with spontaneous episodes of myocardial ischemia or episodes of myocardial ischemia provoked by minimal exertion during recovery from infarction
2. Before definitive therapy of a mechanical complication of infarction such as acute mitral regurgitation, VSD, pseudoaneurysm, or left ventricular aneurysm
3. Patients with persistent hemodynamic instability

Class IIa

1. When myocardial infarction is suspected to have occurred by a mechanism other than thrombotic occlusion at an atherosclerotic plaque. This would include coronary embolism, certain metabolic or hematologic diseases, or coronary artery spasm.
2. Survivors of AMI with depressed left ventricular systolic function (left ventricular ejection fraction

less than or equal to 40 percent), congestive heart failure, prior revascularization, or malignant ventricular arrhythmias.
3. Survivors of AMI who had clinical heart failure during the acute episode but subsequently demonstrated well-preserved left ventricular function.

Class IIb

1. Coronary angiography performed in all patients after infarction to find persistently occluded infarct-related arteries in an attempt to revascularize the artery or identify patients with three-vessel disease
2. All patients after a non-Q-wave myocardial infarction
3. Recurrent VT or VF or both, despite antiarrhythmic therapy, in patients without evidence of ongoing myocardial ischemia

Class III

1. Routine use of coronary angiography and subsequent PTCA of the infarct-related artery within days after thrombolytic therapy
2. Survivors of myocardial infarction who are thought not to be candidates for coronary revascularization

The selection of patients for cardiac catheterization and coronary angiographic studies prior to hospital discharge should be based on identifying patients at risk for ischemic events and on whether the information provided by cardiac catheterization and coronary angiography will change patient management.

Studies analyzing the prognostic utility of cardiac catheterization prior to hospital discharge are from the prethrombolytic era and demonstrate that the angiographic extent of coronary artery disease was related to survival.[628,629] Other trials have addressed the utility of routine coronary angiographic studies in patients who have received thrombolytic therapy.[630-633] The timing of cardiac catheterization during hospitalization has been addressed in several studies. In general, studies that have compared acute or early cardiac catheterization to a more conservative approach of performing cardiac catheterization and coronary angiographic studies only for patients with spontaneous recurrent angina or exercise-induced ischemia have demonstrated no benefit to the strategy of routine catheterization.[1,271]

Figure 42-11 presents a strategy for identifying symptomatic and asymptomatic high-risk patients who should have cardiac catheterization and coronary angiographic studies before discharge. Patients who have a complicated clinical course characterized by refractory cardiac failure, unstable angina, an episode of sustained VT, or cardiac arrest should be studied, as discussed previously. An aggressive approach to these patients is justified because of the observed 1-year mortality rate, ranging from 10 to 25 percent.[634] In the case of patients with symptomatic cardiac failure, right heart catheterization should be included.

The recommended algorithm for selecting asymptomatic, uncomplicated post-AMI patients for cardiac catheterization is also presented in Fig. 42-11. Decision making focuses on the presence or absence of myocardial ischemia. Because of the high incidence of residual ischemia in patients with a non-Q-wave infarction, the task force for guidelines for coronary angiographic studies after myocardial infarction recommended such studies in all non-Q-wave infarctions.[635] The more conservative recommendation here emphasizes evidence of objective ischemia. Where patients have received thrombolytic therapy, it seems reasonable that those who have evidence of residual ischemia are still at increased risk of future ischemic events and should undergo coronary angiography prior to discharge. Consideration of PTCA following coronary angiographic studies should be based on established clinical and anatomic guidelines[1,636] (see Chap. 45). Coronary artery bypass surgery should be considered in those groups in whom it has been shown to be of proven benefit: patients with triple-vessel disease, patients with ischemia, and those with significant left ventricular dysfunction (see also Chap. 48).[637]

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Chapter 42: DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

SECONDARY PREVENTION AND CARDIAC REHABILITATION

Risk Factor Reduction

The relation between the level of activity of the inflammatory response in the arterial wall (which is the characteristic feature of atherosclerosis) and the tendency of the structural integrity of the artery to break down, with the resultant exposure of thrombogenic material and clot formation, is discussed in Chap. 35. The inflammatory response is caused and/or exacerbated by the presence of the classic risk factors. It follows that favorably modifying the risk factors would, intuitively, reduce coronary events. There is now abundant evidence that this is the case. Thus, since those who have had AMI are among those at highest risk for recurrence, management strategies to mitigate this risk are very important in patient management.[638]

SMOKING

Smoking has multiple cardiovascular effects that can promote AMI, including enhanced platelet aggregation, coronary vasospasm, and vascular inflammation. Smoking cessation is an essential goal after AMI, since the recurrence rate and death rate after AMI are doubled by the continuation of smoking (see also Chap. 38).[639] After AMI, however, risk associated with smoking declines rapidly to that of the nonsmoking cohort survivors within 3 years.[640] The psychological and physiologic aspects of smoking should be addressed, and a number of programs have been developed to deal with these needs. Most smokers who have quit, however, have done so without an organized program.[641] The role of the physician in motivating the patient to quit smoking is extremely important and the likelihood of success appears to be directly related to the extent of his or her involvement. Transdermal nicotine patches and oral preparations can be used to aid withdrawal but are not risk-free and should be used temporarily and adjunctively with physician counseling and/or a formal program in behavior modification.[642] The transdermal patches or oral nicotine preparations should not be used during the period just after AMI and should not be used concurrently with smoking. Difficult cases are probably handled best by referral to a formal smoking cessation program. Clonidine hydrochloride has also been used to ameliorate symptoms of smoking withdrawal as well as in conjunction with behavioral intervention.[638]

DYSLIPIDEMIA

Recommendations[1]:

Class I

1. Institute of the American Heart Association (AHA) step II diet, which consists of <7 percent of total calories as saturated fat and <200 mg/day of cholesterol in all patients after recovery from AMI.
2. Patients with low-density lipoprotein (LDL) cholesterol levels >125 mg/dL, despite consuming the AHA step II diet, should be placed on drug therapy with the goal of achieving a target LDL cholesterol <100 mg/dL.
3. Patients with normal plasma cholesterol levels who have a high-density lipoprotein (HDL)

of less than 35 mg/dL should be placed on an exercise regimen to atttempt to increase it.

Class IIa

1. Drug therapy may be added to diet therapy in patients with LDL cholesterol levels <130 mg/dL but >100 mg/dL after an appropriate trial of the AHA step II diet alone.
2. Patients with normal total cholesterol levels, but with HDL cholesterol <35 mg/dL despite dietary and other nonpharmacologic therapy, may be started on drugs such as niacin in an attempt to raise HDL levels to more protective levels.

Class IIb

1. Drug therapy using either niacin or gemfibrozil may be added to diet regardless of LDL and HDL levels when triglyceride levels are >200 mg/dL.

The β-hydroxy- β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors are the most effective drugs in lowering LDL cholesterol. Niacin is effective in raising HDL and, in combination with resins, is also effective in lowering LDL. Triple therapy with a reductase inhibitor, niacin, and resin can be useful in resistant cases. Drug therapy of dyslipidemias is discussed in Chap. 38.

As mentioned earlier, patients who have had an AMI are generally at high risk for recurrence. Furthermore, an abnormally elevated serum cholesterol level is a powerful risk factor for death in this group.[643,644] Early primary prevention studies and relatively small angiographic trials showed decreases in cardiovascular event rates with cholesterol-lowering therapy (see Chap. 38). Large secondary prevention trials have provided compelling evidence that in patients who have had an AMI, therapy with HMG-CoA reductase inhibitors to lower serum cholesterol levels that were either initially elevated-as in the Scandinavian Simvastatin Survival Study (4S)[645] or within "average" range as in the Cholesterol and Recurrent Events (CARE) trial[646]-was effective in reducing both cardiovascular and total mortality as well as cardiovascular events. In CARE, a treatment effect was not observed in the group with baseline LDL values <125 mg/dL. The guidelines of the expert panel of the National Cholesterol Education Program provide target goals for patients with manifest coronary artery disease. These goals are as follows: LDL cholesterol, 100 mg/dL (2.59 mmol/L); HDL cholesterol, >35 mg/dL (0.91 mmol/L).[647]

Serum lipid levels are decreased within several hours after AMI, presumably by the inflammatory response to tissue necrosis.[648] Evaluation of serum lipid levels should be made within the first 6 to 8 h from onset of symptoms or after recovery at 6 to 8 weeks. All AMI patients should have serum lipids evaluated and treated intensively in order to achieve target goals. Treatment should start in the hospital with initiation of the AHA step II diet. With established very high lipid levels (for example, LDL cholesterol >200 mg/dL), many clinicians would have a low threshold for initiating drug therapy early on, anticipating that diet therapy alone might not be sufficient for achieving target LDL goals. Although low HDL is a powerful risk factor for AMI, the benefit of treating it is unproven. It seems prudent to attempt to raise HDL levels by prescribing an exercise regimen. Niacin is also efficacious in raising HDL levels; it may be used, especially if indicated as adjunctive therapy with HMG-CoA reductase inhibitors or with resins, to lower LDL. There is less certainty about indications for treating elevated triglycerides, but it seems prudent to treat levels >400 mg/dL with diet and perhaps with fibrates or niacin (see Chap. 38).

INACTIVITY

There have been numerous studies of post-AMI patients documenting the beneficial effects of

aerobic exercise on functional capacity and myocardial oxygen demand at a given submaximal workload.[649] Such exercise can decrease angina pectoris and ischemia. Conversely, a sedentary lifestyle is a risk factor for coronary artery disease. Meta-analysis of cardiac rehabilitation studies has shown a reduction in mortality in the exercise group as opposed to a control group.[649] These analyses have not permitted separating the effects of exercise per se from the other beneficial aspects of the programs. The greatest benefits of exercise are those observed with moderate, regular exercise as contrasted with the nonexercise group. The benefit can be obtained by exercising about 4200 kJ a week, which can be achieved by walking about 1.5 miles (2.4 km) per day. Long-term, regular exercise training can best be sustained by participating in a supervised exercise program beginning several weeks after discharge from the hospital.[638,649] A standard exercise program might involve three 20- to 30-min sessions three to four times per week at 60 to 75 percent of maximal aerobic capacity. This target activity level should be achieved progressively over several weeks, and progress should be monitored by the physician at regular intervals. The exercise regimen should be initiated and guided by monitored exercise testing.

Regular aerobic exercise should be prescribed for post-AMI patients in stable condition at an intensity, duration, and frequency as determined by formal testing and clinical judgment. Optimum benefit is achieved in a supervised program, although asymptomatic, stable patients can exercise without direct supervision but should receive regular monitoring by a physician (see also Chap. 50).

LOW-ESTROGEN STATES (FEMALES)

Recommendations[1]:

Class IIa

1. Hormone replacement therapy (HRT) with estrogen plus progestin for secondary prevention of coronary events should not be given de novo to postmenopausal women after myocardial infarction.
2. Postmenopausal women who are already taking HRT with estrogen plus progestin at the time of an AMI can continue this therapy.

Estrogen replacement therapy and the primary or secondary prevention of cardiovascular disease continues to be a somewhat contentious and emotional issue that involves weighing the potential efficacy of ERT in reducing cardiovascular risk against the possible increases in breast cancer rates.[650,651] Clinical trials have demonstrated that estrogen with or without progestins lowers both LDL cholesterol and fibrinogen,[652] an effect that would be expected to reduce cardiovascular risk. Contrary to conventional wisdom and expectations, the first large double-blind, placebo-controlled trial to assess the effects of estrogen and progestin treatment on the secondary prevention of coronary heart disease in postmenopausal women showed no reduction in any cardiovascular outcome after 4.1 years of follow-up.[653] Furthermore, the Heart and Estrogen-Progestin Replacement Study (HERS) Research Group reported a significant trend for more primary cardiac events in the treatment group than it did in the placebo group in year 1, although there were fewer events in years 4 and 5 in the treatment group than there were in the placebo group.[653] These observations led to the recommendation that, post-AMI, women on hormone replacement therapy at the time of the event should continue but that initiation of therapy could not be recommended[1].

Drug Therapy

BETA-ADRENERGIC BLOCKERS

Recommendations for long-term therapy in post-AMI patients[1]:

Class I

1. All post-AMI patients except those at low risk without clear contraindications should receive long-term therapy. Treatment should begin early in the course, preferably acutely, and should be continued indefinitely.

Class IIa

1. Low-risk patients without definite contraindications should be considered for beta-adrenergic blocker therapy
2. Survivors of non-ST elevation myocardial infarction

Class IIb

1. Patients with moderate or severe left ventricular failure or other relative contraindications of beta-adrenoceptor blocker therapy, provided they can be monitored closely

Class III

1. None

The benefits of beta-blocker therapy given early in the course of AMI were previously discussed. Multiple clinical trials have also demonstrated the benefits of long-term treatment of post-AMI patients with beta blockers.[654] Long-term efficacy has been demonstrated for propranolol,[13] timolol,[655] and metoprolol.[656] Mortality has been shown to be reduced by about 25 to 35 percent. The beneficial effect is highest in high-risk patients with large (usually anterior) myocardial infarction, and compensated left ventricular dysfunction. The beneficial effects in low-risk patients are less clear, but the consensus is that these patients should probably be treated because of the relatively favorable side-effect profile.[1] This recommendation extends to the patient with NQWMI although, as discussed, the data are less compelling. Beta blockers with intrinsic sympathomimetic activity should not be used in this context.

ASPIRIN

The role of aspirin during the early phases of AMI was discussed earlier. Aspirin use over the long term after AMI is also associated with a reduction in mortality. Meta-analysis of 6 major trials of aspirin treatment showed an overall reduction in vascular mortality in the treated group of 13 percent, with 31 and 42 percent reductions in nonfatal infarction and nonfatal stroke, respectively.[657] These trials used relatively large aspirin doses (300 to 1500 mg/day), but one trial showed efficacy at only 75 mg/day,[658] suggesting that long-term use of more modest doses would be effective. Thus, aspirin at relatively low doses is recommended for all patients with AMI in the absence of contraindications (see also Chap. 44).

ANTICOAGULATION

Anticoagulation can reduce mortality, recurrent myocardial infarction, and stroke after AMI, as indicated by an analysis of multiple trials.[654] Because of relatively high rates of bleeding with warfarin, the need for monitoring, and, in particular, the efficacy and low risk of aspirin, the role of warfarin is rather limited to those at increased risk for developing mural thrombi.[638] In addition, those post-AMI patients with demonstrable left ventricular thrombus and atrial

fibrillation should be anticoagulated. The duration of anticoagulation should be limited to 3 months in the case of left ventricular thrombus.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The ACE inhibitors and recommendations for their use early in the course of AMI were previously discussed. Studies have documented their efficacy in secondary prevention. The reduction in late morbidity and mortality was most obvious in those with large infarctions with reduced ejection fraction and in those with anterior myocardial infarction. In these patients, left ventricular remodeling and progression to heart failure were reduced.[392,396,659] The beneficial effects of ACE inhibitors have been less obvious when low-risk patients were included.[660] The decrease in ischemic events in the SAVE trial[392] and in other ACE-inhibitor trials suggests that the threshold for use of ACE inhibitors for long-term therapy may be lowered by many clinicians to include those with only modest left ventricular dysfunction. Thus, ACE inhibitors have been recommended for chronic use after AMI in those patients with significant left ventricular dysfunction, and their use should be considered in those with only mild-to-moderate left ventricular dysfunction (ejection fraction <45 percent).

The publication of the Heart Outcomes Prevention Evaluation (HOPE) trial in patients with significant risk factors for cardiovascular events showed significant reduction in new events and new-onset diabetes mellitus in those treated with the ACE-inhibitor ramipril.[398] It is likely that the recommendations for use of ACE inhibitors will be extended to all patients at high risk for cardiovascular events regardless of blood pressure or left ventricular function.

Modification of Lifestyle and Cardiac Rehabilitation after Acute Myocardial Infarction

Because of the relatively high risk of recurrence and the need for lifelong modification of lifestyles and risk factors, most post-AMI patients should be enrolled in a cardiac rehabilitation program that emphasizes dietary modification, risk factor reduction, and exercise. The low-risk patient does not require prolonged supervised exercise, as previously discussed. All patients, however, can benefit from a structured environment to launch a lifetime of healthy living. Cardiac rehabilitation is discussed in Chap. 50 and risk factors and the prevention of coronary artery disease are discussed in Chap. 38.

There has been considerable reinvigoration of interest in the potential of dietary interventions in secondary prevention after AMI since the publication of the results of the Lyon Diet Study[661] and of the GISSI-Prevention Study.[662] Both of these studies showed dramatic (>30 percent) reduction in recurrence of cardiovascular events in patients in whom a diet and supplements rich in omega-3 fatty acids was added to adequate conventional therapy. Thus, in view of the minimal or absent risk it seems prudent to recommend that patients incorporate into their dietary regimes sources of omega-3 fatty acids (fish: especially tuna, salmon, and sardines; nuts such as walnuts; and probably fish oil supplements).

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Figure 42-1: Electrocardiographic evolution of acute anterior and inferior myocardial infarction. *A*. Hyperacute phase. There is marked ST-segment elevation in V_2 to V_5 in the anterior infarction and in II, III, and aV_f in the inferior infarction. In the inferior infarction, there are reciprocal changes or posterior involvement as reflected in the ST-segment depression in the precordial leads. There are no QRS changes in either case. *B*. Acute phase. Q waves indicating myocardial necrosis develop during this phase. There is some persis-tent ST-segment elevation and the T-wave vector generally points toward the infarct zone. *C*. Subacute phase. QRS changes are well developed and ST-segment elevation is still present. The T vector, or, more precisely, the terminal portion of the T vector, begins to point away from the infarct zone. *D*. Chronic phase. Minimal or no ST-segment elevation is present, and the T wave is directed away from the infarct zone. (From Wagner et al.,[78] with permission.)

Figure 42-2: Typical plasma profiles for the MB isoenzyme of creatine kinase (MB-CK), aspartate amino transferase (AST), and lactate dehydrogenase (LDH) activities following onset of acute myocardial infarction.

Figure 42-3: Algorithm for the initial assessment and evaluation of the patient with acute chest pain in the emergency department. The emergency department should be organized to facilitate the rapid triage of chest pain patients so that the initial evaluation, the obtainment of a 12-lead ECG, and the establishment of intravenous access and continuous monitoring are accomplished within 10 min. The path in the decision tree is determined by the results of the 12-lead ECG. The presence of ST-segment elevation diagnostic of acute myocardial infarction or of presumptively new bundle branch block suggestive of this diagnosis should lead to the immediate consideration of the suitability of the patient for reperfusion therapy, which, if indicated, should be initiated within 30 min of the patient's arrival. The primary PTCA option is applicable only in those settings in which it is immediately available and can be performed by highly qualified interventional cardiologists. In general, patients should not be transferred for angioplasty if thrombolysis is an option, especially if significant delays will be incurred. Thrombolysis is not indicated in patients with only ST-segment depression.

Figure 42-4: The above analysis is based on a prospective, multicenter, double-blind study involving the consecutive enrollment of 995 patients presenting to the emergency department. Diagnostic sensitivity and specificity for myocardial infarction of all markers (MB-CK subforms, myoglobin, total MB-CK-activity and mass, troponin T, and troponin I) were assessed serially every 1 to 2 h for 24 h. There were 119 (12.5 percent) patients with infarction and 203 (21 percent) with unstable angina. MB-CK subforms were most sensitive and specific (91 and 89 percent) within 6 h of onset versus myoglobin (MG) (78 and 89 percent). For late diagnosis, total MB-CK activity (derived from subforms) was the most sensitive and specific (96 and 98 percent) at 10 h from onset, followed by troponin I (cTnI) (96 and 93 percent), but not until 18 h, and troponin T (cTnT) (87 and 93 percent) at 10 h. In unstable angina, MB-CK subforms were increased in 29.5 percent, myoglobin in 23.7 percent, troponin I in 19.7 percent, and troponin T in 14.8 percent. (Data from Roberts et al.[154])

Figure 42-5: Proportional effects of fibrinolytic therapy on mortality during days 0 to 35 subdivided by presentation features. "Observed minus expected" (O-E) number of events among fibrinolytic-allocated patients (and its variance) is given for subdivisions of presentation features, stratified by trial. This is used to calculate odds ratios (ORs) of death among patients allocated to fibrinolytic therapy to that among those allocated control. The ORs (squares with areas proportional to the amount of "statistical information" contributed by the trials) are plotted with their 99 percent confidence intervals (CIs) (horizontal lines). Squares to the left of the solid vertical line indicate benefit (significant at $2p < 0.01$ only where the entire CI is to left of vertical line). Overall result and 95 percent CI represented by diamond, with overall proportion reduction in the odds of death and statistical significance given alongside. (From Fibrinolytic Therapy Trialists' Collaborative Group,[210] with permission.)

Figure 42-6: Evaluation of patients with ST-segment elevation. Algorithm for initial decision making in regard to reperfusion therapy in patients with suspected acute myocardial infarction and ST-segment elevation. Whether or not to administer thrombolytics or to perform primary PTCA is determined by the time from onset of symptoms. For patients in whom more than 12 h have elapsed since the onset of symptoms, reperfusion should be considered only if there are persistent or recurrent symptoms associated with ST-segment elevation. For patients with ST-segment elevation and duration of symptoms between 7 and 12 h, the decision to proceed with a reperfusion strategy requires careful clinical judgment in weighing the risk/benefit issues, as discussed in the text. (Modified from Ryan et al.,[1] with permission.)

Figure 42-7: Influence of effective anticoagulation on early patency rates with rt-PA. Patency assessed angiographically at an average of 18 to 81 h is significantly greater in patients treated with intravenous heparin.

Figure 42-8: Retrospective analysis of the HART trial showing the relationship between increased PTT and coronary artery patency ($n = 94$). This illustrates the importance of heparin.

Figure 42-9: Kaplan Meier curves for death and infarction in patients assigned to the invasive or conservative strategies in TIMI-2. Routine cardiac catheterization after thrombolytic therapy and revascularization with PTCA or bypass grafting (when anatomically appropriate) was not a superior strategy to catheterization and revascularization when there is development of spontaneous ischemia or ischemia induced by exercise testing. (Reproduced with permission. Williams DO, Braunwald E, Knatterud G, et al.: One-year results of the thrombolysis in myocardial infarction investigation (TIMI) phase II trial. *Circulation* 1992; 85:533-542.[318] Copyright 1992 American Heart Association.)

Figure 42-10: Comparison of the survival of patients with Q-wave infarction (triangles) to that of patients with non-Q-wave infarction with (circles). Early mortality was higher after Q-wave infarction than it was after non-Q-wave infarction and no recurrence (*A*), but survival was identical for patients with Q-wave infarction and those with non-Q-wave infarction and an early recurrent infarction (*B*). Long-term mortality rates are similar in Q-wave infarction and non-Q-wave infarction with or without early recurrence.

Figure 42-11: Strategies for exercise test evaluations soon after myocardial infarction. If patients are at high risk for ischemic events based on clinical criteria, they should undergo invasive evaluation to determine if they are candidates for coronary revascularization procedures (strategy I). For patients initially deemed to be at low risk at time of discharge after myocardial infarction, two strategies for performing exercise testing can be used. One is a symptom-limited test at 14 to 21 days (strategy II). If the patient is on digoxin or if the baseline ECG precludes accurate interpretation of ST-segment changes (e.g., baseline left bundle branch block or left ventricular hypertrophy), then an initial exercise imaging study can be performed. Results of exercise testing should be stratified to determine need for additional invasive or exercise perfusion studies. A third strategy is to perform a submaximal exercise test at 5 to 7 days after myocardial infarction or just before hospital discharge. The exercise test results could be stratified using the guidelines in strategy I. If exercise test studies are negative, a second symptom-limited exercise test could be repeated at 3 to 6 weeks for patients undergoing vigorous activity during leisure or at work. (From Ryan et al.,[1] with permission.)

Figure 42-12: A theoretical view of approaches to identify a postmyocardial infarction population dying of ventricular tachycardia/fibrillation. This concept is presented in a qualitative fashion and represents estimates based on the literature (see text). SCD, sudden cardiac death; NSCD, non-sudden cardiac death; VT, ventricular tachycardia; VF, ventricular fibrillation; MI, myocardial infarction; EMD, electromechanical dissociation; CHF, congestive heart failure.

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Part 6: CORONARY HEART DISEASE
Chapter 43:

THE ELECTROCARDIOGRAM IN ACUTE MYOCARDIAL INFARCTION

Authors: Anton P. Gorgels, Domien J. Engelen, Hein J. J. Wellens

The possibility of treating an acute coronary occlusion by thrombolytic therapy or intracoronary interventions such as percutaneous transluminal coronary angioplasty (PTCA) and stenting makes it necessary to determine, rapidly and precisely, which coronary artery is involved, the size of the area at risk, and the results of the intervention. The larger the area at risk, the more important the attempt to restore or improve perfusion of that area.

In recent years, much effort has been put into correlating electrocardiographic (ECG) changes during the acute ischemic episode with findings from coronary angiography performed at the same time. If specific ECG patterns can be recognized, it will be possible to determine, noninvasively, the culprit coronary artery and the size of the ventricular area that is jeopardized.

This chapter discusses the outcome of such studies. It shows that this information is helpful in decision making during acute myocardial infarction and the chapter is therefore placed in the section on coronary heart disease. Chapter 11 provides a general discussion on the value and limitations of the ECG in the diagnosis of cardiac disease (see also Chaps. 40-42).

CLINICAL PRESENTATION OF ACUTE MYOCARDIAL INFARCTION IN RELATION TO THE INFARCT VESSEL

The presentation of acute myocardial infarction is different depending on the coronary artery involved. The left anterior descending branch (LAD) is the most important coronary artery and supplies the anterior, lateral, septal, and frequently the inferoapical segments of the left ventricle. It also perfuses the proximal part of the bundle branches. The extent of ischemia and the prognosis is dependent on the site of occlusion in the LAD.[1] Involvement of the distal conduction system may result in impaired conduction, varying from right bundle-branch block (RBBB) with or without fascicular block to complete atrioventricular (AV) block.[2-4] The clinical picture may include heart failure and, in the subacute phase, ventricular tachycardia and fibrillation and an increased 1-year mortality.[5] The right coronary artery (RCA) perfuses the sinus node (in 55 percent of patients), the right ventricle, the AV node, the posteromedial papillary muscle, and the inferior part of the left ventricle and variably also the posterior and lateral segments.

Ischemia due to occlusion of the RCA leads to ST elevation in the inferior leads. Usually there is less extensive left ventricular (LV) involvement than in LAD occlusion, but the clinical picture may be impressive due to (1) activation of the vagal nervous system and/or (2) ischemia of the sinus and atrioventricular (AV) node, leading to sinus bradycardia and delay or block in the AV node, (3) right ventricular involvement with cardiogenic shock, and (4) ischemia of the papillary muscle, leading to mitral regurgitation.

The circumflex (CX) branch perfuses the posterior wall and variably the inferior and lateral segments. In case of predominant posterior wall involvement following occlusion of the CX, abnormalities in ventricular activation occur in the second half of the QRS complex and are

therefore difficult to pick up on the 12-lead ECG, frequently causing underestimation of the area at risk and undertreatment of the patient.[6]

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Chapter 43: THE ELECTROCARDIOGRAM IN ACUTE MYOCARDIAL INFARCTION

THE ELECTROCARDIOGRAM IN ANTERIOR WALL INFARCTION

The ECG signs of an anterior wall infarction are ST elevation in precordial leads V_2, V_3, and V_4. The behavior of the ST segments in the other precordial and frontal leads is dependent not only on the anterior area but also on the contribution of the septal, lateral, and inferoapical areas. When they are involved in the ischemic process, the anatomic extent and the amount of ischemia of each of these areas determine the vector of the ST segment. This may result in typical patterns of leads showing ST segment changes, predicting the area at risk, and frequently also pointing to the site of occlusion in the LAD (Table 43-1). The ST segment's behavior in anterior wall infarction will be determined by the presence or absence of ischemia in three left ventricular areas: (1) the basoseptal area, perfused by the proximal septal branch, (2) the basolateral area, perfused by the first diagonal or the intermediate branch, and (3) the inferoapical area, when the distal LAD wraps around the apex. Involvement of the proximal septal and/or diagonal branches will lead to four different types of LAD occlusion: (1) proximal to the septal and first diagonal branch (40 percent of cases), (2) distal to these two branches (40 percent), (3) proximal to the first diagonal but distal to the septal branch (10 percent), and (4) proximal to the septal but distal to the first diagonal (or intermediate) branch (10 percent).

Table 43-1: ECG Identifying the Site of Coronary Vessel Occlusion in Acute Infarction

Anterior wall infarction
Proximal to first septal and/or first diagonal branch of the LAD
Distal to first septal and/or first diagonal branch of the LAD
Inferoposterior wall infarction
1. Distinction between RCA and CX coronary artery 2. Proximal or distal in RCA RV infarction

ABBREVIATIONS: CX = circumflex; LAD = left anterior descending coronary artery; RCA = right coronary artery; RV = right ventricle.

DOMINANCE OF BASAL AREA: PROXIMAL LAD OCCLUSION

An example of an occlusion proximal to the first septal and first diagonal branches is shown in Fig. 43-1. Typical features include ST elevation in aV_R and ST elevation of ≥2.5 mm in V_1, ST depression in the inferior leads and in V_5,[7-9] and an abnormal Q in aV_L. Figure 43-2, Plate 82, depicts the likely mechanism of these findings. There is global involvement of the left ventricle with a contribution to the ECG from all ischemic areas. Because of the larger mass of the basal part of the vector, the ST segment will point in a superior direction (Fig. 43-2, left panel). In the frontal plane, this results in ST elevation in leads aV_R and aV_L (Fig. 43-2, right panel). The cranially positioned lead V_1 will also record ST elevation. This upward orientation of the ST vector causes reciprocal ST depression in the inferior leads[10,11] and also sometimes in the lateral leads (V_5 and V_6). Local conduction delay in the lateral area will lead to widening of the Q wave in lead aV_L.

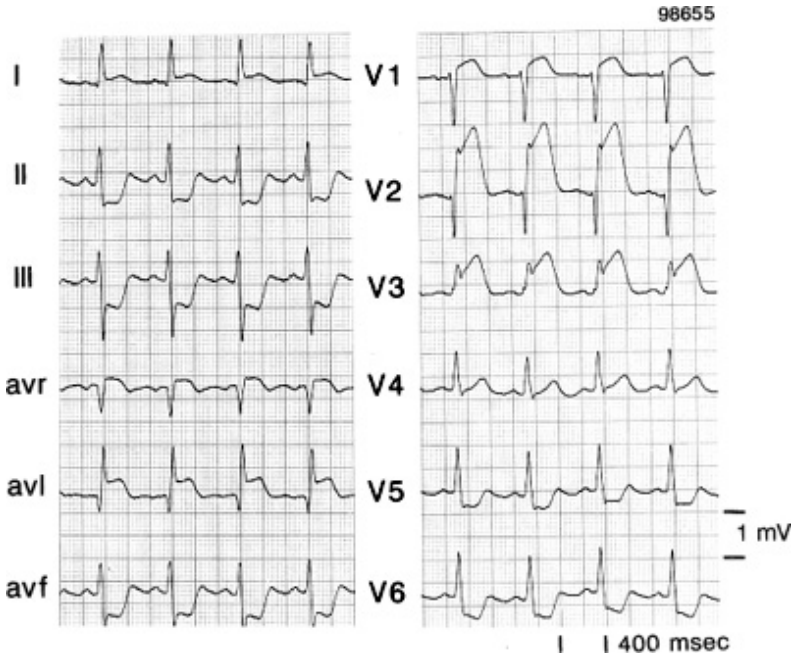

Figure 43-1: Acute anterior wall infarction in proximal LAD occlusion. Anterior wall infarction is present, as indicated by ST-segment elevation in leads V_2 and V_3. In addition, the precordial leads show marked ST-segment elevation in lead V_1 and ST-segment depression in leads V_5 and V_6. The extremity leads show ST-segment elevation in lead aV_R and ST-segment depression in inferior leads II, III, and aV_F.

DOMINANCE OF INFEROAPICAL AREA: DISTAL LAD OCCLUSION

Figure 43-3 shows an example of an acute anterior wall infarction due to a distal LAD occlusion (after the proximal septal and diagonal branches). Typical is the absence of ST-segment depression in the inferior leads.[12,13] Sometimes also, wide Q waves are recorded in V_4 through V_6.

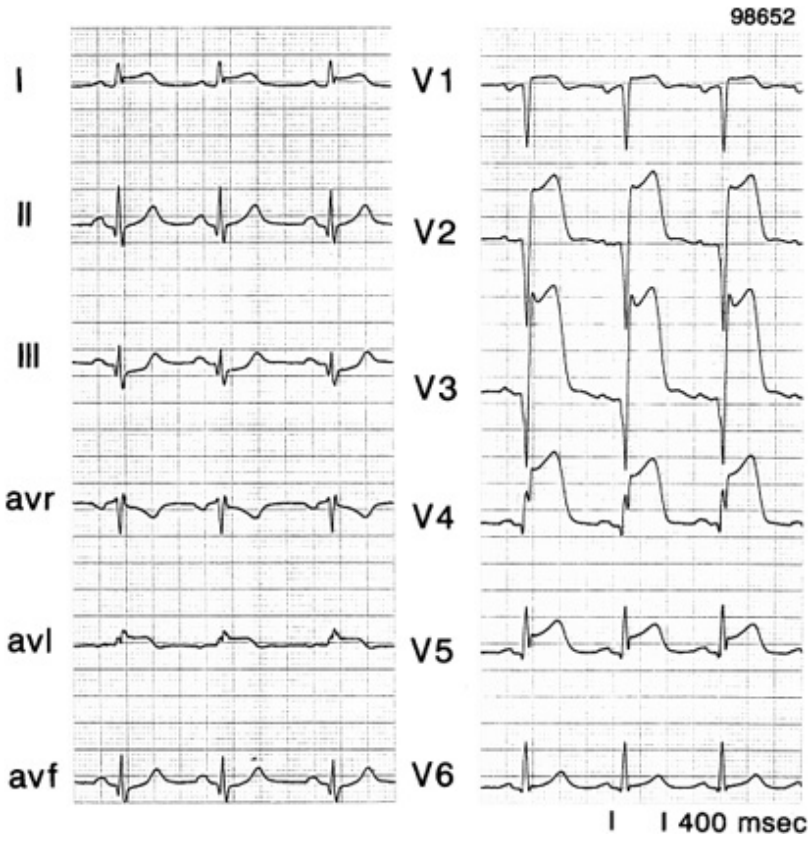

Figure 43-3: Acute anterior wall infarction in distal LAD occlusion. Signs of acute anterior wall infarction are seen, but ST-segment elevation is present in the inferior leads. Note also ST-segment depression in lead aV_R.

In this situation, the inferoapical part is the dominant ischemic area, therefore the ST vector will point inferiorly (Fig. 43-4, left panel, Plate 83). The inferior leads will become isoelectric or even positive (Fig. 43-4, right panel, Plate 83, and Table 43-2). The Q waves in the left precordial leads are likely caused by the combination of local conduction delay in that area combined with persistence of the regular septal Q wave in these leads.

Table 43-2: ECG Criteria Identifying the Site of Occlusion in the LAD Territory

Criterion	Occlusion site	Sensitivity	Specificity	PPA	NPA
CRBBB	Proximal to S1	14	100	100	62
ST ↑ V_1 ≥2.5 mm	Proximal to S1	12	100	100	61
ST ↑ aV_R	Proximal to S1	43	95	86	70
ST ↓ V_5	Proximal to S1	17	98	88	62
Q aV_L	Proximal to D1	44	85	67	69
ST ↓ II ≥1.0 mm	Proximal to S1/D1	34	98	93	68
Q V_5	Distal to S1	24	93	71	53
ST ↓ aV_L	Distal to D1	22	95	87	46
No ST ↓ III	Distal to S1/D1	41	95	92	53

ABBREVIATIONS: D1 = first diagonal branch; NPA = negative predictive accuracy; PPA = positive predictive accuracy; S1 = first septal branch.
SOURCE: From Engelen et al.,[15] with permission.

DOMINANCE OF SEPTAL AREA: FIRST DIAGONAL (OR INTERMEDIATE) BRANCH NOT INCLUDED

Figure. 43-5 presents an example of a case in which a large anterobasal-lateral area is not involved because the occlusion is proximal to the first septal but distal to the first diagonal or intermediate branch. Signs of a proximal first septal branch occlusion are present, such as ST-segment elevation in aV_R, ST-segment elevation ≥2.5 mm in V_1, and ST-segment depression in V_5. As reported elsewhere, the right precordial lead V_{3R} may also show ST-segment elevation.[14] Lead aV_L now shows ST-segment depression and the inferior leads positive ST segments. Figure 43-6, Plate 84, is a diagrammatic presentation of this situation. The left panel shows the rightward orientation of the ST-segment vector, leading (right panel) to the greatest negativity of the ST segment in aV_L and most positivity in lead III, whereas leads aV_R and II are less positive-almost isoelectric. Negativity in lead aV_L is highly specific for an occlusion site behind the first diagonal branch (Table 43-2).

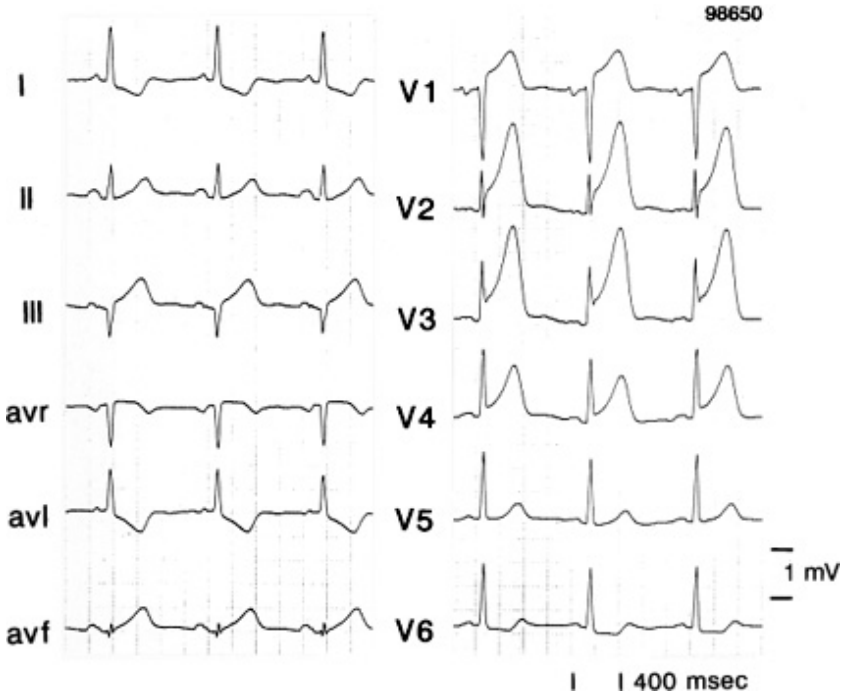

Figure 43-5: Acute anterior wall infarction due to LAD occlusion distal to the first diagonal but proximal to the first septal branch. The precordial leads show evidence of acute anterior wall infarction, but lead aV_L shows ST-segment depression.

DOMINANCE OF THE LATERAL AREA, FIRST SEPTAL BRANCH NOT INCLUDED

Figure 43-7 shows the ECG of an acute anterior wall infarction with an occlusion site distal to the first septal but proximal to the first diagonal branch. Typical features are Q waves in the left lateral leads, ST-segment depression in lead III, and the absence of this finding in lead II. Figure 43-8, Plate 85, shows the distribution of ischemia in that situation, leading to the ST-segment vector, pointing in a left lateral direction (left panel), and leading to the described changes in the ST segment. Local conduction delay in the lateral area with persistence of the septal Q wave results in widening of the Q wave in leads

aV_L and V_5 (right panel).

Electrocardiographic Criteria to Identify the Site of Occlusion in Anterior Wall Infarction

The ECG criteria to identify the site of occlusion in anterior wall infarction, summarized in Table 43-2, are particularly useful in patients presenting with a first acute anterior infarction.[15] In contrast to sensitivity, the specificity of these criteria is high, indicating that their presence accurately predicts the occlusion site, but their absence does not exclude it.

Right bundle-branch block remains, as previously described,[2] a very specific marker of an occlusion site before the first septal branch. ST-segment elevation in V_1 must be considerable to be sufficiently specific ($\geq$ 2.5 mm) for that situation. In contrast, any ST-segment elevation in aV_R, apart from being specific, is the most sensitive marker. ST-segment depression in V_5 is not a very frequent marker, but it is specific. Lead aV_L is the most useful lead to identify an occlusion site, proximal (Q wave) or distal (negative ST segment) to the first diagonal branch.

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THE ELECTROCARDIOGRAM IN INFEROPOSTERIOR WALL INFARCTION

The myocardium of the inferoposterior area of the left ventricle is perfused by the right coronary artery (RCA), and the circumflex (CX) coronary artery. The right ventricle and the AV node are usually supplied by the RCA. As indicated in Table 43-1, the objective of the ECG in inferoposterior infarction is to recognize not only the culprit coronary artery but also whether the right ventricle is involved secondary to an occlusion of the RCA proximal to the right ventricular branch.

The Distinction between a Right Coronary Artery and a Circumflex Coronary Artery Occlusion

As shown in Figs. 43-9 and 43-10, the distinction between an RCA or CX occlusion can be made by determining the ST-segment vector during the acute phase of myocardial infarction. Because RCA occlusion predominantly results in inferoseptal ischemia, the ST-segment vector is directed toward lead III; in CX occlusion, the ischemia is located in the inferoposterolateral region leading to an ST-segment vector pointing toward lead II. Therefore, in RCA occlusion, ST-segment elevation is greater in lead III than lead II (resulting in ST-segment depression in lead I and aV_L). A greater amount of ST-segment depression in aV_L than in lead I further improves the sensitivity in diagnosing anRCA occlusion.[16] In CX occlusion, lead II will show more ST-segment elevation than lead III (with lead I showing an isoelectric ST segment or, in case of important lateral ischemia, ST-segment elevation).

The amount of ST-segment depression in the precordial leads and the number of precordial leads showing ST-segment depression will depend on the extent of posterior wall ischemia. This area is supplied by the posterior descending branch, depending on which coronary artery is dominant-the RCA or CX. The lateral leads V_5 and V_6 are of little value in differentiating between an RCA or CX occlusion. ST-segment elevation in these leads implies a larger perfusion territory of the culprit coronary artery and a need for aggressive reperfusion therapy.[17]

Diagnosing Right Ventricular Infarction

Is the right ventricle (RV) involved in inferoposterior infarction? The RV is supplied by one or more branches of the RCA. Occlusions in the RCA have therefore been classified as occurring before (proximal) or after (distal) the RV branch(es) (Fig. 43-11). RV involvement is of importance because it may lead to cardiogenic shock due to underfilling of the left ventricle, an increased incidence of high degree AV nodal conduction delay during the actue phase, and a higher incidence of sustained ventricular tachycardia in the chronic (scar) phase of MI. As shown in Figs. 43-12 and 43-13, the best way to diagnose RV involvement is to record lead V_{4R}.[18] ST-segment elevation in lead V_{4R} with a positive T wave predicts an RCA occlusion proximal to the right ventricular branch, an isoelectric ST segment with a positive T wave points to a distal RCA occlusion, and a negative T wave indicates an occlusion of the CX.[19,20] Sufficient ST-segment elevation in the inferior leads of the standard ECG is needed to use the findings from V_{4R} reliably (Fig. 43-14).

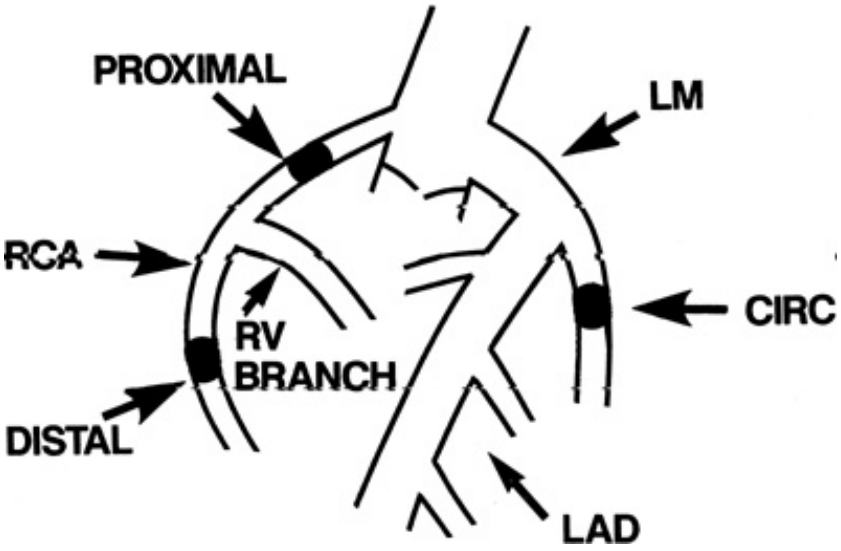

Figure 43-11: Diagram showing the coronary arteries and the possible sites of coronary artery occlusion leading to inferoposterior myocardial infarction. In the right coronary artery (RCA), the occlusion may be before (proximal) the right ventricular (RV) branch or after it (distal). As shown in proximal RCA occlusion, the RV is involved in the infarction.

ST-Segment Depression in the Anterior Leads

ST-segment depression in the anterior leads in inferior wall infarction reflects posterior wall involvement. ST-segment depression may extend from V_1 through V_6 (Fig. 43-10). Recent data indicate that larger infarctions with more postinfarction complications and a higher mortality rate are present in patients with precordial ST-segment depression.[21-23] The extent and amount of ST-segment depression should therefore play a role in decision making about the aggressiveness of reperfusion therapy. Maximal ST-segment depression in leads V_4 through V_6 is more frequently seen in patients with three-vessel disease, and they have a lower LV ejection fraction.[24] ST-segment depression in the precordial leads may occur both with RCA or CX involvement (Fig. 43-10). Absence of ST-segment depression points to the RCA as the infarct vessel.[25] Isolated ST-segment depression may present the difficulty of differentiating acute CX occlusion, resulting in true posterior wall infarction, from nonocclusive myocardial ischemia. In this regard, it has been suggested that localization of maximal ST-segment depression in V_2 or V_3 is predictive of acute CX occlusion.[26] Also, the use of additional leads V_7 through V_9 has been recommended.[27,28]

Isolated Right Ventricular Infarction

Rarely, the ECG shows only minor changes in the inferior leads and the predominant ST-segment elevation is seen in leads V_1, V_2, and the right precordial leads.[29] This picture reflects a predominant RV infarction and is found in case of a small RCA, a collaterally filled RCA, or an isolated occlusion of an RV branch.

Atrioventricular Conduction Disturbances in Acute Myocardial Infarction

ATRIOVENTRICULAR NODAL BLOCK

Different degrees of AV nodal conduction delay and block may occur in inferior wall infarction,

especially when the proximal RCA is involved (Fig. 43-15). High-degree (second or third) AV nodal block is present in about 20 percent of acute inferior infarction ECGs[30] and should suggest a proximal RCA occlusion with RV involvement.[31] AV nodal block is accompanied by a higher in-hospital morbidity and mortality, not only in the prethrombolytic[32] but also in the thrombolytic era.[33] Early reperfusion is indicated to reduce infarct size and restore normal AV conduction.

SUBATRIOVENTRICULAR NODAL BLOCK

The development of bundle-branch block with or without hemiblock during the acute phase of anterior myocardial infarction indicates proximal LAD occlusion and is therefore a marker for the need to reopen the vessel promptly. Also, in the thrombolytic era, the development of bundle-branch block and complete AV block indicates a poor short-term prognosis and stresses the necessity of an aggressive reperfusion attempt.[34-36] When left anterior fascicular block occurs in the setting of acute inferior wall infarction, additional LAD disease should be suspected (Fig. 43-16).[37]

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LIMITATIONS

The findings described above are from studies where occlusion of a single coronary vessel led to the characteristic ECG changes. The presence of multivessel disease, an old myocardial infarction, and occlusion of a vessel that, by collaterals, is perfusing the territory of another coronary artery may affect and change the ECG in such a way that precise identification of the site of occlusion in the culprit coronary artery and the size of the area at risk is no longer possible. This is also the case in the presence of a conal branch from the RCA protecting the superior portion of the interventricular septum in acute anterior wall myocardial infarction.[38] The ECG is also of limited value when ventricular activation is altered, as in preexistent left bun dle-branch block, ventricular preexcitation, and a paced ventricular rhythm.

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CONCLUSION

In acute cardiac ischemia the aggressiveness of (reperfusion) therapy should be determined by the size of the area at risk. As shown in this chapter, the inexpensive electrocardiogram can be of great help in providing that information.

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Figure 43-10: *Left panel:* The typical picture of a RCA occlusion. ST-segment elevation in lead III is higher than in lead II, resulting in ST-segment depression in lead I. In this patient with a dominant RCA complete AV block, right atrial and posterior wall infarction is also present. *Right panel:* An example of a CX occlusion. ST-segment elevation is more marked in lead II than in lead III, leading to a positive T wave in lead I.

Figure 43-11: Diagram showing the coronary arteries and the possible sites of coronary artery occlusion leading to inferoposterior myocardial infarction. In the right coronary artery (RCA), the occlusion may be before (proximal) the right ventricular (RV) branch or after it (distal). As shown in proximal RCA occlusion, the RV is involved in the infarction.

Figure 43-12: Characteristic ST-T-segment changes in lead V_{4R} in cases of proximal RCA, a distal RCA occlusion, or a CX occlusion (see text).

Figure 43-13: Three panels showing the behavior of the right precordial leads in inferoposterior myocardial infarction caused by a proximal RCA, distal RCA, or CX occlusion. See also Fig. 43-12.

Figure 43-14: The relation between ST-segment elevation in leads II, III, and aV_F and in the right precordial leads in proximal RCA. Note that changes diagnostic for RV involvement in lead V_{4R} have disappeared 7½ h after the onset of chest pain. As shown there is a relation between the amount of ST-segment elevation in the inferior leads and lead V_{4R}.

Figure 43-15: Three-to-two AV nodal Wenckebach phenomenon in a patient with an acute inferoposterior myocardial infarction. ST-segment elevation in lead III is higher than in lead II, indicating a right coronary artery (RCA) occlusion. Lead V4R (not shown) indicated an ST-segment elevation of 3 mm with a positive T wave, pointing to a proximal RCA with RV involvement.

Figure 43-16: *Left panel:* Sinus tachycardia with a prolonged PR interval and right bundle-branch block (RBBB) in a patient with an acute anterior wall myocardial infarction. These findings point to a LAD occlusion proximal to the first septal branch. *Right panel:* Same patient after primary PTCA of the proximal LAD occlusion. Note disappearance of PR prolongation and RBBB. The precordial QRS picture indicates a small anterior wall infarction.

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Part 6: CORONARY HEART DISEASE
Chapter 44:

THROMBOGENESIS, ANTITHROMBOTIC, AND THROMBOLYTIC THERAPY

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IMPORTANCE OF THROMBOSIS IN ACUTE CORONARY SYNDROMES

Because nearly 2 million patients annually experience an acute coronary syndrome in the United States, with more than double that figure worldwide, cardiologists and other health care professionals have focused on improving the management of acute coronary syndromes, with one of the most prominent advances being thrombolytic therapy for patients with ST-segment elevation myocardial infarction (MI).[1] More recently, however, there have been numerous advances in antithrombotic therapy, for both patients with ST-elevation MI as well as the much larger group of patients with unstable angina and non-ST-elevation MI.

Rupture or erosion of an atherosclerotic plaque with superimposed nonocclusive thrombus is by far the most common cause of acute coronary syndromes (see also Chaps. 35 and 36). However, angiographic studies have shown a major difference in the severity of the thrombus, based on the presence or absence of ST-segment elevation: In ST-elevation MI the infarct-related artery usually has a 100 percent occlusion,[2,3] whereas in unstable angina/non-ST-elevation MI the culprit artery usually has a severe obstruction (80 to 95 percent) but is patent with coronary perfusion (Fig. 44-1).[4,5] Thus, because of the advent of acute reperfusion therapy, a classification of ST-elevation MI versus unstable angina/non-ST-elevation MI provides the critical information regarding the pathophysiology and acute management of acute coronary syndromes (Fig. 44-1).

Evolution of Athero(thrombo)sclerosis

Atherosclerosis is a silent process that usually commences 20 to 30 years prior to a patient's presentation with a clinical syndrome (see Chaps. 35 and 36).[6,7] Hypercholesterolemia, smoking, hypertension, and other coronary risk factors damage the endothelium and initiate the atherosclerotic process.[6-8] When the endothelium is dysfunctional, macrophages bind to endothelial adhesion molecules and can infiltrate the endothelial cell. Low-density lipoprotein (LDL) molecules are able to penetrate into the vessel wall, and the macrophages digest the LDL, becoming foam cells, which thereby create a lipid-filled atherosclerotic plaque.[7,9] Oxidized LDL may also have a direct toxic effect on the endothelium and smooth muscle cells, which contribute to instability of the atherosclerotic plaque. Such plaques, which usually are lesions with less than 50 percent stenosis, are more prone to rupture.[10-14]

Then, multiple factors contribute to plaque rupture, including endothelial dysfunction, plaque lipid content,[15] local inflammation causing breakdown of the thin shoulder of the plaque,[16] coronary vasoconstriction, local shear-stress forces, platelet activation,[17,18] and the status of the coagulation system (i.e., a potentially prothrombotic state),[19,20] all of which culminate in the formation of a platelet-rich thrombus on the disrupted plaque.[21-23]

It should be noted however, that more than 95 percent of all plaque ruptures are clinically silent.[24,25] Angiographic studies have shown that many high-grade lesions often appear in segments of the coronary artery that were previously normal.[26] The erratic and unpredictable growth of plaques is caused by plaque disruption or fissuring and intracoronary mural thrombosis.[27,28] The mural thrombus then undergoes fibrous organization and contributes, often asymptomatically, to the progression of the disease.[27,28] Thus, this process of plaque disruption and local thrombosis is ongoing in patients with clinically "stable" coronary artery disease, a point that reemphasizes the importance of long-term antithrombotic therapy in patients with coronary artery disease.

Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI) with angioplasty, stenting, or other modalities is associated with denudation of the endothelium and deep vessel injury. This results in exposure of thrombogenic elements in the atherosclerotic plaque and the vessel wall, which predisposes this area to platelet deposition and fibrin formation, leading to intravascular thrombosis.[29,195] Therefore, therapy to prevent acute occlusion following coronary intervention should be directed against both platelets and the coagulation cascade.

Saphenous Vein Bypass Grafting

Disease of the saphenous vein graft is a special case in coronary atherosclerosis. Occlusion rates are 8 to 18 percent per distal anastomosis 1 month postoperatively and 16 to 26 percent at 12 months.[30] Vein graft disease can be divided into three phases: an early postoperative phase (within 1 month after surgery) related to thrombotic occlusion, in which platelet activation and fibrin formation are implicated; an intermediate phase (within the first postoperative year) characterized by intimal hyperplasia, resulting in a form of accelerated atherosclerosis that may have a superimposed thrombotic tendency; and a late phase (after the first postoperative year) characterized by graft atherosclerosis similar to that of the native coronary arteries.[30,196] Therefore, the predominant pathogenetic mechanism in saphenous vein bypass grafting is related to both platelet activation and fibrin generation, particularly in the early postoperative phase.

Role of Endothelial Dysfunction and Inflammation in Early Coronary Atherosclerosis

At areas of plaque injury, there is early adherence of leukocytes and platelets.[31] These early cellular responses lead to the further migration and proliferation of smooth muscle cells, monocytes, and lymphocytes at areas of injury. Vascular endothelial cell injury leads to a cell-mediated response that is very similar to the inflammatory response, which leads to a complex cascade of events that culminate in atherosclerosis and eventually clinical vascular syndromes.[31,32] Activated T cells release cytokines, and monocyte chemotactic factor enhances the adhesion and migration of circulating monocytes and influences lipoprotein uptake by the macrophage and promotes foam cell formation.[31]

In postmortem studies of the atheromatous plaque, disrupted atheromatous plaque were found beneath thrombi in 84 percent of patients,[33] and these culprit lesions contained significantly more macrophages than quiescent lesions.[34] Furthermore, the macrophages and T lymphocytes at the site of plaque disruption were found to be in an activated state.[32] Other studies have localized matrix metalloproteinases to human atherosclerotic plaque, which may contribute to their disruption.[35] Studies of lymphocyte function and expression in patients with unstable angina revealed that this state is associated with the activation of a specific T-cell subset ($CD\text{-}4^{+}$/CD-28 null) that produces interferon-γ, an activator of monocytes, and the production of matrix metalloproteinases.[36] Other complement peptides, including C3-binding protein, localized in areas of endothelial injury and inflammation are chemotactic for monocytes. Clinical studies of patients

with acute coronary syndromes have reflected a heightened systemic inflammatory response as measured by elevated circulating levels of markers such as C-reactive protein and other acute-phase reactants.[37-42]

Role of Platelets and Thrombosis in the Progression to Acute Coronary Syndromes (Figs. 44-1 to 44-6)

The central role of coronary artery thrombosis in the pathogenesis of acute coronary syndromes is supported by six sets of observations: (1) at autopsy, thrombi can usually be identified at the site of a ruptured plaque;[21,22,24,43] (2) coronary atherectomy specimens obtained from patients with acute myocardial infarction (AMI) or unstable angina demonstrate a high incidence of acute thrombotic lesions;[44-47] (3) coronary angioscopic observations indicate that thrombus is frequently present;[48-54] (4) coronary angiography has demonstrated ulceration or irregularities suggesting a ruptured plaque[10,55] and/or thrombus in many patients;[5,56] and (5) evidence of ongoing thrombosis has been noted with elevation of several markers of platelet activity and fibrin formation;[6,57-64] and (6) the clinical outcome of patients with acute coronary syndromes is improved by antithrombotic therapy with aspirin,[65-68] heparin,[67-71] low molecular weight (LMW) heparin,[72-75] and platelet glycoprotein (GP) IIb/IIIa inhibitors.[76-78]

The thrombotic response to plaque disruption/fissuring is primarily determined by five local factors: (1) extent of plaque disruption (e.g., ulcer), (2) character of exposed contents (e.g., lipid pool), (3) degree of stenosis and surface irregularities that activate platelets (i.e., change in geometry after plaque disruption), (4) the surface of residual thrombus (recurrence), and (5) vasoconstriction. In addition, systemic factors appear to enhance thrombogenicity, which may occur in a very stenotic plaque denuded of endothelium without plaque fissuring.[24,79] This balance of local and systemic factors has important effects on outcome, as described below.

Plaque Disruption

NON-PLAQUE-RELATED FACTORS PREDISPOSING PLAQUE TO RUPTURE

Passive plaque disruption is related to physical forces, especially where the fibrous cap is thinnest, i.e., where it is most heavily infiltrated with foam cells and, as a result, the weakest. Pathologic studies have shown that vulnerable plaques are commonly composed of cellular elements and an atheromatous lipid-filled core separated from the arterial lumen by a fibrous membrane or cap.[15,24,25] For eccentric plaques, the shoulder region, that between the plaque and the adjacent vessel wall is most vulnerable.[15,24,54] Based on studies examining both intact and disrupted plaques and in vitro mechanical testing of isolated fibrous cap, vulnerability to rupture depends on three primary factors: (1) circumferential wall stress or cap "fatigue;" (2) location, size, and consistency of the atheromatous core; and (3) blood flow characteristics, such as the impact of flow on the proximal aspect of the plaque.[54]

PREDISPOSING FACTORS IN ACTIVE PLAQUE

Recent evidence points to a large number of inflammatory cells, notably monocyte-derived macrophages, as being present in disrupted plaque.[15,24,25] Macrophage-derived products, such as matrix metalloproteinases (MMPs), collagenases, and other proteolytic enzymes, degrade the matrix of the plaque, weaken the fibrous cap, and thus predispose plaque to rupture.[35] In culture, monocyte-derived macrophages have been found to degrade the collagen of the fibrous cap while simultaneously expressing MMP-1 (interstitial collagenase) and inducing MMP-2 (gelatinolytic).[80] Recent evidence has suggested that circulating oxidized LDL may influence matrix turnover in atherosclerotic plaque by causing macrophages to produce and release more matrix-degrading metalloproteinases (MMP-9), which increase matrix degradation, alter arterial

remodeling, and thus predispose plaque to rupture.[81] It was also found that high-density lipoprotein (HDL) inhibited this process, thus possibly explaining HDL's favorable mechanism of action. When oxidized LDL overloading occurs, macrophages appear to enter into apoptotic death, periods during which induction of MMPs and tissue factor appears to occur. The end result of plaque disruption is acute overlying thrombosis.

Inflammation/Infection

Recent evidence has also pointed to a role for inflammation, which appears to be key in the development of atherosclerosis[82,83] and in the development and recurrence of unstable angina.[37,39,84,85] Infectious agents, notably *Chlamydia pneumoniae*, appear to be one of the underlying causes of diffuse inflammation in the pathogenesis of coronary artery disease.[86-88] Others for which there is some, albeit less strong, evidence include *Heliobacter pylori* and *Cytomegalovirus*.[86] It is important to note that an etiologic relationship between these infectious agents to the development of acute coronary syndromes has not been definitively established.[88-90] On the other hand, evidence from several animal models,[91-94] and pilot treatment trials in patients,[95-97] suggests *Chlamydia pneumoniae* may be an important and *potentially treatable* cause of unstable angina or MI, and larger trials are ongoing.

Acute Thrombosis

Plaque disruption and thrombus formation/remodeling lead to a variable degree of luminal obstruction to blood flow and can present clinically as stable or unstable angina or acute MI or lead to sudden death (Fig. 44-1).[98] At the time of plaque disruption, a number of local and systemic thrombogenic factors may influence the degree and the duration of thrombus deposition. Such a thrombus may then either be partially lysed or become replaced in the process of organization by the vascular repair response.

Substrate and Tissue Factor-Dependent Thrombosis (Figs. 44-2 and 44-3)

The disruption of an atherosclerotic plaque exposes various vessel wall components to the circulating blood, and each have varying degrees of thrombogenicity. Among the various types of plaques, which included normal intima, fatty streaks, sclerotic plaques, fibrolipid lesions, and plaques with lipid-rich cores, it was the lipid-rich plaque (abundant in cholesterol ester) that displayed the highest thrombogenicity and the most intense tissue factor staining compared with the other plaque types.[99]

Tissue factor is a LMW glycoprotein that, after being exposed to circulating blood factors, initiates the extrinsic clotting cascade and is believed to be a major regulator of thrombosis and hemostasis (see Fig. 44-7). Tissue factor forms a high-affinity complex with coagulation factors VII/VII; the tissue factor-factor VIIa complex activates factors IX and X, which in turn lead to thrombin generation.[100] Atherectomy specimens from the culprit lesion in patients with unstable angina demonstrated a strong relationship between tissue factor and macrophages.[16] Experimental studies using a specific inhibitor of tissue factor (tissue factor pathway inhibitor) found that acute thrombus formation was reduced in lipid-rich plaques exposed to this specific inhibitor.[101] Such information supports the important role of tissue factor activity in acute thrombosis after coronary plaque rupture and opens new avenues of possible therapeutic intervention in the treatment and/or prevention of acute coronary syndromes.

Recent observations indicate that after plaque disruption there is a first layer of fibrin formation, as a result of the activation of tissue factor and the coagulation cascade[1]; this precedes significant platelet deposition, as a result of thrombin generation by the coagulation cascade[1]; eventually, if

the fibrin-platelet thrombus occludes the artery, further and significant fibrin formation takes place proximally as a result of stasis. Therefore, the coronary occlusive thrombus is like a "sandwich" composed of fibrin-platelet-fibrin.

Hypercoagulable-Dependent Thrombosis (Table 44-1)

There is evolving evidence that circulating monocytes and white blood cells may be involved in tissue factor expression and thereby influence the thrombogenicity of the circulating blood.[102] Activation of the circulating inflammatory cells in patients leading to acute coronary syndromes has been suggested by high titers of C-reactive protein preceding these events.[85,103-105] Hypercholesterolemia, a high-catecholamine drive such as smoking, emotional stress, cocaine use, certain chemotactic determinants, and perhaps infections may also trigger such hypercoagulable phenomena. In support of this hypothesis are studies evaluating lipid-lowering therapies that have found that normalization of the serum cholesterol reduced blood thrombogenicity.[106]

Several hemostatic determinants, such as fibrinogen, von Willebrand factor, and factor VIIa have been associated with an increased risk of cardiovascular disease. The association with fibrinogen is the most powerful and consistent. Abnormal levels of plasminogen activator inhibitor 1 (PAI-1) and tissue-type plasminogen activator (t-PA) antigen (a marker of endothelial dysfunction) are associated with an increased risk of cardiovascular events.[107] For instance, increased levels of PAI-1 have been found on young survivors of MI.[108] In a healthy cohort of patients, high baseline levels of endogenous t-PA have been found to be significant predictors of the risk of future MI.[108]

Vasoconstriction

Although the vast majority of acute coronary syndromes are caused by the disruption or erosion of a plaque with superimposed thrombus, other mechanisms that alter myocardial oxygen supply and demand must be considered. Studies by Maseri and colleagues have indicated that vasoconstriction has an important role.[109] In acute coronary syndromes, vasoconstriction may occur in response to a mildly dysfunctional endothelium near the culprit lesion or, more likely, may be a response to deep arterial damage or plaque disruption of the culprit lesion itself. Thus, with regard to this second type of vasoconstriction, it seems that a predisposition exists for platelet-dependent and thrombin-dependent vasoconstriction at the site of plaque disruption and thrombosis that may be significant but transient.[109] Thus, platelet-dependent vasoconstriction, mediated by serotonin and thromboxane A_2 (TXA_2),[110] and thrombin-mediated vasoconstriction occur if the vascular wall has been damaged substantially by deendothelialization, which suggests a direct interaction of these substances with the vascular smooth muscle cells.

Mechanism of Thrombosis

Thrombosis is comprised of two interrelated stages: primary hemostasis and secondary hemostasis.[111,112] The first stage of hemostasis is initiated by platelets as they adhere to damaged vessels and form a platelet plug. The second phase involves activation of the coagulation system, which is comprised of a series of inactive proteins (zymogens) that are activated by proteolytic cleavage into active enzymes that ultimately cleave fibrinogen to fibrin to form a hemostatic clot (Fig. 44-7).[113] These two phases are dynamically interactive, however, since activated platelets can provide a surface for coagulation enzymes, and the ultimate enzyme of coagulation, thrombin, is a potent platelet activator.

Platelet Aggregation

Platelets play a key role in the transformation of a stable atherosclerotic plaque to an unstable lesion. With rupture or ulceration of an atherosclerotic plaque, the subendothelial matrix (e.g.,

collagen and tissue factor) is exposed to the circulating blood. Platelets mediate the "primary hemostasis" at the site of a ruptured plaque: the first step is *platelet adhesion* via the GP Ib receptor, as well as von Willebrand factor (Fig. 44-3). This is followed by *platelet activation*, which leads to (1) a shape change in the platelet (from a smooth discoid shape to a spiculated form, which increases the surface area upon which thrombin generation can occur); (2) degranulation of the alpha and dense granules, thereby releasing TXA_2, serotonin, and other platelet aggregatory and chemoattractant agents; and (3) expression of GP IIb/IIIa receptors on the platelet surface with activation of the receptor, such that it can bind fibrinogen. The final step is *platelet aggregation*, i.e., the formation of the platelet plug. Fibrinogen (or von Willebrand factor) binds to the activated GP IIb/IIIa receptors of two platelets, thereby creating a growing platelet aggregate.

Glycoprotein IIb/IIIa Receptor

The platelet GP IIb/IIIa receptor is a member of the integrin receptor superfamily of complexes that mediate cell-protein and cell-cell interactions.[114] The GP IIb/IIIa receptor is a calcium-dependent heterodimer, composed of two different subunits (α_{IIb} and β_3), both of which span the platelet membrane. The GP IIIa subunit contains a four-amino-acid sequence that is crucial for binding of fibrinogen and other ligands.[114] The first three amino acids are arginine-glycine-aspartic acid (RGD). LMW peptide and nonpeptide GP IIb/IIIa inhibitors have been developed to bind to the RGD sequence of the receptor, thereby interfering with the binding of fibrinogen to the GP IIb/IIIa receptor.

Antiplatelet therapy has been directed at decreasing the formation of TXA_2 (e.g., aspirin), inhibiting the adenosine diphosphate (ADP) pathway of platelet activation (e.g., ticlopidine and clopidogrel), and directly inhibiting platelet aggregation (e.g., GP IIb/IIIa inhibitors).

Secondary Hemostasis

Simultaneously with formation of the platelet plug, the plasma coagulation system is activated. Traditionally, the coagulation cascade has been divided into two pathways: the *extrinsic* or contact system and the *intrinsic* system (Fig. 44-7). Recent evidence, however, has revised the understanding of coagulation into a single interrelated system.[115-117] The extrinsic pathway, initiated by release of tissue factor, is now felt to be the predominant mechanism of initiating hemostasis.[115,117] Ultimately, factor X is activated and leads to formation of thrombin, which in turn cleaves fibrinogen to fibrin (Fig. 44-3).

Thrombin plays a central role in arterial thrombosis: (1) it converts fibrinogen to fibrin in the final common pathway for clot formation, (2) it is a powerful stimulus for platelet aggregation, and (3) it activates factor XIII, which leads to cross-linking and stabilization of the fibrin clot.[111] Thrombin molecules are incorporated into coronary thrombi and can form the nidus of rethrombosis (i.e., reocclusion or reinfarction) as the thrombus undergoes fibrinolysis. Accordingly, effective thrombin inhibition is an important part of the therapy for acute coronary syndromes (see page 1394).

Hemostatic System

This is a complex, overlapping system that consists of blood vessels, platelets, procoagulants and anticoagulants, profibrinolytic components, and inhibitors. For clarity, the following sections deal with each component of the hemostatic mechanism individually. However, all of these processes are intimately related and inseparable.

ROLE OF VESSEL WALL CONTRACTION AND ENDOTHELIUM

The immediate control of bleeding from a small severed vessel is vasoconstriction, which is soon followed by local perivascular and intravascular activation of platelets and coagulation components. TXA_2 produced and released by activated platelets may play a role in persistent vasoconstriction, as do products released by stimulated endothelium (e.g., endothelin) or generated during coagulation (bradykinin generated by activated factor XII and fibrinopeptide B).

In normal vessels, circulating platelets do not adhere to normal (unstimulated) endothelial cells in vivo. This may relate to the fact that both platelets and endothelium have a negative charge and thus would be mutually repulsive. The negative electrical charge of endothelial cells is due to a pronounced glycocalyx, consisting of proteoglycans, of which heparan sulfate (a heparin-like substance that binds antithrombin III) is the most important. Stimulated or injured endothelial cells lose their negative surface charge. The nonthrombogenic nature of endothelium is also partly due to the lack of surface molecules as tissue factor.

The thromboresistance of normal endothelium also depends on several substances produced by endothelial cells. They include potent vasodilators and inhibitors of platelet function, such as prostacyclin [prostaglandin I_2 (PGI_2)] and nitric oxide (NO), which serve to prevent platelet adhesion to endothelium.[118,119] Anticoagulant properties include heparin-like glycosaminoglycans and a thrombin-binding protein called thrombomodulin.

The production of prostacyclin by endothelium is stimulated by contact with activated platelets or leukocytes by stretching of the arterial wall (pulsatile pressure) and by some drugs. PGI_1 has strong antiplatelet and vasodilator properties and thus acts as the biological antagonist of TXA_2. A direct link between impaired biosynthesis of PGI_2 in the vessel wall and thrombosis or atherosclerosis is suggested by the decreased capacity of endothelium to generate prostacyclin with age, atherosclerosis, and risk factors such as high cholesterol, heavy smoking, and diabetes. NO is formed from L-arginine by an oxidation pathway that requires several cofactors. NO relaxes smooth muscle cells through stimulation of guanylate cyclase, which, in turn, generates cyclic guanosine monophosphate (cyclic GMP).[120] By the same mechanism, it is also a potent inhibitor of adhesion and aggregation of platelets.

There is a clear synergism between prostacyclin and NO in preventing platelet activation. NO is effective only in the immediate vicinity of its site of release because hemoglobin almost immediately inactivates any NO that enters the bloodstream. It has been suggested that a deficiency in NO production contributes to the pathogenesis of atherosclerosis and to the development of complications of diabetes. Thrombomodulin is a transmembranous protein that serves as an endothelial receptor for free thrombin.[121] In the complex that is formed and which does not require calcium, thrombin loses its procoagulant activity and expresses its anticoagulant role by activating protein C.

ROLE OF PLATELETS

The exterior coat of platelets, the glycocalyx, contains many distinct glycoproteins that are important for platelet function. They include integrins and leucine-rich glycoproteins. These surface glycoproteins mediate platelet adhesion and aggregation as receptors for adhesive proteins and agonists. The platelets contain dense bodies, alpha granules, actin filaments, microtubules, and an open canalicular system, which all have their respective functions in the formation of a hemostatic plug (Fig. 44-2).

In normal conditions, platelets are quiescent and circulate freely in the blood because they do not

attach to a normally functioning endothelium. Vessel injury, however, exposes subendothelial connective tissue to various elements to which platelets can adhere.[122,123] This phenomenon-platelet adhesion-is the initial event and one of the most crucial steps in platelet plug formation. The adhesive proteins collagen and fibronectin (and, to a lesser extent, laminin, microfibrils, and thrombospondin) are present in subendothelium and interact readily with von Willebrand factor, whereby this large protein changes its conformation. This allows platelets to bind to von Willebrand factor via their surface GP Ia/IIa and Ic/IIa receptors (Figs. 44-3 and 44-4). Particularly collagen, a ubiquitous structural component of the vessel wall, is important and may provide scaffolding on which other adhesive proteins assemble. Von Willebrand factor, which has two collagen-binding sites, is an absolute requirement for platelet adhesion but only at high shear rates, whereas fibronectin plays a significant role in platelet adhesion at lower shear rates.

After adhesion, platelets lose their discoid shape, form extended pseudopods, and spread out over the injured surface. Through the action of activators such as collagen and eventually thrombin and norepinephrine, the adhered platelets soon become activated, whereby other platelet receptors are expressed and several mediators stored in platelet granules are released.[124] This release reaction seems to be initiated by contraction of a circumferential band of microtubules. Stored granules are discharged through the open canalicular system after fusion of the granular membrane with the membranes of the open canalicular system. Among the granular agents released are ADP, serotonin, β-thromboglobulin, platelet factor 4, platelet growth factor, and TXA_2.[125,126]

These released substances, particularly ADP and TXA_2, induce binding of platelets to one another, a phenomenon called *platelet aggregation*. This process increases the size of the hemostatic plug at the site of injury and, by recruiting additional circulating platelets, transforms the initial monolayer of platelets into an aggregate. The platelet surface GP IIb/IIIa undergo a conformational change in the aggregation process, so that they can interact with plasma fibrinogen and other adhesive proteins as fibronectin and endothelial thrombospondin, which serve to link platelets together into a tighter aggregate (Fig. 44-7).[124,127]

The prostaglandins also play an important role in mediating the platelet release reaction and aggregation (Fig. 44-4). Collagen and epinephrine appear to trigger the activation of one or more phospholipases in the platelet membrane. Phospholipase A_2 acts on phosphatidylcholine to release arachidonic acid from the platelet membrane. Arachidonic acid is metabolized by cyclooxygenase to unstable proaggregating prostaglandin endoperoxide intermediates (prostaglandins G2 and H2). TXA_2 is formed by the action of thromboxane synthase on PGH_2; it further promotes platelet activation, thrombus growth, and local vasoconstriction.

On the other hand, the vascular endothelial cells synthesize prostacyclin (PGI_2), starting from arachidonic acid or from platelet-derived PGG_2. Prostacyclin stimulates adenylate cyclase and leads to an increased level of cyclic adenosine monophosphate (cyclic AMP) in the platelet (Fig. 44-5). Cyclic AMP, in turn, inhibits the discharge of calcium from the dense tubular system and thus prevents platelet aggregation and secretion. Phosphodiesterase enhances the breakdown of cyclic AMP.

Arachidonic acid also serves as a substrate for the formation of leukotrienes, a pathway mediated by lipoxygenase in the leukocytes. Thus, eicosanoids derived from arachidonic acid in platelets, endothelial cells, and leukocytes provide short-acting biological mediators that further promote not only platelet activation and local vasoconstriction but also platelet inhibition and vasodilatation. In addition, they intervene in local immune-mediated reactions.

ROLE OF BLOOD FLOW

Blood flow influences platelet function by shear stress. Exposure of platelets to very high shear stress leads to spontaneous aggregation even in the absence of exogenous agonists. Furthermore, some coagulation reactions are accelerated in the presence of high shear, and the ability of the endothelium to secrete tissue plasminogen activator over the basal level is increased two- to threefold.

ROLE OF BLOOD COAGULATION

Activated platelets provide a microenvironment that enhances the acceleration of fibrin formation at the site of injury. They rearrange their surface lipoproteins so that phospholipids, on which coagulation factors can concentrate, are now exposed to the bloodstream. This is accompanied by the exposure of high-affinity binding sites for the activated factors V, VIII, IX, and X. Thus, activated platelets provide a suitable surface on which the activation of prothrombin to thrombin is accelerated dramatically. Thrombin occupies a central position in the coagulation process. It is formed as the end product of a complex chain of reactions that transform, in sequence, a number of coagulation factors present as precursors (zymogens) in plasma into activated factors. Table 44-1 lists the well-recognized coagulation factors with their Roman numeral designations and synonyms and some of their properties. The coagulation factors are numbered roughly in the order of their discovery and do not reflect the sequence of reactions. Coagulation factors interact mainly on the membrane of activated platelets and other stimulated cells and tissue factor (a membrane protein exposed to the blood, e.g., after trauma) on which coagulation factors bind. Because of the low concentration of these factors in plasma and the abundant presence of circulating inhibitors, the interaction of procoagulants and their subsequent activation can proceed only slowly in the fluid phase of blood.

Coagulation factors are activated one by one, mainly through limited proteolysis. When the letter "a" accompanies a Roman numeral (e.g., factor VIIa), this indicates that the factor is in its activated form rather than in its naturally occurring precursor form (e.g., factor X). All activated factors are serine proteases: they split arginyl bonds in their specific substrate, and the latter then becomes another activated coagulation factor (waterfall or cascade sequence of events). In contrast, factors V and VIII, tissue factor and high molecular weight (HMW) kininogen are not proenzymes but function rather as cofactors. They can thus be considered as regulatory proteins (cofactors) that influence the reaction rate. These cofactors (except tissue factor) still require activation by minor proteolysis, while tissue factor X, present in extravascular spaces, must make contact with blood to function. The traditional coagulation scheme distinguishes an intrinsic from an extrinsic activation pathway.

The Intrinsic Pathway of the Coagulation System: Activation of Factors XII, XI, X, and IX

All factors participating in the intrinsic pathway are present in circulating blood, and the reaction sequence is initiated by contact of platelets and/or coagulation components with a subendothelial tissue. Antigen-antibody complexes and activated platelets may also serve this purpose, as can fissured atherosclerotic plaques and foreign surfaces, such as those in an extracorporeal circulation or renal dialysis. In vitro, this initial contact phase involves the interaction of factor XII (Hageman factor), factor XI, prekallikrein, and HMW kininogen with a foreign surface (a surface other than normal endothelium or blood cells).

When circulating factor XII meets negatively charged surfaces such as glass and kaolin, it binds via its heavy chain to the surface. Upon adsorption, bound factor XII exerts traces of biological activity. For the mechanisms of this phenomenon, conformation changes of the molecule with exposure of the enzyme site in the light chain have been postulated (Fig. 44-6). Factor XI and prekallikrein exist in plasma as equimolar complexes with HMW kininogen, and these complexes are bound to initiating surfaces via the HMW kininogen moiety. HMW kininogen transports both

factor XI and prekallikrein to an appropriate surface. Surface binding is assumed to serve to bring factor XII, prekallikrein, and factor XI to a close spatial orientation. Binding of factor XII to a negatively charged surface also makes the molecule more susceptible to proteolytic cleavage. Initially, traces of factor XIIa presumably generate traces of kallikrein from prekallikrein by splitting of a single peptide bond. Kallikrein will now activate more rapidly factor XII in a feedback loop, which, in turn, will generate more kallikrein, and the reciprocal activation of these two surface-bound molecules continues until the substrates are locally exhausted. Of note, a potent vasoactive substance, bradykinin, is released from HMW kininogen upon the activation of factor XII and generation of kallikrein. The latter also activates pro-urokinase, enhancing fibrinolytic activity.

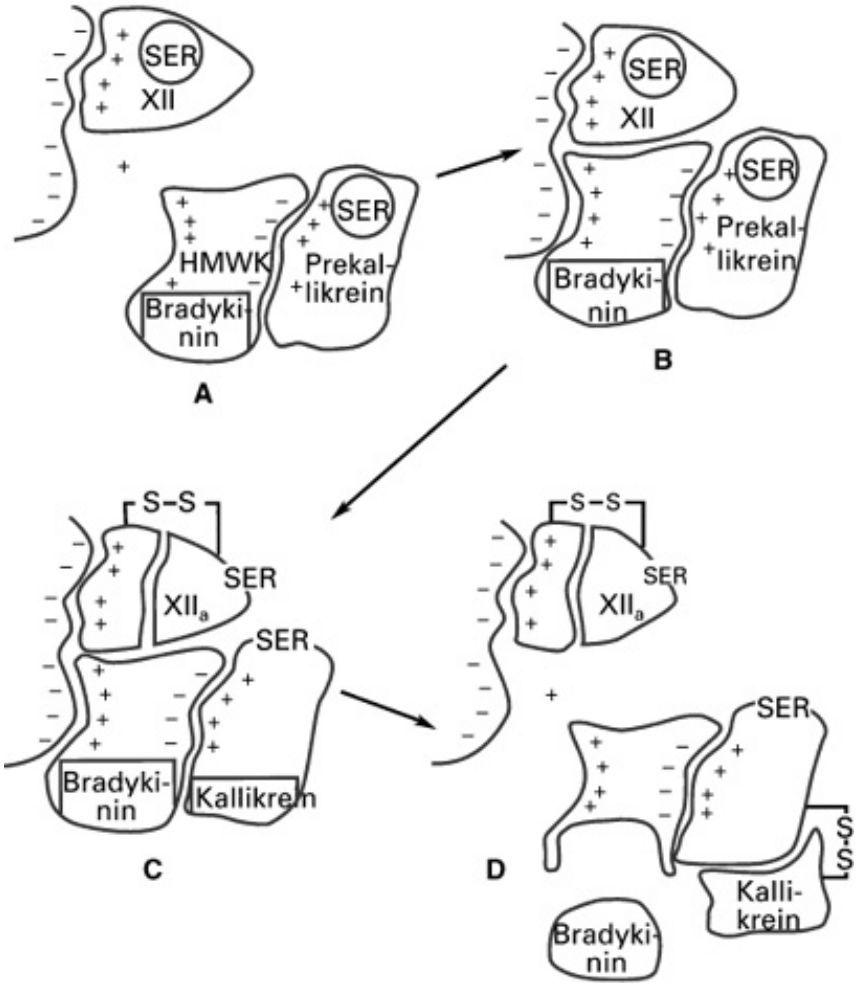

Figure 44-6: In the intrinsic pathway of coagulation, *contact activation* refers to a series of reactions following adsorption of factors XII and XI as well as prekallikrein and high molecular weight kininogen to highly negatively charged surfaces. The contact activation does not require calcium and results in surface-induced conformational changes of the molecules. *A-D*. Sequence of events. SER = serine protease.

Factor XIIa converts in vitro the next factor of the coagulation cascade, factor XI, from its zymogen form to its enzymatic constellation. Factor XI also circulates in plasma complexed with HMW kininogen; the latter protein thus serves as helper protein carrying factors XII and XI in the blood (Fig. 44-7). The in vivo activation of factor XI is less clear. It is possible that factor XII-independent activation of factor XI is mediated by thrombin. Both factor XIIa and thrombin cleave the same internal peptide bond (Arg369-Ile) in each of the two chains of the factor XI molecule, leading to the formation of two heavy and two light chains.

Factor XIa bound to the surfaces by HMW kininogen interacts upon activation with factor IX in a calcium-dependent two-step reaction. Each light chain of factor XIa contains a catalytic site, while its heavy chain has the binding site for factor IX and HMW kininogen. Binding of calcium ions to factor IX (a vitamin K-dependent protein) induces a conformational change in the molecule, which facilitates its binding to the heavy chain of factor XIa, which is essential for the optimal rate of factor IX activation. Platelets can also be reckoned to be important in the intrinsic system as they contain HMW kininogen, which can be expressed when the platelets are activated, as they indeed are on fissured and sclerotic plaques and foreign surfaces.

Activated factor IX, thrombin-modified factor VIII, negatively charged phospholipid (e.g., activated platelets), and calcium ions form a multimolecular complex coined *tenase* because it activates directly factor X; the glutamic acid (Gla) residues of factors IXa and Xa mediate their binding to phospholipid (Fig. 44-7).

Congenital deficiency of the three contact factors (factor XII, prekallikrein, and HMW kininogen) is not associated with bleeding, and only half of factor XI-deficient patients have bleeding problems with an intensity not related to the factor XI level. The significance of the contact phase is, therefore, speculative; however, it may become relevant in particular therapeutic settings. Indeed, extracorporeal circuits may be regarded as a giant test-tube condition, and the contact activation becomes important under these circumstances. Beyond the contact phase, the intrinsic activation system is important, already in physiologic conditions, as individuals with a severe deficiency of factor VIII or IX (two forms of hemophilia) have a serious bleeding condition.

The Extrinsic (Tissue Factor) Pathway of the Coagulation System: Activation of Factors VII and X

In the extrinsic system, membrane-bound tissue factor starts off the chain of events by forming a complex with factor VII in the presence of calcium ions (Fig. 44-7). Tissue factor is as a dimer composed of two identical subunits with interacting enzyme-binding sites.[128,129] It is present on nonvascular cell surfaces and on microvesicles shed from cell surfaces. It was hypothesized that the normal distribution of tissue factor represents a hemostatic envelope ready to activate coagulation when vascular integrity is disrupted. Vascular endothelial cells and monocytes also can produce and express tissue factor activity upon stimulation with interleukin 1 or endotoxin, which suggests that cytokines may modulate tissue factor expression and fibrin deposition at the site of inflammation. Tissue factor is an integral membrane protein composed of protein and phospholipid components, both of which are required for its procoagulant activity. Factor VII is a single-chain protein that, in this form, already has some enzymatic activity and can complex with tissue factor. By cleavage of an Arg-Ile bond, however, the molecule of factor VII splits in a light chain and a heavy chain (containing the active site) linked by two disulfide bonds. This activation increases the coagulant activity of factor VII about 100-fold. However, the activation of factor VII occurs only after it has bound to tissue factor. The tissue factor-factor VIIa complex then combines with the substrate (factor X), producing a further conformational change in factor VIIa, so that it binds still more tightly to tissue factor, precluding dissociation of factor VIIa from tissue factor. The tissue factor-factor VIIa complex activates primarily factor X but also factors IX and XI, which interconnect the intrinsic and extrinsic activation pathways and play a prima ballerina role in the activation of coagulation.[13] Tissue factor accelerates these reactions as a cofactor, apparently by inducing a conformational change in factor VIIa.

It should be noted that phospholipids of the platelet membrane, in conjunction with factor Xa, can also activate factor VII-another bridge between the intrinsic and extrinsic pathways. Thus, the earlier concepts of a clearly separate intrinsic and extrinsic activation system are becoming obsolete. That factor VII is essential to ensure normal hemostasis is underlined by the bleeding condition of patients with severe congenital factor VII deficiency.

The Pathway in Common: The Formation of Prothrombinase, the Enzyme Converting Prothrombin to Thrombin

Factor X stands at the crossroad of the extrinsic and intrinsic activation pathways.[130] This means that factor X can be activated either by the tenase complex (IXa, phospholipid, VIIIa, and Ca ions) or by the tissue factor-factor VIIa complex (Fig. 44-7). In both instances, activation of factor X results from the cleavage of a single peptide bond between Arg and Ile, releasing an activation peptide and unmasking an active site on the heavy chain.[131] This is brought about by the enzymatic activity residing in factor IXa, which is part of the tenase complex. The presence of proteolytically modified factor VIII-whether by thrombin, factor Xa, or factor IXa-by separation of factor VIII from von Willebrand factor enhances 10,000-fold the rate of activation of factor X by factor IXa. Factor VIIIa has no enzymatic activity and is thus a helper protein (a cofactor) which, to exert its function, binds to phospholipid vesicles, provided phosphatidylserine is available on the platelet membrane.[16,132] In fact, specific binding sites are available on activated platelets for factor VIII that are distinct from the binding sites for factor V expressed during stimulation of platelets. As shown below, activated protein C degrades factor VIIIa. Thus, factor VIII must be activated for hemostasis and inactivated for the maintenance of the fluidity of blood.

To be fully active, factor Xa has to form a stoichiometric 1:1 complex with factor Va; the latter molecule enhances the activation of prothrombin by factor Xa 300,000-fold. Normal plasma contains factor V in trace amounts (25 n*M*, while factor X is about 200 n*M*) and in an inactive state; its activation requires three specific enzymatic cleavages, which can be brought about by thrombin or less efficiently by factor Xa. The association of factor Va with factor Xa on an anionic phospholipid is termed *prothrombinase*. Factor Va increases the turnover (k_{cat}) 1000-fold, which means that the number of thrombin molecules generated by the enzyme upon saturation by the substrate is multiplied by a factor of approximately 1000. In contrast to the vitamin K-dependent procoagulation factors (prothrombin and factors VII, IX, and X), which bind to phospholipids via calcium bridges with their Gla domain, factor Va does not bind to phospholipids via calcium bridges but penetrates into the lipid bilayer.

The Action of Prothrombinase on Prothrombin

The multimolecular complex prothrombinase initially cleaves one Arg-Ile bond in the prothrombin molecule, producing meizo-thrombin. This intermediate molecule remains membrane bound through the retained Gla domain linkage and activates the inhibitor protein C but lacks procoagulant properties either on platelets or on fibrinogen. To obtain the latter property, another arginine bond (Arg-Thr) has to be cleaved, yielding alpha-thrombin, which, lacking a Gla-containing region, is released from the cell surface.

For the different reactions pertaining to the coagulation cascade system, it is being assumed that all coagulation factors immobilize on phospholipids (stimulated platelets or perturbed endothelial or white cells) and that reaction products are shuttled between assembled complexes. An alternative but less efficient possibility is that reaction products dissociate from the phospholipid membranes to become free in solution. Single-membrane channeling protects critical enzymes from inactivation by plasma inhibitors (e.g., antithrombin III) as well as from dilution by blood flow.

The Pivotal Role of Thrombin

Thrombin represents the culmination of the coagulation cascade; its action on fibrinogen is most dramatic, because thrombus formation is a visible process. Thrombin itself is responsible for its own nonlinear generation caused by positive feedback activation, whereby thrombin enhances

neoformation of thrombin (Fig. 44-8). In addition, thrombin is a pivotal molecule for numerous other functions. The action of thrombin on platelets results in the release of platelet factor V exteriorization and in the transbilayer movement of its inner membrane surface (flip-flop reaction). Thrombin activates three of the four cofactor or helper proteins (factors V and VIII and thrombomodulin but not tissue factor). Thrombin furthermore activates factor XIII, which increases the strength and renders the fibrin more resistant to thrombolysis. Thrombin can increase the production and release of prostacyclin, NO, ADP, and PAI-1 from the normal endothelium, protecting the microcirculation against thrombosis. Thrombin inhibits its own production by a negative feedback mechanism via the thrombomodulin-protein C and S system. Thrombin is also involved in other biological effects, such as chemotaxis and mitogenesis. It also elicits a potent mitogenic response in fibroblasts and macrophages, thereby modulating inflammatory reactions at the site of vascular injury.

The Conversion of Fibrinogen to Fibrin

Fibrinogen is a large paired molecule held together by disulfide bridges. Each symmetric half-molecule consists of one set of three different polypeptide chains termed Aα, Bβ, and γ. The two half-molecules are joined in the central amino-terminal domain in an antiparallel manner by three interchain disulfide bridges, two of which are between γ chains and the other between α chains.

Thrombin splits an arginine-glycine bond, first at the amino end of the two Aα chains and later at the amino end of each of the two Bβ chains so that each molecule releases in sequence two small aminopeptides A (FPA) and two small fibrinopeptides B (FPB) from fibrinogen and thus converts this molecule to fibrin monomers that are still soluble (Fig. 44-9). The FPA release exposes a polymerization site in the central region of the fibrinogen molecule (E domain) that subsequently aligns with a complementary site in the outer region (D domain) of another fibrin monomer to form staggered overlapping two-stranded fibrils. The slower FPB release exposes an independent site for noncovalent intermolecular interaction, resulting in complementary alignment of fibrin monomers. Subsequently, lateral association of fibrin monomers occurs, and the network becomes thicker and branched, still through a nonenzymatic process. These coupled monomers of fibrin, called *polymers*, are still soluble unless they become too large and precipitate; the resulting gel of fibrin forms the skeleton of a thrombus and traps red and white cells.

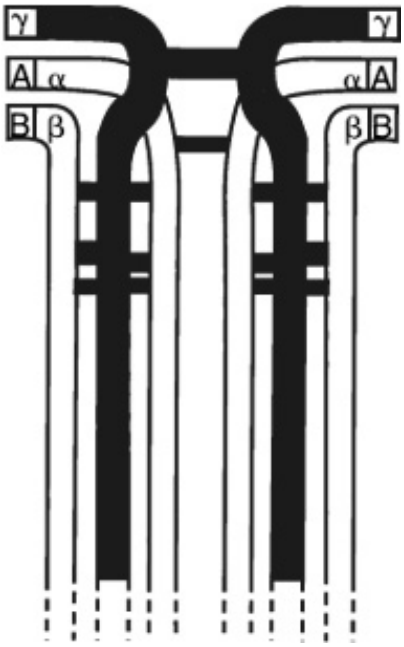

Figure 44-9: Structure of fibrinogen. This glycoprotein is a paired molecule, each half consisting of three homologous chains; Aα, Bβ, and γ. The horizontal connecting lines are disulfide bonds. Thrombin cleaves first the A peptide and then the B peptide. The disulfide knot of the dimer fibrinogen is clearly depicted. The entire sequence of 2946 amino acids has been elucidated.

The structural stability of the fibrin network is achieved through covalent cross-linking.[133] Thrombin activates factor XIII (*fibrin-stabilizing factor*), a transglutaminase that, in the presence of calcium, forms peptide bonds between side chains of suitable lysine (donor) and Gla (acceptor) residues. The result of such a lysine cross-link is that the thrombus becomes firmer and more resistant to thrombolysis. It should be noted that fibrin-bound thrombin (approximately 40 percent of the thrombin generated) retains its coagulant and platelet-activating properties and is protected from inactivation by circulating heparin-antithrombin III.[134] During thrombolysis, fibrin-bound thrombin is released and can cause rethrombosis. Hirudin, hirulog, and similar antithrombin III-independent synthetic thrombin inhibitors, which are smaller than heparin, can inhibit fibrin-bound thrombin. Of note, two other plasma proteins (fibronectin and α2-plasmin inhibitor) are also covalently cross-linked to fibrin by factor XIIIa and are incorporated in the fibrin mesh.

Connections Between the Intrinsic and Extrinsic Pathways of Coagulation

The concept of separating the two pathways of the coagulation system that merge in a common pathway from the activation of factor X on is a didactic schematization that is increasingly blurred as feedback mechanisms and interactions between the two pathways are found.[129] For example, the factor VIIa-tissue factor complex can activate factors IX and XI directly; factors IXa and Xa can activate factor VII. The extrinsic pathway seems to play a major role in the initiation of in vivo coagulation, while the intrinsic pathway is now thought to be required for continuous growth and maintenance of fibrin formation.

Activation of coagulation factors in successive stages is based on the classical cascade. It will be appreciated that the speed with which these reactions develop increases gradually, as in a system of electronic amplification. Also, here one should realize that nature acts in concert rather than in a sequence of solitary actions. Of course, this is a common feature in biological systems. In the case of the coagulation system, it is the more remarkable because it operates largely outside the cell without the controls imposed by intracellular compartmentation.

Coagulation: A Series of Surface-Catalyzed Events

With the exception of fibrinogen, prothrombin, and plasminogen, the coagulation factors are present in the fluid phase of blood at very low concentrations. Their encounter in solution is possible and their interaction slow, though this can be remarkably accelerated, up to 100,000-fold, after adsorption and concentration on surfaces. Modified endothelium, stimulated platelets, denuded subendothelial structures (e.g., collagen), fissured atherosclerotic plaques, and foreign surfaces (extracorporeal circulation conduits) allow the attachment of passing platelets (adhesion) and the absorption of coagulation proteins. One way for this to occur is by binding mediated through calcium bridges between negatively charged phospholipids (tissue factor, activated platelets, and microvesicles) and the γ-carboxyglutamic acid (Gla) residues of the four vitamin K-dependent procoagulants (prothrombin and factors VII, IX, and X), and two endogenous anticoagulants (proteins C and S). Coumarin drugs interfere in the vitamin K cycle, so that less glutamic acid is formed and binding of these proteins to phospholipids is impeded. Assembly on surfaces increases the local concentration of clotting factors considerably and creates an optimal steric relationship (better alignment) for their interaction. This means that a lipid-bound enzyme has a greater affinity for the substrate than the free circulating enzyme. Inhibitors of activated coagulation factors are much less effective in binding to phospholipid surfaces; thus binding of activated coagulation factors to such a surface protects them against endogenous inhibitors.[135] Interaction between coagulation factors is accelerated by the presence of a phospholipid

interphase (decrease of K_m value) and the efficiency is also improved by the presence of the helper protein factors V and VIII (increase of K_{cat}).

NATURAL INHIBITORS OF THE COAGULATION SYSTEM

Several mechanisms help to prevent uncontrolled formation of fibrin in the circulation. First, coagulation remains a strictly localized process because it requires negatively charged surfaces, which are in the first place provided by activated platelets. Platelet activation, in turn, is limited to sites of vessel injury and fissured atherosclerotic plaques. In addition, the flowing blood will rapidly dilute any inadvertently activated clotting factor before it perpetuates the reaction sequence to form fibrin. Finally, a number of proteins circulate in the blood to inhibit the coagulation process at various stages of the cascade. Four of them appear particularly important in preventing thrombosis: antithrombin III, protein C, tissue factor pathway inhibitor, and thrombomodulin.

Antithrombin III inhibits thrombin and the activated forms of several coagulation factors, but inhibition of thrombin and of factor Xa is particularly important and clinically relevant.[136] Thrombin forms a tightly bound, stable complex with antithrombin III; this occurs at a relatively slow rate that is enormously enhanced by heparin (see below) and also appreciably by heparan sulfate, a substance very similar to heparin, which is found on the intraluminal surface of vascular endothelial cells. The inhibition of thrombin is due to ternary complex formation between thrombin, antithrombin III, and heparin. The inhibition of factor Xa is the result of the formation of a binary complex between antithrombin III and factor Xa.

The protein C-thrombomodulin pathway of thrombin inhibition represents the major natural anticoagulant system (Fig. 44-10). Protein C is a proenzyme formed in the liver; vitamin K is required in its synthesis. On the surface of either platelets or endothelium, protein C is activated by thrombin to become a circulating serine protease that inhibits factors Va and VIIIa. Complex formation between thrombin and thrombomodulin, a potent cofactor present on the endothelial surface, catalyzes the activation of protein C. Protein S is another vitamin K-dependent protein that does not possess serine protease properties but appears to function as a cofactor for activated protein C by facilitating its binding to membrane phospholipids.[137] In plasma, protein S circulates free or bound to C4b-binding protein, a component of the complement system. Only free protein S serves as a cofactor of activated protein C. In addition to being a powerful anticoagulant, activated protein C initiates fibrinolysis by releasing t-PA from the endothelium and neutralizing PAI.

Tissue factor-factor VIIa complex is inactivated by the tissue factor pathway inhibitor (TFPI), previously called lipid protein-associated coagulation inhibitor.[129,130,135] TFPI appears to be the only plasma component inhibiting the catalytic activity of factor VIIa-tissue factor complex. Factor VIIa cannot be neutralized effectively unless it is bound to tissue factor.[129] This is in contrast to other coagulation components, which are neutralized more effectively as free reactants than after they interact in complexes.[138] TFPI first interacts with factor Xa to form Xa-TFPI complexes, which then form a quarternary Xa-TFPI-VIIa-tissue factor complex with resulting loss of the activity of VIIa-tissue factor complex. The plasma concentration of TFPI is low, but a larger pool of TFPI bound to vascular endothelium is present from which TFPI can be released into the blood by heparin.

Thrombomodulin is located on the surface of all endothelial cells except those in the microcirculation of the human brain. When thrombin is generated within a vascular space, excess thrombin is bound to thrombomodulin. Thrombomodulin exerts three types of activities: (1) it inhibits thrombin-induced activation of platelets, factor V, and fibrinogen; (2) it promotes the activation of protein C after formation of the thrombomodulin-thrombin complex; and (3) it enhances the inhibition of thrombin by antithrombin III. Thus, thrombomodulin modifies the

substrate specificity of thrombin; the procoagulant activity is switched off, and at the same time its anticoagulant activity is tremendously increased.

The Fibrinolytic System

This system is essential for removing excess fibrin deposits to preserve vascular patency. The role of fibrinolysis in the maintenance of blood fluidity is well illustrated by an increased incidence of venous thromboembolism in patients with abnormal, nonfunctional plasminogen. Similarly, the overproduction of PAI-1 in transgenic mice leads to an increased risk of venous embolism.

COMPONENTS OF THE FIBRINOLYTIC SYSTEM

Plasminogen

This is present in human plasma at a concentration of about 2 μM, which is about twice the concentration of α_2-antiplasmin. The native molecule, denoted Glu-plasminogen, after its NH_2-terminal glutamic acid, is a single-chain glycoprotein, consisting of 791 amino acids.[23] Plasminogen is organized in seven structural domains (Fig. 44-11). From the NH2-terminal end, there is a *preactivation peptide*, five sequential, homologous, looped kringle structures, and the T-proteinase domain with the catalytic site composed of His^{603}, Asp^{646}, and Ser^{741}. The kringle domains contain lysine-binding sites that play a crucial role in the specific recognition of fibrin, cell surfaces, and α_2-antiplasmin.[139-141]

Plasminogen is converted to a two-chain serine protease called *plasmin* by cleavage of a single Arg^{561}-Val^{562} peptide bond between kringle 5 and the proteinase domain. The serine-containing active site is situated in the B or light chain. Plasmin may catalyze the release of the preactivation peptide from Glu-plasminogen, forming degraded plasminogen with amino-terminal lysine, valine, or methionine commonly called *Lys-plasminogen*. Lys-plasminogen is more easily activated to plasmin than Glu-plasminogen.[141] Plasmin digests a number of proteins, including fibrin, fibrinogen, and factors V and VIII, as well as a number of esters and amides.

Natural Plasminogen Activators

Plasminogen may be converted to plasmin by a number of agents called *plasminogen activators*. The principal circulating plasminogen activator in humans is *tissue-type plasminogen activator* (t-PA). This a 70-kDa serine proteinase, which in its native form consists of a single polypeptide chain. t-PA is converted by plasmin to a two-chain form by hydrolysis of the Arg^{275}-Ile^{276} peptide bond. In contrast to most single-chain forms of serine proteinases, single-chain t-PA possesses significant catalytic activity. The amino-terminal region is composed of several domains with homologies to other proteins: a finger domain, a growth factor domain, and two looped kringle structures (Fig. 44-12). The region constituted by residues 276 to 527 represents the serine proteinase part with the catalytic site, composed of His^{322}, Asp^{371}, and Ser^{478}.[142] These distinct domains in t-PA are involved in several functions of the enzyme, including its binding to fibrin, fibrin-specific plasminogen activation, rapid clearance in vivo, and binding to endothelial cell receptors. Binding of t-PA to fibrin is mediated via the finger and the second kringle domains. The presence of fibrin markedly enhances the plasminogen-activating property of t-PA, as it not only binds t-PA and plasminogen but also greatly increases the affinity of t-PA for plasminogen. Thus, fibrin appears to concentrate both t-PA and plasminogen on its surface and to enhance their interaction (see Ambrose et al.[26] and Fuster et al.[28]). Plasmin so formed on fibrin surfaces has its lysine-binding and active sites occupied and is relatively protected from the inhibitory action of α_2-antiplasmin.

Single-chain urokinase-type plasminogen activator (scu-PA) is a 54-kDa glycoprotein containing 411 amino acids (Fig. 44-12). The plasma concentration of scu-PA is about 2 ng/mL. Upon proteolytic cleavage of the Lys^{158}-Ile^{159} peptide bond, the molecule is converted to a two-chain derivative (tcu-PA, urokinase). The catalytic triad is located in the carboxy-terminal polypeptide chain and is composed of Asp^{255}, His^{204}, and Ser^{356}. The amino-terminal chain contains an epidermal growth factor domain and one kringle domain. The epidermal growth factor domain is responsible for the binding of single-chain u-PA to its receptor, which is present on the surface of a variety of cells. The u-PA receptor is essential for localization of u-PA-mediated plasmin formation to the pericellular environment.[143,144] A LMW tcu-PA (33 kDa) can be generated from tcu-PA by hydrolysis of the Lys^{135}-Lys^{136} peptide with plasmin. A LMW scu-PA (32 kDa) can be generated by proteolytic cleavage of the Glu^{143}-Leu^{144} peptide bond.[145]

ENDOGENOUS INHIBITORS OF THE FIBRINOLYTIC SYSTEM

α_2-Antiplasmin (α_2-plasmin inhibitor) belongs to the serine proteinase inhibitor superfamily (serpins). Like other inhibitors of this class, serpins react with their target proteinases by formation of a 1:1 molar reversible complex, followed by covalent binding between the hydroxyl group of the active-site serine residue of the proteinase and the carboxyl group of the P1 residue at the reactive site ("bait region") of the serpin (Fig. 44-11).

α_2-Antiplasmin is present in plasma at a concentration of about 1 μM. It is a 67-kDa glycoprotein containing 464 amino acids and about 13 percent carbohydrate.[146] The reactive site of the inhibitor is the Arg^{364}-Met^{365} peptide bond. α_2-Antiplasmin is unique among serpins by having a carboxy-terminal extension of 51 amino acid residues; this contains a secondary binding site that reacts with the lysine-binding sites of the kringles 1 to 3 of both plasminogen and plasmin. α_2-Antiplasmin (plasminogen-binding form) becomes partly converted in the circulating blood to a non-plasminogen-binding, less reactive form (about 30 percent of the total) that lacks the 26 carboxy-terminal residues. Two forms of α_2-antiplasmin are present in about equal amounts in purified preparations of the inhibitor. The amino-terminal Gln^{14} residue of α_2-antiplasmin can cross-link to Aa chains of fibrin, in a process that requires Ca^{2+} and is catalyzed by activated coagulation factor XIII. This renders the thrombus less sensitive to thrombolysis. Other serpins are α_2-macroglobulin and α_1-antitrypsin.

Two principal inhibitors specific for plasminogen activators have been identified in humans, and a number of additional subsidiary inhibitors of this type have been described. They are also members of the serine protease inhibitors (serpin) family.

PAI-1 is a 52-kDa single-chain glycoprotein consisting of 379 amino acids.[147,148] The reactive site of the inhibitor is the Arg^{346}-Met^{347} peptide bond. PAI-1 is stabilized by a tight binding to the cell-adhesive protein vitronectin. PAI-2 exists in two different forms with comparable kinetic properties and is detected only in pregnant women.[149]

REGULATION OF THE FIBRINOLYTIC SYSTEM

Formed fibrin, whether in normal wound seals or in tissue damaged by any stimulus, is lysed in the body as a result of its unique property of adsorbing small quantities of plasminogen and t-PA and local generation of plasmin, which is protected from inactivation by inhibitors.

Activation of plasminogen by t-PA is enhanced in the presence of fibrin or at the endothelial cell surface. Fibrinolysis may be inhibited at the level of plasminogen activation or at the level of plasmin. Fibrinolysis is also regulated as a result of increased or decreased synthesis and/or

secretion of t-PA and of PAI-1 from the vessel wall[150] or by changes in their rates of elimination by the liver.[151]

Synthesis and Secretion of Tissue-Type Plasminogen Activator

Vascular endothelial cells synthesize and secrete t-PA to the circulating blood.[150] The plasma concentration of free t-PA is less than 1 ng/mL. The half-life of t-PA in the circulation is only about 5 min because of rapid hepatic clearance; some t-PA is inactivated by PAI-1. Various stimuli-such as venous occlusion, physical exercise, catecholamines, bradykinin, or desmopressin-produce a rapid increase (within minutes) in the level of t-PA in the blood. This response is too rapid to represent increased synthesis but may reflect release of t-PA from cellular storage pools, as well as decrease in hepatic clearance due to a reduced hepatic blood flow.[152] A storage pool of t-PA in endothelial cells has not been conclusively identified.[153]

A variety of agents have been shown to increase the synthesis of t-PA by cultured endothelial cells, including thrombin, histamine, butyrate, phorbol myristate acetate, basic fibroblast growth factor, activated protein C, butanol and alcohol derivatives, and retinoids. The increase of t-PA induced by histamine, thrombin, and phorbol myristate acetate in endothelial cells is paralleled by increased levels of t-PA mRNA as a result of enhanced transcription of the t-PA gene.[153] Overexpression of t-PA in endothelial cells using a retroviral expression vector did not alter the morphology, attachment, proliferation, migration, or invasion in the in vitro systems. Potentially such t-PA-transduced cells could increase local fibrinolysis and may thus be useful for in vivo therapeutic interventions.[154]

Synthesis and Secretion of Plasminogen Activator Inhibitor 1

PAI-1 mRNA has been demonstrated in a large variety of tissues, suggesting that common cells in these tissues, such as endothelial or smooth muscle cells, may be the site of production.[155] PAI-1 is found in plasma, platelets, placenta, and extracellular matrix. The concentration in plasma is in the picomolar range but may increase to about 2 n*M* during pregnancy, most likely as a result of release of the inhibitor from placenta. Both active and latent PAI-1 are cleared rapidly, with half-lives in rabbits of approximately 15 and 5 min.[156,157] For unknown reasons, PAI-1 exhibits a circadian variation; the plasma concentration peaks in the morning and reaches a trough in the late afternoon and evening;[158] t-PA exhibits a diurnal variation, which is opposite to that observed for PAI-1.

PAI-1 mRNA is increased and PAI-1 protein detected in endothelial cells juxtaposed to thrombi, in smooth muscle cells adjacent to the neointima, and in macrophages. The augmented arterial wall expression of PAI-1 induced by thrombosis may shift the local balance between fibrinolysis and thrombosis toward the latter.[159]

Only a few studies have reported a downregulation of PAI-1 synthesis in endothelial cells, either by forskolin or by endothelial cell growth factor combined with heparin.[160] PAI-1 is not stored within cells but is rapidly and constitutively secreted after synthesis. An exception is formed by platelets that store PAI-1 in their alpha granules; activation of platelets thus results in release of PAI-1.

α2-Antiplasmin

This forms an inactive 1:1 stoichiometric complex with plasmin. The half-life of plasmin

molecules on the fibrin surface, which have both their lysine-binding sites and active site occupied, is estimated to be 2 to 3 orders of magnitude longer than that of free plasmin (Fig. 44-11).

Plasminogen Activator Inhibitors

PAI-1 reacts very rapidly with single-chain and two-chain t-PA and with two-chain u-PA (tcu-PA).[161,162] PAI-2 primarily inhibits tcu-PA. The inhibition rate of scu-PA, single-chain t-PA, and two-chain t-PA by PAI-2 is about 10, 1200, and 150 times slower, respectively, than that by PAI-1. PAI-1 and PAI-2 do not react with scu-PA.[161]

Like other serpins, PAI-1 inhibits its target proteinases by formation of a 1:1 stoichiometric reversible complex, followed by covalent binding between the hydroxyl group of the active-site serine residue of the proteinase and the carboxyl group of the PI residue at the reactive center ("bait region") of the serpin. The rapid inhibition of both t-PA and u-PA by PAI-1 involves a reversible high-affinity second-site interaction that does not depend on a functional active site. In the presence of fibrin, single-chain t-PA is protected from rapid inhibition by PAI-1. It has, however, also been reported that PAI-1 binds to fibrin and that fibrin-bound PAI-1 may inhibit t-PA-mediated fibrin clot lysis.[163]

The active form of PAI-1 converts to a latent form that can be partially reactivated by denaturing agents. In addition, inhibitory PAI-1 may convert not only to latent PAI-1, which can be reactivated, but also to substrate PAI-1, which may be irreversibly degraded by target proteinases, including t-PA, u-PA, and thrombin.[164]

Plasminogen Activation by Tissue-Type Plasminogen Activator at the Fibrin Surface

The main role of t-PA most likely is in the dissolution of fibrin.[139,165] t-PA is a poor enzyme in the absence of fibrin, but the presence of fibrin strikingly enhances the activation rate of plasminogen.[166] Plasmin formed on the fibrin surface has both its lysine-binding sites and active site occupied and is thus only slowly inactivated by α_2-antiplasmin (half-life of about 10 to 100 s); in contrast, free plasmin, when formed, is rapidly inhibited by α_2-antiplasmin (half-life of about 0.1 s).

During fibrin clot lysis, single-chain t-PA is converted to two-chain t-PA at the fibrin surface. This conversion is probably of little physiologic relevance, since the activity of single-chain t-PA and two-chain t-PA is enhanced to the same extent in the presence of fibrin or fragment-X polymer.[167] Fibrin-bound single-chain t-PA may adopt a conformation similar to that of two-chain t-PA. Whether conversion of Glu-plasminogen to the more easily activatable Lys-plasminogen contributes significantly to the increased plasminogen activation rate during fibrinolysis is still somewhat controversial.

Binding studies[168,169] as well as kinetic studies have revealed that lipoprotein-a- (Lp-a-) competes with plasminogen for binding to fibrin as a result of binding of Lp(a) to fibrin via its lysine-binding domains. As for plasminogen, binding of Lp(a) to fibrin is enhanced by partial proteolytic degradation of the fibrin surface.[168] As a functional consequence of the competition between Lp(a) and plasminogen for binding to fibrin, the fibrin-dependent enhancement of plasminogen activation by t-PA is inhibited.[169,170]

PATHOPHYSIOLOGY OF FIBRINOLYSIS

Increased levels of PAI-1 activity resulting in a decreased fibrinolytic capacity have been reported in several thrombotic disease states, including venous thromboembolism, obesity, sepsis, coronary artery disease, and acute MI.[158,171] Increased levels of PAI-1 have also been found in association with the insulin resistance syndrome in which a significant correlation was found between plasma PAI-1 levels and body mass index, triglyceride levels, insulin levels, and systolic blood pressure. Obese people-particularly those with android obesity-also have high PAI-1 levels.

Increased plasma levels of PAI-1 are one of the major disturbances of the hemostatic system in patients with coronary heart disease, and multiple interrelations with established metabolic risk factors have been observed. Increased PAI-1 levels have also been demonstrated in atherosclerotic lesions within the vessel wall. Therefore, both systemically and locally increased PAI-1 concentrations could have a pathogenic role in the development of atherosclerotic disease.

Many case-control or cross-sectional studies have demonstrated high plasma PAI-1 levels in patients who have had a MI or unstable angina. A relationship between deficient fibrinolysis due to high PAI activity levels and recurrent MI (within 3 years) was demonstrated in young men who had survived their first MI. On the other hand, PAI-1 activity was not predictive for recurrent infarction (nor was t-PA antigen) in a group of older patients followed over 5 years. In a cohort of patients with angina pectoris, high basal t-PA antigen levels were found to be associated with an increased risk of MI, while no correlation was observed with PAI activity.[172,173]

Attempts to demonstrate a relationship between plasma PAI-1 levels and the severity of vessel wall damage have led to conflicting results in cross-sectional studies. Analysis of the data of the European Concerted Action on Thrombosis (ECAT) angina pectoris study demonstrated that there was a weak distinction between patients with and patients without significant coronary stenosis; the former had significantly higher plasma levels of PAI-1. NO association could be observed with the extent of coronary atherosclerosis. There are multiple interrelations between plasma PAI-1 levels and other risk factors of atherothrombosis, such as those involved in the metabolic syndrome of insulin resistance. In the ECAT angina pectoris study, in which insulin determination was available for almost 1500 patients, two- to threefold differences in PAI-1 levels were observed in comparing the lowest and the highest quintile of insulin, body mass index, or triglyceride.[174]

NEXT

Chapter 44: THROMBOGENESIS, ANTITHROMBOTIC, AND THROMBOLYTIC THERAPY

ANTITHROMBOTIC DRUGS

Given the importance of thrombosis in acute coronary syndromes, thrombolytic and antithrombotic therapy has become the primary therapy for most conditions. This chapter reviews the numerous agents in clinical use or expected for clinical use in the coming years. The mechanism of action of the agent and the major evidence supporting its use in clinical medicine are reviewed; readers will also be referred to the specific chapter of that clinical syndrome for additional perspective on its use in context with the full treatment strategies.

Platelet Inhibitors

Platelet inhibition can be achieved in numerous ways (Fig. 44-12). These include inhibition of platelet cyclooxygenase (aspirin or sulfinpyrazone), inhibition of ADP receptors (ticlopidine or clopidogrel), or inhibition of the platelet GP IIb/IIIa receptor. Platelet inhibition can also be achieved by inhibition of thromboxane synthase with or without blockade of endoperoxide-thromboxane receptors, modulation of platelet adenylate or guanylate cyclase (prostacyclin analogs), interference with the function of the platelet GP Ib-IX receptor (monoclonal antibodies to GP 1b-IX), synthetic peptides to the A1 von Willebrand factor domain, recombinant von Willebrand fragments covering the A1 domain, and peptides that bind to but do not activate the platelet-receptor domain that interacts with thrombin. In this chapter, only platelet inhibitors that have been investigated in clinical trials are reviewed.

Aspirin

This permanently acetylates cyclooxygenase, thereby blocking the synthesis of TXA_2 by the platelet (Fig. 44-5). By decreasing the amount of TXA_2 released, which would act to stimulate other platelets, this decreases overall platelet aggregation at the site of the thrombus. This inhibition of cyclooxygenase is permanent-and thus the antiplatelet effects last for the lifetime of the platelets-on order of 7 to 10 days. Aspirin selectively inhibits TXA_2 formation (Fig. 44-5) but only partially impedes platelet aggregation induced by ADP, collagen, and low concentrations of thrombin.[175]

Aspirin does not inhibit adherence of the initial layer of platelets to the subendothelium or atherosclerotic plaques, and the release of granule contents is not opposed. Thus, the effects of platelet-derived growth factors and other mitogens on smooth muscle cells are not inhibited.[176] Aspirin also impairs thrombosis by a mechanism that seems to be unrelated to platelet cyclooxygenase, as, for instance, the acetylation of guanosine triphosphate-binding proteins, thrombin receptors, and prothrombin.[177] The salicylate moiety of aspirin also antagonizes the lipoxygenase pathway of arachidonate metabolism in platelets, and the demonstration of two cyclooxygenase enzymes (COX-1 and COX-2)[178] may further elucidate the antithrombotic mechanism of aspirin.[179] Aspirin is known to have an anti-inflammatory effect at high doses, but whether an anti-inflammatory effect is present at doses used in acute coronary syndromes is not clear.

DOSE

The ideal dose of aspirin for the primary or secondary prevention of cardiovascular disease is not determined. A dose of 40 mg was found to achieve maximal inhibition of TXA_2. Doses between 75 and 1300 mg/day have produced similar reductions in cardiovascular event.[65-68] Thus, there does not appear to be a dose response in efficacy of aspirin. In the Second International Study of Infarct Survival (ISIS-2), a dose of 160 mg/day was shown to have a mortality benefit, so this dose is the minimum initial dose recommended for acute therapy.[180] For safety (e.g., gastrointestinal bleeding), the rate of bleeding appears

to be slightly higher with higher doses, and thus a dose of 75 to 81 mg daily could be an appropriate dose for long-term therapy, although major bleeding is relatively rare (<1 percent) even at a dose of 325 mg daily.[181]

ADVERSE EFFECTS

Absolute contraindications for aspirin therapy are few but include documented aspirin allergy (e.g., asthma), active bleeding, severe thrombocytopenia (<20,000 cells/mL), or a known platelet disorder. In patients with gastrointestinal complaints (e.g., dyspepsia) with long-term aspirin therapy (i.e., aspirin intolerance), this would not be expected to be an acute problem of in-hospital treatment, and aspirin therapy is recommended for acute therapy, with evaluation of the cause of the disorder or consideration of alternate antithrombotic therapy in the subacute phase of the patient's acute coronary syndrome.

CLINICAL USE

Aspirin is a critical antithrombotic agent in coronary artery disease. In the setting of acute ST-elevation MI, aspirin decreased reocclusion by over 50 percent in a meta-analysis of 32 angiographic trials[182] (Fig. 44-13). Aspirin also was found to decrease reinfarction significantly in the large ISIS-2 trial and most importantly reduced mortality by 23 percent.[180]

Several major studies have demonstrated clear beneficial effects of aspirin in patients with unstable angina and non-ST-elevation MI, with an approximately 50 percent reduction in the risk of death or MI in patients presenting with unstable angina or non-Q-wave MI (Fig. 44-13).[65-68] The first study from the Veterans Administration (VA) Cooperative Study Group documented a 51 percent reduction in the risk of death or MI in patients presenting with unstable angina, and the overall benefits of aspirin were maintained during the 1-year follow-up period.[65] The Canadian multicenter trial confirmed the large risk reduction by aspirin for the development of death or MI among patients with unstable angina/non-ST-elevation MI.[66] The Montreal Heart Institute study demonstrated the effectiveness of both aspirin, as well as heparin, in reducing the incidence of death or MI.[67] A more recent study by the Research on Instability in Coronary Artery Disease Group (RISC) extended these observations to all patients with acute coronary syndromes, showing an approximately 70 percent reduction by aspirin in subsequent risk of death or MI in patients with either unstable angina or non-ST-elevation MI.[68]

Following MI, aspirin reduces subsequent cardiac events, providing secondary prevention (Table 44-2).[183,184] These benefits have now been observed to persist for up to 4 years of follow-up with chronic antiplatelet therapy.[184] Thus, aspirin has had a dramatic effect in reducing adverse clinical events and is primary therapy for all acute coronary syndromes.

In PCI, aspirin has been used as background therapy in most trials, and one small trial did find a reduced rate of thrombotic cardiac events in patients randomized to aspirin compared with placebo.[185] In coronary artery bypass grafting (CABG), aspirin is also an important component of therapy. Without aspirin therapy, graft occlusion occurred in 16 to 26 percent of patients by 1 year.[30] The VA Cooperative Study randomized patients to five treatment arms: (1) aspirin 325 mg/day, (2) aspirin 325 mg three times daily, (3) 325 mg daily of aspirin and dipyridamole 75 mg daily, (4) sulfinpyrazone 267 mg daily, or (5) placebo. Early graft patency was significantly higher in patients randomized to aspirin at any dose, with benefit persisting at 1 year. The dose of 325 mg daily of aspirin was as effective as the 325 mg three times daily. Sulfinpyrazone and dipyridamole added no benefit to aspirin.[186]

PRIMARY PREVENTION OF ACUTE MYOCARDIAL INFARCTION

Two studies examining the use of aspirin in primary prevention of MI (Table 44-3) were conducted. In the United States, in the Physicians' Health Study, more than 22,000 male physicians of ages 40 to 84 were randomized to receive 325 mg of aspirin every other day or placebo for 5 years. There was a 44 percent relative reduction in MI in the aspirin-treated group, although the absolute incidence of such event was less than 1 percent in the low-risk population (Fig. 44-13). This effect was limited to those older than 50

years. The incidence of cardiovascular death was not different.[187] In a British primary prevention trial of more than 5000 male physicians, two-thirds were randomized to receive 500 mg/day of aspirin and one-third were advised to use no aspirin. After 6 years, there was no difference in the rate of MI.[188] However, a large number of protocol crossovers (both physicians stopping aspirin in the aspirin group, and physicians taking aspirin in the placebo group) diluted the power of the study to show a significant difference.

Table 44-3: Aspirin in Primary Prevention (U.S. Physicians' Health Study and British Doctors' Trial Results)

	Reduction (% ± SD)			
	United States	British	Overview	
End Point	Physicians' Health Study	Doctors' Trials	Both Trials	*p*
Nonfatal myocardial infarction	44 ± 9	3 ± 19	32 ± 8	<.0001
Nonfatal stroke	↑19 ± 15	↑13 ± 24	↑18 ± 13	NS
Total cardiovascular deaths	2 ± 15	7 ± 14	5 ± 10	NS
Any vascular event	18 ± 7	4 ± 12	13 ± 6	NS

Source: Fuster et al.,[493] with permission.

In summary, aspirin has been shown to be beneficial in essentially every condition in which it has been tested. Its use is strongly recommended in all guidelines of management of coronary artery disease.[189,190]

Thienopyridines: Ticlopidine and Clopidogrel

The thienopyridines are inactive in vitro but potent antiaggregating agents in vivo, indicating the importance of at least one active transient metabolite. The metabolic activation takes place in the liver as a portojugular shunt abolishes the antiaggregating effect. Ticlopidine and its chemical analog clopidogrel are noncompetitive but selective antagonists of ADP-induced platelet aggregation and act by specifically blocking GP IIb/IIIa activation (Fig. 44-5) specific for the ADP pathway. Since the two compounds are chemically related, their mechanisms of action are considered similar. Ex vivo studies indicate that the antiaggregating effect is concentration dependent; the rate of recovery is linked to platelet survival, suggesting a permanent effect on platelets.[191]

The two agents are believed to inhibit the binding of adenosine 5′-diphosphate (ADP) to its platelet receptor.[191-195] Initial studies reported that this ADP receptor blockade led to direct inhibition of fibrinogen binding to the GP IIb/IIIa complex.[196,197] There is also evidence that ticlopidine may interfere with von Willebrand factor, resulting in less binding of von Willebrand factor to platelet receptors.[197-199] Recent studies suggest there are at least two types of ADP receptors.[191,193,200] The first type is a low-affinity type 2 purinergic receptor that is G-protein coupled and results in mobilization of calcium from internal stores.[201] This leads to a conformational change in and activation of the GP IIb/IIIa receptor complex, fibrinogen binding, and platelet aggregation. The second type of ADP receptor (P2Y1) is of high affinity and is responsible for platelet shape change and rapid calcium influx.[201,202] Because ticlopidine and clopidogrel do not affect shape change or calcium influx, they appear to achieve their effect by interacting with the low-affinity type 2 purinergic receptor.[191,193,201] This interference with a specific ADP-dependent

step of GP IIb/IIIa complex activation results in less platelet aggregation and, thus, ultimately impairs thrombus formation.[193,203,204] Despite these numerous in vitro studies, the mechanism(s) of action of ticlopidine and clopidogrel<@>are still not fully characterized. Further insights would be greatly facilitated by the cloning of the type 2 purinergic ADP receptor.

Ticlopidine and clopidogrel have been tested in several animal models of platelet-dependent arterial or venous thrombosis and found to be more effective than sulfinpyrazone, dipyridamole, and aspirin. Other effects are a reduction in fibrinogen levels and blood viscosity and improvement in decreased erythrocyte deformability.

TICLOPIDINE

This was studied in a randomized trial of patients with unstable angina involving 652 patients. The control group did not receive aspirin because at the time of protocol design it was not routinely used to treat unstable angina. At 6-month follow-up, ticlopidine led to a significant 46 percent reduction in vascular death or nonfatal MI.[205] Of note, there was no difference in the number of events over the first 10 days, consistent with the delayed onset of the antiplatelet effect of ticlopidine. Thus, ticlopidine appears to be comparable to aspirin for secondary prevention of events after unstable angina/non-ST-elevation MI.

The effectiveness of ticlopidine has been shown in patients with transient ischemic cerebral attacks and stroke, and peripheral arterial or ischemic heart disease.[195] The first large trial of its effectiveness in 3069 patients with recent transient or mild persistent focal cerebral or retinal ischemia has shown that ticlopidine has a more pronounced effect on death from all causes or nonfatal stroke than aspirin.[206]

Ticlopidine has also been demonstrated to be effective in combination with aspirin for prevention of thrombosis and recurrent ischemic events in patients undergoing coronary stent implantation. The first randomized trial [Intracoronary Stenting and Antithrombotic Regimen (ISAR)] confirmed the advantage of an antiplatelet regimen over an anticoagulant regimen.[207] A total of 517 patients were randomized to intravenous heparin for only 12 h and ticlopidine, 250 mg twice daily, and aspirin, 100 mg twice daily, for 4 weeks; or to intravenous heparin for 5 to 10 days, aspirin, 100 mg twice daily, and phenprocoumon [target international normalized ratio (INR) = 3.5 to 4.5] for 4 weeks. At 30-day follow-up, the ticlopidine group had 75 percent fewer cardiac end points than the phenprocoumon group (1.6 versus 6.2 percent, p = .01) and no episodes of stent thrombosis (versus 5.0 percent, $p < 0.001$).

A larger, adequately powered study has now shown an impressive benefit of a ticlopidine-containing regimen over both anticoagulation and aspirin-only regimens. The Stent Antithrombotic Regimen Study (STARS) trial randomized 1653 patients to either aspirin, 325 mg once daily, plus warfarin (target INR = 2.0 to 2.5); aspirin plus ticlopidine, 250 mg twice daily; or aspirin alone for 1 month.[208] The primary end point was death, MI, target vessel revascularization, or stent thrombosis to 30 days. The primary end point was significantly lower among patients treated with aspirin plus ticlopidine, 0.5 percent, compared with 3.6 percent for those treated with aspirin alone, and 2.7 percent for those who received aspirin plus warfarin (p = .001).[208] Two other randomized trials have also found significant benefit favoring ticlopidine plus aspirin, compared with aspirin and warfarin regimens.[209,210]

A recent analysis has shown added benefit in patients who are pretreated with ticlopidine for several days prior to PCI.[211] A series of 175 patients treated with ticlopidine prior to stenting were evaluated. Ticlopidine pretreatment of at least 3 days was associated with a significant reduction in periprocedural MI [odds ratio = 0.18; 95% confidence interval (CI) = 0.04 to 0.78; p = .01] compared with pretreatment of less than 3 days. Thus, patients with effective ADP inhibition at the time of PCI appear to have greater benefit from the drug.

SIDE EFFECTS

The most common adverse effects associated with ticlopidine are gastrointestinal: diarrhea affects about 20 percent of treated patients. Other effects are skin reactions (urticaria, pruritus, and erythema) and hemorrhagic disorders (epistaxis, ecchymoses, and menorrhagia). These effects are generally not severe and

resolve after discontinuation of ticlopidine. Ticlopidine has also been reported to increase total cholesterol by 9 percent.[206]

The most potentially serious problem is bone marrow depression (leukopenia, thrombocytopenia, and pancytopenia); close monitoring is therefore essential for at least the first 12 weeks of ticlopidine therapy.[212,213] Ticlopidine-associated neutropenia and thrombocytopenia occur in approximately 1 percent of patients. Of these, a small percentage develop thrombotic thrombocytopenic purpura (TTP), which can be fatal in 25 to 40 percent of cases.[214,215] In a recent survey of 43,322 patients, the incidence of TTP following ticlopidine use for stenting was 1 case per 4814 patients treated (0.02 percent; 95% CI = 1 case per 2533 to 1 case per 10,541 patients treated).[215] Thus, if ticlopidine is used, short courses (2 to 3 weeks) and biweekly monitoring of complete blood count are generally recommended.

CLOPIDOGREL

This is chemically related to ticlopidine, and their mechanisms of action are considered similar. Clopidogrel is approximately six times as potent as ticlopidine in the inhibition of ADP-induced aggregation of human platelets. The onset of action of clopidogrel is more rapid than ticlopidine, especially when using a loading dose of 300 mg or more, which achieves effective platelet inhibition within 2 to 5 h.[216]

Clopidogrel has been tested for secondary prevention in a broad population of patients with atherosclerosis in the Clopidogrel Versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial, which enrolled 19,185 patients, of which one-third had experienced an MI within 35 days and had documented peripheral arterial disease or an ischemic stroke from 1 week to 6 months prior to randomization.[181] Patients were randomized to either clopidogrel, 75 mg once daily, or aspirin, 325 mg once daily; mean follow-up was 1.9 years. Overall, clopidogrel was associated with an 8.7 percent reduction relative to aspirin in the combined end point of ischemic stroke, MI, or vascular death (5.32 versus 5.83 percent per year; $p = .042$) (Fig. 44-14).[181]

Curiously, among the 6302 patients who had an MI within 35 days of randomization (mean, 17.6 days), there was a statistically insignificant 3.7 percent increase in the combined end point of MI, stroke, and vascular death ($p = .66$).[181] Of the patients in the peripheral vascular disease and stroke strata, however, 2144 had a history of MI. In a post hoc secondary analysis of all 8446 patients with a history of MI, clopidogrel was associated with a 7.4 percent decrease in the combined end point, which is similar to the benefit of clopidogrel observed in the overall trial (combined end point reduction of 8.7 percent).[181] In addition, the relative benefit of clopidogrel on the components of the primary end point was greatest in preventing MI: clopidogrel produced a significant 19.2 percent reduction in MI ($p = .008$), while there were nonsignificant 5.2 and 7.6 percent reductions in stroke and vascular death, respectively (Fig. 44-14).[217] Based on these data, the Food and Drug Administration (FDA) approved clopidogrel for secondary prevention of vascular events among patients with symptomatic atherosclerosis. Very recent data have shown that selected high-risk subgroups of patients in the CAPRIE trial, such as those with prior CABG or diabetes, had a much greater benefit. For patients with prior CABG, clopidogrel reduced the annual rate of vascular death, MI, or stroke from 22.3 to 15.9 percent ($p = .001$).[218] Thus, clopidogrel is a suitable alternative to aspirin and appears to afford some benefit over aspirin. Clopidogrel is also the drug of choice in patients who have a true aspirin allergy.

Interest now has turned to the combination of clopidogrel plus aspirin. Experimental data have shown synergy between the two agents in their antithrombotic effects.[219] Trials are currently ongoing for patients with unstable angina/non-ST-elevation MI testing the combination of clopidogrel plus aspirin compared with aspirin alone.

Clopidogrel also appears to be as effective as ticlopidine in preventing stent thrombosis.[195,220-225] As previously noted, current regimens usually begin with a loading dose of 300 mg, which achieves effective platelet inhibition within 2 to 5 h,[216] followed by 75 mg daily. The current duration of treatment following stenting is 30 days, but a trial is currently examining whether there is added benefit from longer treatment.

SIDE EFFECTS

Clopidogrel is not associated with neutropenia and an extremely low (3 to 4 per million) rate of thrombotic thrombocytopenic purpura, and it was associated with a lower rate of gastrointestinal bleeding compared with aspirin.[181] In the CAPRIE study, adverse events with clopidogrel were proportionally less frequent than those previously reported for ticlopidine.[181] In CAPRIE, of 19,185 patients followed up for a mean of 1.91 years, only 0.10 percent in the clopidogrel group developed a significant reduction in neutrophil count (<1.2 × 10 g/L) compared with 0.17 percent in the aspirin group.

Thromboxane Synthase Inhibitors

These have been developed with the expectation not only of suppressing TXA_2 biosynthesis (Fig. 44-5) but also of sparing or even enhancing the formation of prostacyclin by the vascular endothelium. Thromboxane synthase inhibition offers the potential advantage over aspirin-type cyclooxygenase inhibitors of reorienting the arachidonic cascade toward an overproduction of inhibitory prostanoids (PGI_2 and PGD_2) and a reduction in TXA_2 formation. However, specific inhibition of TXA_2 synthase produces an accumulation of cyclic prostaglandin endoperoxides, which occupy and activate TXA_2 and endoperoxide receptors on platelets and endothelium and thus attenuate the inhibitory effect of PGI_2 and PGD_2.

Most thromboxane synthase inhibitors have moderate potency and brief duration of action and do not result in a sufficiently sustained inhibition of TXA_2 production to be clinically effective. Moreover, some individuals are poor responders to drugs of this type. The increased generation of endoperoxides that share the same receptors as TXA_2 is another problem that will not be solved by more potent and long-acting drugs of this class.[226] Although thromboxane synthase inhibitors have shown some benefit in experimental models, their effects in clinical trials in patients with coronary artery disease have been disappointing.

Thromboxane Receptor Blockers

The more recently developed thromboxane receptor blockers specifically impede the action of both TXA_2 and endoperoxides on their presumed common receptors on platelets (Fig. 44-5) and prevent vasoconstriction induced by TXA_2. These agents leave the normal pattern of thromboxane and prostacyclin formation unaltered. Thromboxane receptor antagonists prolong bleeding time more than thromboxane synthase inhibitors. As expected, TXA_2 synthesis is not inhibited and PGI_2 generation not augmented by specific thromboxane/endoperoxide receptor antagonists. Unfortunately, the results of the initial clinical studies with such agents have been disappointing.[227]

Combined Thromboxane Synthase Inhibitors and Receptor Blockers

Some compounds have a dual activity. Ridogrel is a potent TXA_2 synthase inhibitor with modest additional TXA_2/prostaglandin endoperoxide receptor antagonist properties (at least 100-fold less).[228] Although the animal pharmacology was very promising, the preclinical evaluation was deceptive. Ridogrel was testing as adjunctive antiplatelet therapy with thrombolysis in the Ridogrel Aspirin Patency Trial (RAPT).[229] A total of 907 patients with acute MI treated with streptokinase were randomized to aspirin or ridogrel. The primary end point was coronary patency [Thrombolysis in Myocardial Infarction (TIMI) flow grades 2 and 3] at predischarge angiography to be performed between 7 and 14 days after admission. No difference was observed between the two groups: 72.2 percent in the ridogrel and 75.5 percent in the aspirin group. The incidence of major in-hospital clinical events during hospital stay was similar in both groups. However, in a post hoc analysis, a lower incidence of new ischemic events (reinfarction, recurrent angina, or ischemic stroke) was observed with ridogrel: 13 versus 19 percent in the aspirin group (p = .025). There was no excess in major bleeding complications, including hemorrhagic stroke. With only modest results, this agent has not been developed for widespread clinical use.

Dipyridamole

This is a pyrimidopyrimidine compound whose antithrombotic action is not well understood. It is felt to decrease platelet aggregability but also decrease platelet adhesion to prosthetic valves, increase platelet survival, and decrease red blood cell deformability.[230] It has been shown in one study to reduce embolism from prosthetic cardiac valves when combined with warfarin.[230] In CABG, neither dipyridamole (nor sulfinpyrazone) added to the benefit of aspirin in maintaining graft patency.[186] Thus, its role in coronary artery disease is limited.

Sulfinpyrazone

This is a weak antiplatelet agent that, after metabolism to a sulfide form, acts as an incomplete and reversible inhibitor of platelet cyclooxygenase, although other actions may exist. In one trial of unstable angina, patients were randomized to receive 1300 mg/day of aspirin, 800 mg/day of sulfinpyrazone, the combination of both, or placebo. After 18 months, the incidence of death and MI was reduced in the aspirin group, but sulfinpyrazone demonstrated no benefit.[231]

Platelet Glycoprotein IIb/IIIa Receptor Blockers

This is a potent class of platelet inhibitors. GP IIb/IIIa receptor antagonists block the binding of fibrinogen to specific membrane GP IIb/IIIa integrin receptors, thus preventing platelet aggregation induced by various platelet agonists. Whereas platelet activation is produced by a wide variety of stimuli, the final common step to platelet aggregation is fibrinogen binding. Thus, no matter what stimuli there are for platelet activation, the platelet is inhibited by the GP IIb/IIIa inhibitor-making it an order of magnitude more effective than aspirin (or ticlopidine) at inhibiting platelet aggregation. When testing platelet aggregation in the laboratory, aspirin inhibits ADP-induced platelet aggregation by approximately 5 to 10 percent, ticlopidine and clopidogrel inhibit platelet aggregation by approximately 30 percent, and the doses of the GP IIb/IIIa inhibitors being tested clinically inhibit platelet aggregation by approximately 80 to 90 percent.

Types of Glycoprotein IIb/IIIa Inhibitors

There are three broad categories of GP IIb/IIIa inhibitors: (1) the monoclonal antibody fragment to the IIb/IIIa receptor, abciximab; (2) the intravenous peptide and nonpeptide small molecule inhibitors, such as eptifibatide and tirofiban; and (3) the oral GP IIb/IIIa inhibitors, such as xemilofiban, orbofiban, sibrafiban, and roxifiban.

The first platelet GP IIb/IIIa antagonists to be developed were murine monoclonal antibodies.[232] In vitro, these antibodies completely inhibit platelet aggregation and, in animal models of angioplasty injury and thrombolysis, prevent thrombosis and augment the activity of thrombolytic agents. Because of concerns about their immunogenicity, the derivative product chimeric monoclonal 7E3 Fab (c7E3 Fab, abciximab) was created via genetic recombination. This new molecule consists of the mouse-derived variable regions from the original molecule linked to the constant region derived from human immunoglobulin G. Abciximab binds to the GP IIb/IIIa receptor and to a broader group of integrins, such as the vitronectin receptor, which appears to be important in neointimal proliferation. In addition, abciximab has been shown to inhibit thrombin generation by tissue factor most likely due to its dual blockade of GP IIb/IIIa and $\alpha_v\beta_3$.[233]

Abciximab binds very tightly to the GP IIb/IIIa receptor.[234] Thus, the antiplatelet effect lasts much longer than the infusion period-a potential benefit on improving efficacy. On the other hand, if bleeding occurred, stopping the drug will not reverse the antiplatelet effect immediately; transfusion of platelets, however, will allow the antibodies to redistribute among all the platelets, thereby reducing the level of platelet inhibition. Abciximab also binds to other integrins on the platelet receptor, such as the vitronectin receptor,[114] but the clinical significance of this cross-reactivity is not yet established.

The peptide and peptidomimetic inhibitors (e.g., tirofiban and eptifibatide) are competitive inhibitors of the GP IIb/IIIa receptor.[235,236] Tirofiban and eptifibatide are RGD- and KGD-containing agents that bind to the fibrinogen binding site of the GP IIb/IIIa receptor. The level of platelet inhibition is directly related to the

drug level in the blood. With these short-acting agents the ratio of drug molecules to GP IIb/IIIa receptors is greater than 250, whereas for the "tight-binding" agents (e.g., abciximab) the ratio is approximately 2.

Since both inhibitors have short half-lives, when the drug infusion is stopped,[235,236] the antiplatelet activity reverses after a few hours, which is a potential benefit for avoiding bleeding complications. On the other hand, for prolonged antiplatelet effect, the drug needs to be given intravenously for a longer period. The inhibitors developed to date have been specifically targeted to the GP IIb/IIIa receptor and not to cross-react other integrins.

The third group of GP IIb/IIIa inhibitors are the oral agents. These are also competitive inhibitors and are usually pro-drugs, which are absorbed and then converted to active compounds in the blood.[237-241] The oral agents all have longer half-lives, such that they can be given once, twice, or three times daily to achieve relatively steady levels of GP IIb/IIIa inhibition. With oral dosing, long-term therapy (i.e., longer than 1 year) is possible. As with the intravenous compounds, two major groups of drugs exist in the oral class: those with competitive inhibition and short "off time" from the receptor-where a high drug level is critical to achieving high levels of platelet inhibition-and those that have "tight" binding to the platelet (similar to abciximab) with the majority of the drug circulating bound to platelets.

Potential Mechanisms of Benefit of Glycoprotein IIb/IIIa Inhibitors

Several potential mechanisms exist for how GP IIb/IIIa inhibition may improve clot resolution and clinical outcome in patients' acute coronary syndromes. First, by blocking platelet aggregation in the platelet-rich arterial thrombus, it prevents propagation of the thrombus. GP IIb/IIIa inhibitors may also be able to *disaggregate* a recently formed platelet plug. Second, by preventing accumulation of a large number of platelets at the lesion, it decreases the amount of platelet phospholipid membrane, a cofactor needed for thrombin generation in the clotting cascade. Third, a thrombus rich in platelets may resist thrombolysis (either thrombolytic therapy or endogenous thrombolysis), owing in part to the increased presence of PAI-1, a potent natural inhibitor of fibrinolysis that exists in high concentrations in platelets.

Glycoprotein IIb/IIIa Inhibition During Coronary Angioplasty

The FDA had approved three agents for use during PCI, including abciximab (ReoPro) and eptifibatide (Integrilin) for elective and urgent PCI. In addition, tirofiban (Aggrastat) is approved for the treatment of patients with unstable angina and non-ST-elevation MI undergoing PCI. Abciximab is administered as a 0.25-mg/kg bolus and an infusion of 0.125 μg/kg per minute for 12 h following PCI. Although lower doses are approved, the most widely used dose is that from the unstable angina trial,[76] a dose of eptifibatide is 180-μg/kg bolus and infusion of 2.0 μg/kg per minute. A recent trial also showed benefit of this regimen with an added second bolus of 180 μg/kg 10 min after the first. The dose of tirofiban used in the angioplasty trial Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE), and an ongoing trial, is a bolus of 10 μg/kg over 3 min followed by 0.15 μg/kg per minute.

ABCIXIMAB

Initial testing of GP IIb/IIIa inhibitors began in patients undergoing PCI. In the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial of patients undergoing high-risk PCI, abciximab bolus and infusion had a 35 percent lower rate of death, MI, or urgent revascularization at 30 days compared with the placebo group (8.3 versus 12.8 percent, $p = .008$).[241a] In long-term follow-up, significant benefit has been observed at 6 months and 3 years.[242,243] Similar reductions in major cardiac events were observed in the Evaluation in PTCA to Improve Long-Term Outcomes with Abciximab Glycoprotein IIb/IIIa Blockade (EPILOG) trial of elective PCI. Death, MI, or urgent revascularization at 30 days for abciximab plus low-dose heparin group was 5.2 versus 11.7 percent for heparin alone, a 58 percent risk reduction ($p < 0.001$).[243a] The abciximab plus standard-dose heparin also had a significant reduction in ischemic complications to 5.4 percent ($p < 0.001$).[243a] Death or MI was similarly reduced by more than 50 percent when adding abciximab (Fig. 44-15). When using a lower dose of heparin with abciximab, there was no difference in the incidence of major bleeding or the need for transfusion between abciximab-treated

patients and placebo. Thus, a low-dose heparin regimen can be recommended with abciximab (70-U/kg initial bolus with an additional 20 U/kg if the activated clotting time is less than 200 s).

Abciximab was also found to be beneficial when started 24 h *prior* to a PCI in the Chimeric 7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, which studied 1265 patients with refractory angina undergoing PCI.[253] All patients had undergone cardiac catheterization and had a planned PCI the following day. Death, MI, or urgent revascularization was reduced by abciximab from 15.9 to 11.3 percent ($p = .012$).[253] As in all the trials, the major benefit is in reductions of periprocedural MI as well as the need for urgent revascularization. A meta-analysis, however, has shown that there is a significant reduction in *mortality* when GP IIb/IIIa inhibition is used.[243b] These data highlight the clinical importance of thrombosis and of effective antithrombotic therapy in PCI.

The benefit of GP IIb/IIIa inhibition with coronary stenting was shown in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial.[243c] Compared with stenting alone, the rate of death, MI, or urgent revascularization at 30 days was significantly reduced in both abciximab groups-from 10.8 to 5.3 percent for stent plus abciximab ($p < 0.001$) and 6.9 percent for balloon angioplasty with abciximab ($p = .007$).[243c] Benefits were maintained at 6 months[244] and 1 year, with a significant reduction in 1-year mortality among patients treated with stent plus abciximab compared with stent alone.[245]

EPTIFIBATIDE

This has been studied in two PCI trials and one large unstable angina trial. In the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT-II) trial of patients undergoing elective or urgent PCI, patients were randomized to eptifibatide at one of two doses or placebo, continued for 20 to 24 h after the procedure. These doses (infusion rates of 0.5 and 0.75 mg/kg per hour) however were found after the trial was completed to achieve only 50 to 60 percent platelet inhibition. The primary end point of the trial was a composite of death, MI, urgent need for revascularization, or stent placement for abrupt vessel closure at 30 days. There was a trend toward a lower composite event rate in the low-dose and high-dose eptifibatide-treated groups compared with placebo (9.2 and 9.9 percent versus 11.4 percent, respectively; $p = .063$ for low-dose eptifibatide).[8]

More recently, the Enhanced Suppression of the Platelet Receptor IIb/IIIa with Eptifibatide Therapy (ESPRIT) trial tested a higher dose, 180-μg/kg bolus followed by an infusion of 2.0 mg/kg per hour, with a second bolus of 180 μg/kg given 10 min after the first bolus. This dose was similar to that used in the Platelet IIb/IIIa Underpinning the Receptor for Suppression of Unstable Angina Trial (PURSUIT)[76] (see also page 1397) and was targeted to achieve 85 to 95 percent platelet inhibition. The second bolus was added to ensure no fall in the level of inhibition of platelet aggregation at the early periprocedural time point. In this trial, patients enrolled had either stable angina or unstable angina or a recent, but not acute, MI. The primary end point was death, MI urgent revascularization, or thrombotic bailout at 48 h. There was a 37 percent reduction in death or MI (10.5 versus 6.6 percent, $p = .0017$) (Fig. 44-16).[246] Death or MI at 48 h was reduced from 9.2 to 5.5 percent ($p = .0013$), a relative 40 percent reduction. Death, MI, or target vessel revascularization was reduced from 9.3 to 6.0 percent ($p = .0045$).[246] Thus, eptifibatide in the new double-bolus and infusion regimen led to a substantial reduction in early complications from PCI.

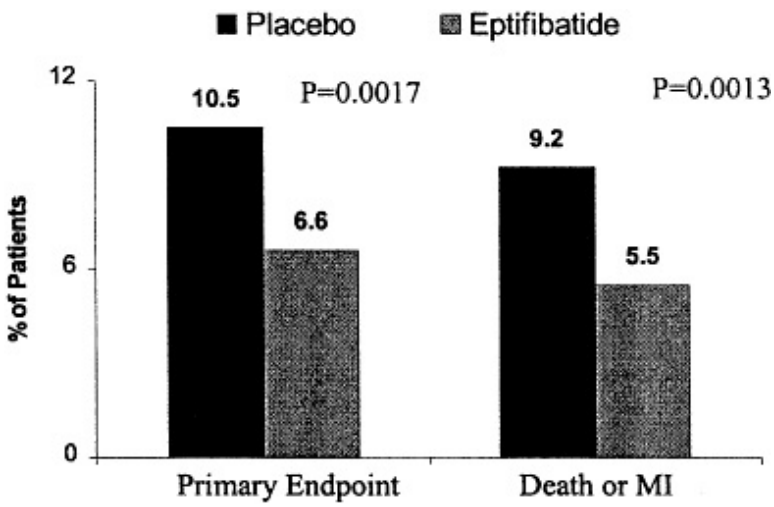

Figure 44-16: Primary Results from the ESPRIT trial of eptifibatide in coronary stenting. (Presented by Tcheng J at American College of Cardiology, March 2000.)

TIROFIBAN

This is a nonpeptide GP IIb/IIIa receptor antagonist. The compound has a short half-life (approximately 3 h).[247] Intravenous infusion of tirofiban for 1 or 4 h in healthy male volunteers dose-dependently inhibited ADP-, collagen-, arachidonic acid-, and thrombin-induced platelet aggregation.[247,248] Bleeding time was also significantly increased.

The RESTORE trial enrolled 2139 patients undergoing high-risk PCI and randomized patients to tirofiban (10-mg/kg bolus followed by infusion of 0.15-mg/kg per hour for 36 h). Tirofiban led to a lower, but not statistically significant, rate of the primary composite end point (death, MI, revascularization for target vessel ischemia, or stent placement for abrupt vessel closure at 30 days), (10.3 versus 12.2 percent, a 16 percent risk reduction, $p = .16$).[249] Death, MI, or urgent revascularization to 30 days was reduced by tirofiban by 24 percent (8.0 versus 10.5 percent, $p = .052$). In this trial, however, systematic collection of cardiac enzymes periprocedurally was not carried out, and thus a major end point was not ascertained as in the other trials. A trial is currently under way that will directly compare abciximab and tirofiban in PCI.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

The final area of coronary intervention that has been tested is for *primary* PCI, i.e., for acute ST-elevation MI. After favorable results in a subgroup of the EPIC trial were observed,[250] the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) trial was conducted, comparing abciximab with placebo.[251] Although the prespecified 6-month end point of death, MI, or any target vessel revascularization was not significantly reduced, abciximab was able to reduce the 30-day incidence of death, MI, or urgent revascularization by 48 percent, from 11.2 to 5.8 percent ($p = .03$). This beneficial effect was sustained at 6 months (17.8 versus 11.6 percent, $p = .05$).[251] Two other randomized trials have also shown benefit of abciximab in primary PCI, each with a similar 50 percent reduction in death, MI, or urgent revascularization at 30 days.[251a,251b]

Another important observation has been made regarding treatment of patients with ST-elevation MI with GP IIb/IIIa inhibitors in the emergency department 30 to 90 min *prior* to performing a PCI. Early TIMI grade 3 flow is achieved in 20 to 30 percent of patients, with a TIMI grade 2 or 3 flow achieved of approximately 50 percent.[251a-251c,281,283] Thus, use of GP IIb/IIIa inhibitors can "facilitate" the PCI by providing better preprocedural flow and consequently better procedural outcomes.

Thus, given this broad experience with GP IIb/IIIa inhibitors in PCI (Fig. 44-15), and with reductions in death or MI of approximately 50 percent, their use has become a new therapeutic standard for PCI.

Glycoprotein IIb/IIIa Inhibitors in Unstable Angina and Non-ST-Elevation Myocardial Infarction

As of the time of this printing, the FDA had approved three agents for the treatment of unstable angina and non-ST-elevation MI: tirofiban and eptifibatide (Integrilin); abciximab (ReoPro) is approved for use in patients with unstable angina with a planned PCI. For unstable angina, abciximab can be administered as a 0.25-mg/kg bolus and an infusion of 0.125 μg/kg per minute for 12 to 24 h. Although in the CAPTURE trial it was administered for 24 h prior to, and only 1 h after, the procedure, in all the other trials abciximab was continued for 12 h after PCI. The approved dose of tirofiban is that used in the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial: a loading dose of 0.4 μg/kg per minute over 30 min, followed by 0.1 μg/kg per minute. Patients with renal insufficiency (creatinine clearance < 30 mL/min) should receive half the usual rate of infusion. The dose of eptifibatide is 180-μg/kg bolus and infusion of 2.0 μg/kg per minute.

TIROFIBAN

PRISM-PLUS studied 1915 patients with documented unstable angina and non-ST-elevation MI with either electrocardiographic changes or positive enzymes.[78] The combination of tirofiban, heparin, and aspirin significantly lowered the rate of death, MI, or recurrent refractory ischemia at 7 days (primary end point) compared with heparin plus aspirin (12.9 versus 17.9 percent, respectively, a 32 percent risk reduction, p = .004).[78] This benefit was predominantly due to a 47 percent reduction in MI (p = .006) and a 30 percent reduction in refractory ischemia (p = .02). These benefits were achieved early and include a significant 66 percent reduction in death or MI at 48 h (0.9 versus 2.6 percent, p = .01).[78] Importantly, these benefits were preserved during follow-up: the 30-day rate of death or MI was also reduced by 30 percent (from 11.9 to 8.7 percent, p = .03).[78] Long-term follow-up to 6 months also showed a significant reduction in events (32.1 versus 27.7 percent, p = .02).[78]

The benefit of tirofiban plus heparin and aspirin was found across all subgroups evaluated, including men and women, elderly and young, unstable angina and non-ST-elevation MI patients, and those with ST-segment depression or elevation, *and* in those with no ST-segment or T-wave changes.[78] As expected, the absolute benefit in number of events prevented was greater in higher-risk patient subgroups, such as the elderly, diabetics, those who were already taking aspirin, and those with ST-segment changes or positive cardiac markers. The benefit of tirofiban plus heparin was also found in all types of management strategies: patients managed medically derived a 25 percent reduction in death or MI rate at 30 days, those who also had angioplasty had a 34 percent reduction, and those who were sent on to bypass surgery also derived a 30 percent benefit. Thus, benefit of adding tirofiban to aspirin plus heparin is derived in all patient groups treated.

A beneficial effect of tirofiban was also observed in the PRISM study, which randomized 3232 patients with unstable angina and non-ST-elevation MI to either heparin or tirofiban, with all patients receiving aspirin.[77] The primary goal of this study was to examine the effects of GP IIb/IIIa inhibition during medical therapy only; thus, the end point was a composite of death, MI, and refractory ischemic conditions at 48 h, and coronary procedures were not permitted by the protocol during the first 48 h. Tirofiban-treated patients had a significantly lower composite event rate than the placebo group (3.8 versus 5.6 percent, representing a 32 percent reduction, p = .01).[77] At 30 days, the improvement on the composite end point of death or MI was no longer statistically significant (death or MI, relative risk = 0.80, p = .11). Thus, the effects of GP IIb/IIIa inhibition with tirofiban appear to have greater long-term effects when used in conjunction with heparin (as was done in the PRISM-PLUS trial) (see below).

EPTIFIBATIDE

This was studied in the PURSUIT trial involving 10,948 patients with unstable angina and non-Q-wave MI. Patients received aspirin and heparin and were randomized to in one of three arms: high-dose eptifibatide, low-dose eptifibatide, or placebo. By study design, the low dose was dropped after an interim analysis because of a reasonable safety profile of the high dose. Eptifibatide (180-μg/kg bolus and infusion of 2.0 μg/kg per minute) reduced the rate of death or MI at 30 days from 15.7 to 14.2 percent (p = .042).[76] This

benefit of reducing 15 events per 1000 patients treated was achieved after only 72 h (while the patients were on study drug): 7.6 percent for placebo compared with 5.9 percent for eptifibatide (p = .001). Among patients undergoing early angioplasty or stenting while on study drug, benefits were more dramatic: 16.7 percent for placebo compared with 11.6 percent for eptifibatide (p = .01).[76] In this group, there were reductions in death or MI observed both prior to PCI and during the first 24 h after PCI.[252] Severe or moderate hemorrhage was more common in the eptifibatide group, 12.8 versus 9.9 percent ($p < 0.001$).

ABCIXIMAB

The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IV-Acute Coronary Syndromes (ACS) trial recently reported (Topol, European Congress of Cardiology, Amsterdam 2000) no benefit of Abciximab in patients with unstable angina and non-Q-wave MI, who did not undergo PCI. On the other hand, among patients with unstable angina who undergo PCI (i.e., those managed with an early invasive strategy), abciximab has been shown to be beneficial. In the CAPTURE trial, 1265 patients with refractory angina had undergone cardiac catheterization and had a planned PCI the following day. They were then randomized to abciximab or placebo (in addition to aspirin and heparin) that was administered for 24 h *prior* to a PCI. Death, MI, or urgent revascularization was reduced by abciximab from 15.9 to 11.3 percent (p = .012).[253]

LAMIFIBAN

This nonpeptide synthetic compound that binds reversibly to the integrin IIb/IIIa with a K_D of 5 nM has been effective in several animal models of thrombosis.[254] The inhibition of the ADP-induced aggregation curve parallels the receptor occupancy obtained during in vitro radioligand-binding studies (approximately 50 percent inhibition with 50 percent receptor occupancy of GP IIb/IIIa). The half-life of the free drug is 40 min and that of the bound drug is 9 h. A dose-finding study was conducted in patients with unstable angina.[255]

The Canadian Lamifiban Study of 365 patients with unstable angina showed a lower rate of death or MI at 30 days (2.5 versus 8.19 percent for placebo, p = .03).[256] These results were not observed in the larger Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndromes in a Global Organization Network (PARAGON) A study, which involved 2282 patients. In that study, death or MI at 30 days was 11.7 percent for placebo (aspirin plus heparin) compared with 10.6 percent for low-dose (1 μg/min) lamifiban and 12.0 percent for high-dose (5 μg/min) lamifiban (p = NS).[257] The findings on 6-month follow-up, however, suggest a possible benefit of low-dose lamifiban plus heparin: death or MI to 6 months was 12.6 percent for low-dose lamifiban plus heparin compared with 17.9 percent for placebo (p = .025).[257]

The PARAGON-B trial evaluated a dose of lamifiban based on renal function, so as to ensure optimal dose level. In this trial, 5225 patients with unstable angina or non-ST-elevation MI were enrolled and treated with lamifiban versus placebo. The primary end point, death, MI, or severe recurrent ischemia, was not significantly reduced in the overall group (11.8 versus 12.8 percent for heparin, p = .329).[258] In those with positive troponin T at baseline, however, there was a significant reduction in events (from 19 to 11 percent for lamifiban, p = .018). This agent is not being developed for commercial use.

Meta-analysis

Figure 44-15 shows a meta-analysis of all the large GP IIb/IIIa inhibitor trials through 1999 in PCI or unstable angina.[259] The results show a consistent benefit on death or MI rate at 30 days (highly statistically significant, $p < 0.0000001$).[259] Although some differences exist in the relative benefits, it is currently believed that these may relate more to trial design and end-point assessment than differences between the drugs. Thus, it is felt that the benefit in reducing death or MI is a class effect of all the GP IIb/IIIa inhibitors. Direct comparisons between the agents are ongoing to determine the relative benefits of one agent compared with another. Thus, GP IIb/IIIa inhibition in patients with unstable angina/non-ST-elevation MI or PCI reduced death or MI rate at 30 days, representing a significant advance in the treatment of these acute coronary syndromes. These data highlight the importance of acute thrombosis and of platelet

inhibition in acute coronary syndromes and establish GP IIb/IIIa inhibition as a new standard of care in the treatment of these conditions.

Need for Heparin with Glycoprotein IIb/IIIa Inhibitors

The data from several of the trials suggest that GP IIb/IIIa inhibitors should be administered with concomitant heparin. This notion was first suggested by the dropping of the tirofiban-alone arm from the PRISM-PLUS trial, as compared with the superiority of the heparin plus tirofiban arm in that trial. Subsequently, the two other trials in unstable angina have found very similar results: In the PARAGON-A trial, there was a greater benefit when using triple antithrombotic therapy (aspirin, heparin, and the GP IIb/IIIa inhibitor), and this has also recently been reported in a dose-ranging study with lamifiban.[257] The third trial that recently demonstrated the need for heparin was the PURSUIT. A recent abstract found that, among the 90 percent of patients in whom physicians decided to use heparin, a greater benefit on reduction in death or MI rate was observed (14 percent reduction, from 16.9 to 14.6 percent, $p = .013$) compared with a 41 percent *increase* in death or MI rate among the patients not treated with heparin.[260] Although these data may be confounded by other issues, they are consistent with the other trials. Thus, it appears important to use heparin with GP IIb/IIIa inhibitors when treating patients with unstable angina and non-ST-elevation MI. This fits our understanding of the pathophysiology of thrombus formation in acute coronary syndromes, which involves both platelets and the clotting cascade. Since one agent is a potent antiplatelet and the other is an anticoagulant, it follows that both together will have greater benefit. The next question in the field is the safety and efficacy of LMW heparin in combination with GP IIb/IIIa inhibitors.

Angiographic Observations: Establishing the Paradigm of Benefit

Data on thrombus resolution are available from two trials: PRISM-PLUS and CAPTURE. An angiographic substudy was performed as part of the PRISM-PLUS trial to investigate the mechanism of benefit of tirofiban.[261] It was observed that the coronary thrombus was smaller in patients treated with tirofiban plus heparin and aspirin compared with heparin and aspirin. The percentage of patients who had definitive thrombus was reduced from 24 to 17 percent, and there was a 23 percent improvement in overall thrombus grade ($p = .022$).[261] Similarly, coronary flow, using the TIMI flow grading system,[3] was significantly improved, with TIMI grade 3 flow improving from 74.5 to 81.9 percent, with a 35 percent overall improvement in flow ($p = .002$).[261] Similar data are also available from the CAPTURE trial.[262] Together these data establish the pathophysiologic link between the potent platelet inhibition achieved by tirofiban, a reduction in thrombus, and improvement in coronary blood flow, and consequent improvement in clinical outcome for patients.

Reducing Infarct Size with Glycoprotein IIb/IIIa Inhibition

A new concept in the field of GP IIb/IIIa inhibition is that these agents appear to be able to reduce the size of an evolving non-ST-elevation MI or even prevent the development of myocardial necrosis, based on evidence from two trials.[263,264] In the PRISM-PLUS troponin substudy, patients randomized to tirofiban plus heparin had a significantly lower peak troponin than did patients who received heparin and aspirin alone.[264] This was also true among patients who had a negative CK-MB on admission. In the PURSUIT trial, it was observed that the size of the MI (either index or recurrent MI) measured by peak CK-MB, was significantly smaller in patients treated with eptifibatide. Thus, these potent antiplatelet therapies appear to have an immediate effect in reducing the severity of the presenting illness, something that has been observed for patients who develop acute coronary syndromes while already taking aspirin.[265-267]

Another new concept in GP IIb/IIIa inhibition is that there appears to be a greater benefit of treatment when administered earlier relative to the onset of pain. In an analysis from PURSUIT, the absolute reduction in death or MI rate with eptifibatide was 2.8 percent for patients treated within 6 h from the onset of pain and was less for those treated between 6 to 12 and 12 to 24 h after onset of pain. No benefit was observed in patients treated 24 h after the onset of pain. Similar data have been observed in PRISM-PLUS (unpublished data).

Glycoprotein IIb/IIIa Inhibitors Plus Thrombolysis for Treatment of Acute Myocardial Infarction

Although thrombolytic therapy has proved to be a major advance in the treatment of patients with acute MI,[180,268] current thrombolytic regimens have several limitations: (1) failure of initial reperfusion,[269,270] (2) inadequate perfusion with delayed flow (TIMI grade 2 flow),[269,270] (3) imperfect myocardial perfusion,[271] and (4) infarct-related artery reocclusion/reinfarction in a significant percentage of patients.[270,272] Because platelets play a central role in coronary thrombosis-especially failed reperfusion, reocclusion, and reinfarction-attention has turned to the GP IIb/IIIa inhibitors as a means of improving current reperfusion regimens.[259,273]

MECHANISMS OF THROMBOLYTIC RESISTANCE

Lack of initial reperfusion, which could be termed *thrombolytic resistance*, appears to be due to several mechanisms (Table 44-4): (1) Fibrinolytic agents act only on the fibrin portion of the thrombus, leaving activated platelets as a source of rethrombosis. (2) Platelets elaborate PAI-1, which inhibits the action of the thrombolytic agent; platelets also release other agents, such as TXA_2, which causes local vasoconstriction.[274] (3) Lysis of clot-bound fibrin exposes clot-bound thrombin, which remains catalytically active and can cleave fibrinogen to fibrin, facilitating rethrombosis.[275] In addition, thrombosis can stimulate further thrombin production and activation of platelets.[276] (4) thrombolytic therapy also has a direct platelet-activating effect, leading to increased levels of TXA_2 and platelet-activating factor.[274,277] The presence of aspirin does not abolish the platelet-activating effect of fibrinolytic therapy.[274] Thus, thrombolysis promotes platelet activation and therefore actually creates an environment that may lead to subsequent rethrombosis and/or reocclusion.

Table 44-4: Potential Mechanisms of Thrombolytic Resistance

1. Only fibrin is lysed by thrombolytic agent
2. Plasminogen activator inhibitor 1
3. Thromboxane A_2
4. Clot-bound thrombin
5. Activation of platelets

INITIAL STUDIES

Preclinical studies were performed that first tested GP IIb/IIIa receptor inhibitors with thrombolytics to accelerate reperfusion time and reduce the risk of reocclusion.[278,279] The Thrombolysis and Angioplasty in Myocardial Infarction 8 (TAMI-8) trial[280] established the clinical feasibility of combining GP IIb/IIIa inhibitors with thrombolytic therapy. After receiving t-PA plus heparin and aspirin, patients received incremental doses of m7E3, a murine monoclonal antibody to the GP IIb/IIIa receptor. A consistent dose-dependent increase in platelet aggregation was observed, and a clear relationship between GP IIb/IIIa receptor occupancy and extent of platelet inhibition was established.[280]

Concomitant Full-Dose Thrombolytic Therapy Plus Glycoprotein IIb/IIIa Inhibition

The combination of eptifibatide and t-PA, as tested in the Integrilin to Manage Platelet Aggregation and Combat Acute Myocardial Infarction (IMPACT-AMI) trial, significantly increased the rate of TIMI grade 3 infarct related artery (IRA) flow upon angiography at 90 min (66 percent, as compared with 39 percent in the placebo group, $p = .006$).[281] A subsequent trial combining full-dose streptokinase with ascending dosages of eptifibatide found modest improvements in TIMI grade 3 flow in the infarct-related artery, but there was an increased rate of major bleeding.

The Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) trial compared different lamifiban dosage levels to placebo in 353 patients presenting within 12 h of acute MI symptom onset. Patients received aspirin and heparin and either t-PA or streptokinase at standard doses.[282] Lamifiban was associated with improved myocardial reperfusion as measured by early resolution of ST-segment elevation, but no difference in the composite clinical end point was noted. Lamifiban also was associated with increased rates of gastrointestinal, coronary bypass related, and catheterization access-site bleeding complications.

In summary, with the strategy of concomitant full-dose thrombolytic therapy and full-dose GP IIb/IIIa inhibition, it has been difficult to balance efficacy and safety, so attention has turned to combining full-dose GP IIb/III inhibitors with reduced doses of thrombolytic agents.

Reduced-Dose Thrombolysis Plus Glycoprotein IIb/IIIa Inhibition

The combination of a *reduced*-dose thrombolytic agent and a GP IIb/IIIa inhibitor was tested in the TIMI-14 trial using t-PA, streptokinase, and reteplase, and in Strategies for Patency Enhancement in the Emergency Department (SPEED) using reteplase.

The international TIMI-14 trial dose-ranging phase enrolled 681 patients with ST-elevation MI who met standard eligibility criteria.[283] The patients were randomized within 12 h of acute ST-elevation MI symptom onset to one of four reperfusion regimens (each encompassing several dosage levels): standard-dose t-PA alone (the control arm), reduced-dose t-PA plus abciximab, reduced-dose streptokinase plus abciximab, or abciximab alone. All patients received aspirin and heparin. The initial heparin dosage was a 70-U/kg bolus and an infusion of 15 U/kg per hour in the t-PA control arm, and a 60-U/kg bolus with an infusion of 7 U/kg per hour in the arms that included abciximab.

Abciximab alone was associated with 90-min TIMI grade 3 flow rates in 32 percent of patients and 90-min patency in 48 percent of patients.[283] The combination of streptokinase and abciximab produced only modest improvement in early TIMI grade 3 flow. TIMI grade 3 flow at 90 min was achieved in 42 percent of patients in the 0.5-MU (million units) group, 39 percent of patients in the 0.75-MU group, and 47 percent of patients in the 1.25-MU group. The 1.5-MU regimen, plus abciximab, was discontinued after four of six patients developed a major hemorrhage, one of whom developed an intracranial hemorrhage (ICH).

Dose ranging with t-PA found that the best angiographic results were obtained using a 50-mg dose given as a 15-mg bolus and a 35-mg infusion over 60 min. At 90 min, TIMI grade 3 flow was achieved in 77 percent of patients compared with 62 percent for t-PA alone ($p = .02$). Overall patency of the IRA was achieved in 93 percent of patients with the combination of abciximab and t-PA compared with 78 percent for t-PA ($p = .09$). An even greater difference was observed at 60 min when adding GP IIb/IIIa inhibition: the standard t-PA dose achieved only 43 percent TIMI grade 3 flow at 60 min compared with 72 percent for 50 mg t-PA plus abciximab ($p = .0009$). Major hemorrhage was similar among the t-PA plus abciximab and control groups, approximately 6 percent in each. In-hospital mortality was similar in all groups, ranging from 3 to 5 percent.

Thus, the addition of the GP IIb/IIIa receptor inhibitor abciximab to 50 mg of t-PA increased the rate of TIMI grade 3 flow at 60 min by an absolute 29 percent, representing a relative 67 percent improvement over standard therapy. At 90 min, the addition of the GP IIb/IIIa receptor inhibitor improved TIMI grade 3 flow by an absolute 15 percent (a relative 25 percent improvement). These results indicate that the combination of GP IIb/IIIa receptor inhibition with reduced-dose thrombolytic therapy appears to be a promising new regimen for enhancing both the speed and extent of reperfusion in acute ST-elevation MI.

Results from the SPEED trial[283a] similarly demonstrated improvements in early TIMI grade 3 flow with reteplase, indicating that the combination of low-dose thrombolytic therapy with t-PA or reteplase appears to be a potentially promising new regimen for improving both the speed and extent of thrombolysis in acute MI. There are numerous other ongoing angiographic and larger mortality trials that are exploring further the potential role of GP IIb/IIIa inhibitors with reduced-dose thrombolytic therapy.

SAFETY

One of the concerns with any antithrombotic agent is bleeding. Although the initial EPIC study showed increased bleeding when using abciximab plus heparin during angioplasty compared with heparin alone,[284] a strong interaction with the dose of heparin was observed. In the subsequent EPILOG trial, the rate of major bleeding was identical between heparin control patients and those receiving abciximab and low-dose heparin.[285] Similarly, the rate of major bleeding has generally not been significantly increased in other trials with intravenous administration.[77,78,249,286] Thus, use of lower doses of heparin and careful monitoring of the level of anticoagulation help avoid bleeding complications in patients receiving GP IIb/IIIa inhibitors. With regard to monitoring the degree of platelet inhibition, trials to date have used weight adjusted dosing of the GP IIb/IIIa inhibitors, but investigation is currently ongoing to determine when and where monitoring of platelet function might be useful clinically.[287,288]

Another concern, especially when adding GP IIb/IIIa inhibition to thrombolytic therapy, is the risk of ICH. Fortunately, GP IIb/IIIa inhibitors generally have a low risk of ICH when used alone, and no apparent increase compared with aspirin and heparin in the major trials.[76-78,249,257,284-286,289] The risk of ICH when combined with thrombolytic therapy may be largely due to the risk from the latter agent, but larger trials will be needed to define the exact rate.

THROMBOCYTOPENIA

This is an uncommon but important complication of GP IIb/IIIa inhibitors: For tirofiban in PRISM-PLUS, the rate of severe thrombocytopenia (<50,000 cells/mm^3) was 0.5 percent compared with 0.3 percent for heparin (p = NS)[78]; in the PURSUIT trial, thrombocytopenia (<20,000 cells/mm^3) occurred in 0.2 percent compared with <0.1 percent for heparin.[76] Thrombocytopenia is associated with increased bleeding and, in a smaller proportion of patients, recurrent thrombotic events.[290,291] This syndrome bears resemblance to heparin-induced thrombocytopenia (HIT) and indicates a need to monitor platelet count daily during the GP IIb/IIIa infusion.

Oral Glycoprotein IIb/IIIa Inhibition

Oral GP IIb/IIIa inhibitors are peptidomimetic agents that are competitive inhibitors of the GP IIb/IIIa receptor. They are usually pro-drugs, which are absorbed and then converted to active compounds in the blood.[237-241] The oral agents all have longer half-lives, such that they can be given once, twice, or three times daily to achieve relatively steady levels of GP IIb/IIIa inhibition. With oral dosing, long-term therapy (i.e., longer than 1 year) is possible. As with the intravenous compounds, two major groups of drugs exist in the oral class: those with competitive inhibition and short "off time" from the receptor (where a high drug level is critical to achieving high levels of platelet inhibition) and those which have "tight" binding to the platelet (similar to abciximab) with the majority of the drug circulating bound to platelets.

INITIAL CLINICAL EXPERIENCE

Pharmacokinetics and Pharmacodynamics

A number of orally active platelet GP IIb/IIIa inhibitors have been studied in clinical trials (Table 44-5). Currently available data suggest that most of these agents inhibit ex vivo platelet aggregation in response to various agonists [ADP, collagen, or Thrombin Receptor Activator Peptide (TRAP)] that correlates closely with plasma level of active metabolite. In addition, the dose/concentration response is maintained without evidence for tolerance or tachyphylaxis over time. Differences in drug half-life may result in drug accumulation and more pronounced platelet inhibition during chronic therapy, depending on the dose interval employed. The pharmacokinetic and pharmacodynamic response to most oral GP IIb/IIIa inhibitors can be illustrated by comparing and contrasting the responses of short-acting (xemilofiban, half-life 4.1 h), moderate-acting (sibrafiban and orbofiban, half-lives approximately 10 to 11 h), and longer-acting agents (roxifiban and cromofiban, half-lives approximately 24 h).

Xemilofiban

The first experience with oral GP IIb/IIIa inhibition was with xemilofiban.[237,292,293] High degrees of platelet inhibition were achieved with this oral GP IIb/IIIa inhibitor. It has a relatively short half-life and thus is given three times daily. The Oral Glycoprotein IIb/IIIa Receptor Blockade to Inhibit Thrombosis (ORBIT) trial was a randomized dose-ranging trial of xemilofiban in patients undergoing percutaneous intervention.[294] Peak inhibition of platelet aggregation was similar following the same dose of xemilofiban administered on days 14 and 28 of the trial. The time to peak blood level following the same dose of xemilofiban was reduced from 4 h following the first dose of drug to 2 h with steady-state dosing during chronic therapy.[294] Most bleeding events were observed during the first 2 weeks of therapy on a three-times daily dosing regimen.[294] Further bleeding events were uncommon during the final 2 weeks of treatment on a twice-daily dosing regimen, and the requirement for blood transfusion was infrequent.

TIMI-12 Trial

This was a phase II, double-blind, dose-ranging trial designed to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of sibrafiban in 329 patients after acute coronary syndromes.[238] In the pharmacokinetics/pharmacodynamics cohort of TIMI-12, a total of 106 patients were randomized to receive one of seven dosing regimens of sibrafiban, ranging from 5 mg daily to 10 mg twice daily for 28 days. In the safety cohort, 223 patients were randomized to one of four dose regimens of sibrafiban (ranging from 5 mg twice daily to 15 mg once daily) or aspirin for 28 days.

High levels of platelet inhibition were achieved: mean peak values ranged from 47 to 97 percent inhibition of 20 μ*M* ADP-induced platelet aggregation on day 28 across the seven doses. Twice-daily dosing provided more sustained platelet inhibition (mean inhibition, 36 to 86 percent on day 28), while platelet inhibition returned to baseline levels by 24 h with once-daily dosing.[238] Major hemorrhage was rare in patients treated with sibrafiban (1.5 percent) or aspirin (1.9 percent). However, protocol-defined "minor" bleeding, usually mucocutaneous, occurred in 0 to 32 percent of patients in the various sibrafiban groups, compared with none of the aspirin-treated patients. In a multivariate model, minor bleeding was related to total daily dose ($p = .002$), once-daily compared with twice-daily dosing ($p < .0001$), renal function ($p < .0001$), and presentation with unstable angina ($p < .01$).[238]

Thus, the oral GP IIb/IIIa antagonist sibrafiban achieved effective, chronic platelet inhibition with a clear dose response but at the expense of a relatively high incidence of minor bleeding. The mucocutaneous bleeds appeared to be related to plasma drug concentrations, the degree of platelet inhibition, and other patient factors (weight and renal function). One lesson learned is that dosing of sibrafiban (or other oral agents) based on such clinical factors might help improve the safety profile of the drug with regard to minor bleeding.

Peak-to-Trough Ratios

In TIMI-12, approximately double the rate of minor bleeding occurred with once-daily dosing, as compared with similar total daily dose of twice-daily dosing (e.g., 15 mg once daily versus 7 mg twice daily). This may indicate that the higher peak drug concentrations and degree of platelet inhibition (sometimes 100 percent) may be related to the bleeding episodes. The bleeding appeared to occur approximately 6 h after study drug ingestion, which correlates with the peak blood level. Thus, these data suggest that using dosing regimens that avoid high peaks may decrease the risk of bleeding.

Variability

In addition, interpatient variability has been observed in drug level and degree of platelet inhibition. In contrast, the 24- to 72-h infusions of intravenous GP IIb/IIIa inhibitors have doses selected to achieve 80 to 95 percent inhibition-and a very steady level of inhibition is achieved. This is one of the major differences in the pharmacokinetics between the intravenous and oral GP IIb/IIIa inhibitors, and it may be an explanation for differences in clinical outcomes observed to date. This variability might lead to too low a level of inhibition at the trough level or too high a level of inhibition in some patients at peak times.

One potential strategy for dosing oral GP IIb/IIIa antagonists is to monitor the degree of platelet inhibition or drug level achieved in individual patients and adjust the dose to a target level, as is currently done with anticoagulant therapy. By avoiding higher levels of platelet inhibition, this strategy may reduce bleeding complications. This could potentially be accomplished with a bedside assay for platelet inhibition.[287] An alternate strategy for adjusting the dose of an oral GP IIb/IIIa inhibitor is to begin using fixed dose initially but lower the dose if the patient experiences minor bleeding. Such strategies may improve the overall safety profile of these potent platelet antagonists.

Thrombocytopenia

This is another key area of tolerability. Data from the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS)-TIMI-16 trial suggest that, with oral therapy, thrombocytopenia generally occurs early, within the first 2 weeks, with very low rates during long-term follow-up.[295] Among patients who developed thrombocytopenia, however, higher rates of both bleeding and cardiac events were seen. Thus, a very small percentage of patients treated with oral GP IIb/IIIa inhibitors developed thrombocytopenia, and a proportion of those developed thrombosis or bleeding. This pattern bears some resemblance to that for heparin and for intravenous GP IIb/IIIa inhibitors, suggesting the pathophysiology may relate to a more general drug-induced thrombocytopenia ± thrombosis (DITT) syndrome.

Degree of Platelet Inhibition and Efficacy

Previous animal and clinical studies have suggested that the maximum benefit of GP IIb/IIIa inhibition occurs when the degree of platelet inhibition is greater than 80 percent.[284,285] Currently, it is not clear whether lower levels of platelet inhibition would also be beneficial. The IMPACT-II study showed a strong trend toward the reduction of recurrent ischemic events after coronary angioplasty at a dose of eptifibatide that achieved only 50 to 60 percent inhibition.[286] In contrast, a greater benefit was observed with a higher dose of eptifibatide (that targeted 85 to 90 percent platelet inhibition) in the ESPRIT trial (Tcheng J, presented at the American College of Cardiology, March 2000). Thus, it appears that greater benefit, at least in the acute setting, is achieved with doses that achieve more than 80 percent inhibition of 20 μ*M* ADP-induced platelet aggregation, but this is not truly a "threshold" below which no benefit is achieved. For long-term therapy, a high level of blockade will need to be balanced with the potential of increased bleeding, and thus a slightly lower level of inhibition may be optimal.

Degree of Platelet Inhibition and Bleeding

As observed in TIMI-12, increasing the degree of platelet inhibition may produce a higher incidence of minor bleeding events.[238] This suggests that a lower degree of platelet inhibition may be better tolerated during chronic, oral therapy. Nevertheless, major hemorrhage appears to be within an acceptable range in the initial trials with oral GP IIb/IIIa inhibitors, even at high levels of platelet inhibition. Therefore, one possible dosing strategy for GP IIb/IIIa inhibitors may be to tailor the dose to the risk of recurrent ischemic events, thus optimizing the degree of platelet inhibition and minimizing the risk of minor bleeding. For example, patients might be given a higher dose during the early phase of their acute coronary syndrome, when they are at highest risk of recurrent ischemic events. The dose could then be lowered during the chronic phase, when the risk of recurrent ischemic events is lower, thereby decreasing the risk of bleeding.

Need for Aspirin

An important aspect of oral GP IIb/IIIa inhibition is concomitant therapy with aspirin. Several factors suggest the benefit of the combination of aspirin and an oral GP IIb/IIIa inhibitor. First, synergism has been demonstrated for inhibition of platelet aggregation in response to collagen, with a greater degree of platelet inhibition with the combination of aspirin plus the GP IIb/IIIa inhibitor.[296] Second, the action of aspirin is to decrease the synthesis of TXA_2 by the platelet, which decreases platelet *activation*, a step proximal to platelet aggregation. Thus, aspirin and GP IIb/IIIa inhibitors inhibit different steps in the formation of a platelet thrombus. In addition, reduction in TXA_2 reduces local coronary vasospasm, which helps reduce ischemia. Additional factors favoring the combination are aspirin's efficacy for primary and secondary

prevention of ischemic events,[184] its relatively good safety profile, and its low cost. Finally, aspirin would provide antiplatelet effects during the troughs in GP IIb/IIIa blockade that may occur between doses. The potential adverse effect of concomitant aspirin is increased risk of bleeding, particularly gastrointestinal bleeding. In addition, it has been argued that the effects of a GP IIb/IIIa inhibitor are an order of magnitude stronger than those of aspirin-and thus adding aspirin is redundant to the antiplatelet effects of the GP IIb/IIIa inhibitor.

Four Large Phase III Trials

The first phase III trial of an oral GP IIb/IIIa inhibitor in patients with acute coronary syndromes was the OPUS-TIMI-16. This trial involved 10,288 patients randomized at 888 hospitals in 28 countries worldwide. The inclusion criteria were onset within the last 72 h of an acute coronary syndrome defined as rest ischemic pain lasting at least 5 min associated with either ECG changes, positive cardiac markers, or a prior history of vascular disease. Major exclusion criteria included renal insufficiency (creatinine >1.6 mg/dL or an estimated creatinine clearance <40 mL/min, increased bleeding risk, or need for warfarin).

Eligible patients were treated with 150 to 162 mg of acetylsalicylic acid (aspirin) and were randomized, in double-blind fashion, to one of two dosing strategies of orbofiban given twice daily or to placebo. In one dose, orbofiban was given 50 mg twice daily throughout the trial (50/50 group); in the other, the 50 mg twice daily dose was given for the first 30 days (the highest risk period), and then the dose was reduced to 30 mg twice daily (50/30 group). Other medical and interventional therapy was at the discretion of the treating physician. Patients were seen at 14 and 30 days and every 3 months. The primary end point was a composite of death, MI, recurrent ischemia leading to rehospitalization or urgent revascularization, or stroke. The planned sample size was to be 12,000 patients, but the trial was stopped prematurely after an unexpected increased mortality rate at 30 days was observed in one of the orbofiban groups.[297]

The composite end-point rates at 30 days were 10.8 percent in the placebo group compared with 9.9 percent in the two orbofiban groups ($p = 0.12$).[297,298] The mortality rate at 30 days was 1.4 percent in the placebo group compared with 2.3 percent in the 50/30 group and 1.6 percent in the 50/50 group. Through follow-up, 10-month event rates were 22.9, 23.1 and 22.8 percent, respectively (p = NS).[297,298] The safety profile was acceptable, with the rate of major hemorrhage and thrombocytopenia (0.6 percent) greater than with aspirin but within the expected range for this class of drugs. Subsequent exploratory analyses found greater benefit for patients who underwent PCI while on study drug and those who were stable on admission (Killip class I).

Substudies from OPUS-TIMI-16 demonstrated that this agent led to increases in measures of platelet activation, such as P-selectin.[299,300] These data are consistent with the observations in vitro of an apparent prothrombotic effect, with increases in platelet activation and aggregation at low levels of platelet inhibition.[301] In contrast, in TIMI-12, no increase in P-selectin was observed with sibrafiban therapy.[18] Further research in this field is ongoing, but it appears that there may be differences among the oral GP IIb/IIIa inhibitors with regard to the potential prothrombotic effects.

Many lessons were learned from OPUS-TIMI-16, the first large trial of oral GP IIb/IIIa inhibition in acute coronary syndromes, which will be helpful in planning future trials of other GP IIb/IIIa inhibitors. First, it appears that it will be beneficial to optimize the dosing strategy used with the oral agents, potentially to mimic the stable antiplatelet effect achieved by the intravenous drugs. This would mean trying to reduce the interpatient and intrapatient variability, potentially adjusting the dose by weight and/or renal function. One might also use the plasma drug level and/or the bedside platelet function test to adjust the dose. Second, our data suggest that one could target stabilized patients. In addition, several new and planned trials will be testing different drugs (e.g., with tight IIb/IIIa receptor binding).

EXCITE Trial

The Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial studied the agent xemilofiban in patients undergoing PCI. This trial followed the promising results demonstrated by two pilot studies in PCI.[292,294] In the EXCITE trial, 7232 patients undergoing elective PCI (angioplasty or stent)

without adjunctive intravenous GP IIb/IIIa inhibition were randomized in a double-blind fashion to receive one of two xemilofiban regimens or placebo: 20 mg of oral xemilofiban 30 to 90 min prior to percutaneous coronary revascularization, followed by 10 mg or 20 mg xemilofiban or placebo for both were subsequently administered three times daily for 6 months.[302]

Death, MI, or urgent revascularization at 6 months, the primary end point, occurred in 13.6 percent of patients in the placebo group, 14.1 percent of patients in the 10-mg xemilofiban group, and 12.6 percent of patients in the 20-mg xemilofiban group (p = NS).[302] A trend toward fewer periprocedural MIs in the first 48 h following PCI was not sustained.[302] On the other hand, mortality tended to be higher in 10-mg xemilofiban dose group: The mortality rate at 6 months was 1.0 percent for placebo, 1.6 percent for the 10-mg xemilofiban dose group, and 1.1 percent in the 20-mg dose group.[302] Major hemorrhagic events were significantly more common among the xemilofiban-treated patients.[302] Thus, administration of the oral GP IIb/IIIa receptor inhibitor xemilofiban immediately prior to percutaneous revascularization in patients with acute and stable coronary artery disease, and chronically for up to 6 months thereafter, did not significantly reduce the primary composite end point of death, MI, or need for urgent revascularization. Xemilofiban did reduce the incidence of periprocedural MIs during the first 48 h of dosing.

SYMPHONY-I Trial

Following the phase II trial, TIMI-12,[238] the first Sibrafiban Versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes (SYMPHONY) trial was a randomized, double-blind, aspirin-controlled trial of two regimens of sibrafiban for the treatment of patients following an acute coronary syndrome. A total of 9233 patients with either AMI or high-risk unstable angina (with ST deviation of 0.5 mm or more) who were stabilized for at least 12 h were randomized to receive either aspirin (80 mg every 12 h) or high-dose or low-dose sibrafiban (without aspirin) every 12 h for a total of 3 months. The dose of sibrafiban was either 3, 4.5, or 6 mg, based on body weight and renal function. The primary efficacy end point was a composite of death, MI, and severe recurrent ischemia.

There was no difference in the primary end point between aspirin (9.8 percent), low-dose sibrafiban (10.1 percent), and high-dose sibrafiban (10.1 percent). Similarly there were no differences in mortality alone, MI, or recurrent ischemia. Major bleeding was more common with the two sibrafiban groups, high dose (5.7 percent) and low dose (5.2 percent) compared with aspirin (3.9 percent). In conclusion, sibrafiban without aspirin was not superior to aspirin alone for secondary prevention of cardiac events following acute coronary syndromes.

SYMPHONY-II Trial

The second SYMPHONY trial, which was terminated early at the time the SYMPHONY-I results were available, studied the combination of low-dose sibrafiban plus aspirin, high-dose sibrafiban, and aspirin alone. A total of 6671 patients with stabilized acute coronary syndromes were randomized. Follow-up was on average for 90 days. The primary efficacy end point of death, MI, or severe recurrent ischemia showed no difference in the high-dose sibrafiban group (10.5 percent) compared with 9.3 percent for aspirin alone and 9.2 percent for low-dose sibrafiban plus aspirin. The mortality rate was significantly higher with the high-dose sibrafiban group: 2.4 compared with 1.3 percent for placebo and 1.7 percent for the low-dose sibrafiban plus aspirin group. A similar pattern was seen for recurrent MI: 6.9 percent for high-dose sibrafiban compared with 5.3 percent for aspirin and 5.3 percent for the low-dose plus aspirin group. Major bleeding was more common with the two sibrafiban groups, 4.6 percent with high-dose sibrafiban compared with 4.0 percent for aspirin and 5.7 percent for low-dose sibrafiban plus aspirin.

NEW AGENTS ON THE HORIZON

Another agent, lotrafiban, has been studied in phase II and is currently being studied in a large phase III trial-Blockade for the GP IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO)-in which all patients will receive aspirin and be randomized to lotrafiban or placebo. Another agent, cromafiban, has a very long half-life and thus may have more predictable and stable levels of platelet inhibition. Lefradafiban has been tested in a phase II study, with intriguing trends toward benefit among patients with a positive troponin T at

baseline,[303] which is similar to the findings seen with intravenous GP IIb/IIIa inhibitors in the CAPTURE[304] and PRISM trials.[305] These data suggest that identification of the ideal patients with risk-stratification methods may assist in targeting therapy to patients who will benefit most.

Two agents to date have been evaluated as both intravenous *and* oral compounds: Klerval[306,307] and (le)fradafiban.[308] In the TIMI-15B trial, a transition from initial intravenous treatment to prolonged oral treatment with Klerval achieved a smooth transition in the level of platelet inhibition in patients with acute coronary syndromes. Because of low bioavailability, however, the development of this drug was discontinued. Lefradafiban (oral) and fradafiban (intravenous) await further testing.

Roxifiban is an oral agent that binds tightly to platelet receptor and is slow to dissociate.[240,241,309,310] The half-life of dissociation is 7 min, more than 40 times longer than the short-acting molecules like tirofiban (approximately 10 to 20 s) (Table 44-6).[310] Roxifiban's tight binding is similar to that of abciximab, which also has a long half-life of dissociation.[310] This prolonged antiplatelet effect would avoid the possibility of "on-off" proaggregatory effects of the drug binding to the GP IIb/IIIa inhibitor,[301] which may have explained some of the findings from previous trials with oral GP IIb/IIIa inhibitors. Indeed, experimental models have shown that roxifiban has superior antithrombotic effects as compared with other short-acting GP IIb/IIIa inhibitors.[240] With its long half-life, roxifiban is administered once daily. It also has a very high potency and affinity for the GP IIb/IIIa receptor. As such, the oral doses needed are only 0.5 to 1.5 mg once daily. It has a very stable antiplatelet effect over time (i.e., a low peak to trough level of platelet inhibition), and blood levels do not appear to be affected significantly by renal function.

CONCLUSION

Thus, initial disappointment has been seen for the testing to date with oral GP IIb/IIIa inhibitors. Numerous questions remain, such as what level of platelet inhibition is optimal, how efficacy and safety can best be balanced, whether other adjunctive agents are needed, and whether monitoring of platelet function will assist in the use of these agents. In addition, identification of the optimal patients by using tools of risk stratification may assist in targeting therapy to patients who will benefit most. As with other classes of drug, such as beta blockers in congestive heart failure or cholesterol-lowering drugs (beginning with resin drugs 20 years ago), the road toward identifying appropriate patients, doses, and drugs is frequently a long one. With ongoing trials and "second generation" agents (Table 44-6) it is hoped that this class of drugs will be found to be clinically useful.

PREVIOUS | NEXT

Chapter 44: THROMBOGENESIS, ANTITHROMBOTIC, AND THROMBOLYTIC THERAPY

ANTICOAGULANT DRUGS

Unfractionated Heparin

Heparin refers not to a single molecule but rather to a family of mucopolysaccharide chains of varying length and composition. Heparin by itself has no anticoagulant property but rather is a cofactor to antithrombin (formerly referred to as antithrombin III). Heparin accelerates the action of two naturally occurring plasma inhibitors, forming a 1:1 stoichiometric complex with antithrombin III (an inhibitor of thrombin and activated factors X, IX, XI, and XII) and, at very high doses, with heparin cofactor II, which acts only on thrombin decay. Heparin contains a unique pentasaccharide that has a high-affinity binding sequence for antithrombin III. This sequence is present in only one-third of heparin molecules and is not required for binding to heparin cofactor II.

Factor Xa bound to platelets and thrombin bound to the endothelium or to fibrin (thrombus) are protected from inactivation by heparin-antithrombin III complex.[311,312] In plasma, approximately 20 times more heparin is needed to inactivate fibrin-bound thrombin than to inactivate free thrombin [311] This explains why more heparin is needed to prevent the extension of venous thrombosis than to prevent formation of the initial thrombus.

When in the bloodstream after parenteral administration, heparin binds to endothelial cells, mononuclear macrophages, and numerous plasma proteins. Some of these neutralize anticoagulant activity (e.g., platelet factor 4 and vitronectin), whereas others such as von Willebrand factor lose their function. Elevated levels of these heparin-binding proteins explain the different individual heparin dose requirements to obtain the same antithrombotic effect and the so-called "heparin resistance" in patients with inflammatory and malignant diseases.[312] Binding of heparin to the endothelium and various plasma proteins reduces bioavailability at low concentrations and causes variability of response to fixed doses of anticoagulant[312] (Table 44-7).

Table 44-7: Advantages and Disadvantages of Unfractionated Heparin, Low-Molecular-Weight Heparin, and Recombinant Hirudin

Unfractionated Heparin	LMW Heparin	Hirudin
Inhibits to the same extent thrombin and factor VII, much less IXa and XIa	Inhibits mainly factor Xa, thrombin to some extent	Specific and potent inhibitor of thrombin
Antithrombin III-dependent	Antithrombin III-dependent	Antithrombin III-independent
Neutralized by heparinase, several plasma proteins, platelet factor 4, and endothelium	Neutralized by heparinase, weak endothelium binding	Not neutralized by heparinase, endothelium, macrophages, fibrin monomer, and plasma proteins
Does not inactivate clot-bound thrombin and factor VII	Does not inactivate clot-bound thrombin and factor VII	Inactivates clot-bound thrombin
Inhibits platelet function	Inhibits platelet function	Prevents thrombin induced aggregation but not other platelet agonists

Induced thrombocytopenia is not rare	Can induce thrombocytopenia	Does not induce thrombocytopenia
Bioavailability after subcutaneous injection, 30%	Bioavailability after subcutaneous injection, >90%	Good bioavailability after subcutaneous injection, circa 85%
Poor dose-effect response	Fair dose-effect response	Fair dose-effect response
Not immunogenic	Not immunogenic	Not or barely immunogenic
Transient increase of liver enzymes is common	Transient increase of liver enzymes possible	No liver toxicity
Increases vascular permeability	No increase of vascular permeability	No increase of vascular permeability

The pharmacokinetics of heparin are complicated. In brief, the anticoagulant response increases disproportionately in intensity and duration as the dose increases. This explains why the anticoagulant effect of heparin has to be closely monitored. At present, no completely satisfactory test measuring the generation of thrombin and the levels of antithrombin is available. The most commonly used test is the activated partial thromboplastin time (APTT), which is sensitive to the inhibitory effect of heparin on thrombin, factor X, and factor IX. Unfortunately, the different commercial APTT reagents vary in their response to heparin, and there are technical variables. The therapeutic level of the APTT should therefore be established in each clinical laboratory to correspond to 0.2 to 0.4 U of heparin per milliliter plasma by protamine titration or to 0.2 to 0.7 IU factor Xa per milliliter of plasma by the chromogenic substrate assay for the determination of anti-factor-Xa activity.

SIDE EFFECTS

The most common and major side effect of heparin is bleeding. The risk is higher when unfractionated heparin is given by intermittent infusion (14.2 percent) rather than continuous infusion (6.8 percent) or subcutaneously (4.1 percent). Also, the dose of heparin, the patient's anticoagulant response, serious concurrent illness, and chronic consumption of alcohol may predispose the patient to bleeding. HIT occurs in 2.4 percent of patients receiving therapeutic heparin and 0.3 percent for prophylactic heparin. In addition, vascular occlusion occurs in 0.4 percent. Rare complications are osteoporosis (usually with prolonged treatment), alopecia, skin necrosis, urticaria, and transient elevation of hepatic transaminases.

CLINICAL USE

Adjunct to Thrombolytic Therapy: Subcutaneous Heparin

Heparin has been studied in numerous trials in conjunction with thrombolytic therapy, and its role and dosing are still being debated. One of the first trials, which pre-dated the use of aspirin, was the Studio sulla Calciparina nell'Angina e nella Trombosi ventricolare nell'Infarcto (SCATI)[224,313] group, which randomized 711 patients to either heparin or no heparin; 433 of these patients also received streptokinase. These patients did not receive aspirin. This study found a 44 percent reduction in mortality rate when 12,500 U subcutaneous heparin was given to patients with acute MI. This reduction in mortality was significant both in the group receiving streptokinase and in those who did not receive the thrombolytic agent.

The use of heparin in those receiving aspirin as adjunctive therapy with thrombolytic agents (Table 44-8) was examined in many studies, including Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) 2, ISIS-3, and GUSTO. In the GISSI-2/International Study, patients who received streptokinase and heparin beginning 12 h after the infusion of the thrombolytic agent had a non-statistically significant trend toward a decrease in mortality rate as compared with those who received streptokinase alone.[314] The mortality rate for those receiving t-PA was the same whether or not heparin was added to the regimen.[315,316]

Table 44-8: Data from Direct Comparison of Antithrombotic Regimens: GISSI-2, ISIS-3, and GUSTO-I

Outcome	GISSI-2 AND ISIS-3, ASPIRIN PLUS ANY THROMBOLYTIC AGENT		GUSTO-I, ASPIRIN PLUS SK	
	No Heparin (*n* = 31,050), %	SC Heparin (*n* = 31,017), %	SC Heparin (*n* = 9971), %	IV Heparin (*n* = 10,377), %
Death	10.2	10.0	7.2	7.4
Reinfarction	3.3	3.0	3.4	4.0
Total stroke	1.2	1.2	1.3	1.4
Hemorrhagic stroke	0.4	0.5	0.5	0.5
Major bleeding	0.7	1.0	0.3	0.5

ABBREVIATIONS: SK = streptokinase; SC = subcutaneous; IV = intravenous.
SOURCE: Hennekens et al.,[314] with permission.

ISIS-3 found that heparin given subcutaneously (12,500 U every 12 h starting 4 h after the start of thrombolytic therapy) and aspirin given with t-PA or streptokinase resulted in a nearly significant decrease in mortality.[317] There was also a trend toward a decrease in hospital reinfarction rate in the heparin group. However, this early benefit was lost when the primary end point of 35 days was reached. Heparin was associated with a very small excess of major bleeding (0.2 percent of patients: 1.0 percent compared with 0.8 percent for no heparin, $p < .01$). Intracerebral hemorrhage also seemed very slightly increased (0.056 versus 0.40 percent, $p < .05$).[317]

Intravenous Heparin

This is an important adjunctive agent in decreasing reocclusion following t-PA for acute ST-elevation MI. Infarct-related artery patency has been studied in four angiographic trials evaluating whether heparin improves patency. No difference in patency was seen at 90 min.[318] Between 18 h and 5 days, however, there was higher patency among patients randomized to receive intravenous heparin.[319-321] Since early patency was similar, the benefit of heparin is felt to be due largely to decreased reocclusion. All trials with novel variants of t-PA [i.e., r-PA (reteplase) and TNK-t-PA, (tenecteplase)] have used adjunctive heparin in the clinical trials.

Following streptokinase or anistreplase (anisoylated plasminogen-streptokinase activator complex [APSAC]), the role of heparin is less clear. One study with APSAC found no difference in coronary artery patency in those receiving heparin plus aspirin compared with aspirin alone.[322] In the GUSTO-I trial, patients treated with streptokinase with intravenous or subcutaneous heparin had similar infarct-related artery patency at 90 min and 24 h, but those receiving intravenous heparin had significantly higher patency at 5 to 7 days (84 versus 72 percent, $p = .04$).[270] Nonetheless, the overall 30-day mortality and the rate of clinical reinfarction were the same between these two groups.[323] It should be noted, however, that patients randomized to the subcutaneous arm did receive intravenous heparin when recurrent ischemia developed. Therefore, intravenous heparin may be considered optional in streptokinase-treated patients. Of note, however, the American College of Cardiology/American Heart Association guidelines do recommend intravenous heparin for patients receiving streptokinase or APSAC if they are at high risk of developing systemic emboli (e.g., large anterior MI or atrial fibrillation).

Very recent preliminary data on the 5-year follow-up of United States' patients only from GUSTO-I showed

that the streptokinase group with intravenous heparin had a survival similar to that of t-PA. Thus, the late (days 5 to 7) patency advantage observed in the GUSTO angiographic substudy for intravenous heparin as compared with subcutaneous heparin might have translated into only a late mortality benefit. Further analysis of these preliminary data is needed, however.

Unstable Angina/Non-ST-Elevation Myocardial Infarction

In unstable angina and non-ST-elevation MI, heparin is an important component of primary therapy. Two initial small studies suggested a reduction in cardiac events by heparin.[324,325] Three studies of heparin in unstable angina and non-ST-elevation MI also suggest benefit: The Montreal Heart Institute trial showed that heparin reduced refractory angina and MI compared with placebo.[67] A follow-up report extending enrollment in that trial found a reduction in the risk of subsequent MI by heparin compared with aspirin alone.[69] The RISC study failed to demonstrate a beneficial effect of heparin compared with aspirin but noted that, during heparin therapy, patients receiving both aspirin and heparin had the lowest rate of death or MI.[68]

The Antithrombotic Therapy for Acute Coronary Syndromes (ATACS) Study Group evaluated the role of combination antithrombotic therapy compared with aspirin alone in patients with acute ischemic syndromes who were not prior aspirin users.[70] They observed a trend toward fewer ischemic events (death, MI, or recurrent ischemia with ECG changes) in patients receiving aspirin and heparin and warfarin at 12 weeks (19 percent) compared with aspirin alone (28 percent) (p = .09).[70] They went on to perform a meta-analysis of the Theroux, RISC, and their own trial, and found that during the 5 days of active treatment with aspirin and heparin the risk of death or MI was lower than for aspirin alone (odds ratio = 0.44; 95% CI = 0.21 to 0.93).[70] A more recent and comprehensive meta-analysis showed a 33 percent reduction in death or MI at 2 to 12 weeks (7.9 versus 10.4 percent; relative risk = 0.67; 95% CI = 0.44 to 1.02) (Fig. 44-17).[71] These data support the use of aspirin plus heparin in unstable angina/non-ST elevation MI.

HEPARIN RESISTANCE

Variability in the anticoagulant effects of heparin, so-called heparin resistance,[326,327] is thought to be due to the heterogeneity of heparin molecules and to the neutralization of heparin by circulating plasma factors and by proteins released by activated platelets.[328-332] Clinically, frequent monitoring of the anticoagulant response by using APTT is recommended, with titrations made according to a standardized nomogram.[190] The use of a standardized nomogram minimizes the variability in the dosing adjustments given by various physicians and has been shown to improve the achievement of a target APTT.[328,333,334]

THERAPEUTIC RANGE

The exact level of anticoagulation that constitutes the therapeutic range is not yet established. Pilot studies in unstable angina[335] and acute MI[336-339] have suggested that lower APTT values are maybe related to recurrent ischemic events or lower infarct-related artery patency,[340,341] suggesting that the lower limit of the target range of APTT is at least 1.5 to 2 times control. On the upper boundary of the target range, higher APTT values are associated with an increased risk of hemorrhage.[342] In the large GUSTO-I trial of thrombolytic therapy, the lowest rate of bleeding (and mortality) was observed in patients who had a 12-h APTT between 50 and 70 s.[339] Furthermore, in unstable angina, in the TIMI-3B trial, there was no apparent benefit of higher levels of anticoagulation.[343]

HEPARIN DOSING

Standard heparin dosing involves a 5000-U bolus followed by a 1000-U/h infusion, which is then titrated according to the APTT.[328,344] The use of weight-adjusted heparin has been suggested as a means of improving APTT control and safety.[345] In one randomized trial, a high percentage of patients "overshot" in the initial APTT at 6 h (median, 150 s).[346] Another trial that examined a 60-U/kg bolus and an infusion of 12 U/kg per hour compared with fixed dosing found a higher percentage of patients within range without a

large number of APTTs above range at 6 h.[347] A third trial that tested standard dosing versus weight-adjusted dosing (70-U/kg bolus and initial infusion of 15 U/kg per hour) found no significant difference in control of APTT with weight-adjusted dosing.[348] Another approach uses on-line feedback of APTT data to a computer algorithm using a pharmacodynamic model of heparin response in the individual patient, with promising results in an initial pilot trial.[349]

An important lesson learned from recent trials is that lower initial doses of heparin in the setting of thrombolytic therapy are associated with a lower rate of intracranial hemorrhage. In the TIMI-10B and Assessment of the Safety of a New Thrombolytic (ASSENT-I) trials,[350] and in TIMI-9 and GUSTO-II trials,[351-354] when the doses of heparin were reduced in the first part of the trial to the second part of the trial, the rates of ICH and major hemorrhage were reduced. A recent overview of all major thrombolytic trials, and of detailed information from the TIMI trials and the Intravenous n-PA for Treatment of Infarcting Myocardium Early II (InTIME-II) trial, confirmed that lower doses of heparin are associated with reduced ICH.[355]

Further very compelling evidence of the benefit of lower doses of heparin comes from the InTIME-II trial, which compared the single-bolus thrombolytic agent, lanoteplase, and accelerated t-PA in 15,078 patients worldwide. The heparin dose was 70-U/kg bolus with a maximum of 4000 U (i.e., 4000 U/kg/h for all patients weighing more than 57 kg) and 15-U/h (max 1000 U/h) infusion. The rate of ICH for t-PA was the lowest ever reported in a large trial for accelerated t-PA: 0.62 percent.[355]

CURRENT RECOMMENDATION

Based on the emerging data, the 1999 update to the American College of Cardiology/American Heart Association guidelines for the management of acute MI will recommend a new lower dose of heparin: a bolus of 60 U/kg (maximum, 4000 U) and an initial infusion of 12 U/kg per hour (maximum, 1000 U/h).[356] No maximum is needed in nonthrombolytic treated patients. The guidelines also call for frequent monitoring of APTT (every 6 h until in the target range and every 12 to 24 h thereafter) and for titration of heparin by using a standardized nomogram, with a target range of APTT between 1.5 to 2 times control or approximately 50 and 70 s.[356]

CORONARY REVASCULARIZATION PROCEDURES

Use of adequate heparinization with aspirin throughout the procedure is strongly recommended.[357] The exact level of anticoagulation with unfractionated heparin has been debated, but current recommendations are to achieve an activated clotting time between 300 and 350 s in patients *not* receiving a GP IIb/IIIa inhibitor.[358] This can generally be achieved using a weight-adjusted dose of a 100-U/kg bolus, with 20-U/kg additional boluses if needed.[359] For patients who do receive a GP IIb/IIIa inhibitor, the target should be approximately 200 to 250 s, based on data from the EPILOG trial.[285]

LMW Heparins

Some of the limitations of unfractionated heparin can be overcome with LMW heparin (mean molecular weight, 4000 to 5000; range, 1000 to 10,000). LMW heparins produce their major anticoagulant effect by binding to antithrombin through the same high-affinity pentasaccharide sequence of unfractionated heparin, which, however, is present in only one-third of the LMW heparins. A minimum additional chain length of 15 saccharides (MW > 5400) is required for the inactivation of thrombin, but the inactivation of factor X requires only the pentasaccharide (Fig. 44-18). Unfractionated heparin has an anti-factor Xa to anti-factor II ratio of 1:1, which is between 4:1 and 2:1 for the various LMW heparins. Drugs with a high anti-factor Xa activity were indeed designed based on the hypothesis that inhibition of earlier steps in the blood coagulation system would be associated with a more potent antithrombotic effect than inhibition of subsequent steps. This is because of the amplification process inherent in the coagulation cascade; that is, a single factor Xa molecule can lead to the generation of hundreds of thrombin molecules.

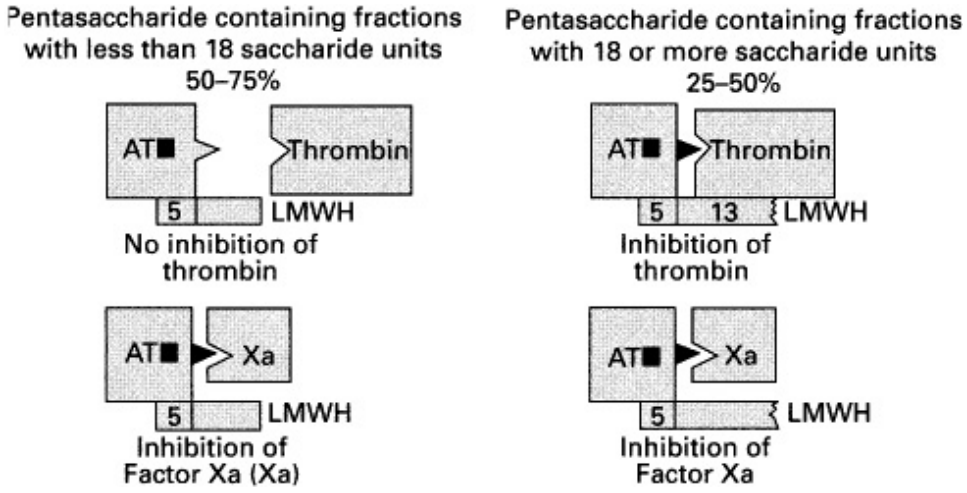

Figure 44-18: Mechanism of action of heparin and low molecular weight heparin (LMWH): Heparin acts as a cofactor to antithrombin to (1) change the conformation of its active site and (2) serve as a "bridge" to bring together an antithrombin (AT) and thrombin. Heparin is a catalyst: after it facilitates the binding of one pair of thrombin and antithrombin molecules, it is released and facilitates another thrombin-antithrombin interaction. LMWH also binds to antithrombin and changes the conformation of its active site, but does not act as a bridge to thrombin. Approximately 25 to 50 percent of the LMWH molecules of different commercial preparations contain at least 18 saccharide units, which allows binding to the heparin-binding site of thrombin, and thus both these molecules inhibit thrombin and factor Xa. The remaining 50 to 75 percent of LMWH molecules contain fewer than 18 saccharide units and inhibit only factor Xa.

The advantages of LMW heparins over unfractionated heparin are numerous (Table 44-7). Factor Xa bound to the platelet membrane in the prothrombinase complex is resistant to inactivation by unfractionated heparin but is not resistant to inactivation by LMW heparins. Also, LMW heparins have lesser binding characteristics to platelet factor 4, other plasma proteins, and endothelial cells, resulting in a higher bioavailability (after subcutaneous injection, greater than 90 versus 30 percent for unfractionated heparin); reduced plasma clearance, which is independent of dose and plasma concentration; a longer half-life (anti-factor Xa activity between 3 and 4 h for LMW heparins compared with 30 to 150 min for unfractionated heparin); and less interindividual variability of the anticoagulant response.[360] LMW heparins have a lower affinity for von Willebrand factor,[361] increase vascular permeability less than unfractionated heparin, and have a weak effect on platelet function. These differences could explain why LMW heparins produce less bleeding than unfractionated heparin with equivalent or higher antithrombotic effect in experimental animals[360] and in some clinical studies.

The long half-life of LMW heparins and their predictable anticoagulant response to weight-adjusted doses allow a twice daily subcutaneous administration without laboratory monitoring.[360]

HEPARINOIDS: MIXTURE OF LMW SULFATE GLYCOSAMINOGLYCANS

Danaparoid sodium (Org 10172) is a LMW heparinoid (6 kDa) and consists of a polydispersed mixture comprising sulfated glycosaminoglycuronides derived from animal mucosa; heparan sulfate (83% wt/wt), of which 4 to 5 percent has high affinity for antithrombin III; dermatan sulfate (12% wt/wt); and a minor amount of chondroitin sulfate (5% wt/wt).[362] There is uncertainty whether the low-affinity fraction of danaparoid sodium has an antithrombotic function[363] or not.[364] Danaparoid sodium was more efficacious than heparin and was associated with less and briefer bleeding than heparin in various animal models of thrombosis.

The complex mechanism of the antithrombotic activity of danaparoid sodium can so far be only partially explained. Its anticoagulant profile is characterized by a high ratio of anti-factor Xa/antithrombin activity (14 over < 0.5), resulting in an effective inhibition of thrombin generation. The anti-factor Xa activity is

mediated by antithrombin and is not inactivated by endogenous heparin-neutralizing factors. The low antithrombin activity is mediated by heparin cofactor II and antithrombin III. The heparan sulfate fraction with low affinity for antithrombin III, despite lacking significant effects on coagulation factors Xa and IIa (thrombin) in vitro, has been shown in animal studies to contribute substantially to the antithrombotic activity. In contrast to heparin, danaparoid sodium shows hardly any or no effect on platelet function in vitro or in vivo. Danaparoid sodium is essentially free of contaminating heparin, has minimal cross-reactivity in in vitro assays for HIT, and has been used successfully in patients with this complication.

Pharmacokinetic studies have been primarily based on the kinetics of relevant anticoagulant activities because no specific chemical assay methods are available. In comparison with heparin, danaparoid sodium has a prolonged elimination half-life of anti-factor Xa activity. After intravenous and subcutaneous administration of danaparoid sodium, the antithrombin activity half-life is shorter (1.8 h) than its anti-factor Xa half-life (17.6 h). Danaparoid sodium has an absolute bioavailability of 100 percent after subcutaneous administration. The kidneys play an important role in the elimination of the anti-factor Xa activity of danaparoid sodium, but a cellular metabolism seems unlikely, since the liver does not affect the anti-factor Xa activity and there is only slight and reversible binding to the endothelium.[71,364]

Danaparoid sodium is effective in the prevention of deep venous thrombosis in patients with thrombotic stroke and after elective hip surgery or hip fracture.[365] The long half-life of danaparoid sodium, which is not effectively neutralized by protamine, has been rather difficult to manage clinically.

Clinical Use of LMW Heparin

LMW heparin has been studied extensively in the prevention and more recently for the treatment of venous thrombosis. In the United States, it is approved for prophylaxis against deep venous thrombosis based on results from several trials.[344,366-368] Other trials for the *treatment* of deep venous thrombosis have also been promising.[344,369-372] Several of these trials have demonstrated a lower rate of major hemorrhage with LMW heparin than with standard heparin.[344]

LMW HEPARIN IN UNSTABLE ANGINA

In recent years, LMW heparin has been studied extensively in unstable angina. Two pilot trials were encouraging.[373,374] A second, open-label pilot trial in unstable angina and non-Q-wave MI has also suggested that LMW heparin may be superior to aspirin and heparin.[375] This study used nadroparin (Fraxaparin), which has a 3:1 ratio of factor Xa-thrombin inhibition.

DALTEPARIN

In the first large trial of LMW heparin in unstable angina, the Fragmin During Instability in Coronary Artery Disease (FRISC) study, dalteparin plus aspirin was found to reduce death or MI dramatically over the first 6 days compared with aspirin alone (1.8 versus 4.8 percent, $p = .001$).[72] (Note that this is a significant reduction compared with aspirin alone, whereas the meta-analysis for unfractionated heparin had a risk reduction of 33 percent and $p = .06$.)[71] Beyond 6 days, dalteparin was continued versus placebo and, at 40 days, the composite of death, MI, or need revascularization was significantly reduced (2.2 versus 5.7 percent, $p < 0.001$).[72] A subsequent trial of patients with unstable angina for less than 72 h, the Fragmin in Unstable Coronary Artery Disease (FRIC) trial, found no difference in clinical outcomes between intravenous heparin and dalteparin, indicating it was a suitable alternative to unfractionated heparin, although it was not shown to be superior in this trial.[376]

ENOXAPARIN

The Evaluation of the Safety and Efficacy of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events (ESSENCE) trial compared enoxaparin (a LMW heparin with 3.8:1 factor Xa-thrombin inhibition ratio) with intravenous heparin in 3000 patients with unstable angina and non-Q-wave MI. A 2 to 3 day course of enoxaparin was superior to unfractionated heparin with regard to the primary end point, the occurrence of

death, MI, or recurrent ischemia at 14 days (16.6 versus 19.8 percent, $p = .019$).[73] The rates of this end point at 30 days were 19.8 versus 23.3 percent ($p = .016$).[73] Death or MI to 30 days also favored enoxaparin (6.2 versus 7.7 percent, $p = .08$).

Interestingly, in this double-blind trial, the rates of catheterization (43 versus 46 percent, $p = .08$ for enoxaparin compared with heparin) and PCI (13 versus 17 percent, respectively, $p = .001$) were lower in patients treated with enoxaparin. A subsequent cost-effectiveness analysis found that there was a minimal increase in the cost for the drug (enoxaparin compared with unfractionated heparin with APTT measurements) ($75)-but with lower rates of catheterization and revascularization, treatment with enoxaparin led to a *savings* of $1172 per patient treated. Thus, both improved outcomes, and lower costs were observed with enoxaparin compared with unfractionated heparin.

TIMI-11 Trials These also studied enoxaparin in unstable angina and non-Q-wave MI. In TIMI-11A, the first goal was to determine the appropriate dose of enoxaparin-whether to use a dose that previously had been shown to be effective in venous thrombosis (1.0 mg/kg subcutaneously twice daily) or whether higher doses would be beneficial in arterial thrombosis. In TIMI-11A, a higher dose (1.25 mg/kg) was found to have an unacceptably high rate of major hemorrhage, 6.5 percent to 14 days, as compared with a rate of 1.9 percent for patients treated with 1.0 mg/kg.[377] There was no difference in the rate of recurrent ischemic events between the two doses. Thus, the dose of 1.0 mg/kg appeared to be appropriate and was used in the TIMI-11B trial.

The TIMI-11B trial studied high-risk patients with unstable angina and non-ST-elevation MI. They were required to have ST deviation or positive cardiac serum markers (CK-MB or troponin) to be enrolled. TIMI-11B compared intravenous unfractionated heparin with enoxaparin (1.0 mg/kg subcutaneously twice daily in hospital and a fixed dose b.i.d. as an outpatient) for a total of 43 days. Death, MI, or severe recurrent ischemia requiring urgent revascularization through day 14 occurred in 16.6 percent of patients treated with heparin and in 14.2 percent of patients treated with enoxaparin ($p = .03$), a 15 percent relative risk reduction.[75] The rate of the primary end point to 43 days was 19.6 percent for unfractionated heparin and 17.3 percent for enoxaparin ($p = .049$).[75] Parallel reductions in death and MI were also observed.

A meta-analysis of the TIMI-11B and ESSENCE trials showed that, at 43 days, enoxaparin reduced the rate of death, MI, or urgent revascularization from 18.7 to 15.6 percent ($p = .0006$). Death or MI at 43 days was reduced from 8.6 to 7.1 percent ($p = .02$) (Fig. 44-19).[74] Thus, enoxaparin has been shown in two large randomized trials to be superior to unfractionated heparin for the treatment of unstable angina and non-ST-elevation MI. The FDA has approved enoxaparin for the treatment of patients with unstable angina and non-ST-elevation MI.

LMW HEPARIN IN ANGIOPLASTY, STENTS, AND ACUTE MYOCARDIAL INFARCTION

There is emerging experience with LMW heparin in angioplasty. One study found that LMW heparin did not reduce restenosis.[378] However, LMW heparin may play a role in preventing thrombotic complications after complicated angioplasty. A recent nonrandomized experience of patients with suboptimal angioplasty or stent results treated some patients with LMW heparin for 4 weeks and others with standard care (aspirin). They found a reduced rate (1.5 versus 8.2 percent, $p < 0.05$) of death or recurrent MI during follow-up.[379] Thus, LMW heparin appears to have great promise and further randomized trials are under way.

Similarly, trials of LMW heparin in acute MI treated with thrombolytic therapy are under way.[380,381] In the setting of ST-elevation MI treated with thrombolytic therapy, one recent study found a significant reduction in the rate of death, MI, or readmission for an acute coronary syndrome.[380] A total of 300 patients treated with thrombolysis (predominantly streptokinase, but also anistreplase and t-PA) were randomized to intravenous unfractionated heparin (5000-U bolus and 1250 U/h titrated to an APTT of 2 to 2.5 times control) or enoxaparin (40-mg intravenous bolus, followed by 40 mg subcutaneously every 8 h) for 4 days. The rate of the composite end point at 3 months was 36.4 percent for heparin and 25.5 percent for enoxaparin ($p = .04$).[380] It appeared that rebound was reduced by enoxaparin, with the rate of reinfarction

from days 4 to 6 of 6.6 percent for heparin and 2.2 percent for enoxaparin (p = .05).[380]

In a second recent study, dalteparin was compared with placebo in streptokinase-treated patients. TIMI grade 3 flow 20 to 28 h later tended to be higher in patients treated with dalteparin (68 versus 51 percent, p = .10), and the number of ischemic episodes on continuous ECG monitoring was lower (16 versus 38 percent, p = .04).[381]

Most recently, Heparin Aspirin Reinfarction (HART-II) trial compared enoxaparin with unfractionated heparin as adjuncts to t-PA and aspirin for patients with acute MI.[382] There was a strong trend toward improved early TIMI grade 3 flow with enoxaparin (53 versus 48 percent for unfractionated heparin, p = .06). There was an even greater effect on reocclusion (5.9 versus 9.8 percent).[382] Thus, LWM heparins appear to be beneficial in these pilot trials with thrombolysis, and larger studies are underway to try to confirm these results.

Direct Thrombin Inhibitors

These have also undergone extensive evaluation in conjunction with thrombolytic therapy. The prototypic agent is hirudin, a 65-amino-acid polypeptide that is derived from the leech *Hirudo medicinalis*, which acts as a potent and selective inhibitor of thrombin.[383] Hirudin selectively binds thrombin in a 1:1 fashion at two sites: (1) the carboxy terminus of hirudin binds to the substrate recognition site, the domain of thrombin that recognizes fibrinogen[384] or the platelet;[385] and (2) the amino terminus of hirudin binds to the catalytic site of thrombin.[384] Hirudin does not inhibit other enzymes in the coagulation or fibrinolytic pathways such as factor Xa, IX, kallikrein, activated protein C, plasmin, or tissue plasminogen activator.[383] Hirudin does not bind covalently to thrombin; however, the dissociation rate is extremely slow, making hirudin an essentially irreversible inhibitor of thrombin.[383,386]

In patients with established coronary artery disease with normal renal function (serum creatinine, 1.0 ± 0.2 mg/dL), the plasma half-life of hirudin was found to be 2 to 3 h,[387] in agreement with the half-life of the effect of hirudin on the APTT of about 2 to 3 h. Hirudin is produced in yeast by recombinant DNA technology. Several different hirudin preparations are available, including desirudin[352,354,388] and lepirudin.[389]

Other analogs are also available, including bivaluridin (Hirulog),[390-392] argatroban,[393] efegatran,[394] and inogatran.[395] Hirulog contains three domains: the 12-amino-acid carboxy terminus derived from hirudin; a four-amino-acid sequence, D-Phe-Pro-Arg-Pro, which binds to the catalytic site of thrombin; and a linker region with the optimal length to allow binding of both inhibitory sites.[390] The hirulog-thrombin complex is transient, as thrombin can slowly cleave the Pro-Arg bond in the N-terminal extension. This metabolic cleavage contributes to its half-life on the APTT of about 40 min. Only 20 percent of hirulog is excreted in the urine, indicating an extensive hepatic catabolism or proteolysis at other sites. Argatroban is an arginine derivative that binds to thrombin with intermediate affinity.

Direct thrombin inhibitors have been shown to inhibit all of the major actions of thrombin, including thrombin-induced generation of fibrin and thrombin-induced platelet activation, as well as thrombin's autocatalytic reaction.[383,396] Potential advantages of hirudin over heparin are that hirudin can inhibit clot-bound thrombin,[275] it is not inhibited by activated platelets,[397] and it does not require a cofactor and thus may provide a more stable anticoagulant response.[396]

ADJUNCT TO THROMBOLYTIC THERAPY

The effects of desirudin in the setting of thrombolysis were tested in TIMI-5, 6, and 9 and GUSTO-II.[352,354,388,398] Hirudin provided a more stable APTT, within the target range almost twice as frequently. No episodes of thrombocytopenia were reported for hirudin.

In TIMI-5, a lower rate of recurrent MI was observed (4.3 versus 11.9 percent, for hirudin and heparin, respectively, p = .03), as well as a trend toward lower reocclusion (1.6 versus 6.7 percent, p = .07).[388] In the

phase III TIMI-9B trial, a similar trend in lower reinfarction was observed in hospital (2.3 versus 3.4 percent, $p = .07$), but no difference was observed in the primary end point (death, MI, or severe congestive heart failure/shock) at 30 days (12.9 percent for hirudin and 11.9 percent for heparin, p = NS).[352] Similarly, death or MI was not different between the two anticoagulants (9.7 versus 9.5 percent, p = NS).[352] Hirudin was tested in over 12,000 patients across the full spectrum of acute coronary syndromes in the GUSTO-IIb trial. There was a reduction in reinfarction (5.4 versus 6.3 percent for heparin, $p = .04$) but only a trend toward reduction in death or MI at 30 days (8.9 versus 9.8 percent, $p = .06$).[354] In patients with ST-elevation MI, death or MI was slightly lower (9.9 versus 11.3 percent, $p = .13$). An intriguing trend to benefit was seen in streptokinase-treated patients in GUSTO-II,[399] but this was not observed in TIMI-9B.[352]

In the HIT-III trial, excess ICH was observed with lepirudin (3.4 versus 0 percent). In the subsequent HIT-4 trial, involving 1208 patients and using a lower dose of lepirudin, TIMI flow grade 3 was observed in 40.7 percent in the lepirudin and in 33.5 percent in the heparin group ($p = .16$), No differences were seen between lepirudin and heparin in the rates of hemorrhagic stroke (0.2 versus 0.3 percent), reinfarction (4.6 versus 5.1 percent), or mortality (6.8 versus 6.4 percent) at 30 days. Thus, lepirudin in conjunction with streptokinase did not significantly improve reperfusion or clinical outcomes in this study.

Angiographic trials with other direct thrombin inhibitors in conjunction with thrombolytic therapy have also been conducted. In a pilot study and the Hirulog Early Rerfusion/Occlusion (HERO) trial, a trend toward improved early (90 to 120 min) TIMI grade 3 flow was observed with the higher dose of Hirulog as compared with heparin in patients receiving streptokinase.[391,392] Testing with other agents found modest or no improvements compared with heparin.[393,394,400]

UNSTABLE ANGINA

The hirudin desirudin was tested in the GUSTO-IIb trial involving 12,142 patients with unstable angina/non-ST-elevation MI and ST-elevation MI. In the entire cohort, the 30-day rate of death or MI tended to be lower (8.9 versus 9.8 percent, $p = .06$),[354] with no difference in mortality and a modest reduction in reinfarction (5.4 versus 6.3 percent for heparin, $p = .04$). In the 8011 patients with unstable angina or non-ST-elevation MI, the rate of death or MI was not significantly reduced at 30 days (8.3 versus 9.1 percent, $p = .22$).[354]

Lepirudin was compared with heparin in the Organisation to Assess Strategies for Ischemic Syndromes 2 (OASIS-2) trial,[389] and there was a strong trend toward reduction in cardiovascular death or MI at 7 days (3.6 versus 4.2 percent, respectively, $p = .08$). Major bleeding requiring transfusion was infrequent but more frequent with lepirudin (1.2 versus 0.7 percent for heparin, $p = .01$). The authors performed a meta-analysis of all the hirudin trials and observed a modest 10 percent benefit favoring hirudin, although this was not statistically significant for patients with unstable angina.

Other synthetic direct thrombin inhibitors have also been tested [e.g., argatroban and bivaluridin (Hirulog)], and again only modest or no improvements were observed compared with heparin,[400,401] although lower rates of bleeding have been observed with bivalirudin.[401] The direct thrombin inhibitors have been observed to provide a very stable level of anticoagulation, as measured by APTT,[354,402,403] and no episodes of thrombocytopenia were reported for the hirudin class. Of note, lepirudin is approved by the FDA for use as an anticoagulant in patients with HIT and associated thromboembolic disease.

USE DURING CORONARY ANGIOPLASTY

Following a pilot trial of hirudin in low-risk patients undergoing angioplasty, which showed a reduction in early abrupt closure,[404] a larger randomized, double-blind study compared hirudin (40-mg bolus followed by 0.2 mg/kg per hour) with heparin in the prevention of restenosis after coronary angioplasty.[405] The primary end point was event-free survival (freedom from cardiac death, MI, coronary bypass surgery, bailout procedure, repeat percutaneous transluminal coronary angioplasty, or elective stent placement). At 7 months, event-free survival was 67.3 percent in the group receiving heparin, 63.5 percent in the group

receiving intravenous hirudin, and 68.0 percent in the group receiving both intravenous and subcutaneous hirudin (p = .61). However, the administration of hirudin was associated with a significant reduction in early cardiac events, which occurred in 11.0, 7.9, and 5.6 percent of patients in the respective groups. Although significantly fewer early cardiac events occurred with hirudin than with heparin, hirudin had no apparent benefit with longer-term follow-up. Two retrospective analyses have recently shown that patients with unstable angina, treated with hirudin, and who undergo PCI on the study drug, have a dramatic reduction in death or MI. In the OASIS-2 trial, there was a 60 percent reduction in death or MI in those undergoing PCI compared with 5 percent in those who did not.[406] Thus, these data are consistent with those with GP IIb/IIIa inhibitors, which show a benefit both before and after the procedure.[407]

The direct thrombin inhibitor bivalirudin (Hirulog) was studied in a double-blind, randomized trial of over 4000 patients with unstable angina or recent MI undergoing angioplasty. Patients were assigned to receive either heparin or bivalirudin immediately before angioplasty. Overall, bivalirudin did not significantly reduce the incidence of the primary end point (death, MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin: 11.4 versus 12.2 percent for heparin). In the prospectively stratified subgroup of 704 patients with postinfarction angina, however, bivalirudin therapy did lead to a significant reduction in the primary end point (9.1 versus 14.2 percent, p = .04). In addition, bivalirudin was associated with a lower incidence of bleeding (3.8 versus 9.8 percent, p 0.001). No differences in recurrent ischemic events were seen at 6 months. Thus, bivalirudin appeared to be as effective as heparin but with a better safety profile during angioplasty. This study pre-dated coronary stenting and GP IIb/IIIa inhibitors, so more information is needed to assess its potential role. The FDA recently approved bivalirudin for use during angioplasty.

Thus, to date, the direct thrombin inhibitors have not produced a dramatic improvement in clinical outcome as adjuncts to thrombolytic therapy. The benefits in unstable angina have been modest and almost reached statistical significance on the primary end point in one trial and in angioplasty one agent is approved for use. There are several large ongoing trials evaluating the direct thrombin inhibitor bivalirudin HERO-2 is comparing bivalirudin with heparin as an adjunctive agent to streptokinase, and another is comparing bivalirudin plus bailout abciximab with heparin plus abciximab.

Warfarin/Oral Anticoagulants

Warfarin sodium and related coumarin congeners are effective antithrombotic compounds that differ in speed in the inhibition of vitamin K-2,3-epoxide within hepatic chromosomes. These compounds depress the synthesis of four vitamin K-dependent procoagulants (factors II, VII, IX, and X) and of two natural inhibitor proteins C and S (Fig. 44-20). The plasma concentration of these proteins will decrease in accord with their half-lives. The coagulation components with the shortest half-lives are the procoagulant factor VII and the endogenous anticoagulant protein C. This may cause a frank imbalance between procoagulants and anticoagulants at the start of treatment and lead to thrombosis of skin capillaries and venules with cutaneous necrosis.[408]

MONITORING OF WARFARIN TREATMENT

The intensity of the effect of warfarin on the synthesis of coagulation factors differs among patients; moreover, in the same individual, it may, over time, vary considerably. This explains the need for close monitoring by having daily blood tests in the first week of treatment with warfarin. The test used is the *prothrombin time*, a term that leads to confusion because the assay depends in fact on the global activity of five coagulation factors (prothrombin and factors V, VII, IX, and X). Among the six factors whose synthesis is inhibited by coumarin derivatives, three (prothrombin and factors VII and X) are effectively measured by this test, but not factor IX and the anticoagulant proteins C and S. On the other hand, the prothrombin time is also sensitive to factor V, a coagulation protein independent of vitamin K.

To perform the prothrombin time, a tissue extract (thromboplastin) and calcium are added to citrated plasma and the time to fibrin formation is measured. Commercial thromboplastin reagents extracted by different methods from various organs and species vary extensively in their sensitivity to reductions in levels of vitamin K-dependent factors. To standardize determinations of prothrombin time and thus allow direct comparison of results obtained with different thromboplastins, the INR is recommended.[409]

At the start of warfarin treatment, the prothrombin time is first prolonged by factor VII depletion because factor VII has a half-life much shorter than that of the other vitamin K-dependent coagulation factors (prothrombin and factors IX and X). Thus, in the beginning of warfarin treatment, the prothrombin time is prolonged, while the intrinsic and common coagulation pathways are still uninfluenced. This explains why, in switching from heparin to warfarin, heparin should be continued unabated for at least 1 day after the prothrombin time (INR) has reached therapeutic values. Also, during long-term warfarin therapy, prothrombin times should be checked regularly, as many drugs and foods can enhance or decrease the warfarin effect. Certain intercurrent diseases (liver insufficiency, heart failure, and hyperthyroidism) may also modify warfarin dose requirements.

Bleeding is the most important side effect, and the risk may vary from patient to patient, depending on the presence of comorbid conditions (hypertension, malignancy, older age, recent surgery) and the intensity of anticoagulation. Patients with intensive anticoagulation (INR = 2.5 to 4) have, during the first 3 months, a risk of clinically important bleeding over two times greater (14 versus 6 percent) than those with less intensive anticoagulation (INR = 2.0 to 2.5).[410] On average, the annual overall risk of bleeding is 6 percent, with the incidence of major and fatal bleeding estimated to be 2 and 0.8 percent, respectively.

A rare, nonhemorrhagic side effect of warfarin is coumarin-induced skin necrosis, an unexplained complication that occurs between days 3 and 8 of therapy. The rapid decline in protein C level is postulated to play a role in the obscure pathogenesis of thrombosis of skin venules and capillaries within the subcutaneous fat, usually in the lower part of the body. Coumarin drugs readily cross the placenta and may be teratogenic, particularly during the first trimester of pregnancy. In conclusion, vitamin K antagonists are effective antithrombotic drugs with a narrow risk-benefit ratio that require regular monitoring and a disciplined patient (Table 44-9). Their main virtues are oral administration and low cost.

Table 44-9: Drawbacks of Coumarin Drugs and Profile of an Ideal Antithrombotic Drug

Delayed action
Need for blood monitoring prothrombin time (PT)
PT test does not fully reflect the drug effect
Interaction with many commonly used drugs leading to:
Potentiation of anticoagulation
Decreasing anticoagulation level
Sometimes modifying the activity of the other inter- acting drug
Anticoagulation level influenced by diet
Annual risk of bleeding: Total 6%
Major 2%
Fatal 0.8%
Narrow benefit-to-risk ratio
Embryotoxicity during first trimester of pregnancy

CLINICAL STUDIES

Anticoagulant therapy with warfarin has been shown to be beneficial following MI. In pooled data from seven randomized trials between 1964 and 1980, oral anticoagulant therapy over a 1- to 6-year period

reduced the rate of death or MI by 20 percent.[411] Subsequently, there have been three large studies evaluating warfarin after MI (both ST-elevation MI and non-ST-elevation MI). In Warfarin Reinfarction Study (WARIS), mortality was reduced by 24 percent (p = .027) and reinfarction was reduced by 34 percent. More recently, the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial demonstrated a similar reduction in reinfarction (53 percent benefit of warfarin compared with placebo) in patients following acute MI.[412] Thus, warfarin monotherapy appears to be at least as effective as aspirin after MI.

Two clinical trials compared warfarin therapy with antiplatelet therapy in secondary prevention of MI. In the German Austrian Myocardial Infarction Study (GAMIS), 946 patients 38 to 42 days after acute MI were randomized to open-label phenprocoumon (target INR = 2.5 to 5.0), aspirin 1.5 g/day, or placebo.[241,413] No difference was observed between groups in mortality or reinfarction. The French Enquete de Prevention Secondaire de l'Infarctus de Myocarde (EPSIM) study[243,414] revealed no difference in death or reinfarction in patients receiving either oral anticoagulants or aspirin, but there were 54 percent more patients with gastrointestinal events with aspirin and four times more severe hemorrhagic events with warfarin. In the Aspirin Versus Coumadin in the Prevention of Reocclusion and Recurrent Ischemia After Successful Thrombolysis (APRICOT) trial, 300 patients were randomized to either 325 mg of aspirin per day or heparin followed by warfarin (target INR = 2.8 to 4.0) after an initial angiogram less than 48 h after acute MI revealed a patent infarct-related artery.[414] At 3 months, there was no significant difference in reocclusion rates among the warfarin, aspirin, and placebo arms. Aspirin significantly reduced reinfarction compared with placebo but not with warfarin. The mortality rates did not differ between the groups.

The Coumadin Aspirin Reinfarction Study (CARS) evaluated the combination of aspirin (80 mg) and fixed-dose warfarin (1 or 3 mg, not adjusted to a prothrombin time) compared with aspirin alone (160 mg). No benefit was observed with the combinations of fixed-dose warfarin plus aspirin with regard to recurrent MI, cardiac death, or nonfatal ischemic stroke.[415] More recently, a trial involving men at risk for ischemic heart disease, using a slightly higher dose of warfarin (4.1 mg on average titrated to an INR of 1.5), found a significant reduction compared with placebo in coronary death or MI with the combination of warfarin and aspirin 75 mg daily.[416] In this trial, there was an increase in hemorrhagic strokes among patients treated with the combination (0.9 versus 0.1 percent for warfarin alone, 0.2 percent for aspirin alone, and 0 percent for placebo; p = .009).[416] The Combination Hemotherapy and Mortality Prevention (CHAMP) study randomized patients to receive either 160 mg/day of aspirin or 80 mg of aspirin plus coumadin to achieve an INR of 1.5 to 2.5. Results of this study found no difference in mortality or recurrent events with the addition of warfarin to aspirin.[417] Major bleeding was more common in the combination group: 1.25/100 patient years compared with 0.69/100 patient years for aspirin alone. Preliminary results of two studies (APRICOT II and ASPECT II) have shown benefit with the combination of coumadin (higher INR than in previous studies) plus aspirin as compared to aspirin alone (Verhevgt et al., European Congress of Cardiology, Amsterdam, 2000).[418]

There are several other areas for benefit or potential benefit with warfarin therapy. First, warfarin is superior to aspirin in prevention of systemic emboli in patients with atrial fibrillation.[411,419] In addition, beneficial effects in reducing systemic emboli have also been observed in patients after MI with documented left ventricular dysfunction.[420] Thus, in selected patients at risk for systemic emboli, warfarin affords a second beneficial effect. Thus, at present, warfarin is a suitable alternative to aspirin following MI, and is indicated if there is a risk for systemic embolization.

PREVIOUS | NEXT

Chapter 44: THROMBOGENESIS, ANTITHROMBOTIC, AND THROMBOLYTIC THERAPY

THROMBOLYTIC DRUGS

All thrombolytic drugs are plasminogen activators, and, as indicated in Fig. 44-21, some are natural activators endogenous to the human fibrinolytic system and others are not.

Streptokinase

Thus is a nonenzyme protein produced by several strains of hemolytic streptococci: it consists of a single polypeptide chain of 414 amino acids with a molecular weight of about 50,000.[421] Streptokinase cannot directly cleave peptide bonds, but it activates plasminogen to plasmin indirectly, following a three-step mechanism.[421] In the first step, streptokinase forms an equimolar complex with plasminogen. This complex undergoes a conformational change, resulting in the exposure of an active site in the plasminogen moiety. In the second step, this active site catalyzes the activation of plasminogen to plasmin. In a third step, plasminogen-streptokinase molecules are converted to plasmin-streptokinase complexes.[422] The active-site residues in the plasmin-streptokinase complex are the same as those in the plasmin molecule, but plasmin is unable to activate plasminogen, whereas the plasmin(ogen)-streptokinase complex is not inhibited by α_2-antiplasmin.

Most individuals have measurable circulating streptokinase-neutralizing antibodies, which may result from previous infections with B-hemolytic streptococci. Therefore, during thrombolytic therapy, sufficient streptokinase must be infused to neutralize these antibodies. A few days after streptokinase administration, the antistreptokinase titer rises rapidly to 50 to 100 times the preinfusion value and remains high for 4 to 6 months, during which renewed treatment with streptokinase is impracticable.[423]

Clinical trials have shown intravenous streptokinase, administered as an infusion of 1.5 million units over 1 h, leads to a significant reduction in mortality rate. In the GISSI-I trial, for patients with acute MI within 12 h, there was a 19 percent reduction in mortality rate.[268] In ISIS-2, there was a 25 percent reduction in mortality rate.[180] In the ISIS-3 trial, streptokinase was found to have an identical mortality rate as the 3-h regimen of t-PA with either subcutaneous or no heparin.[317] In the GUSTO-I trial, however, streptokinase was inferior to t-PA when the latter was administered as an accelerated 90-min bolus and infusion with concomitant intravenous heparin[323] (see also Chap. 42).

Anistreplase (Anisoylated Plasminogen-Streptokinase Complex)

APSAC (anistreplase) was constructed with the aim of controlling the enzymatic activity of the plasmin(ogen)-streptokinase complex by a specific reversible chemical protection of its catalytic center (i.e., by titration with a *p*-anisoyl group).[148,424] Anistreplase, which is an equimolar noncovalent complex between human Lys-plasminogen and streptokinase, has a catalytic center located in the carboxy-terminal region of the molecule, whereas the lysine-binding sites are found within the amino-terminal region of plasminogen. Reversible acylation of the catalytic center would thus not affect the weak fibrin-binding capacity of Lys-plasminogen in the complex. The plasmin(ogen)-streptokinase complex is an efficient activator of plasminogen. Deacylation of anistreplase uncovers the catalytic center, which converts plasminogen to plasmin. Deacylation of anistreplase does, however, occur both in the circulation and at the fibrin surface, and the fibrin specificity of thrombolysis with anistreplase is only marginal at best. A plasma half-life of 70 min was found for anistreplase, compared with 25 min for the plasminogen-streptokinase complex formed in vivo after administration of streptokinase.[425] Patients with high streptokinase antibodies do not respond to anistreplase, and anistreplase causes a marked increase in the streptokinase antibody titer within 2 to 3 weeks, which persists for months.

Clinical studies have shown anistreplase to reduce mortality compared with placebo[426] and to have equivalent mortality to streptokinase and the 3-h regimen of t-PA.[317] In the TIMI-4 trial, TIMI grade 3 flow at 60 and 90 min was inferior to accelerated t-PA, as were clinical outcomes.[427] Because it is a bolus drug, administered as 30 U over 2 to 5 min), anistreplase was used in several trials of prehospital thrombolysis, which showed benefit compared with hospital-based treatment.[428,429] Due to its high cost (approaching that of t-PA) yet inferior patency profile, its use has waned greatly.

UROKINASE

Two-chain urokinase-type plasminogen activator (tcu-PA), a trypsin-like serine proteinase composed of two polypeptide chains (20,000 and 34,000 Da), has been isolated from human urine[430] and from cultured human embryonic kidney cells.[431] The tcu-PA activates plasminogen directly following Michaelis-Menten kinetics but has no specific affinity for fibrin and activates fibrin-bound and circulating plasminogen relatively indiscriminantly. Extensive plasminogen activation and depletion of α_2-antiplasmin may occur following treatment of thromboembolic diseases with tcu-PA, leading to degradation of several plasma proteins, including fibrinogen, factor V, and factor VIII.

PRO-UROKINASE

Single-chain urokinase-type plasminogen activator (scu-PA, pro-urokinase) is a naturally occurring human protein first isolated from natural sources and then produced through recombinant DNA technology.[432] The human gene responsible for its synthesis is located on chromosome 10 and is about 6.4 kb long, organized in 11 exons; it gives rise to a 2.5-kb-long messenger RNA, which transcribes a single-chain glycosylated polypeptide. Evidence for the signal transduction pathways involved in regulation of the urokinase gene has to date demonstrated three mechanisms, which are dependent respectively on activation of c-AMP protein kinase, protein kinase C, and an as yet uncharacterized protein kinase.[433]

The single-chain protein is synthesized principally by renal and vascular endothelial cells but also by a variety of cultured normal, transformed, and malignant cell types. The protein scu-PA has also been expressed by gene-cloning techniques in *E. coli* bacteria[154,434] and mouse hybridoma cells.

The glycosylated natural scu-PA is a single-chain glycoprotein with a molecular weight of 54,000 Da and containing 411 amino acid residues. The N-terminal domain has a homology with the growth factor domain of other proteins, followed by a kringle domain, homologous to plasminogen, t-PA, and other proteins involved in coagulation.[435] However, the single-disulfide-bonded kringle domain of scu-PA does not contain a lysine-binding site, and it does not confer fibrin-binding properties to the enzyme. The single glycosylation site of the glycoprotein is located at asparagine 302. The molecule expressed by *E. coli* lacks the glycosyl group, which reduces the molecular weight to 47,000 Da.[434] The scu-PA is the native zymogenic precursor of urokinase. Limited hydrolysis by plasmin or kallikrein of the Lys^{158}-Ile^{159} peptide bond converts the molecule to tcu-PA (urokinase), which is held together by one disulfide bond essential for the thrombolytic activity[436] (Fig. 44-22). A fully active tcu-PA derivative is obtained after additional proteolysis at position Lys^{135}-Lys^{136}. In purified systems, scu-PA has some intrinsic plasminogen-activating potential, but it is 1 percent of that of tcu-PA. Conversion of scu-PA to tcu-PA in the vicinity of a fibrin clot apparently constitutes a significant positive feedback mechanism for clot lysis in human plasma in vitro. Specific hydrolysis of the Glu^{143}-Leu^{144} peptide bond in scu-PA yields a LMW scu-PA of 32,000 (scu-PA-32k). Thrombin, on the other hand, cleaves the Arg^{156}-Phe^{157} peptide bond in scu-PA, resulting in an inactive double-chain molecule.

Tissue-Type Plasminogen Activator

Native t-PA is a serine proteinase with a molecular weight of about 70,000, composed of one polypeptide chain containing 527 amino acids with serine as the amino-terminal amino acid.[142,157] t-PA is converted by plasmin to a two-chain form by hydrolysis of the Arg^{275}-Ile^{276} peptide bond. The two-chain form is held together by one interchain disulfide bond. t-PA for clinical use is presently produced by recombinant DNA

technology [Activase (Genentech) or Actilyse (Boehringer Ingelheim)] and consists mainly of the single-chain form.

The NH_2-terminal region of t-PA is composed of four domains with homologies to other proteins: residues 4 to 50 (F domain) are homologous to the *finger domains* in fibronectin, residues 50 to 87 (E domain) are homologous to human epidermal growth factor, and two regions comprising residues 87 to 176 and 176 to 262 (K1 and K2 domains) are both homologous to the five "kringle" loop structures of plasminogen (Fig. 44-22). The region comprising residues 276 to 527 is homologous to that of other serine proteinases and contains the catalytic site, which is composed of His^{322}, Asp^{371}, and Ser^{478}. t-PA has a specific affinity for fibrin. The structures involved in the fibrin binding of t-PA are fully contained within the A (heavy) chain. Evidence obtained with deletion mutants suggests that binding of t-PA to fibrin is mediated both via the finger domain and via the second kringle region. A lysine-binding site is involved in the interaction of K2 domain with fibrin but not in the interaction of the finger domain with fibrin. The structures required for the enzymatic activity of t-PA are fully contained within the B chain.

The activation of plasminogen by t-PA, both in the presence and in the absence of fibrin, follows Michaelis-Menten kinetics.[166] There is a consensus that the presence of fibrin enhances the efficiency of plasminogen activation by t-PA by 2 to 3 orders of magnitude.[166] Fibrin provides a surface to which t-PA and plasminogen adsorb in a sequential and ordered way, yielding a cyclic ternary complex. Fibrin essentially increases the local plasminogen concentration by creating an additional interaction between t-PA and its substrate. The high affinity of t-PA for plasminogen in the presence of fibrin thus allows efficient activation on the fibrin clot, while no efficient plasminogen activation by t-PA occurs in plasma. Plasmin formed on the fibrin surface has both its lysine-binding sites and active site occupied and is thus only slowly inactivated by α_2-antiplasmin (a half-life of about 10 to 100 s); in contrast, free plasmin, when formed, is rapidly inhibited by α_2-antiplasmin (a half-life of about 0.1 s). The fibrinolytic process thus seems to be triggered by and confined to fibrin.

Several mutants of recombinant tissue-type plasminogen activator (rt-PA) have been constructed with interesting properties, including slower clearance from the circulation, more selective binding to fibrin, stronger stimulation by fibrin, and resistance to plasma protease inhibitors (see below).

Clinical Studies

After a series of patients were treated with t-PA,[437] t-PA was compared with intravenous streptokinase in the TIMI-1 trial, in which 290 patients with acute MI underwent initial diagnostic coronary angiography and then were treated with either streptokinase or t-PA in addition to intravenous heparin. The primary end point, reperfusion of initially occluded coronary arteries after 90 min, was achieved in 62 percent of t-PA-treated patients compared with 31 percent of streptokinase-treated patients ($p < 0.001$).[3,438] The patency rate at 90 min independent of findings on baseline arteriogram was 70 percent for t-PA and 43 percent for streptokinase ($p < 0.001$). Nearly identical results were observed in the European study.[439] t-PA was studied in numerous angiographic trials, as reviewed by Granger and coworkers, who observed that the 3-h dosing regimen of t-PA had superior patency and TIMI grade 3 flow,[3] at both 60 and 90 min, compared with streptokinase or anistreplase.[440] Neuhaus and colleagues developed the *accelerated* 90-min dosing regimen,[441] which was found to achieve even higher rates of early reperfusion when compared with the 3-h t-PA dosing regimen,[442] anisteplase,[427,443] or streptokinase.[270]

Given the importance of rapid reperfusion, one would expect that a more aggressive thrombolytic regimen that achieves a higher rate of early infarct-related patency would be associated with a lower mortality rate. This notion was called into question following the results of GISSI-2/International Study[315,316] and ISIS-3[317] (Table 44-10).

Table 44-10: Results from GISSI-2/International Study and ISIS-3

	Streptokinase	t-PA (3-h Regimen)	Anistreplase
GISSI-2/International		10,372	-
No. of patients	10,396		
Mortality (%)	8.4	8.9	-
Total stroke	1.0	1.6	-
ICH	0.4	0.6	-
ISIS-3		13,746	13,773
No. of patients	13,780		
35-Day mortality.(%)	10.6	10.3	10.5
Total stroke	1.04	1.39	1.26
ICH	0.2	0.7	0.6

ABBREVIATIONS: ICH = intracranial hemorrhage; t-PA = tissue-type plasminogen activator.

GUSTO-I Trial

In contrast, in the GUSTO-I trial, the accelerated dosing of t-PA was used in conjunction with intravenousheparin. As shown in Table 44-11, the mortality rate at 30 days was significantly lower in the front-loaded t-PA arm as compared with each of the three other arms.[323] The improvement in mortality was already seen after only 24 h, with t-PA-treated patients having a significantly lower mortality rate. In addition, other major complications were decreased by t-PA. There was less cardiogenic shock, congestive heart failure, and ventricular arrhythmia. Higher patency rate was seen with t-PA (Table 44-12).

Table 44-11: Results from the GUSTO Trial

Outcome	SK and sq Heparin	SK and IV Heparin	Front-Loaded t-PA and IV Heparin	t-PA and SK and IV Heparin	*p* Value t-PA vs. Both SK Regimens
No. of patients	9796	10,377	10,344	10,328	
30-Day mortality (%)	7.2	7.4	6.3	7.0	0.005
Net clinical benefit (death or disabling stroke) (%)	7.7	7.9	6.9	7.6	0.006
24-h Mortality (%)	2.8	2.9	2.3	2.8	0.005
Intracranial hemorrhage	0.5	0.5	0.7	0.9	0.03
Congestive heart failure	17.5	16.8	15.2	16.8	<0.001
Cardiogenic shock	6.9	6.3	5.1	6.1	<0.001

ABBREVIATIONS: IV = intravenous; SK = streptokinase; t-PA = tissue-type plasminogen activator; sq = subcutaneous.
SOURCE: Data from the GUSTO Investigators.[270323]

Table 44-12: GUSTO Angiographic Substudy

No. of patients	293	283	292	299	
Infarct-related artery patency (TIMI grade 2 or 3 flow) at 90 min (%)	54	60	81	73	<0.001
TIMI grade 3 flow at 90 min (%)	29	32	54	38	<0.001

ICH is the dreaded complication of thrombolysis, although it is fortunately a rare complication despite aggressive regimens of thrombolysis, aspirin, and heparin. For each of these streptokinase arms, 0.5 percent of patients suffered an ICH as compared with 0.7 percent of patients treated with front-loaded t-PA and 0.9 percent of patients treated with combination thrombolytic therapy.[323] To put their results in full perspective, the GUSTO investigators developed the concept of *net clinical benefit*, i.e., the occurrence of either death or a disabling stroke. When comparing the net clinical benefit between the four regimens, t-PA had a significantly lower rate compared with the other three regimens.

The explanation of the benefit of t-PA in the GUSTO and TIMI-4 trials and the lack of benefit in GISSI-2 and ISIS-3 is based on two factors: the t-PA regimen and the heparin dosing. The use of the front-loaded t-PA regimen achieves a higher rate of early patency compared with the older 3-h regimen.[440] The use of early intravenous heparin has been shown to improve late infarct-related artery patency (Table 44-12). In contrast, the GISSI-2 and ISIS-3 trials used the slower infusion regimen of t-PA and either no heparin or delayed, subcutaneous heparin, which does not elevate APTT until approximately 24 h after the start of treatment. Because the initial 24 h hold the highest risk of reocclusion of an open infarct-related artery (which is associated with a threefold increase in mortality), the subcutaneous heparin regimen is inadequate at preventing this important complication.

Double-Bolus Tissue-Type Plasminogen Activator

Initial interest in a double-bolus regimen of t-PA came from a series of patients, in which two 50-mg boluses of t-PA were administered 30 min apart, and TIMI grade 3 flow was observed in 88 percent of patients.[444] In a subsequent randomized trial, however, double-bolus t-PA achieved only 58 percent TIMI grade 3 flow, compared with 66 percent for the accelerated 90-min infusion of t-PA.[445] The Continuous Infusion Versus Double-Bolus Administration of Alteplase (COBALT) trial compared double-bolus t-PA with the accelerated infusion of t-PA but was terminated prematurely because of concern about the safety of the double-bolus regimen. The 30-day mortality rate was higher in the double-bolus group than in the accelerated-infusion group: 7.98 percent as compared with 7.53 percent.[446] Rates of hemorrhagic stroke were 1.12 percent after double-bolus alteplase as compared with 0.81 percent after an accelerated infusion of alteplase (p = .23).[446] Statistically, double-bolus t-PA was *not* equivalent to t-PA.[446] Thus, based on this trial, double-bolus t-PA is not recommended for general clinical use,[446] and the accelerated, 90-min infusion of t-PA remains the current standard dosing for acute MI.

Tissue-Type Plasminogen Activator (Reteplase)

This is a single-chain nonglycosylated deletion variant of rt-PA consisting of only the K2 and the protease domains of human t-PA (Fig. 44-23). The active site of the protease domain of reteplase and that of t-PA, and their plasminogenolytic activity in the absence of a stimulator, do not differ, but the plasminogenolytic activity of reteplase in the presence of fragments of fibrinogen as a stimulator was

fourfold lower compared with t-PA, whereas the binding of reteplase to fibrin was five times lower. These differences in plasminogenolytic activity and fibrin binding between the two molecules might be due to the missing finger domain in reteplase. It is known that fibrin binding is mediated through both the finger domain and the lysine-binding site in the K2 domain of t-PA. Reteplase and t-PA are inhibited by PAI-1 to a similar degree, but the affinity of reteplase for binding to endothelial cells and monocytes is reduced, probably as a consequence of deletion of the finger and epidermal growth factor domains in reteplase, which seem to be involved in the interaction with endothelial cell receptors. The thrombolytic properties of reteplase and alteplase (rt-PA) were compared in the rabbit jugular vein thrombosis model.[447] The effective dose for 50 percent thrombolysis (ED_{50}) was 163 kU/kg (0.28 mg/kg) for reteplase and 871 kU/kg (1.09 mg/kg) for alteplase, indicating a 5.3-fold higher potency of reteplase. At equipotent doses (50 percent thrombolysis), the residual concentration of fibrinogen was 74 percent with reteplase and 76 percent with alteplase. Pharmacokinetic analysis of plasma activity at a dose of 400 kU/kg in rabbits revealed a half-life of 18.9 ± 1.5 min for reteplase and 2.1 ± 0.1 min for alteplase. Plasma clearance for reteplase was 4.3-fold slower than for alteplase (4.7 versus 1.2 mL/min per kilogram).[448] One may therefore conclude that the higher potency of reteplase is due to the slower clearance. An initial half-life of 14 to 18 min was also observed with reteplase in healthy human volunteers[449] and in patients with acute MI.[450]

Dose-ranging studies of bolus reteplase were performed in a multicenter trial.[451] With a dose of 10 MU of reteplase, a patent infarct-related coronary artery (TIMI-3 grade) was obtained at 30 min in 46 percent, at 60 min in 48 percent, at 90 min in 52 percent, and at 24 to 48 h in 88 percent of patients with acute MI. With 15 MU, a higher angiographic patency rate at the same time intervals was obtained (38, 58, 69, and 85 percent). Because there was a 20 percent (10 MU) and 12.5 percent (15 MU) reocclusion rate between the 30- and 90-min angiograms, the administration of a second smaller bolus of reteplase (5 MU) 30 min after the initial bolus (10 MU) was investigated in an open uncontrolled study.[452] Patency rates (TIMI-3) reached 50 percent at 60 min, 58 percent at 90 min, and 84 percent at 24 to 48 h. Only one of the 50 patients studied had reocclusion in the first 24 to 48 h.

In the Reteplase versus Alteplase Infusion in Acute Myocardial Infarction (RAPID-I) trial involving 605 patients with acute MI, different bolus doses of reteplase (a single dose of 15 MU, 10 MU, and 5 MU 30 min later; and 10 MU and 10 MU 30 min later) were compared with the conventional dose regimen of alteplase (100 mg over 3 h). TIMI-3 patency rates at 90 min were obtained with the given reteplase regimen in 42.7, 45.4, and 62.9 percent, respectively, and in 47.6 percent of patients treated with alteplase.[453] The difference between the 10 MU + 10 MU reteplase and alteplase arms is significant ($p = .01$).

The RAPID-II trial was a randomized open-label angiographic study of 324 patients with acute MI that was designed to compare the effect of 10 + 10 U reteplase with that of an accelerated, front-loaded dose of alteplase (100 mg over 90 min) on the TIMI grade of the infarct-related coronary artery 90 min after the initiation of thrombolytic therapy.[454] There was no age limit, and patients were recruited up to 12 h after onset of symptoms; all received aspirin. The heparin regimen consisted of a 5000-IU intravenous bolus that was administered before thrombolytic therapy, followed by an infusion of 1000 IU/h for at least 24 h. In this study, reteplase achieved earlier and more complete reperfusion than did accelerated-dose alteplase.[454] TIMI grade 2 or 3 patency and TIMI grade 3 flow rates of the infarct-related artery at 90 min were significantly higher for reteplase relative to the alteplase control (83.4 versus 73.3 percent and 59.9 versus 45.2 percent, respectively).[454] At 60 min, both the TIMI grade 2 or 3 patency and the TIMI grade 3 flow rates were significantly higher for reteplase than for alteplase.[454] Reteplase-treated patients required significantly fewer additional coronary interventions within the first 6 h of treatment (13.3 versus 26.5 percent). As expected in a trial of this size, there were no significant differences between the reteplase and the alteplase groups with respect to 35-day mortality (4.1 versus 8.4 percent) and hemorrhagic stroke (1.2 versus 1.8 percent).[454]

Two mortality trials with reteplase were planned in patients with acute MI. The International Joint Efficacy Comparison of Thrombolytics (INJECT) study was designed to determine whether reteplase was at least as effective in mortality reduction as a standard streptokinase regimen.[455] In this double-blind study, 3004 patients were randomized to a double bolus of 10 + 10 U of reteplase 30 min apart, and 3006 patients were randomized to 1.5 MU of streptokinase over 60 min. Treatment could be started up to 12 h from onset of symptoms. All patients received intravenous heparin for at least 24 h and aspirin. The 35-day mortality rate

was 9.0 percent in the reteplase group and 9.5 percent in the streptokinase group, a nonsignificant difference. That did meet predefined criteria for equivalence.[455] At 6 months, mortality rates were 11.0 percent for reteplase and 12.0 percent for streptokinase.[455] Bleeding events were similar in the two groups (0.7 percent for reteplase and 1.0 percent for streptokinase). The in-hospital stroke rates were 1.23 percent for reteplase and 1.0 percent for streptokinase. The incidence of recurrent MI was similar in the two groups.

In the GUSTO-III mortality trial, reteplase was administered in two bolus injections 30 min apart and compared with front-loaded alteplase (100 mg in 90 min) in 15,059 patients treated within 6 h of symptoms of acute MI. The GUSTO-III trial compared reteplase with front-loaded alteplase (t-PA).[456] Mortality (7.47 versus 7.24 percent, r-PA versus t-PA), ICH (0.91 versus 0.87 percent), and net clinical benefit (death or disabling stroke) were very similar clinically (7.9 percent in each group) between double-bolus reteplase and alteplase infusion, respectively.[456] When applying post hoc criteria for equivalence (evaluating the upper boundary of the 95% CI), reteplase is statistically equivalent for death or disabling stroke when a 1 percent absolute boundary is used [derived from the difference observed between streptokinase (SK) and t-PA]. Thus, clinically, the simpler double-bolus regimen of r-PA appears clinically equivalent to accelerated t-PA.

TNK-Tissue-Type Plasminogen Activator (Tenecteplase)

TNK-t-PA (tenecteplase) is a new thrombolytic agent that is a genetically engineered variant of t-PA (Fig. 44-24). TNK-t-PA is similar to wild-type t-PA, but has amino acid substitutions at three sites, which give it its name: a threonine (T) is replaced by asparagine, which adds a glycosylation site to position 103; an asparagine (N) is replaced by a glutamine, thereby removing a glycosylation site from site 117; and four amino acids-lysine (K), histidine, arginine, and arginine-are replaced by four alanines at the third site. Together, these substitutions lead to, in animal models, a prolonged half-life of the molecule,[457,458] increased fibrin specificity,[457] and increased resistance to inhibition by PAI-1.[459-461]

Pharmacokinetics

Clinical testing of TNK-t-PA began in the TIMI-10A trial, with doses ranging from 5 to 50 mg.[457] TNK-t-PA was demonstrated to have a slowed plasma clearance relative to values for t-PA. The corresponding plasma half-life of elimination of TNK-t-PA ranged from 11 to 20 min, as compared with 3.5 min as previously reported for t-PA.[462] These results were duplicated in the TIMI-10B trial.[458,463]

Fibrin Specificity

TNK-t-PA is much more fibrin specific than t-PA, which is itself more fibrin specific than streptokinase or reteplase. Systemic fibrinogen and plasminogen levels fell by only 5 to 15 percent over the first 6 h at the 30- to 50-mg doses of TNK-t-PA compared with 40 to 50 percent drops following t-PA. Similarly, the consumption of α2-antiplasmin, the fluid-phase inhibitor of plasmin, and a resultant increase in plasmin-α2-antiplasmin complexes was four to five times greater with t-PA as compared with TNK-t-PA. This high level of fibrin specificity of TNK-t-PA compared with t-PA helps explain its efficacy when administered as a 5- to 10-s bolus, and the fact that it does not induce the *plasminogen steal* phenomenon.[464] Furthermore, these benefits in preserving the systemic coagulation factors appear to translate into lower rates of major bleeding in the large phase III trial (see below).

TIMI Grade 3 Flow

In the dose-ranging trial TIMI-10A, the rate of TIMI grade 3 flow at 90 min was achieved in 57 to 64 percent of patients at the 30- to 50-mg TNK-t-PA doses, which was higher than in patients treated with the lower doses ($p = .032$).[457] In TIMI-10B, a total of 886 patients were randomized to receive either front-loaded (90-min infusion) t-PA or a single 5- to 10-s bolus of TNK-t-PA at 30- or 50-mg bolus.[463] The 50-mg dose was discontinued due to increased bleeding and replaced with a 40-mg dose of TNK-t-PA. The 40-mg dose of TNK-t-PA produced a similar rate of TIMI grade 3 flow at 90 min compared with t-PA (63

percent). The 30-mg dose of TNK-t-PA had a significantly lower rate of TIMI grade 3 flow at 90 min than did t-PA (54.6 percent, $p = .04$), whereas the 50-mg dose showed 65.8 percent (p = NS).[463] TIMI grade 2 or 3 flow at 90 min and TIMI frame counts were similar between TNK-t-PA and t-PA. At 60 min, there were no differences in the rates of TIMI grade 3 flow or overall patency.[463]

Weight-Adjusted Dosing

In TIMI-10B and ASSENT-I, a prespecified weight-based analysis was carried out.[463,465,466] The rate of TIMI grade 3 flow was 62 to 63 percent for doses of TNK-t-PA of approximately 0.53 mg/kg and higher but was 51 to 54 percent at doses lower than this ($p = .028$ across quintiles). Further analysis into covariates of the degree of perfusion achieved revealed that, when stratifying dose/weight into tertiles, the median corrected TIMI frame count was significantly lower (i.e., faster flow) in patients who received the higher "weight corrected" dose.[465]

Safety Results in the TIMI-10B Trial

During the initial phase of the trial, i.e., prior to the reduction of heparin dosage previously described, there were three ICHs among the 78 patients (3.8 percent, 95% CI = 0.8 to 10.8) treated with the 50 mg TNK-t-PA dose. In the parallel ASSENT-I trial, however, there were no ICHs at this dose. This dose was dropped from further testing and, at the same time, the doses of heparin were reduced. Further analysis demonstrated that the concomitant heparin may have played a larger role than that of dose of TNK-t-PA in defining the rate of ICH.

Initially in TIMI-10B and ASSENT-I, heparin dosing was at the discretion of the treating physicians, but a protocol amendment mandated that patients receive the following dose of heparin: for patients weighing more than 67 kg, a 5000-U bolus and 1000-U/h infusion, and, for patients weighing 67 kg or less, a 4000-U bolus and 800-U/h infusion. In addition, adjustment of the heparin dose according to the nomogram was mandated to begin with the 6-h APTT.

The rates of both ICH and serious bleeding were lower after the protocol amendment: for TNK-t-PA 30 mg, the ICH rate fell from 2.2 to 0 percent ($p = .047$), and, for t-PA, the rate fell from 2.8 to 1.2 percent ($p = .29$) (overall combined $p = .04$).[463] Similar observations and statistically significant reductions in ICH rate were observed in overall TNK-t-PA experience combining the TIMI-10B and ASSENT-I trials.[350] The rate of severe bleeding also decreased with the reduced heparin dosing: from 3 to 0 percent ($p = .02$) for 30 mg TNK-t-PA, and from 8 to 2 percent ($p = .01$) for t-PA (combined $p = .001$).[463] Thus, for the subsequent phase III trial (ASSENT-II), the lower heparin regimen was used.

Another observation on safety involved the rates of serious (noncerebral) bleeding in TIMI-10B, where lower rates of serious bleeding requiring transfusion were noted. For t-PA, 7.0 percent of patients required transfusion compared with 1.0 percent of TNK-t-PA patients treated with the 30-mg dose ($p < 0.001$) and 1.3 percent treated with the 40-mg dose ($p < 0.01$).[467] Similar low rates of serious bleeding requiring transfusion were observed in the ASSENT-I trial.[467] Thus, there appeared to be early evidence that the very fibrin specific agent TNK-t-PA might have lower rates of bleeding than t-PA.

ASSENT-I Trial

This was a randomized trial of three doses of TNK-t-PA, with the primary goal to determine the rate of ICH of the three doses, to assist in determining the appropriate dose for a large phase III trial. A total of 3235 patients randomized: to receive either 30 mg TNK-t-PA ($n = 1705$), 40 mg ($n = 1457$), or 50 mg ($n = 73$).[468] As noted previously, the 50-mg dose was discontinued and replaced by 40 mg because of increased bleeding observed in the TIMI-10B study. ICH occurred in 0.77 percent of patients overall: 0.94 percent in the 30-mg arm and 0.62 percent in the 40-mg arm. No strokes were found among the 73 patients treated with 50 mg TNK-t-PA. In patients treated within 6 h after symptom onset, the rates of ICH were 0.56 percent (30 mg TNK-t-PA) and 0.58 (40 mg TNK-t-PA). Death, death or nonfatal stroke, or severe bleeding

complications occurred in a low proportion of patients: 6.4, 7.4, and 2.8 percent, respectively, without differences among the 3 doses.

ASSENT-II

TNK-t-PA was compared with accelerated t-PA in a large mortality trial of patients with acute ST-elevation MI presenting within 6 h of the onset of pain. This trial enrolled 16,950 patients worldwide. TNK-t-PA was administered as a weight-adjusted dose of 0.53 mg/kg given in 5-mg increments, ranging from 30 to 50 mg.

Overall mortality was essentially identical between the two agents: 6.17 percent for TNK-t-PA and 6.15 percent for t-PA (p = NS).[469] This trial was an *equivalence* trial[470] and, using its predefined criteria, TNK-t-PA was shown to be equivalent to t-PA (relative risk = 1.00; 90% CI = 0.91 to 1.10; p for equivalence = 0.028). The equivalence of TNK-t-PA to t-PA on reducing mortality was shown in nearly every subgroup tested.

There was an intriguingly *better* outcome for patients treated with TNK-t-PA compared with t-PA more than 4 h after the onset of chest pain. This benefit may relate to the greater fibrin specificity of TNK-t-PA. The first observation of the benefit of greater fibrin specificity in later-treated patients came from the TIMI-1 trial, in which 90-min patency was preserved in patients treated with t-PA with time to treatment of less than or more than 4 h, whereas, for those treated with streptokinase, patency was significantly worse if time to treatment was more than 4 h.[3,438] Similar findings were seen in an analysis of the German angiographic thrombolytic trials.[471,472] The same pattern favoring the more fibrin-specific agent was seen in the GUSTO-III trial, where t-PA had significantly lower mortality than reteplase, a less fibrin-specific agent, in patients treated more than 4 h after the onset of pain.[456] It is hypothesized that the clot may be more resistant the longer it has been able to mature, and the greater fibrin specificity of the thrombolytic agent may enhance the ability to lyse the clot.

Safety Observations

In ASSENT-II, the rate of ICH was also identical for TNK-t-PA and t-PA (0.93 versus 0.94 percent, p = NS). Total stroke was also similar (1.78 percent for TNK-t-PA versus 1.66 percent for t-PA, p = NS). However, there was an intriguingly lower rate (albeit not statistically significant) of ICH in patients older than 75 years of age treated with TNK-t-PA (1.7 percent versus 2.6 percent for those treated with t-PA). Further detailed analysis found that the highest-risk group for ICH was elderly female patients weighing 67 kg or less.[473] This group has been found in two previous multivariate analyses to be at high risk for ICH.[474,475] Most encouragingly, the rates for ICH in this high-risk group were only 1.1 percent following treatment with TNK-t-PA compared with 3.0 percent for those treated with t-PA. The multivariate adjusted odds ratio was 0.30 (95% CI = 0.09 to 0.98, $p < 0.05$).[473] In all other patients, the rates of ICH were similar between the two thrombolytic groups.

Importantly, these benefits on ICH were paralleled by significantly lower rates of major bleeding. In the trial as a whole, the rates of major bleeding were 4.7 percent for TNK-t-PA and 5.9 percent for t-PA (p = .0002).[469] Total bleeding also occurred in fewer patients (p = .0003).[469,476] Similarly, the rate of bleeding requiring transfusion was significantly lower with TNK-t-PA.

Desmodus Salivary Plasminogen Activator The subsistence of vampire bats on a diet of fresh blood is apparently contingent on their ability to interfere with the hemostatic system of the blood donor. The saliva of vampire bats contains a variety of factors that presumably satisfy two essential requirements: to maintain prolonged bleeding from the wound and to preserve blood fluidity following ingestion of a meal.[477] Different molecular forms of the *Desmodus* salivary plasminogen activator (DSPA) have been purified, characterized, cloned, and expressed. Two HMW forms exhibit about 85 percent homology to human t-PA: DSPAα1 (M_r 43) and DSPAα2 (M_r 39), which contain neither a kringle 2 domain nor a plasmin-sensitive processing site. DSPAβ lacks the finger-like structure and DSPAγ lacks the finger and epidermal growth factor structures.[405,478] The two HMW forms exhibit a specific activity in vitro equal to or higher than that

of t-PA, a relative PAI-1 resistance, and a greatly enhanced fibrin specificity with a strict requirement for polymeric fibrin as a cofactor.[479-481] In animal models (rats, rabbits, and dogs) of thrombolysis, DSPAα1 is superior to t-PA in terms of potency (2.5 times higher), terminal half-life (three times longer), and clearance (four- to eightfold slower).[481] Interestingly, the fibrin cofactor requirement of DSPAα1 and DPSAα2, which both bind to fibrin, may not solely depend on fibrin binding, as the two smaller forms, DPSAβ and DSPAγ, are also fibrin dependent but lack fibrin affinity.[481]

ZK152387 is recombinant DSPAα1 produced in mammalian cell culture; its amino acid sequence is identical to that of its natural counterpart.[478] DSPAα1 may be suitable for bolus administration; its long half-life and high specific activity may allow a marked reduction of the absolute dose of drug required for effective thrombolysis as compared with t-PA.

Staphylokinase Mature staphylokinase consists of 136 amino acids in a single polypeptide chain without disulfide bridges. Staphylokinase, like streptokinase, is not an enzyme but forms a 1:1 stoichiometric complex with plasmin(ogen) that activates other plasminogen molecules. Streptokinase and plasminogen produce a complex that exposes the active site in the plasminogen molecule without proteolytic cleavage, whereas generation of plasmin is required for exposure of the active site in the complex with staphylokinase.[482,483]

Staphylokinase does not bind to fibrin, and fibrin stimulates the initial rate of plasminogen activation by staphylokinase only fourfold as compared with twofold by streptokinase. In purified systems α_2-antiplasmin rapidly inhibits the plasmin-staphylokinase complex (second-order inhibition rate constant of approximately $2 \times 10^6\ M^{-1}s^{-1}$), although it does not inhibit the plasmin(ogen)-streptokinase complex. Addition of 6-aminohexanoic acid or of fibrin-like substances (e.g., CNBr-digested fibrinogen) induces a more than 100-fold reduction of the inhibition rates of the plasmin-staphylokinase complex by α_2-antiplasmin. Rapid inhibition by α_2-antiplasmin indeed requires the availability of the lysine-binding sites in the plasminogen moiety of the complex. More detailed studies on the interaction between staphylokinase, plasmin(ogen), and α_2-antiplasmin have shown that neutralization of the plasmin-staphylokinase complex by α_2-antiplasmin results in dissociation of functionally active staphylokinase from the complex, followed by its recycling to other plasminogen molecules.[482]

In plasma, the conversion of plasminogen-staphylokinase to plasmin-staphylokinase complex does not occur at a significant rate because it is prevented by α_2-antiplasmin; without plasmin-staphylokinase complex, no significant plasminogen activation occurs. In the presence of fibrin, generation of the plasmin(ogen)-staphylokinase complex is facilitated, and inhibition of plasmin-staphylokinase by α_2-antiplasmin at the clot surface is delayed. Recycling of staphylokinase to fibrin-bound plasminogen, after neutralization of the complex, will result in more efficient generation of the active complex. This mechanism is mediated via the lysine-binding sites of plasminogen and results in significantly enhanced plasminogen activation at the fibrin surface. These regulatory properties of fibrin and α_2-antiplasmin suggest that the fibrin specificity of staphylokinase is due to rapid inhibition of generated plasmin-staphylokinase complex by α_2-antiplasmin and by a more than 100-fold reduced inhibition rate at the fibrin surface.[482,484]

Recombinant staphylokinase (STAR)[485] was found to have a potency for venous clot lysis in hamsters and rabbits comparable to that of streptokinase. Repeated administration of STAR, in contrast to streptokinase, did not induce resistance to clot lysis in this model. In addition, STAR was found to be significantly more efficient than streptokinase for the dissolution of platelet-rich arterial eversion graft thrombi.[485]

These encouraging results have formed the basis for the evaluation, on a pilot scale, of the pharmacokinetic, thrombolytic, and immunogenic properties of STAR in patients with acute MI.[486] In four of five patients with acute MI, 10 mg of STAR given intravenously over 30 min was found to induce angiographically documented coronary artery recanalization within 40 min. Plasma fibrinogen and α_2-antiplasmin levels were unaffected, and allergic reactions were not observed. In a second series of five patients with acute coronary occlusion, intravenous administration of 10 mg of STAR over 30 min induced recanalization in all patients within 20 min without associated fibrinogen degradation.[190,487] In these patients, however,

neutralizing antibodies were consistently demonstrable in plasma at 14 to 35 days. Thus, with respect to immunogenicity, the initial observations in humans are not as encouraging as the experience in baboons. A subsequent trial was conducted in 100 patients with MI of less than 6-h duration who were allocated to accelerated and weight-adjusted t-PA over 90 min (52 patients) or to recombinant staphylokinase (STAR) (the first 25 patients to 10 mg and the next 23 patients to 20 mg given intravenously over 30 min).[488] All patients received aspirin and intravenous heparin. TIMI-3 flow grade at 90 min was achieved in 62 percent of STAR patients compared with 58 percent of t-PA patients (risk ratio = 1.1; 95% CI = 0.76 to 1.5). With 10 mg STAR, TIMI-3 patency was 50 percent (risk ratio = 0.86; 95% CI = 0.54 to 1.4 versus rt-PA); with 20 mg STAR, it was 74 percent (risk ratio = 1.3; 95% CI = 0.90 to 1.2 versus rt-PA). Residual fibrinogen levels at 0 min were 118 ± 47 percent (mean ± SD) of baseline with STAR and 68 ± 42 percent with rt-PA ($p < .0005$). STAR therapy was not associated with an excess mortality rate or electrical, hemorrhagic, mechanical, or allergic complications, but patients developed antibody-mediated STAR-neutralizing activity from week 2 after STAR treatment.

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CONCLUSION

Thus, with an understanding of the pathogenesis of and risk of thrombus formation,[489] we can formulate a rational approach to the use of antiplatelet, anticoagulant, and thrombolytic agents.[489-491] Many advances have occurred in the treatment of acute coronary syndromes over the past 75 years.[492,493] In ST-elevation MI, new aggressive thrombolytic regimens improve early reperfusion and improve survival. The current focus is on bolus thrombolysis, the combination of reduced-dose thrombolytic therapy with GP IIb/IIIa inhibitors, and the use of LMW heparin in place of unfractionated heparin. In unstable angina and non-ST-elevation MI, two major advances are GP IIb/IIIa inhibition and LMW heparin. The direct thrombin inhibitors have also shown promise. Following acute coronary syndromes, use of the more potent antiplatelet agent than aspirin, clopidogrel, appears to decrease recurrent ischemic events, whereas disappointing results have come thus far from the oral GP IIb/IIIa inhibitors. With a great number of new thrombolytic and antithrombotic therapies for patients with acute coronary syndromes, it is hoped that their use will continue to improve clinical outcomes in the years ahead.

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Figure 44-18: Mechanism of action of heparin and low molecular weight heparin (LMWH): Heparin acts as a cofactor to antithrombin to (1) change the conformation of its active site and (2) serve as a "bridge" to bring together an antithrombin (AT) and thrombin. Heparin is a catalyst: after it facilitates the binding of one pair of thrombin and antithrombin molecules, it is released and facilitates another thrombin-antithrombin interaction. LMWH also binds to antithrombin and changes the conformation of its active site, but does not act as a bridge to thrombin. Approximately 25 to 50 percent of the LMWH molecules of different commercial preparations contain at least 18 saccharide units, which allows binding to the heparin-binding site of thrombin, and thus both these molecules inhibit thrombin and factor Xa. The remaining 50 to 75 percent of LMWH molecules contain fewer than 18 saccharide units and inhibit only factor Xa.

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Figure 44-20: Vitamin K in its reduced form (vitamin K hydroquinone) is essential for the gamma-carboxylation reaction of glutamic acid (Glu)-to gamma-carboxyglutamic acid (Gla-). In this carboxylation, vitamin K hydroquinone is converted to vitamin K_1 epoxide and an epoxide-reductase regenerates active vitamin K hydroquinone. It is this regeneration step that is blocked by all coumarin-type anticoagulant drugs (e.g., warfarin).

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Figure 44-23: Schematic representation of the primary structure of reteplase (Retavase) (amino acids Ser1-Gln3 and Gly176-Pro527 of tissue-type plasminogen activator). The amino acids are represented by their single-letter symbols; black bars indicate disulfide bonds and the asterisks indicate the active-site residues in the protease part. The arrow indicates the plasmin cleavage site.

Figure 44-24: Schematic representation of the primary structure of recombinant tissue-type plasminogen activator-TNK (TNK-t-PA, tenecteplase) (substitution on rt-PA of Thr103 by Asn, Asn111 by Gln, and Lys296-His-Arg-Arg by Ala-Ala-Ala-Ala). The amino acids are represented by their single-letter symbols, black bars indicate disulfide bonds, and the asterisks indicate the active site residues in the protease part. The arrow indicates the plasmin cleavage site.

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Part 6: CORONARY HEART DISEASE
Chapter 45:

PERCUTANEOUS CORONARY INTERVENTION

Authors: John S. Douglas, Jr., Spencer B. King III

The treatment of patients with coronary heart disease changed dramatically with the advent and refinement of coronary artery surgical techniques in the 1970s and percutaneous coronary intervention in the next decade. This chapter addresses the development and contemporary use of catheter-based coronary artery intervention, including selection of patients and devices, procedural issues, results, complications, and long-term outcome.

DEVELOPMENT OF BALLOON ANGIOPLASTY

Percutaneous transluminal coronary angioplasty (PTCA) was conceived and shepherded into worldwide acceptance and application by Andreas R. Gruentzig, but the stage was set by the pioneering effort of others. Gruentzig's ideas were a direct extension of the work of Dotter and Judkins,[1] who in 1964 mechanically dilated femoral arteries with a coaxial double-catheter system, and of Zeitler,[2] who applied this technique successfully in West Germany and introduced it to Gruentzig. After Gruentzig's development of a polyvinyl chloride balloon catheter with fixed maximal inflated diameters in 1974, modern balloon angioplasty evolved rapidly. With further balloon catheter miniaturization and building on the coronary arteriography techniques of Sones and Judkins, Gruentzig succeeded in dilating experimental stenoses in canine coronary arteries[3-5] and then in dilating human arteries during bypass surgery. In September 1977, the first PTCA was performed in Zurich in a 37-year-old insurance salesman with severe angina pectoris and high-grade stenosis of the proximal left anterior descending (LAD) coronary artery.[6-8] Balloon angioplasty was successful in relieving the stenosis, and on the tenth anniversary of this landmark procedure, coronary arteriography revealed angiographically normal coronary arteries (Fig. 45-1). Over 20 years later, the patient remained asymptomatic.

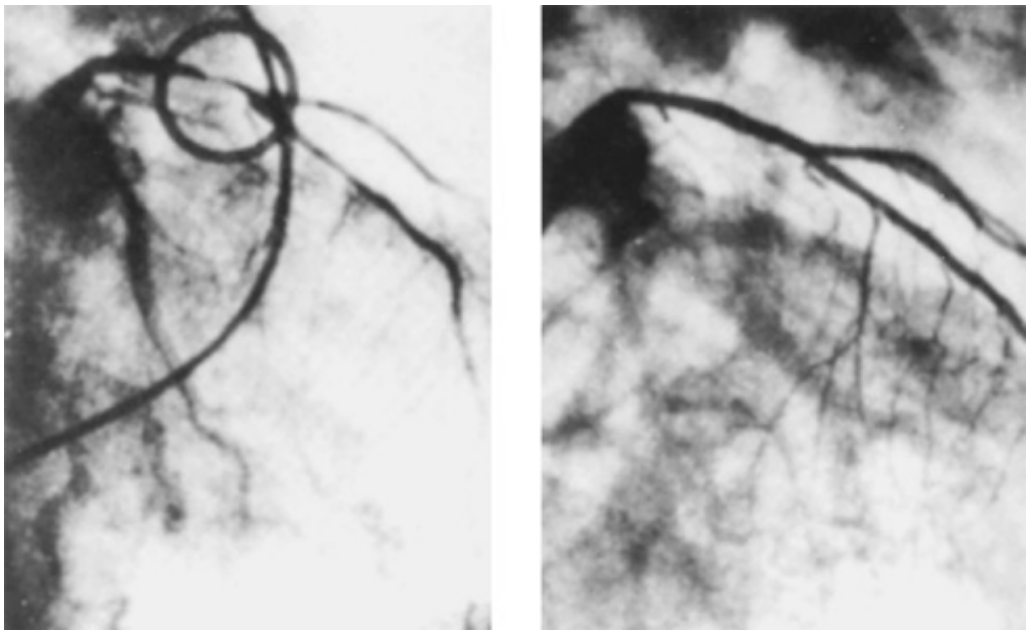

Figure 45-1: Right anterior oblique coronary arteriogram of the first patient who underwent transluminal coronary angioplasty on September 16, 1977 (*left*) and on September 16, 1987 (*right*). During this 10-year period, the patient remained completely asymptomatic, and the arteriogram at 10 years showed no narrowing in the coronary arteries. Over 20 years later, the patient is free of symptoms.

Following the report of Gruentzig's first five patients in 1978[9] and 50 patients in 1979,[10] worldwide interest in the technique was assured. Under the auspices of the National Heart, Lung, and Blood Institute (NHLBI), multicenter registries were formed to report experiences with the evolving technique of balloon coronary angioplasty.[11-13] Development of an over-the-wire balloon catheter by Simpson et al.,[14] combined with advances in guidewire and balloon catheter technology, resulted in a steerable balloon catheter system capable of crossing and dilating heretofore unreachable coronary stenoses (Fig. 45-2). The use of percutaneous revascularization increased dramatically, exceeding 130,000 procedures in the United States in 1986, 400,000 in 1995, and 600,000 in 1999. By 1986 at Emory University Hospital, catheter-based revascularization techniques were performed more frequently than coronary artery bypass grafting (CABG) for relief from symptoms of ischemic heart disease (Fig. 45-3).

Initially, coronary balloon angioplasty was performed for discrete, proximal, noncalcified, subtotal lesions located in one coronary artery. Gruentzig was able to dilate successfully 64 percent of the initial 50 patients and 78 percent of the first 169.[10,15] Most of the patients dilated successfully were improved symptomatically. A 10-year follow-up of Gruentzig's early Zurich series revealed an overall survival rate of 90 and 95 percent for those with single-vessel disease.[15,16] Five-year survival in the NHLBI Registry was 93 percent for single-vessel disease and 87 percent for patients with multivessel disease,[17] and 70 percent of patients were free of target vessel revascularization at 10 years.[18] Large observational studies comparing medical, surgical, and PTCA therapy suggested that revascularization surpassed medical therapy for most anatomic subsets and that surgery provided a survival benefit over PTCA in severe multivessel disease.[19,20] Recently published observational data from the 1993-1995 New York State Cardiac Procedure Registry of 60,000 CABG and PTCA procedures reported better 3-year survival with CABG in patients with three-vessel disease and those patients with two-vessel disease/proximal LAD stenosis treated with CABG, whereas those with one-vessel disease/no LAD stenosis had better survival with PTCA. All other patients had similar survival with PTCA and CABG.[21] Only now are outcomes for similar anatomic subsets being reported from randomized trials,[22] and these

results do not indicate a superiority of CABG over PTCA except in diabetics with three-vessel disease (see "Randomized Trials of Balloon Angioplasty," below).

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Chapter 45: PERCUTANEOUS CORONARY INTERVENTION

RANDOMIZED TRIALS OF BALLOON ANGIOPLASTY

PTCA versus Medical Therapy

The favorable results of these observational studies and others reporting single-vessel and multivessel $ir23,9p6sease patients[23,24] led to a series of randomized trials comparing balloon angioplasty with medical therapy[25-31] and with CABG.[32-38] The Angioplasty Compared to Medical Therapy Evaluation (ACME), involving 212 patients with single-vessel disease and abnormal stress tests, revealed greater freedom from angina in the angioplasty group at 6 months (64 versus 46 percent) as well as better treadmill performance (2.1- versus 0.5-min increase). There was no difference in death or myocardial infarction (MI).[25] The Second Randomized Intervention Treatment of Angina (RITA-2) trial randomized 1018 patients with stable angina to PTCA or medical therapy.[28] The majority (60 percent) had single-vessel disease, and 33 percent had two-vessel disease. Angina relief and treadmill performance were significantly better in the PTCA patients, but complications also were more frequent; death or myocardial infarction occurred in 6.3 percent of PTCA patients compared with 3.3 percent of medically treated patients. Symptomatic benefit was greater in the patients with severe angina at baseline. In the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial, 920 patients were randomly assigned to either an invasive strategy (routine coronary angiography and myocardial revascularization) or conservative management (medical therapy and noninvasive testing).[26] Although there was no difference in mortality during 12 to 44 months of follow-up, there was a higher incidence of a composite end point (death or nonfatal infarction) in the invasive group at 1 month and at 1 year (111 versus 85 events; $p = 0.05$). Although stents, ticlopidine, and IIb/IIIa inhibitors were not used, there were no deaths at 30 days in the invasive group treated with PTCA but an 11.6 percent 30-day mortality in this group treated with CABG. Whereas the VANQWISH investigators recommended the conservative approach, the recently reported, larger Fast Revascularization During Instability in Coronary Disease (FRISC II) study strongly supported an invasive approach.[30,31] Among men at 6 months, the invasive strategy in FRISC II resulted in a 34 percent reduction in death or MI ($p = 0.002$) and a 52 percent reduction in mortality (1.5 versus 3.2 percent; $p = 0.03$). Although there was no reduction in death or MI in women, there was an approximately 50 percent reduction in symptoms of angina and need for readmissions during 6 months of follow-up.

In 341 mildly symptomatic patients (59 percent asymptomatic or class I, 40 percent class II) in the Atorvastatin versus Revascularization Treatment (AVERT) trial, PTCA was compared with aggressive lipid-lowering therapy (atorvastatin 80 mg).[29] At 18-month follow-up, angina relief was significantly better ($p < 0.009$) in the PTCA group, with 54 percent having improvement, versus 41 percent in the aggressive lipid-lowering group, but quality-of-life scores were similar, and there was a trend toward more events (primarily hospitalization for ischemia) in the PTCA group. In AVERT, stents were used in 30 percent of patients. This study suggests that in low-risk patients with no or mild symptoms, aggressive lipid lowering is as effective as PTCA in reducing subsequent ischemic events and emphasizes the importance of extending aggressive lipid lowering in all patients with obstructive coronary artery disease. The Medicine, Angioplasty or Surgery Study (MASS) randomized 214 patients with stable angina, normal left ventricular function, and severe proximal LAD stenosis to bypass surgery [with left internal mammary artery (LIMA)

graft], PTCA, or medical therapy.[27] At 3 years, there was no difference in death or MI. Both revascularization strategies yielded better symptom relief, but subsequent procedures were more common in the PTCA group.

PTCA versus CABG

Over 5000 patients have been randomized in nine trials comparing angioplasty with CABG surgery. Two of these trials were sponsored by the NHLBI and performed in the United States. The first, the Emory Angioplasty versus Surgery Trial (EAST), was a single-center study,[32] whereas the larger Bypass Angioplasty Revascularization Investigation (BARI)[33,34] involved 18 centers. In-hospital mortality was similar for angioplasty and bypass surgery (approximately 1 percent) in these two studies of patients with multivessel disease, and 5-year survival also was similar (Table 45-1). Repeat revascularization procedures, however, were more common in the angioplasty group. Freedom from angina was better in the CABG group in both EAST and BARI. Meta-analyses of eight randomized published trials comparing PTCA and CABG (BARI not included) reported no difference in mortality or MI at 1 year after angioplasty or CABG, but 18 percent of the angioplasty patients had required bypass surgery and 20 percent had an additional angioplasty, a significantly higher rate of repeat revascularization than in the surgery group.[35,36] This increased need for additional revascularization procedures in angioplasty patients, largely due to restenosis, eroded the initial cost advantage of angioplasty; by 3 years in the EAST study, angioplasty had been 95 percent as costly as bypass surgery.[37,38]

Considerable interest was generated by a subset analysis of treated diabetics in BARI. Among the 353 diabetics treated with insulin or oral hypoglycemic agents, 5-year survival was significantly better in patients who underwent surgery compared with that of patients who underwent PTCA (80.6 versus 65.5 percent; $p = 0.003$).[39] Analysis of 7-year survival for all patients in BARI revealed for the first time a significantly better survival with CABG compared with PTCA-treated patients (84.4, 80.9 percent; $p = 0.0425$) (Fig. 45-4*A*). This difference was accounted for entirely by the poorer survival of treated diabetics revascularized with PTCA (55.7 versus 76.4 percent for CABG; $p = 0.0011$)[40] (see Fig. 45-4*B*). There was no difference in the survival of nondiabetics (see Fig. 45-4*C*). Further analysis of treated diabetics in BARI revealed that the survival benefit with CABG was conferred only to those patients who received an internal mammary artery (IMA) graft. The 7-year survival of patients treated with an IMA graft was 83.2 percent compared with 54.5 percent for saphenous vein graft only patients, a figure comparable with that attained with PTCA. EAST, which initially showed no difference between PTCA and CABG in diabetics, now at 8 years shows the same trend as BARI [41] (see Fig. 45-4*D-F*). Considering the rather late manifestation of these outcome differences, it is likely that factors other than early restenosis must be operative. Development of new lesions, perhaps unrecognized, probably accounts for those events occurring many years after revascularization. Poorer outcomes also were reported for diabetics in the BARI registry[42] and in the Emory University Hospital database.[43] In these randomized trials and observational reports, balloon angioplasty was the predominant interventional strategy. Use of stents has been shown to reduce restenosis, and their use in trials of stents versus CABG (see "Stents: After a Decade of Use the Dominant Strategy," below) and in diabetic patients is discussed below. Pending clarification by these trials, caution should exercised in the use of PTCA in diabetic patients with multivessel disease[44] and use of arterial grafts emphasized in diabetic patients.[45,46]

Only recently have data become available from BARI analyzing long-term outcomes based on more specific anatomic subsets.[22] At 7 years, there was no difference in survival of PTCA-treated versus CABG-treated patients with three-vessel disease without diabetes (85 versus 87 percent; *p*

= 0.4, *n* = 592), three-vessel disease with decreased left ventricular ejection fraction (LVEF) (70 versus 74 percent; *p* = 0.6, *n* = 176), two-vessel disease with proximal LAD stenosis (87 versus 84 percent; *p* = 0.9, *n* = 352), and two-vessel disease with proximal LAD stenosis and decreased LVEF (78 versus 71 percent; *p* = 0.7, *n* = 72). Contrary to the New York State Cardiac Procedure Registry data, these findings of a prospective, randomized trial tend to support the appropriateness of PTCA in nondiabetics with multivessel disease when the anatomy is permissive and the patient prefers a percutaneous approach.

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Chapter 45: PERCUTANEOUS CORONARY INTERVENTION

NEW DEVICES AND STRATEGIES FOR CORONARY INTERVENTION

Atherectomy, Laser, and Thrombectomy Devices

The directional atherectomy catheter (Fig. 45-5*A*) developed by Simpson[47] was, in 1990, the first nonballoon device approved for coronary intervention and the first to undergo randomized comparison with balloon angioplasty. In native coronary artery[48,49] and saphenous vein graft lesions[50] judged suitable for either procedure, however, the more costly directional atherectomy did not show a substantive advantage over balloon angioplasty. Additional trials using techniques to achieve optimal atherectomy (<20 percent residual stenosis) have been completed.[51,52] The randomized Balloon versus Optimal Atherectomy Trial (BOAT) showed no increase in in-hospital death, Q-wave MI, or CABG with directional atherectomy, but a higher rate of non-Q-wave infarction occurred (16 versus 6 percent; $p < 0.0001$).[51] Restenosis was lower in the atherectomy arm (31 versus 39.8 percent; $p = 0.016$), but there was no difference in late clinical events. The use of directional atherectomy has declined dramatically in most but not all centers[53,54] because of its complexity, added cost, and marginal benefit. In some centers, this technique is used to debulk lesions prior to stenting with the hope of reducing restenosis[55,56] and for lesions at bifurcations and ostial lesions of the LAD coronary artery.[57,58] Excimer laser angioplasty was approved by the Food and Drug Administration (FDA) in 1992 for lesions not favorable for balloon angioplasty, but this technology has not been shown superior to balloon angioplasty[59] and is used infrequently in most centers and then primarily for treating in-stent restenosis, where it is safe and initially effective but has no proven superiority.[60] In 1994, two additional atherectomy devices, the Rotablator (Heart Technologies, Bellevue, WA; see Fig. 45-5*B*) and the Transluminal Extraction Catheter (TEC) (Interventional Technologies, San Diego, CA; see Fig. 45-5*C*) were approved for marketing by the FDA The Rotablator's principal advantage is in the treatment of calcified and undilatable stenoses, but it is also used to treat bifurcation lesions and in-stent restenosis and to debulk prior to stenting.[61-64] The TEC device is used principally in saphenous vein grafts, where aspiration of thrombus is its unique attribute. In 1999, a rheolytic thrombectomy device known as the Angiojet (POSSIS Medical, Inc., Minneapolis, MN; see Fig. 45-5*D*) also became available for treatment of intracoronary thrombus, and it has proved useful in the setting of acute coronary syndromes associated with large thrombi and in treatment of stent thrombosis.[65-69]

Stents: After a Decade of Use, the Dominant Strategy

None of the devices described earlier had the impact on interventional cardiology that was produced by the development of the stainless steel intracoronary stent. The first coronary stents were implanted in patients in 1986 by Puel in Toulouse and Sigwart in Lausanne for restenosis prevention,[70,71] an unproven hypothesis at the time, whereas the initial implantation in a patient in the United States was performed by the authors at Emory University in 1987 in the setting of abrupt closure,[72,73] following encouraging results in a canine model by Roubin et al.[74] The initial European experience was with a self-expanding mesh stent, whereas the experience at Emory was with a balloon-mounted coil stent that subsequently was marketed as the Gianturco-Roubin flex stent (Cook, Inc., Bloomington, IN) following FDA approval for abrupt or threatened closure in 1993. This stent made balloon angioplasty considerably safer by providing effective therapy for coronary dissections and reducing the need for emergency coronary bypass surgery, but the use of

this stent, despite intensive anticoagulation with heparin and warfarin, was complicated by stent thrombosis in 5 to 10 percent of patients, and bleeding was a common complication. The device that ultimately revolutionized interventional cardiology was the Palmaz-Schatz stent (Johnson & Johnson Interventional Systems, Warren, NJ) (Fig. 45-6). On the basis of two carefully conducted randomized trials that showed reduced restenosis compared with balloon angioplasty,[75,76] this device was granted FDA approval for marketing in 1994 for the elective treatment of *de novo* lesions in native coronary arteries. Over 100,000 implantations of this stent were performed in the first year of its availability. The interest in stenting was greatly heightened by a pivotal observation by Colombo that complete stent expansion by high-pressure balloon inflation, confirmed by intravascular ultrasound (Fig. 45-7), when aspirin and ticlopidine were substituted for warfarin, yielded a very low thrombosis rate.[77] A randomized trial of stent placement without ultrasound guidance comparing aspirin and ticlopidine with phenprocoumon (a warfarin derivative) (ISAR) revealed a low 30-day incidence of cardiac events and bleeding rates in the aspirin-ticlopidine patients, supporting this simplified antithrombotic strategy[78,79] (Fig. 45-8). This finding was confirmed and extended by the Stent Anticoagulation Restenosis Study (STARS) investigation, which showed that aspirin and ticlopidine resulted in a lower rate of stent thrombosis than aspirin alone or a combination of aspirin and warfarin[80] (see Fig. 45-8), by a multicenter comparison of aspirin and ticlopidine with aspirin and oral anticoagulation in medium-risk (FANTASTIC, Fig. 45-8) and high-risk patients showing better outcome with the simpler approach,[81,82] and by a report of Mayo Clinic experience suggesting that 14 days of ticlopidine and aspirin was adequate for prophylaxis against stent thrombosis in most patients.[83] However, rare reports of thrombotic thrombocytopenia purpura related to ticlopidine use accounting for at least 20 deaths[84,85] led most centers to abandon ticlopidine in favor of clopidogrel, also an antagonist of platelet ADP receptors with similar pharmacologic activity but with far fewer side effects.[86] Clopidogrel proved equal to ticlopidine in observational reports,[87,88] and in a randomized investigation, the Clopidogrel Aspirin Stent Interventional Cooperative Study (CLASSICS), it was observed that neutropenia, thrombocytopenia, or early discontinuation of the drug was more common in the ticlopidine group (9.1 versus 2.9 percent) than in the clopidogrel group, which received 300 mg as a loading dose and 75 mg subsequently,[89] and that major cardiac events were similar at 1 month.[90] Currently, most centers use a loading dose of 300 to 525 mg clopidogrel when prolonged pretreatment is not possible plus aspirin 160 to 325 mg daily and 75 mg clopidogrel plus aspirin for 15 to 30 days after stent implantation.

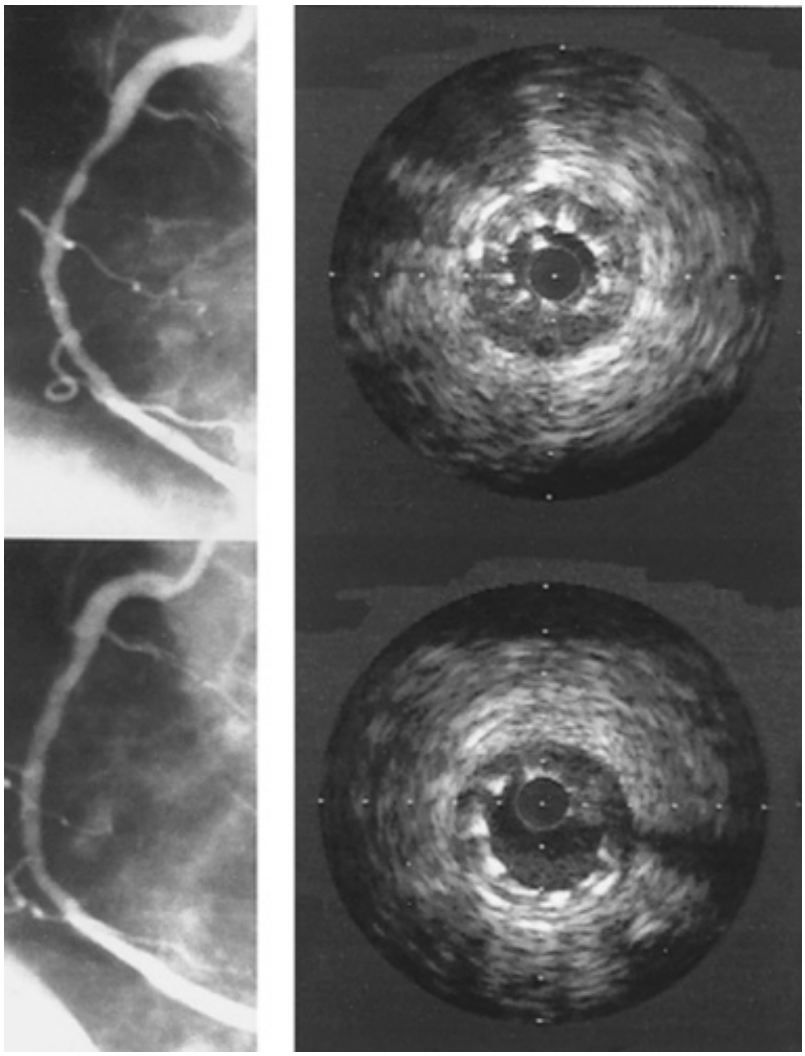

Figure 45-7: A 74-year-old woman developed early recurrence of angina after balloon angioplasty of the right coronary artery. Coronary arteriography revealed a severe, long stenosis of the right coronary artery (*top left*). Stenting was advised, and a Wallstent was deployed and dilated with a 3.5-mm balloon to 15 atm with an excellent angiographic result (*bottom left*). IVUS, however, showed that the distal end of the stent had been missed with the balloon and was poorly expanded (*top right*). This area was "redilated" to 16 atm with no change in the angiogram but much better stent expansion and wall apposition by ultrasound (*bottom right*). Following repeat dilation, the lumen cross-sectional area increased from 4.2 to 6.4 mm2.

A number of randomized trials have been conducted using the simpler antiplatelet therapy. The important Belgium Netherlands Stent II (BENESTENT II) study that randomized the heparin-coated Palmaz-Schatz stent and standard balloon angioplasty found better event-free survival at 12 months in the stent group (89 versus 79 percent; $p = 0.004$), lower restenosis (16 versus 31 percent; $p = 0.0008$), and higher costs in stent patients by $1020 at 1 year.[91] This study raised fundamental questions as to whether a strategy of elective stenting is justified in all patients, and further analysis of long-term follow-up suggested that stent implantation in some subsets was both superior and cost-effective (i.e., unstable angina, proximal LAD stenosis). To investigate these issues, the Optimal Angioplasty versus Primary Stenting (OPUS-1) trial randomized 479 patients to primary stenting or balloon angioplasty followed by provisional stenting only when necessary and reported that after 6 months the combined incidence of death, MI, and target-vessel revascularization was significantly lower in the primary stenting arm (6.1 versus 14.9 percent; $p = 0.003$), and at 6 months primary stenting was slightly less expensive ($10,206 versus $10,490).[92] This provocative study in which 99 percent of patients in the primary stent arm received a stent compared with 37 percent in the provisional stenting arm supported routine stenting when the

anatomy is appropriate as opposed to primary balloon angioplasty with stent backup, a strategy that has been advocated by some investigators[93-95] and, of course, was the dominant strategy in the early days of stenting. The use of coronary stents was reviewed extensively in a recent American College of Cardiology Expert Consensus Document[96] and in other reports.[96a,96b] This document and these newer studies provide perspectives on which to base everyday decisions regarding contemporary coronary intervention.

Stents versus CABG in Multivessel Disease

The issue of whether to recommend CABG or PTCA in patients with multivessel disease will be significantly influenced by the long-term outcome of randomized trials comparing stents with bypass surgery. Intermediate-term data are available from the Arterial Revascularization Therapy Study (ARTS), which randomized 1205 multivessel disease patients in 68 clinical centers to stent or standard CABG. At 1 year, there was no difference in death or MI; however, repeat interventions were higher in the stent group.[97] One-year survival free of death, MI, and reintervention was seen in 87.6 percent of the surgical group and 73.7 percent of the stent group ($p < 0.04$), but at a higher total 1-year cost (13,645 versus 10,860 euros). The occurrence of late events in 26 percent of ARTS stented patients was approximately one-half the incidence seen following balloon angioplasty in multivessel disease in BARI and EAST due to a reduced need for repeat revascularization in stented patients. As in BARI, the mortality rate in ARTS of diabetics treated percutaneously was significantly higher than that of nondiabetics (6.3 versus 3.1 percent; $p < 0.01$).[98] In the smaller Argentine Randomized Study of Stents versus CABG in Multivessel Disease (ERACI II), 450 patients were randomized, and at 14.7 months, survival was better in the stent group (97.4 versus 92.5 percent; $p < 0.015$) and freedom from MI was higher (97.7 versus 93.4 percent; $p < 0.017$), but repeat revascularization was needed more often in the stent group and costs were similar.[99] The Stent or Surgery Trial (SOS) will soon be completed and should offer additional insights.

Adjunctive Strategies

Intravascular ultrasound (IVUS) also has been used extensively in some centers to evaluate coronary lesions for device therapy and to assess the results of device and balloon treatment,[77,100] but the increased cost of this approach is a limiting factor. Although IVUS has had significant impact on the evolution of interventional cardiology, on the understanding of restenosis, and in evaluation of difficult lesions, its routine use in most centers is limited. See Chap. 47 for a detailed discussion.

IIb/IIIa Platelet Receptor Inhibitors

The latest arrows in the quiver of the interventionalist are the new, potent antiplatelet agents.[101-113] The first approved by the FDA was a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor. This agent, abciximab (ReoPro, Centocor, Malvern, PA), was shown to reduce ischemic complications and late clinical events in high-risk angioplasty.[105] The other IIb/IIIa receptor inhibitors approved by the FDA, unlike the antibody abciximab, are competitive inhibitors; eptifibatide (Integrilin, COR Therapeutics, San Francisco, CA) is a peptide, and tirofiban (Aggrastat, Merck, White House Station, NJ) is a small nonpeptide molecule. Each of these IIb/IIIa agents has been shown to consistently reduce a composite end point of death or nonfatal MI in the setting of coronary intervention and in acute coronary syndromes[79,101-105] (Fig. 45-9). Further, at 3-year follow-up in the EPIC trial, the first major study of abciximab during coronary intervention, a subgroup of 555 patients with acute coronary syndromes treated with bolus abciximab and infusion had a significant reduction in mortality at 3 years.[106] For a detailed discussion of IIb/IIIa platelet receptor inhibitors, see Chap. 44. In a recent

review of the use of the three FDA-approved IIb/IIIa receptor inhibitor agents in acute coronary syndromes, it was noted that they were each effective in reducing a composite end point of death or MI when administered prior to or at the time of percutaneous coronary intervention[107] (Fig. 45-10). In most centers, the use of these agents, slowed initially by bleeding complications and high costs, has been increasing especially in high-risk patients. Also contributing to this trend is the favorable outcome of IIb/IIIa receptor inhibitor-treated patients in the Evaluation of Platelet IIb/IIIa Inhibitors of Stenting (EPISTENT) trial, in which abciximab therapy in patients undergoing stent implantation or balloon angioplasty was evaluated.[108,109] At 6 months, the incidence of a composite end point of death or MI was 5.6 percent in patients receiving a stent and abciximab compared with 11.4 percent in those receiving a stent and placebo ($p < 0.001$) and 7.8 percent in patients treated with balloon angioplasty and abciximab (Fig. 45-11). There was a further advantage in diabetics, in whom the combination of abciximab and stenting was associated with a lower rate of repeat target vessel revascularization (8.1 percent) than was observed with stenting and placebo (16.6 percent; $p = 0.02$) or angioplasty and abciximab (18.4 percent; $p = 0.008$), and this benefit persisted through 1-year follow-up.[110] The mechanism by which target-vessel revascularization was reduced in the abciximab-treated patients is unclear.[111] Previous reports indicate that abciximab did not prevent neointimal proliferation or reduce in-stent restenosis.[112] EPISTENT does, however, raise the question regarding whether all diabetic patients and further all patients receiving stents should receive IIb/IIIa platelet inhibitors. Ongoing trials of these agents in stented patients may shed light on this important question. Clearly, however, these potent new strategies enhance the ability to provide safe and effective percutaneous revacularization.[113] Recently published data from CAPTURE indicated the presence of a gradient in the benefit obtained from IIb/IIIa receptor inhibition with abciximab in unstable angina. Death or MI was significantly less frequent in patients with elevated baseline troponin treated with abciximab compared with placebo (9.5 versus 23.9 percent; $p = 0.002$), but this end point was not different in troponin-negative patients (7.5 versus 9.4 percent; $p = 0.47$).[114] Stated differently, without an elevated troponin level, there was no benefit of treatment with respect to risk of death or MI. While there was no difference in death, MI, or urgent intervention in simple lesions, there was for complex lesions (ACC/AHA classes B2 and C) an incidence of this end point of 19.1 percent for placebo versus 11.5 percent for abciximab ($p = 0.055$).[115] The benefit gradient was steepest for bifurcation lesions in young patients. Occlusion of a side branch of more than 1.5 mm diameter, orginating from the angioplasty site, occurred in 2.8 percent of placebo-treated patients and 1.0 percent of abciximab-treated patients ($p = 0.03$). Also of interest, when flow in the culprit artery was less than TIMI grade 3 after angioplasty, the incidence of death and MI at 30 days was 11.5 percent with placebo and 4.1 percent with abciximab, supporting a role for abciximab in ameliorating the consequences of postprocedure slow flow. These observations that IIb/IIIa receptor inhibitors appear to be more effective in patients with refractory unstable angina, complex anatomy, and slow flow, results not observed previously,[104,105,116] may help in the design of trials to better determine the place of these agents.

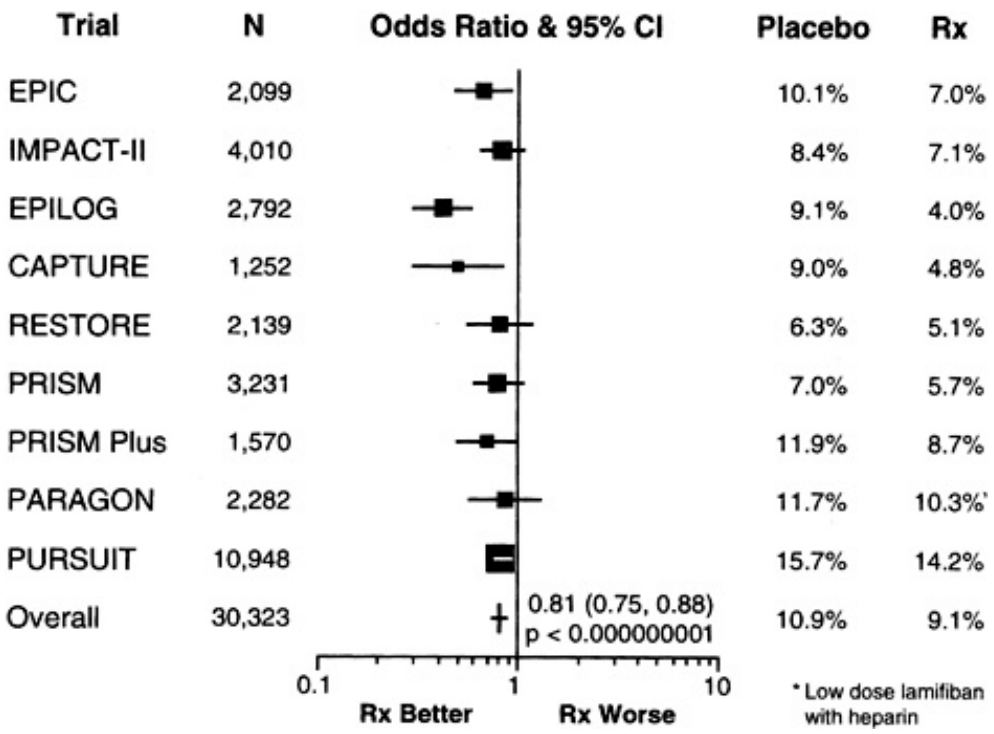

Figure 45-9: Odds ratios and 95 percent confidence intervals for nine large-scale randomized trials of IIb/IIIa platelet receptor inhibitors for percutaneous coronary interventions or unstable angina/non-Q-wave MI. Overall, in 30,323 patients, a 19 percent reduction in death or MI at 30 days was demonstrated. (From ref. 79 with permission.)

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Chapter 45: PERCUTANEOUS CORONARY INTERVENTION

INDICATIONS FOR CORONARY INTERVENTION

In general, when one is selecting percutaneous coronary intervention, there should be assurance that the operator can treat, with a high probability of success, the coronary lesion(s) accounting for the symptoms or signs of myocardial ischemia. Further, the associated risk and durability of the revascularization should be acceptable as compared with bypass surgery or medical therapy during both early and long-term follow-up. The latter estimate requires consideration of the likelihood and consequences of abrupt vessel closure, restenosis, and incomplete revascularization. In addition, one cannot disregard the comparative costs of the initial intervention, its complications, and the need for subsequent revascularization procedures. The American College of Cardiology/American Heart Association Guidelines for Percutaneous Transluminal Coronary Angioplasty and Coronary Bypass Surgery provide a detailed analysis of many of these issues.[45,117,118]

Selection of Patients

SINGLE-VESSEL DISEASE

Percutaneous revascularization is an attractive option for many symptomatic patients who are anatomically suitable, having single-vessel coronary disease. It is important, however, to remember that there are no large studies comparing angioplasty with surgery in this group of patients and none that show a statistically significant survival benefit of angioplasty compared with surgery or medical therapy. Data from Emory University indicate that of 692 single-vessel disease patients newly diagnosed in 1988, a total of 46 percent underwent angioplasty, 50 percent were treated medically, and 4 percent underwent coronary bypass surgery. Of 7604 patients with single-vessel disease treated at Emory with angioplasty between 1980 and 1991, angiographic success was 90 percent and complications were infrequent (Q-wave MI, 0.8 percent; emergency CABG, 1.7 percent; and death, 0.2 percent).[119] In these patients with single-vessel disease, 1-, 5-, and 10-year survival was 99, 93, and 86 percent, respectively, whereas 80, 69, and 58 percent were PTCA-free and 92, 87, and 77 percent were CABG-free at 1, 5, and 10 years. In the Duke Data Bank experience, 5-year survival with angioplasty in single-vessel disease compared favorably with bypass surgery (95 versus 93 percent with CABG).[120]

The ACME study showed that angioplasty in single-vessel disease can lead to improved quality of life compared with medical therapy at 6 months, with reduced angina and improved exercise performance out to 3 years.[25,121,122] Clearly, it is improvement in symptoms rather than prolongation of life that is achieved by angioplasty in this patient subset. The ACME data suggest, however, that using the angioplasty techniques available at that time resulted in a slightly increased risk of acute complications (2 percent emergency CABG, 1 percent Q-wave MI) and repeat revascularization (23 versus 9 percent) at 6 months but no difference in late revascularization at 3 years.[122]

In an observational report from Kansas City of 704 patients with single-vessel LAD artery revascularization, 2-year mortality was 3.9, 2.6, and 1 percent in PTCA, stent, and LIMA-LAD revascularization groups, respectively ($p = 0.33$), and repeat procedures occurred in 30, 24, and 5 percent, respectively ($p = 0.001$).[123] In the randomized Medicine, Angioplasty, or Surgery Study (MASS) of isolated LAD disease, there was no difference in MI or mortality at 5 years but fewer late events in the surgery group.[124] In a relatively small, randomized trial of angioplasty and IMA surgery for isolated disease of the LAD artery, there was no difference in mortality or MI, but angioplasty patients had more repeat revascularizations (25 versus 3 percent; $p < 0.01$).[125] Clear superiority of stenting over balloon angioplasty for isolated LAD disease was demonstrated in a randomized comparison of these strategies in 120 patients.[126] One-year rates of event-free survival were 87 percent after stenting and 70 percent after

angioplasty ($p = 0.04$), and restenosis rates were 19 and 40 percent, respectively ($p = 0.02$).

Studies from the Cleveland Clinic analyzing the importance of repeat procedures in determining 2-year cardiac cost suggest that coronary intervention is more cost-effective than medical and surgical therapy when the probability of repeat procedures is low.[127] One would infer from this analysis that the presence of multiple or complex lesions, which are likely to recur, may tilt the scale sufficiently to modify adversely the favorable comparative cost-effectiveness of percutaneous intervention in single-vessel disease.

MULTIVESSEL DISEASE

A dramatic increase in the use of percutaneous intervention in multivessel disease, fueled by improved angioplasty technology and new devices, accounts for the growth in these procedures worldwide. *Rational selection of patients, however, requires a careful analysis of multiple issues, including a risk-benefit assessment of each ischemia-producing lesion, a projection of the possible completeness and durability of the physiologic revascularization, and an estimate of resource consumption compared with surgery and medical therapy.*

In general, as stated in "Guidelines for PTCA,"[118] patients selected for intervention are symptomatic, have evidence of ischemia, need noncardiac surgery, are recovering from cardiac arrest or malignant arrhythmia, or have compelling anatomy. Patient preferences must be considered, since repeat interventions are a common and an integral aspect of percutaneous intervention in multivessel disease (see Table 45-1). Complete revascularization, which has been shown in the surgical experience to produce superior long-term results, has been associated with fewer late interventions after angioplasty,[128] but it is not frequently attained due to the presence of total occlusions, noncritical stenoses, and diffuse disease. In the 1985-1986 NHLBI PTCA Registry, complete revascularization was achieved in 19 percent of multivessel patients.[129]

At Emory University among 10,783 patients who underwent coronary intervention, complete revascularization was achieved in 84 percent of patients with single-vessel disease and 25 percent with two-vessel disease but in only 5 percent with triple-vessel disease.[119] In the experience of EAST, 71 percent of index segments were revascularized in PTCA patients.[130] Culpritlesion angioplasty is clearly an accepted strategy, but care must be taken to avoid significant residual ischemia after intervention. This approach was reflected in EAST, where revascularization was attempted in 96 percent of high-priority lesions in PTCA patients and in 99 percent of surgical patients. (*High-priority lesions* were defined as 70 to 100 percent stenoses located proximally or in large vessels ≥ 2.5 mm). This strategy yielded similar 3-year EAST primary end points for CABG and PTCA and an identical frequency of patients with all index segments free of stenosis of 70 to 100 percent (82 versus 82 percent).[130] Recently published data from BARI indicated that planned incomplete revascularization was unrelated to 5-year risk of cardiac death or death/MI but was related to risk of CABG.[131]

The risks of percutaneous coronary intervention are increased in the presence of unstable angina, advanced age, poor left ventricular function, extensive coronary artery disease, comorbid conditions, and female gender.[132] At Emory, in-hospital mortality for one-, two-, and three-vessel disease was 0.2, 0.4, and 1.2 percent, respectively ($p < 0.0001$), and emergency bypass surgery was needed in 1.7, 3.0, and 3.2 percent, respectively.[119] In general, the risk of intervention is directly related to the probability and consequences of abrupt closure. In multivessel disease, both are frequently higher, and impaired left ventricular function is commonly present. Recent application of stenting in multivessel percutaneous intervention has improved outcomes significantly.[133-136] In a report from the Washington Hospital Center, in-hospital and long-term outcomes of 398 consecutive patients undergoing multivessel stenting were quite similar to those of patients undergoing single-vessel stenting with respect to mortality (1.4 versus 0.7 percent; $p = 0.26$), repeat revascularization (20 versus 21 percent; $p = 0.73$), and Q-wave MI (0 versus 1.2 percent; $p = 0.02$). Overall event-free survival was similar.[135] Although the major randomized trials of angioplasty versus bypass surgery also showed no overall difference in mortality on long-term follow-up, BARI reported that patients being treated for diabetes had significantly worse 5-year mortality with angioplasty compared with surgery (35 versus 19 percent).[39] In a smaller cohort of diabetic patients in EAST, however, there were no differences in outcome until almost 8 years following revascularization. The BARI findings question the safety of angioplasty in the diabetic population, who frequently have diffuse multivessel disease, more

frequent restenoses, more rapid disease progression, and in many cases a reduced recognition of recurrent ischemia.[44,137] ARTS extended this cautionary theme in multivessel diabetics with observations that stented diabetics had roughly twice the mortality of nondiabetics[98] (see "Randomized Trials of Balloon Angioplasty," above).

UNSTABLE ANGINA

Patients with unstable angina, who account for a majority of coronary interventions, are at increased risk for ischemic complications, particularly abrupt closure.[117,118,132] These complications, which are presumed to be related to the presence of thrombus and ruptured complex plaque[138] (see Chaps. 40 and 44), as demonstrated elegantly by angioscopy,[139,140] have led many operators to defer intervention for a few days while stabilizing the patient on aggressive antianginal therapy, including aspirin and heparin[141-143] (particularly in the presence of angiographic thrombus).[144] Alternatively, the favorable results achieved with angioplasty within 18 to 48 h after hospitalization in randomized trials of interventional strategies in unstable angina (96 percent angiographic success, 0.4 percent mortality, 2.9 percent MI, 0.7 percent emergency CABG, 2.2 percent abrupt closure)[145] and the recently reported FRISC II study of invasive management of non-Q-wave MI[30,31] have encouraged some to pursue a more aggressive approach, particularly in patients at highest risk of a coronary event-i.e., those with postinfarction angina[146] and angina refractory to medical therapy.[147] The use of direct antithrombins[148] and platelet glycoprotein IIb/IIIa inhibitors[105] has been shown to be effective in reducing complications of intervention in unstable angina, whereas the routine administration of thrombolytic agents has reduced the thrombus burden but with an unfavorable impact on complications (i.e., in hospital ischemic events; 12.9 versus 6.3 percent without thrombolytics; $p = 0.02$).[149] At present, the optimal adjunctive therapy in unstable angina is unclear, but recent trials of the currently available IIb/IIIa platelet receptor inhibitors and of low-molecular-weight heparin have shown important reductions in complications in patients with non-ST-segment elevation acute coronary syndromes during medical therapy[101-103,114-116,150-153] and additional protection with IIb/IIIa receptor inhibitors during coronary intervention[107,154] (see Fig. 45-10 and Chap. 41). Data from CAPTURE in patients with unstable angina indicated that the benefit of IIb/IIIa receptor inhibition was greatest in troponin-positive patients and those with complex coronary anatomy.[114,115,155]

Selection of Lesions

LESION CHARACTERISTICS

The importance of coronary stenosis angiographic morphology in predicting the outcome of coronary angioplasty is reflected in the American College of Cardiology/American Heart Association "PTCA Guidelines."[117,118] Lesions were classified as type A for anticipated high success, low risk; type B for anticipated moderate success, moderate risk; and type C for anticipated low success, high risk (Table 45-2). The general validity of this classification in predicting outcome of balloon angioplasty was confirmed in low-risk patients,[156] in patients with multivessel disease,[157] and in patients undergoing directional atherectomy, in whom success and complication rates were 93 and 3 percent for type A lesions, 88 and 6 percent for type B_1, and 75 and 13 percent when more than one B characteristic was present (type B_2).[158] More recent analysis of this lesion scoring system using balloon angioplasty technology of the 1990s suggests rates of 96, 93, and 80 percent can be achieved with type A, B, and C lesions, respectively, and that certain morphologic characteristics (i.e., long lesions, calcified lesions, stenosis severity 80 to 90 percent, angulated lesions, and presence of thrombus)[159] may have higher predictive value in determining success and complications. The ABC classification also was reported to be useful in predicting outcome after contemporary angioplasty in a population of unstable angina patients in whom early adverse events occurred in 4 percent of type A, 7.7 percent of type B_1, 15.3 percent of type B_2, and 17.9 percent of type C lesions in patients treated with heparin.[160] It does appear, however, in many centers that the complexity of lesions being attempted has increased and that new devices (especially stents) and antithrombotic strategies have, to a certain extent, weakened the prognostic value of this scoring system. In one recent report of 1085 lesions treated in the era of new devices (type A, 8 percent; type B_1, 42 percent; type B_2, 35 percent; type C, 15 percent), procedural success was 100 percent for type A, 97.3 percent for type B_1, 97 percent for type B_2, and 87.4 percent for type C lesions. Predictors of procedural failure were lesion length greater than 20

mm, TIMI-I flow, calcification, angle greater than 90 percent, and chronic total occlusion.[161] In an effort to update this classification based on results of contemporary coronary intervention using stents and IIb/IIIa platelet receptor inhibitors, Ellis and colleagues analyzed results from 10,907 lesions and proposed a new classification scheme for risk stratification.[162] Over 4000 patients treated in 1995 through 1996 constituted a training set (40.7 percent received stents, 26 percent abciximab, 18.9 percent Rotablator, 0.9 percent directional atherectomy, 0.2 percent excimer laser, and 0.2 percent TEC). Nine preintervention variables were independently correlated with adverse outcome (non-chronic total occlusion, degenerated vein graft, vein graft age greater than 10 years, lesion length greater than 10 mm, severe calcium, lesion irregularity, large filling defect, angulated greater than 45 degrees plus calcium, and eccentricity). A proposed classification (Table 45-3) validated against 2146 patients treated in 1997 had greater predictive value than the ACC/AHA classification, but not by as much as expected. Importantly, lesion characteristics previously thought to be associated with a heightened risk but absent in the new classification include lesion angulation per se, bifurcation location, ostial site, proximal tortuosity, and small thrombus. When the new model was tested against the 1997 validation set, adverse outcomes [death, MI > 3 × creatine kinase (CK) or emergency CABG] occurred in 2.1 percent of low-risk patients, 3.4 percent at moderate risk, 8.2 percent at high risk, and 12.7 at highest risk (compared with 2.5, 3.0, 5.2 and 6.6 percent for ACC/AHA types A, B_1, B_2, and C, respectively). Whether bifurcation location should be included as a predictor of complications is debatable. In our own experience, bifurcation has represented increased risk, and this was confirmed in CAPTURE, where placebo-treated patients with bifurcations had a higher rate of death, MI, or early revascularization than placebo-treated patients without bifurcations (23 versus 11.7 percent; $p < 0.05$).[115] Importantly, this increased risk of complications with bifurcations was neutralized by treatment with abciximab. It should be recognized, however, that other factors are important in determining risk in the stent and IIb/IIIa inhibitor era, including patient age, LVEF, acute MI presentation, and operator experience, and these also must be considered.[163-165]

Table 45-3: New Risk-Assessment Schema Based on Analysis of 10,907 Lesions Treated in the Stent and IIb/IIIa Era

Strongest correlates:	Nonchronic total occlusion
	Degenerated saphenous vein graft (SVG)
Moderately strong correlates:	Length ≥10 mm
	Lumen irregularity
	Large filling defect
	Calcium + angle ≥45°
	Eccentric
	Severe calcification
	SVG age ≥10 years
Highest risk:	Either of strongest correlates
High risk:	≥3 moderate correlates and the absence of strong correlates
Moderate risk:	1-2 moderate correlates and the absence of strong correlates
Low risk:	No risk factors

SOURCE: Ellis et al.[162]

LEFT MAIN CORONARY ARTERY LESIONS

Whereas percutaneous intervention in protected left main coronary artery disease has been an accepted strategy for many years,[166] significant narrowing of an unprotected left main coronary artery has been considered a contraindication to this approach since Gruentzig's early recognition of increased mortality.[9,10] With the advent of improved technology in the form of atherectomy devices and stents, percutaneous revascularization has been applied increasingly in patients with unprotected left main coronary artery lesions.[167-170] Although reports of unprotected left main angioplasty/stenting indicated reasonably good results in carefully selected patients,[168,170] CABG remains the treatment of choice according to ACC/AHA guidelines.[45] Patients considered for percutaneous intervention in an unprotected left main coronary artery lesion in our hospital include those with significant comorbidity, making CABG impractical, and patients experiencing abrupt left main coronary artery closure as a complication of coronary angiography or presenting in cardiogenic shock without immediately available surgery.[170,171]

PREDICTORS OF RESTENOSIS

Lesion characteristics that were associated with increased restenosis rates following balloon angioplasty alone or after stent implantation include length, total occlusion (Fig. 45-12), vessel size less than 3 mm, ostial location, previous angioplasty to the same site, and saphenous vein grafts.[172-174] The assessment of lesion characteristics by IVUS and angioscopy also has been shown to have prognostic value for determining angioplasty success and long-term outcome,[175-179] and in some centers these strategies are used frequently to guide therapy (see Chap. 47). Selection of lesions for intervention is strongly based on the operator's assessment of his or her ability to treat the ischemia-producing lesion safely and in a cost-conscious manner and to achieve long-term patency and symptomatic benefit.

IN-STENT RESTENOSIS

One of the most vexing lesions confronting the interventionalist is in-stent restenosis, a new "disease" created by the explosion of stent use worldwide. This lesion, solely the result of neointimal proliferation as opposed to a combination of negative remodeling and intimal proliferation seen in nonstented lesions,[179] was reported by Yokoi et al.[180] to have an overall recurrence rate of 37 percent, but this rate is up to 85 percent for diffuse in-stent restenosis. Among 288 lesions, recurrent restenosis was highly correlated with the pattern of restenosis (target lesion revascularization in 19 percent of focal lesions less than 10 mm, 35 percent for lesions larger than 10 mm but confined to the stent, 50 percent for lesion larger than 10 mm and extending beyond the stent, and 83 percent for total occlusions; $p < 0.0001$). Additional correlates were the presence of diabetes (odds ratio, 2.8) and previous in-stent restenosis (odds ratio, 2.7).[181] In-stent lesions have been shown by IVUS to have significant reintrusion of tissue shortly after catheter-based intervention not apparent by quantitative angiography.[182] Debulking with atherectomy and laser techniques has been advocated and, although safe and associated with a larger postprocedure minimal lumen diameter (MLD), has not been shown to be superior to balloon angioplasty.[183-186] Although preliminary results from a U.S.-based multicenter randomized comparison of rotational atherectomy and balloon angioplasty were encouraging,[187] results of ARTS indicated that rotablation was inferior to balloon angioplasty (restenosis in 70 percent compared with 50 percent with balloon; $p = 0.008$).[188] Yokoi[189] reported results of repeated balloon angioplasty of in-stent restenosis in 310 patients, observing a first recurrence in 51 percent and subsequent recurrences following repetitive procedures in 68, 78, 74, and 92 percent of patients. Although 98 percent of patients were free of death and 90 percent were free of death/MI/CABG at 3 years, the increasingly high restenosis rate makes this approach impractical. The investigational use of radiation to inhibit neointimal proliferation has produced the most promising strategy for potential use in the treatment of this difficult problem. In randomized trials, beta and gamma radiation has reduced restenosis rates of 50 to 60 percent to approximately 20 percent[190,191] with reduction in 2-year death, MI, or target vessel revascularization (TVR) from 52 to 23 percent ($p = 0.03$).[192]

Selection of Devices

Conventional balloon angioplasty is a simple, relatively low in cost, and effective method of reducing coronary stenosis, but new devices (especially stents) are being used with increasing frequency, particularly in conditions where balloon angioplasty has been proved not to be highly effective (Table 45-4). At Emory University Hospital in 1990, balloon angioplasty was the sole technique used in 88 percent of 1863 patients

who underwent coronary intervention (directional atherectomy, 3 percent; excimer laser, 3 percent; stents, 2 percent; laser balloon, 1 percent), whereas in 1998, a majority of lesions that were discrete and not involving bifurcations were treated with stent implantation (66 percent of all patients), and the atherectomy procedures performed were prinicipally with the Rotablator for calcified, rigid, or bifurcation lesions (accounting for 8 percent of patients). At the Cleveland Clinic in 1997, device use frequency was as follows: stents, 64 percent (62.6 percent planned and 1.6 percent bailout); rotational atherectomy, 18 percent; directional atherectomy, 0.6 percent; excimer laser, 0.5 percent; and TEC 0.1 percent.[162]

Table 45-4: New Coronary Interventional Strategies Compared with Balloon Angioplasty

Technique	Indications	Contraindications	Advantages and Limitations
Balloon angioplasty	Focal stenosis	Insignificant narrowing, no ischemia, unimportant artery	Broad applicability, lower cost; poor outcome in thrombotic, ostial, and calcified lesions; significant restenosis
Stents	Focal stenosis	Heavy calcification or thrombus, vessel diameter <2.5 mm	Reduced emergency CABG and restenosis; more expensive, rare stent thrombosis
Directional atherectomy	Focal noncalcified	Diffuse disease, severe tortuosity or bend	Debulks, reduced restenosis; more frequent non-Q-wave MI, more expensive, technically difficult
Rotational atherectomy	Focal calcified stenosis, ostial site	Thrombus, large plaque burden, severe tortuosity or bend	Effective in calcified lesions, reduced elastic recoil; more expensive, similar restenosis, transient left ventricular dysfunction
Laser	Ostial lesion, SVG, in-stent restenosis	Severe calcification, tortuosity or bend	Debulks effectively; increased cost, similar restenosis
Transluminal extraction atherectomy	Thrombotic lesion, bulky SVG lesion	Severe tortuosity or bend, calcification	Thrombus and plaque removed; high complication rate in native vessels, distal embolization
Rheolytic thrombectomy	Thrombus	No thrombus	Effective thrombus removal; no plaque removal

PROVISIONAL STENTING

The practice of performing balloon angioplasty as an initial strategy in a majority of patients and using stents for suboptimal results is supported by observations from the BENESTENT trial that stentlike results (30 percent residual narrowing) were achievable in 35 percent of patients with balloons and that they had a long-term outcome comparable with that of stented patients.[193] This strategy has been reported to be cost-

effective,[194] but the recent OPUS-1 study of primary stenting suggested that primary stenting was cost-effective after 6 months because of reduced reinterventions.[92] Adjunctive stents placed for bailout have been shown clearly to reduce Q-wave infarction and emergency bypass surgery.[72,73] Although subacute thrombosis was substantially higher in patients with stents placed emergently in the early experience, the employment of high-pressure balloon inflations in recent studies and the use of antiplatelet agents such as ticlopidine and clopidogrel plus aspirin instead of warfarin have reduced this complication substantially to about 1 percent.[195]

PRIMARY STENTING

In our hospital, stents frequently are selected for primary treatment of complex lesions, aortoostial sites, shelflike lesions, early recurrence, total occlusions, and lesions with high restenosis rates (proximal LAD artery and saphenous vein grafts) (Figs. 45-7, 45-12, and 45-13). It is important to point out that restenosis rates obtained with stents in complex lesions are not as favorable as in simple lesions[196,197] and that these applications have not been subjected to rigorous comparison with balloon angioplasty. Randomized comparison has been carried out, however, in saphenous vein grafts, where 6-month MLD was significantly larger with stents (1.75 versus 1.47 mm; $p = 0.05$), and a composite end point of death, MI, CABG, or target lesion revascularization was less frequent (26 versus 38 percent; $p = 0.05$).[198] Stents also were shown in randomized trials to be superior to balloon angioplasty in total occlusions (TVR in 8.4 versus 15.4 percent; $p = 0.03$)[199] and in restenotic lesions (TVR in 10 versus 27 percent; $p = 0.001$).[200]

Given the superb results reported in the BENESTENT II study[91] with heparin-coated stents (overall clinical success 99 percent, stent thrombosis 0.2 percent, restenosis 16 percent, and 1-year mortality 1 percent) and the large number of new stent designs currently available, one would anticipate broadened use of improved and cheaper stents due to competitive market forces. Decreased cost may permit stenting to rival or prove more cost-effective than simple balloon angioplasty for most lesions.[201-203]

ATHERECTOMY

Currently, directional coronary atherectomy (DCA) is used infrequently in most centers as primary therapy but may be applied effectively in STRESS and BENESTENT-equivalent lesions[54] or used adjunctively prior to stent implantation based on registry data indicating that this strategy can yield restenosis rates as low as 11 percent.[56] Suitable lesions are generally proximal in vessels larger than 3 mm in diameter and have features that predict poor outcome with primary stenting such as high-bulk stenoses, ostial site, proximal LAD artery lesion, and protected left main coronary lesions[170,204] and include carefully selected bifurcation lesions[205-209] and complex postinfarction lesions (where histology frequently shows partially organized thrombus; see Fig. 45-10). Pretreatment of calcified lesions with rotational atherectomy may permit successful DCA in selected patients,[209] but in general moderate angiographic calcification and significant superficial calcification on IVUS are predictors of failure.[175]

Rotational atherectomy has proved useful in the presence of calcium, in treatment of aortoostial and branch ostial lesions, and in nondilatable lesions. In some series, it has been used in long, ulcerated, and complex lesions with excellent acute results,[210,211] and in some reports, long-term outcome of stenting was improved by rotablation pretreatment.[63] Highly angulated or thrombotic lesions or those with impaired distal runoff (recent infarction, fixed thallium defect) and segments with myocardial bridging should be avoided.[210-213] Rotational atherectomy also has been used in total occlusions, but restenosis rates have not been demonstrated to be better than those of balloon angioplasty. Elective intraaortic balloon pump placement has been shown to improve systemic blood pressure and to be associated with a lower non-Q-wave MI rate in high-risk patients.[214] Care is needed in selection of rotablation in patients with reduced left ventricular function due to the transient regional ventricular dysfunction shown to persist for over 2 hours after the procedure.[215]

The TEC, which is unique in its ability to cut and aspirate plaque and thrombus, is used primarily in saphenous vein grafts containing thrombus, where acute success rates are high, but embolic MI and

restenosis are not uncommon.[216-218] In some centers, high-risk patients with MI have been treated successfully with TEC either acutely or following postinfarction angina due to thrombotic coronary occlusion with results comparable with those of balloon angioplasty.[219] When used in the treatment of complex native coronary artery lesions not associated with acute MI, the outcome also appears similar to that of balloon angioplasty,[220] but use of TEC doubles the cost. In carefully selected patients with large intracoronary thrombi and ongoing ischemia, TEC has proved useful, as has the Dispatch catheter (Scimed Life Systems, Maple Grove, MN), a device for localized intracoronary infusion.[221] The Angiojet (Possis Medical, Inc., Minneapolis, MN) is the most effective thrombectomy device currently available and is used principally to treat large intracoronary thrombi.[65-69,222]

LASER ANGIOPLASTY

Although ablative laser angioplasty (XeCl excimer and holmium Nd:YAG) has been shown to be effective in the treatment of aortoostial sites, undilatable lesions, total occlusions, calcification, long lesions, and saphenous vein grafts,[223-226] its superiority to simpler and less costly balloon strategies has not been demonstrated.[227-229] Lesions that should not be selected for ablative laser angioplasty include those on bend points or in tortuous segments, those associated with severe calcification or thrombus, or lesions with a suspected subintimal wire passage. In general, bifurcation lesions should not be selected for ablative laser therapy unless an eccentrically directed device can be used to avoid perforating at the flow divider of the vessel. The use of a laser guidewire to cross total occlusions has been advocated.[230]

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Chapter 45: PERCUTANEOUS CORONARY INTERVENTION

PERFORMANCE OF CORONARY INTERVENTION

Operator Proficiency

Current guidelines recommend that cardiologists who wish to become competent in coronary intervention receive special training in diagnostic and therapeutic catheterization during an additional year after the standard fellowship training program and maintain skills by performance of a minimum of 75 procedures per year.[231-237] Adequate case mix is an important aspect of a physician's training in interventional cardiology that has not yet been addressed by practice guidelines.[238,239] Assurance of quality by surveillance of procedural outcomes is made difficult by such complex issues as a need to adjust for high-risk patients, low incidence and subjectivity of major adverse events, and low volume of many operators.[163-165,240-242]

Interventional Laboratory

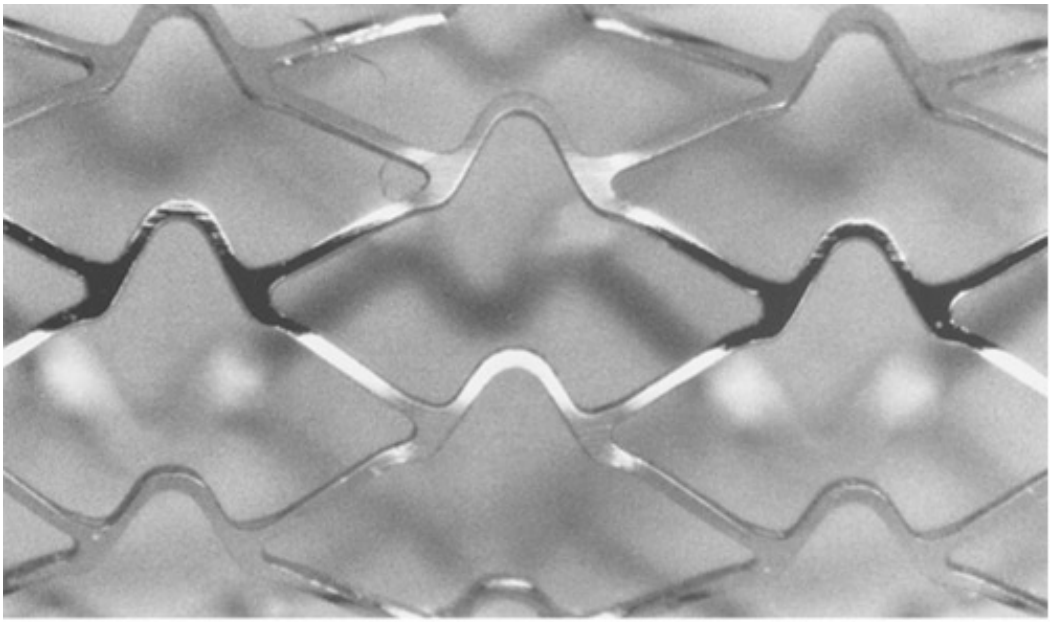
Optimal conditions for performance of coronary angioplasty procedures require sophisticated imaging systems; trained personnel; a large inventory of dilation, atherectomy, and stent hardware and software; and a variety of therapeutic safety nets to protect the patient when intervention fails or is complicated. Most studies suggest that laboratory procedural volume is important and inversely related to adverse procedural outcomes.[163,243-245] The quality of the video image of the coronary arteries is an important determinant of angioplasty success. A freeze-frame storage and display capability is required for use during the procedure, as is a high-quality video replay with slow-motion and stop-frame capability. The ability to solve specific problems-such as lesion eccentricity or rigidity, vessel tortuosity, and unusual position or orientation of the coronary ostia-often depends on specific device characteristics. Consequently, it is necessary to have available dilating catheters, stents, atherectomy devices, guidewires, and guiding catheters in a variety of shapes and sizes. Cardiac surgery should be available in the institution if needed for emergency situations.

Interventional Equipment

The over-the-wire steerable catheter system used in most coronary interventions is illustrated in Fig. 45-14. In atherectomy, ablative laser, or stent procedures, the device replaces or is mounted on a balloon catheter. The balloon or device is introduced through a guiding catheter that extends through the arterial puncture site (femoral, brachial, or radial) to the coronary artery or graft ostia, where coaxial alignment of the catheter and vessel is highly desirable. In the past, the Judkins right and left coronary shapes were used most frequently, but many other shapes are currently available to address specific anatomic problems (Figs. 45-15 and 45-16). The size (5-11 French) and shape of the guide catheter may be determined by the arterial size at the entry site, the guide catheter lumen requirement of the device used, and other factors such as a need for optimal vessel opacification. Balloon catheters for coronary use are available in an array of balloon lengths (8-40 mm), diameters (1.5-5 mm), shaft sizes, and special features, including active and passive perfusion, high-pressure capability, and local intracoronary infusion.

In the United States, the most frequently used stent in early experiences, the Palmaz-Schatz stent (see Fig. 45-6), was provided with a sheath delivery system that necessitated an 8 French guide catheter, whereas most currently used stents are accommodated by 6 French catheters, and

use of these smaller catheters for radial artery or femoral approaches has increased dramatically.[246] A large number of new stent designs have cleared FDA approval and are available for use (Fig. 45-17). Although these new stent designs offer considerable advantage over first-generation devices in terms of their deliverability, profile, variety of sizes, and strength of balloon, stent versus stent comparisons have not been performed in a manner that helps the interventionalist in choosing the best device for a given problem.[247]



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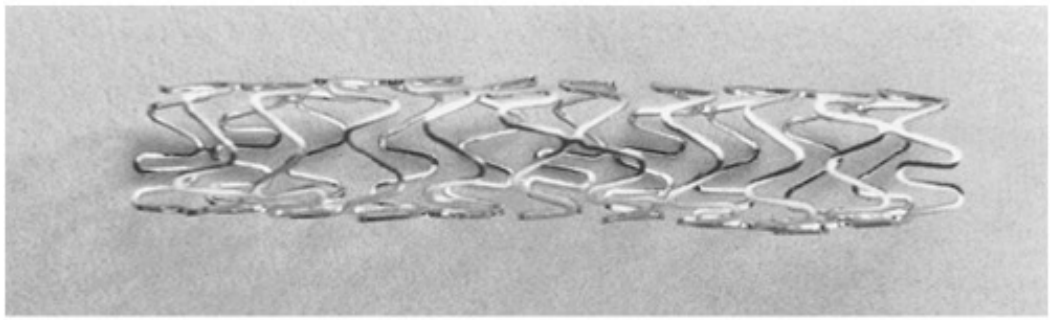

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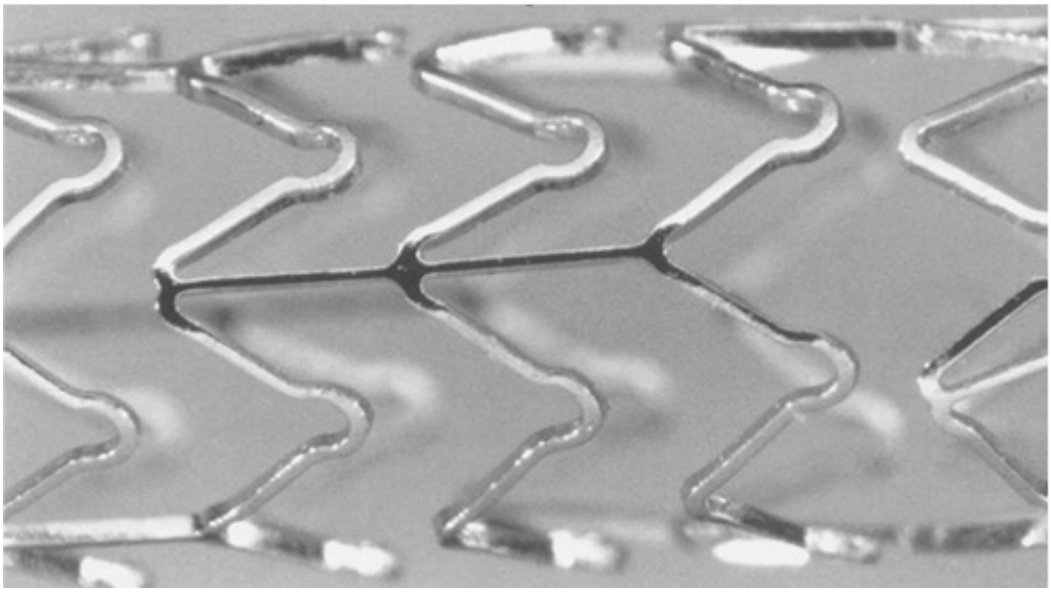

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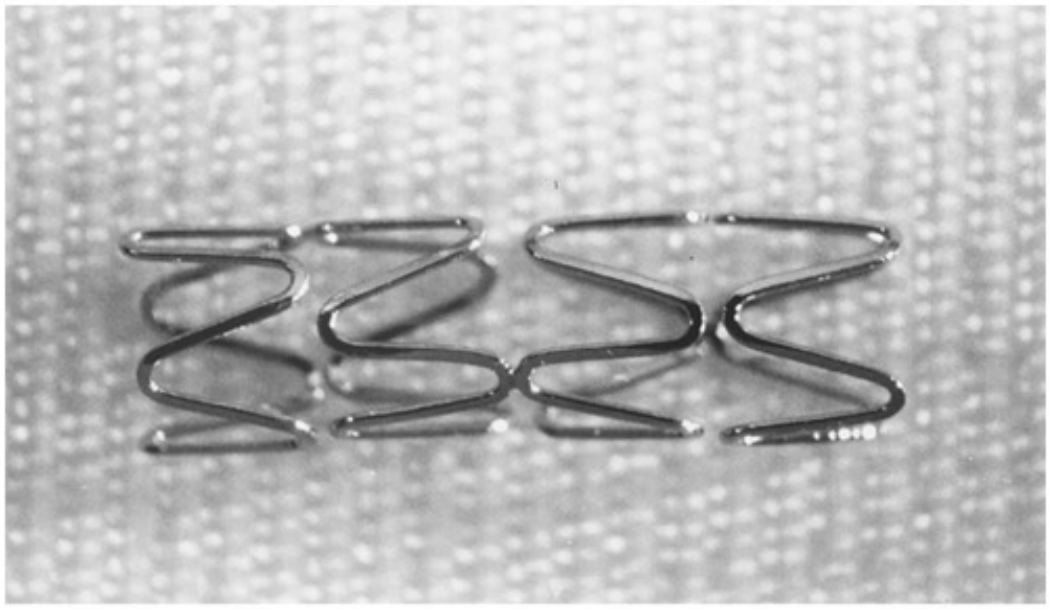

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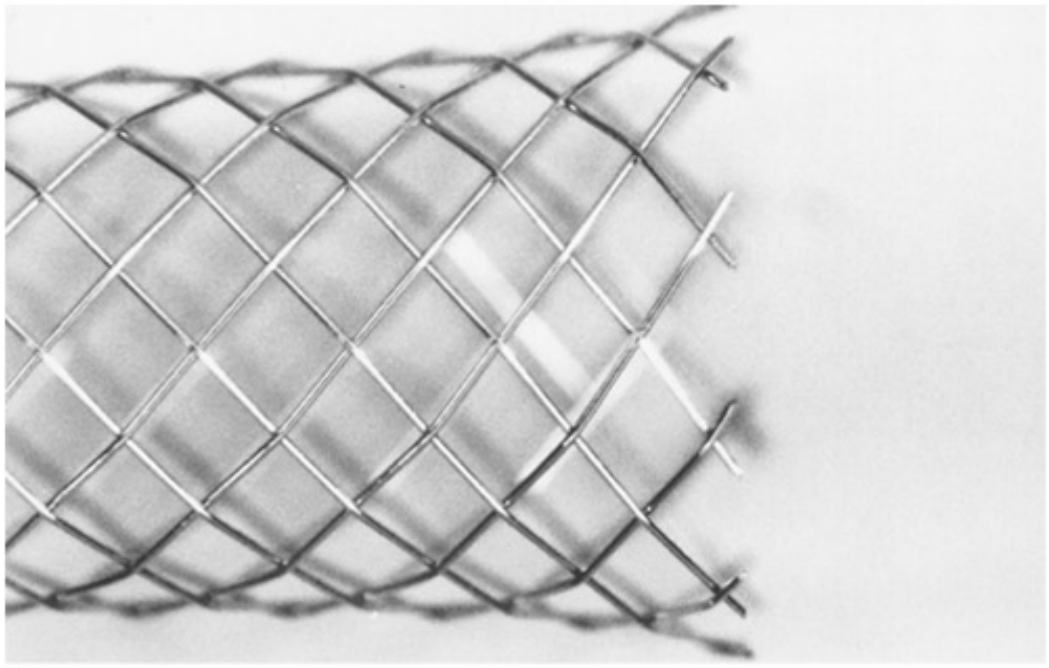

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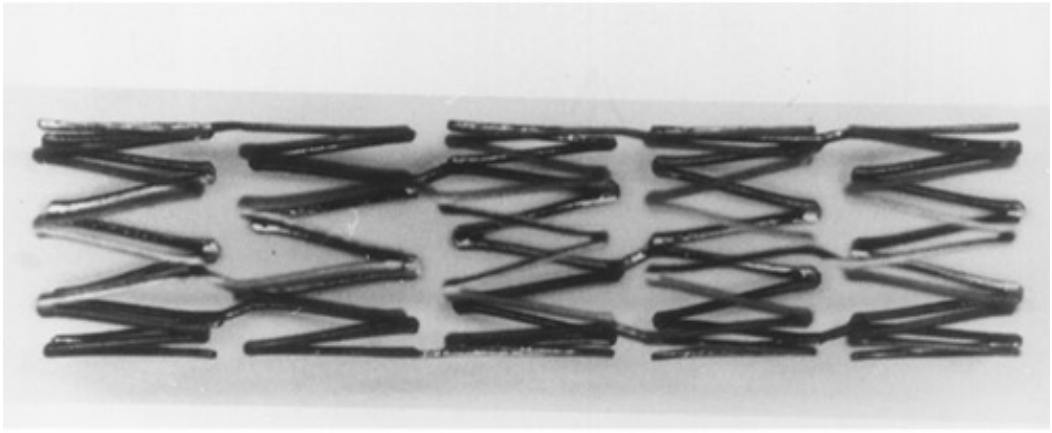

F

F

Figure 45-17: Currently available newer-generation stents. *A.* Nir stent (Medinol-Scimed, Maple Grove, MN). *B.* Cross-Flex LC stent (Cordis-Johnson & Johnson, Warren, NJ). *C.* Multi-Link Duet stent (Guidant, Santa Clara, CA). *D.* AVE-GFX stent (Medtronic-Applied Vascular Engineering, Santa Rosa, CA). *E.* Magic Wall stent (Schneider-Scimed, Maple Grove, MN). *F.* Radius stent (Scimed, Maple Grove, MN).

The high-speed rotational atherectomy device (see Fig. 45-5*B*), an olive-shaped burr with embedded diamond chips, requires a special 0.009-in. stainless steel guidewire, whereas the directional atherectomy cutter and laser catheters pass over conventional 0.014-in. steerable guidewires. The transluminal extraction catheter requires a unique 0.014-in. stainless steel guidewire that has a 0.21-in. ball at its tip.

The use of IVUS to guide therapy varies widely; it is almost routine practice in some centers and is rarely used in others. Ultrasound assessment of the adequacy of stent deployment (see Fig. 45-7), pioneered by Colombo and colleagues,[77] and evaluation of calcified lesions are probably the most frequent applications (see Chap. 47).

The Coronary Interventional Procedure

Prior to coronary intervention, patients receive an explanation of the procedure, including the operator's estimate of success, possible complications, risks, and benefits. A booklet and videotape describing the procedure and an explanation by the nursing staff help to reduce anxiety and ensure that both patient and family are well informed.

Antiplatelet therapy is used routinely. The therapy most widely used is aspirin 160 to 325 mg daily. Patients in whom stenting is planned also receive clopidogrel, usually in 300- to 525-mg loading dose unless pretreatment for several days has been performed. In a significant percentage of patients in our hospital, a platelet glycoprotein IIb/IIIa receptor antagonist is used when there is perceived to be an increased risk of abrupt closure or distal embolization (e.g., suspected or definite thrombus, acute coronary syndrome, complex lesion, diabetes, atherectomy procedure, or multisite intervention).[105] Restenosis trials have failed to show a clear advantage of one antiplatelet regimen over another and have not shown inhibition of restenosis by calcium channel-blocking agents, warfarin anticoagulation, angiotension-converting enzyme (ACE) inhibitors, steroids, or other agents.

Some operators administer a calcium channel-blocking agent prior to coronary intervention for prophylaxis against coronary artery spasm and to reduce ischemia during the procedure. Once the patient is in the catheterization laboratory, electrocardiographic monitoring leads are applied, a peripheral intravenous line is started, and midazolam 1 mg or an equivalent drug is given intravenously. In most laboratories, a femoral approach is employed; use of a radial artery approach, however, is increasing. Heparin is administered intravenously (100 units/kg, or 70 units/kg if IIb/IIIa receptor-inhibiting agents are used concomitantly). Maintenance of an activated clotting time (ACT) of greater than 300 s is recommended unless IIb/IIIa inhibitors are used, where 200 to 250 s is accepted. IIb/IIIa platelet receptor inhibitors are used selectively in our hospital for higher-risk patients (see "IIb/IIIa Platelet Receptor Inhibitors," above). Use of low-molecular-weight heparin during intervention is under investigation. Patients with a history of allergy to contrast material are premedicated with prednisone 40 to 60 mg orally the night before and the day of the procedure and with diphenhydramine (Benadryl) 50 mg intravenously at the time of the procedure. Ionic hyperosmolar contrast material is used commonly in our hospital for elective coronary angioplasty because of the extraordinary cost of low-osmolar agents and the lack of proved benefit to warrant their routine use.[248-250] Due to the reported increased thrombotic complications with nonionic agents (attributed to comparatively less thrombin inhibition and

enhanced platelet activation), ionic agents have been preferred in patients with unstable ischemic syndromes or frank intracoronary thrombus.[249] Recently published studies comparing ionic (Ioxglate) and nonionic (Iomeprol) agents in a randomized format,[251] ionic versus nonionic contrast material in EPIC, EPILOG, and CAPTURE in a metaanalysis,[252] and ionic versus nonionic in stenting,[253] however, revealed no increase in thrombotic complications, whereas nonionic agents were associated with more bailout stenting in a randomized study.[254] These studies reported outcomes with contrast agents with osmolalities in the 600 to 700 mosmol/kg range. Recent preliminary reports of the use of the isosmolar nonionic dimer iodixanol in high-risk PTCA were promising,[255] and further evaluation of this agent is warranted. Contrast-induced bradycardia, more common with ionic agents, is treated with atropine. Patients selected for use of a low-osmolar contrast agent include those with renal insufficiency or severe left ventricular dysfunction. Nonionic agents generally are reserved for patients with known allergy to the available ionic agents or with a history of severe bradycardia with ionic agents.

Coronary arteriograms are performed in two approximately orthogonal views selected to demonstrate the lesion(s) to be treated and the course of the parent artery without overlap by other vessels. The angles chosen are recorded, and freeze frames demonstrating the anatomy are stored and displayed during the procedure. A balloon catheter or device is selected based on the diameter of the target coronary artery to be treated and the length of the stenotic segment as determined by comparison with the guiding catheter of known diameter. The balloon diameter is chosen to approximate closely the diameter of the normal adjacent vessel, since oversizing the angioplasty balloon has been associated with increased complications and no reduction in the rate of restenosis.[256] In general, an over-the-wire catheter system is preferred because of the ability to exchange easily for alternative guidewires, balloons, or stents. The operator's impression of the difficulty of the case may influence selection of a particularly low profile catheter to cross severe stenoses, a flexible catheter or device to negotiate tortuous segments, or rotational atherectomy to treat a fibrotic, calcified lesion. Balloon-on-a-wire devices are especially useful when an ultra-low-profile balloon or simultaneous use of two balloons is required (see Fig. 45-2). Because of the current availability of very low profile and flexible balloon-mounted stents that are securely attached, direct stenting without predilating has increased dramatically in some centers. The coronary ostium is engaged with the guiding catheter, and the steerable guidewire is cautiously advanced into the target artery. In patients requiring angioplasty of more than one coronary artery, the most difficult lesion is commonly treated first. A clean crossing of the stenosis with the guidewire is critical and is accomplished by aligning the steerable wire tip with the entry point of the stenosis and gently advancing it across the lesion. The intraluminal position of the wire in the distal artery is confirmed by free rotation of the guidewire tip and by contrast angiography. If there is difficulty in crossing the stenosis with the guidewire, reshaping the tip commonly will lead to success. Changing the wire to one with different characteristics, such as a hydrophilic coating or one that is stiffer, may be necessary in the case of total occlusions.

With the steerable guidewire securely in the distal coronary artery, injections of contrast material are made through the guiding catheter to locate and mark the position of the stenosis to be treated. While fixing the position of the guidewire, the operator advances the balloon catheter or device to the lesion. If it is not possible to push the balloon or device across the stenosis, it may be wise to exchange it for rotational atherectomy or the lowest-profile over-the-wire balloon system available. If balloon angioplasty is being performed, the balloon is inflated to an initial pressure of 2 atm. Indentation of the inflated balloon by the lesion confirms proper placement. The balloon is subsequently inflated until the "waist" caused by the lesion is obliterated, and then the balloon is fully inflated. When using a compliant balloon, the operator may inflate the balloon to higher pressures to produce the balloon diameter desired. During these inflations, an attempt is made not to exceed the burst pressure of the balloon. The balloon is reinflated as needed to achieve an adequate dilation.

There is no clear evidence regarding the optimal number or duration of balloon inflations or the

maximal balloon pressure. Occasionally, if two to four inflations of 30 to 60 s do not yield the desired result, prolonged inflations up to 5 to 10 min may be helpful. Tolerance of the longer inflations may be enhanced by distal perfusion of arterial or venous blood through the dilatation catheter or by use of an autoperfusion balloon catheter.[257] Balloon inflations are limited by evidence of ischemia, as indicated by symptoms of chest discomfort or by ST-segment elevation. Some investigators have monitored intracoronary electrocardiograms from the steerable intracoronary guidewire and found these to be more sensitive in detecting ischemia than surface electrocardiograms. One also can use the intracoronary wire for temporary pacing.[258]

When performing directional atherectomy, the "window" of the atherectomy device is oriented toward the lesion, and the balloon is inflated to 1 atm. The cutter is then withdrawn, allowing the lesion to enter the open window. The motor is activated, and a cut is performed by slowly advancing the spinning cutter to the distal end of the device housing, thereby packing the shavings into the nose cone of the device. The balloon is then deflated, the window reoriented, and the sequence repeated. To minimize the possibility of perforation, the window is not oriented toward normal portions of the vessel wall. It is important to note that overzealous atherectomy may lead to an increased risk of perforation or aneurysm formation.

Intracoronary stenting may be conducted either as a primary strategy or for suboptimal outcomes after balloon angioplasty or other interventions. Deployment strategies vary depending on stent designs, since some are balloon-mounted and others are self-expanding. Stent deployment with a properly sized balloon is performed (usually to >12 atm) to expand the stent optimally throughout its length. A recently reported randomized trial of stent implantation showed no advantage to inflation to more than 15 atm.[259] Although some operators advocate IVUS guidance, there is no consensus regarding its routine use.[260,261]

With rotational atherectomy and ablative laser procedures, many operators use special infusion or flushing strategies (using saline and/or vasodilators) to optimize laser debulking by blood displacement, reduce acoustic shock and dissection with the laser, and avoid no-reflow phenomena.[210,262] Proper sizing of these debulking devices is under investigation. Recent studies suggest that lower rotational atherectomy speeds (<160,000 rev/min) produce less platelet activation and comparable atheroablation and that IIb/IIIa receptor inhibitors block this activation.[263,264]

If there is concern about the adequacy of the lumen at the treatment site, use of a Doppler flow wire, angioscopy, or pressure gradients may be helpful in addition to ultrasound in assessing the result. Studies suggest that a normal coronary hyperemic flow response and a low transluminal gradient are associated with reduced risk of restenosis. *It is clear that optimizing the lumen size is the goal, since final lumen size is an important determinant of the probability of restenosis*. When the operator is confident that the best possible result has been obtained, the patient is returned to his or her room, where an electrocardiogram is obtained and the patient is placed on telemetry. Puncture-site closure devices are used with increasing frequency. Creatine kinase determinations are performed immediately and every 8 h for three determinations. Because of the dehydrating effect of the osmotic load, most patients receive at least 1 L of intravenous fluids after the procedure. Delayed sheath removal is performed at 2 to 4 h when the ACT is below 150 s. If an intimal tear, suboptimal result, or intraluminal thrombus is present, or if multiple stents are implanted, a IIb/IIIa receptor inhibitor is often used.[265] There is evidence that routine heparin administration following uncomplicated angioplasty is not helpful in reducing acute occlusion or restenosis.[266] Postprocedure medications in-hospital include aspirin, a calcium channel-blocking agent, topical nitrates, and clopidogrel in stented patients. Most patients are discharged on the first day following the procedure after receiving instructions on lipid-lowering therapy (see Chap. 38), exercise, and cessation of smoking and are given an outline of follow-up procedures.

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Chapter 45: PERCUTANEOUS CORONARY INTERVENTION

RESULTS OF CORONARY INTERVENTION

The results obtained with coronary intervention procedures have been influenced significantly by technological advances, operator experience, and the difficulty of patients selected. With pioneering equipment, Gruentzig was able to dilate 64 percent of the first 50 patients and 78 percent of the first 169 patients.[10,15] Defining primary success as less than 50 percent residual stenosis and freedom from complications, a success rate of 91 percent in over 26,000 patients treated at Emory University Hospital was seen between 1980 and 1998 (Table 45-5). Note that complication rates generally declined despite increasingly difficult cases. Experienced operators should achieve primary success rates in excess of 95 percent in ideal proximal lesions compared with a reduced success rate of approximately 75 percent in recent (<3 months) total occlusions or when attempting to treat fibrotic, calcified, eccentric stenoses located distally in tortuous coronary arteries. In all techniques, including stenting,[196] lesion characteristics are a major determinant of the outcome of the procedure.[117,118,157-162] Long-term outcome has been reported out to 10 years in patients treated in Zurich, Atlanta, and Rotterdam,[15-17,119,267] and detailed 5- to 8-year follow-up data are available from randomized trials,[25-41,130,131] (see above and Table 45-1 and Fig. 45-4).

Complications

Patients undergoing coronary intervention are subject to the same complications encountered with the performance of coronary arteriography. In addition, because instrumentation of the atherosclerotic lesion takes place, coronary artery dissection, thrombus formation, and coronary artery spasm may occur, leading to acute occlusion of the coronary artery or of side branches arising from it. Atheroembolism may occur and lead to MI in an otherwise successful procedure. Occlusion of the treated artery is the most common serious complication of coronary angioplasty and accounts for most of the morbidity and mortality related to the procedure.

Of Gruentzig's first 50 patients, 5 experienced an acute deterioration necessitating emergency bypass surgery and 3 showed electrocardiographic evidence of MI.[10] The results of 3500 patients undergoing elective balloon angioplasty at Emory were analyzed and reported in detail.[268] Angioplasty was attempted in 3933 lesions, with a success rate of 91 percent. No complications occurred in 89 percent of patients, minor complications occurred in 6.9 percent, and major complications (emergency surgery, MI, death) occurred in 4.1 percent. Emergency CABG was performed in 2.7 percent of patients, who had an MI rate of 49 percent and a Q-wave MI rate of 23 percent. In patients sent for emergency surgery, the mortality rate was 2 percent. The overall MI rate was 2.6 percent. There were two nonsurgical deaths, giving a total mortality rate of 0.1 percent (4 of 3500). *Five preprocedural predictors of a major complication were identified: multivessel coronary artery disease, lesion eccentricity, presence of calcium in the lesion, female gender, and lesion length. The strongest predictor of a major complication was the appearance of an intimal dissection during the procedure*. Intimal dissection was evident in 29 percent of patients, and its presence resulted in a sixfold increase in the risk of a major complication. Minor complications tabulated in this study included the following: side branch occlusion (1.7 percent), ventricular arrhythmia requiring dc shock (1.5 percent), emergency recatheterization (0.8 percent), femoral artery repair (0.6 percent), transfusion requirement (0.3 percent), coronary embolus (0.1 percent), cardiac tamponade (0.1 percent), and stroke (0.03 percent). This early series of patients was treated with balloon angioplasty alone. In 1995 at Emory University Hospital, over 1600

patients were treated (76 percent with balloon alone), with angiographic success in 94 percent, Q-wave MI in 1.1 percent, non-Q-wave MI in 2.9 percent, and death in 0.6 percent. Stents have played an increasing role, being used in 66 percent of patients in 1998 with an improvement in acute outcome (see Table 45-5).

Although angiographic variables are important predictors of abrupt closure, of equal or greater importance is an estimate of the consequences of abrupt closure. This estimate is determined in large part by the amount of myocardium that is supplied by the artery in jeopardy. Occlusion of a small diagonal branch is of little consequence compared, for example, with the occlusion of a large LAD coronary artery that is also supplying collateral vessels to an occluded right coronary artery. In the first case, a small non-Q-wave MI is likely, whereas in the latter, occlusion would likely result in abrupt anterior and inferior ischemia and be associated with hypotension and possibly cardiogenic shock. Immediate stenting or bypass surgery may be lifesaving, but MI will occur in up to one-half of patients, and there is a significant risk of mortality in this subgroup of patients.

An analysis of 294 acute occlusions occurring during 8207 consecutive coronary angioplasty procedures performed in two centers revealed 13 cardiac deaths (4.4 percent of acute occlusions) and an overall cardiac mortality of 0.16 percent.[269] Of 13 patients who died, 12 were women. Multivariate analysis identified three independent predictors of death: collaterals originating from the dilated vessel, female gender, and multivessel disease. In an analysis of 32 deaths associated with 8052 PTCA procedures in three centers, left ventricular failure due to vessel occlusion, the most common cause of death, was independently correlated with female sex, "jeopardy score," and PTCA of a proximal right coronary artery (RCA) site but not ejection fraction or presence of multivessel disease.[270] Right ventricular failure due to occlusion of the proximal RCA and left main coronary dissections accounted for most of the remaining deaths.

The use of stents in the course of a failing angioplasty (Fig. 45-18) and prospectively in patients with unfavorable anatomy has significantly reduced the risk of urgent bypass surgery and Q-wave MI.[72,73,113] The increasing use of stents and adjunctive measures including new, powerful antithrombotic agents may herald a "new era" of coronary intervention.[113] New complications specifically related to the use of nonballoon devices include coronary perforation, distal atheroembolization, arterial access complications, and "domino stenting" (additional stents to treat end-of-stent dissections). The risk of coronary perforation is a limiting factor in achieving optimal atherectomy and significantly restricts use of the TEC device in native vessels. Among 8932 patients treated at William Beaumont Hospital, perforation was reported in 0.4 percent (balloon, 0.14 percent; TEC, 1.3 percent; DCA, 0.25 percent; excimer laser 2 percent).[271] This risk of perforation is highest in tortuous and smaller vessels and in laser angioplasty of right coronary lesions. In patients experiencing free perforations, Ellis reported that 75 percent required surgery, 29 percent had a Q-wave MI, and 14 percent died.[272] Perforation was reported in 10 of 432 stent patients (2.3 percent), resulting in cardiac tamponade (50 percent), MI (40 percent), emergency surgery (50 percent), and death (30 percent).[273] The manifestations of perforation were delayed (5-24 h) in 20 percent of patients. Angiographic features associated with stent-related perforation were complex lesion morphology, small vessel diameter (2.6 ± 0.2 mm), oversized stents (stent/artery ratio 1.4 ± 0.1), tapering vessel (40 percent), and recrossing dissections (20 percent).[273] These results should engender a cautious approach to stenting in small vessels and when there is uncertainty regarding wire position. One of the newest causes of perforation is the hydrophilic coronary guidewire, which easily penetrates the wall of small distal arteries causing bleeding and cardiac tamponade, especially when IIb/IIIa receptor inhibitors have been used. Prompt application of strategies for the management of vessel perforation can be lifesaving, and device angioplasty operators must be facile with them.

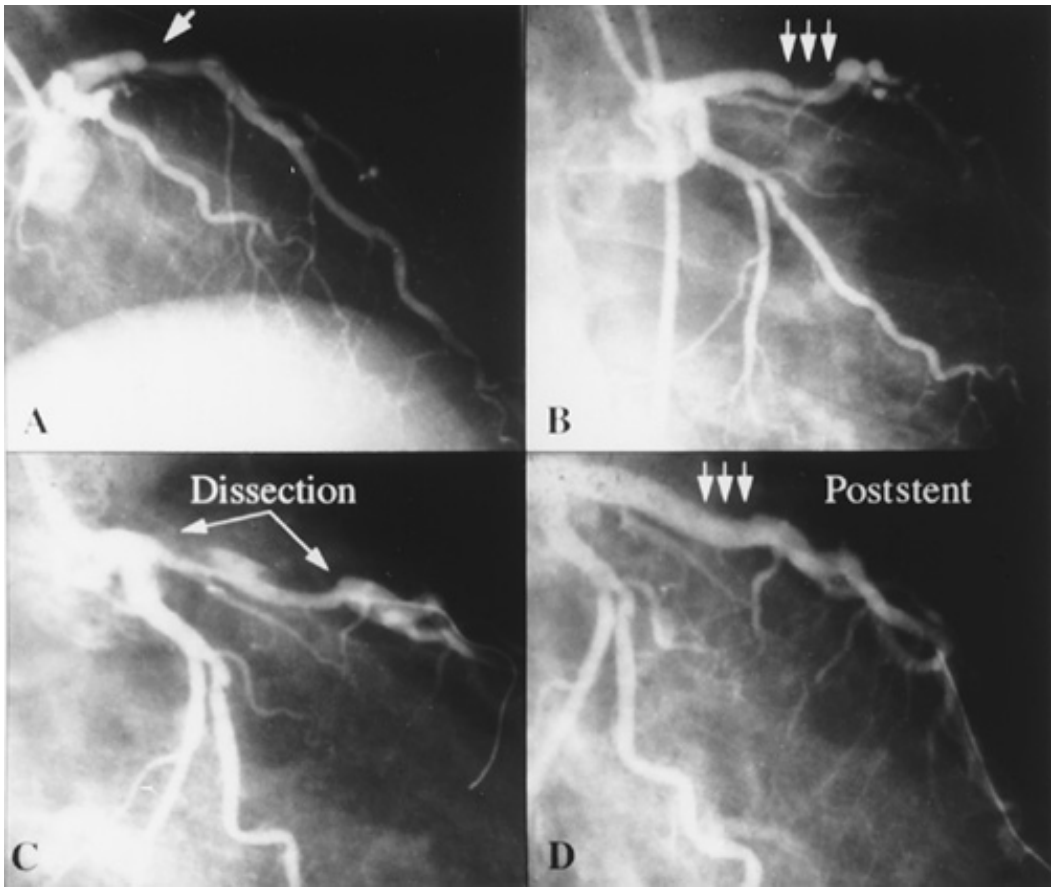

Figure 45-18: Complex stenosis of tortuous proximal LAD. *A.* Right anterior oblique, cranial angulation. *B.* Caudal angulation. Following an initial attempt at treatment of the lesion, a long dissection occurred. *C.* Prompt stent implantation stabilized the patient, preventing the need for emergency CABG (*D*).

Fortunately, the risk of vascular access-site complications, a frequent accompaniment of stenting when heparin and warfarin anticoagulation is used adjunctively, has been reduced with less aggressive antithrombotic strategies. In our experience, complications at the femoral artery puncture site were more often related to advanced age, female sex, hypertension, and postprocedure heparin use than to the size of the catheter.[274-276] Prolonged compression of pseudoaneurysms using ultrasound guidance and in some cases local thrombin injection obviates surgery in many patients with this complication.[277-279] Closure devices are used actively in some centers but add significantly to the cost of the procedure and have their own complications, including infection.

Distal coronary atheroembolization is only occasionally recognized clinically with balloon angioplasty but probably occurs moderately frequently[280] and is a clinically important limitation of debulking strategies such as atherectomy and laser ablation, where its manifestations are slow coronary flow, ischemia, and infarction.[281,282] Reports from CAVEAT indicate that creatine kinase elevations postprocedure were associated with worse long-term outcomes (death, MI, repeat intervention).[282] Although procedural modifications with rotational atherectomy appear to have reduced the immediate impact of microparticulate embolization,[210] the issue remains a source of concern and needs further study. Patients at increased risk include those with bulky or long native vessel lesions and nonfocal or thrombotic saphenous vein graft lesions, where embolization with TEC was noted in about 20 percent, and about one-third of patients with this complication died.[283,284] Atheroembolization also complicates stenting, accounting for an

increased rate of non-Q-wave MI compared with balloon angioplasty. Particulate embolism to the coronary microcirculation may lead to otherwise silent infarction reflected by creatine kinase elevation, a topic of intense interest due to the finding of adverse late outcome, even with small elevations,[285] and the recognition that IIb/IIIa platelet receptor inhibitors, filters, and "occlusion-aspiration" systems can protect against this complication.[105,106,286,287] Not all studies, however, have found a correlation between enzyme elevations and adverse late outcome,[288] and this issue of when to use IIb/IIIa platelet receptors inhibitors is actively debated.[289]

Acute contrast nephropathy requiring dialysis is a costly complication of coronary intervention, which occurred in 15 of 1828 (0.8 percent) patients and was associated with a high (33.8 percent) in-hospital mortality.[290] Independent predictors of contrast nephropathy included decreased baseline creatinine clearance, diabetes, and contrast dose (no dialysis was required in patients receiving less than 100 mL of contrast material). Adequate periprocedural hydration and limitation of contrast volume are the most important measures in high-risk patients.[291]

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Chapter 45: PERCUTANEOUS CORONARY INTERVENTION

FUTURE DIRECTIONS

The future of coronary intervention is bright indeed. The problem of subacute stent thrombosis, greatly diminished by current deployment strategies, should be solved by nonthrombogenic stents and/or more effective antithrombotic agents, thus opening the arena of small-vessel stenting (2- to 2.5-mm vessels) and further expanding intervention for multiple lesions in multiple vessels. The major impediments are cost and restenosis. The former should be ameliorated somewhat by market competition. Restenosis, which has been reduced by stenting of *de novo*[75,76,201] and restenotic lesions,[292] remains a challenge that is currently being addressed on multiple fronts with good prospects for meaningful solutions,[192293-296] but new and sometimes unsuspected problems continue to arise, as in the recognition of the threat of late-late occlusion following brachytherapy.[297,298] Improved strategies to protect the microcirculation from atheroembolization are on the immediate horizon.[286]

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Chapter 45: PERCUTANEOUS CORONARY INTERVENTION

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Figure 45-17: Currently available newer-generation stents. *A.* Nir stent (Medinol-Scimed, Maple Grove, MN). *B.* Cross-Flex LC stent (Cordis-Johnson & Johnson, Warren, NJ). *C.* Multi-Link Duet stent (Guidant, Santa Clara, CA). *D.* AVE-GFX stent (Medtronic-Applied Vascular Engineering, Santa Rosa, CA). *E.* Magic Wall stent (Schneider-Scimed, Maple Grove, MN). *F.* Radius stent (Scimed, Maple Grove, MN).

Figure 45-18: Complex stenosis of tortuous proximal LAD. *A.* Right anterior oblique, cranial angulation. *B.* Caudal angulation. Following an initial attempt at treatment of the lesion, a long dissection occurred. *C.* Prompt stent implantation stabilized the patient, preventing the need for emergency CABG (*D*).

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Part 6: CORONARY HEART DISEASE
Chapter 46:

MECHANICAL INTERVENTIONS IN ACUTE MYOCARDIAL INFARCTION

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The history of mechanical reperfusion therapy is fascinating and has important lessons concerning the application of radical new treatments in modern medicine. Confluences of pathologic, clinical, and technical advances were required for this treatment to be initiated and validated. Lack of understanding of the pathophysiologic basis for acute myocardial infarction (AMI), lack of adequate understanding of clinical subsets, and lack of adequate medical devices led to multiple early pioneering attempts that were akin to the early rocket programs of the late 1950s. Ultimately, however, this treatment modality has been refined, tested, and validated and has the promise to dramatically decrease mortality for increasingly large segments of the population. This chapter will review the historical development of mechanical reperfusion, summarize the results of randomized clinical trials, define subsets most likely to be benefited or harmed by this approach, and offer a glimpse into future research directions.

HISTORICAL DEVELOPMENT

Mechanical reperfusion had its inception with the initial treatise of Fletcher et al.[1] that described the use of intravenous thrombolytic therapy in thromboembolic disorders, including myocardial infarction. The authors presented results on their experience with treatment of 22 patients with AMI. Unfortunately, no methodology for testing efficacy existed. A suggestion that the SGOT enzyme curves peaked earlier was entertained. Crude descriptors including chest pain relief, blood pressure response, and electrocardiographic changes were highly variable and did not provide consistent patterns to demonstrate harm or benefit. Importantly, autopsies were performed in three of the four patients who died. The autopsy results were confusing. One patient who died suddenly 3 weeks after treatment had evidence of a large healing infarction but no evidence of residual thrombus in the infarct artery. A fresh thrombus in a separate artery was perceived to be the cause of death. A second patient died shortly after cessation of streptokinase infusion, and at autopsy, a very fresh microscopic thrombus was found in an ulcerated plaque in the left main artery. A third patient with a history of atrial fibrillation was found to have a massive posterolateral infarction but only mild atherosclerotic plaque and no residual thrombus. These autopsy findings failed to demonstrate that failure of therapy to recanalize vessels lead to death or that thrombus was in fact related to any of these cases. The results of this initial study helped fuel a controversy that raged for 20 years in the scientific community on the role of thrombus formation in myocardial infarction.

Bouchek et al.[2] published the second pioneering observation concerning reperfusion therapy and the initial attempt at developing a platform for local treatment in 1960. This intrepid group performed emergency brachial cut-downs and used subselective catheters to apply fibrinolytic therapy to the aortic root of patients presenting with AMI. Unfortunately, they were unaware of Sones[3] work in selective coronary angiography. Bouchek et al. were astute enough to use the electrocardiogram (ECG) as a localizing tool so that right or left coronary subselective infusions could occur. Although this group presented similar enzymatic results, like Fletcher, they could not clearly establish that their treatment was beneficial. If only their catheters could have been advanced another 3 or 4 mm and angiographic documentation of clot lysis established, the history of reperfusion therapy would have been accelerated by 20 years!

Thus the lack of consensus concerning the inciting role of thrombotic occlusion in AMI, lack of equipment to visualize thrombus in vivo, and lack of clearly defined subgroups for treatment lead investigators to abandon invasive approaches in the 1960s. Later that decade, Favaloro[4] et al. made major contributions to the development of saphenous vein aortocoronary bypass and early on applied it to patients presenting with AMI.[4,5] This group quickly realized that due to enormous logistic and time constraints, this treatment was not practical in referral centers. Fortunately, two groups, one in Spokane[6] and one in Goettingen,[7] attempted to apply emergency surgical revascularization as management for myocardial infarction in a community setting. Preoperative emergency catheterization was required, and thus, for the first time, knowledge of the coronary anatomy during AMI became available. Both groups made seminal observations that served as cornerstones for reperfusion therapy. DeWood et al.[8] described the high prevalence of total coronary occlusion in the early hours after acute transmural myocardial infarction and the decreased incidence of total occlusion in the later hours of presentation. These authors concluded that total coronary occlusion occurred early and that spontaneous lysis explained the lower prevalence during later presentation. They concluded that total thrombotic occlusion was the cause and not the consequence of AMI. Perhaps equally important, this initial report and a subsequent report[9] clearly defined the role of electrocardiographic transmural injury current in identifying a population of patients most likely to have acute total occlusion and thus most likely to benefit from emergency revascularization.

At the same time that the Spokane group was testing surgical revascularization, Rentrop and associates were developing techniques to safely catheterize and study patients with AMI and cardiogenic shock. In June 1978, based on lessons learned from balloon angioplasty, they performed emergency guidewire recanalization of a catheter-related acute thrombotic coronary occlusion.[10] The instantaneous gratifying clinical and electrocardiographic results led this group to initiate mechanical reperfusion in AMI. They reported on the first 13 patients treated with mechanical reperfusion in 1979.[11] In June 1979, this group initiated a second phase of their investigation, selective catheter infusion of intracoronary streptokinase. They presented their work at the American Heart Association Meetings in November of 1979, and the modern era of reperfusion therapy was born. American investigators were largely uninterested in thrombolytic therapy of AMI in the 1960s and 1970s. The pathologic findings of Roberts and Buja[12] and the National Heart Lung and Blood Institute (NHLBI) consensus conference[13] swayed scientific conventional wisdom. The importance of thrombotic occlusion was unclear, and attention was focused on methods to limit infarct size by decreasing oxygen demand.[14] Once the works of DeWood et al. and Rentrop et al. were disseminated, enormous research interest was generated in both Europe and the United States. Randomized trials were quickly organized. Khaja et al.[15] first demonstrated the efficacy of intracoronary streptokinase administration. The western Washington group demonstrated the mortality advantage of intracoronary streptokinase therapy.[16] Because of the necessity of selective coronary angiography for this treatment, it became apparent that a severe residual stenosis persisted in most patients after successful recanalization. The Ann Arbor group first demonstrated that balloon angioplasty could more effectively relieve the residual stenosis than could thrombolytic therapy alone.[17] This resulted in less recurrent ischemia, less exercise-induced ischemia,[18] and more effective preservation of ventricular function.[19] Lack of trained operators, lack of catheterization facilities, and logistic constraints, however, led most investigators to abandon primary angioplasty in the mid-1980s.

Both intracoronary streptokinase and primary percutaneous transluminal coronary angioplasty (PTCA) lost momentum once intravenous thrombolytic therapy was validated in the mid-1980s.[20] Research interest focused on new thrombolytic drugs that could be administered intravenously. Many investigators were still concerned about the severe underlying residual stenosis remaining after thrombolytic therapy. Therefore, three major randomized trials the TAMI, TIMI-2a, and European Cooperative trials were performed.[21-23] Each trial attempted to determine the value of

routine PTCA after thrombolytic therapy. In aggregate,[24,25] these studies gave surprising and disappointing results. Routine PTCA not only failed to improve results but actually appeared to be harmful. Angioplasty thus was abandoned as an adjunct to thrombolytic therapy in 1990.

Although routine, postthrombolytic PTCA was proven to be detrimental, interest still persisted in the use of PTCA without antecedent thrombolytic therapy and in cases of persistent chest pain after thrombolytic therapy. A great deal of the credit must be given to the pioneering work of Hartzler et al.[26] This group demonstrated that angioplasty alone may have outcomes superior to thrombolytic therapy.[27] At the same time, Brodie et al.[28] and O'Neill et al.[29] concluded that lone angioplasty had been inadequately tested as a reperfusion modality. These three groups joined forces and organized the original Primary Angioplasty in Myocardial Infarction (PAMI) study group. This group first formally compared intravenous thrombolytic therapy with primary PTCA. The results of this trial and the Zwolle and Mayo Clinic studies have largely defined the value of mechanical reperfusion in the 1990s.

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Chapter 46: MECHANICAL INTERVENTIONS IN ACUTE MYOCARDIAL INFARCTION

RESCUE ANGIOPLASTY

In the early 1990s, intravenous thrombolytic therapy became the overwhelmingly preferred reperfusion strategy.[30-32] Unfortunately, with current fibrinolytic regimens, successful reperfusion after thrombolytic therapy is achieved in only 54 to 81 percent of patients, and TIMI 3 flow is achieved in only 29 to 54 percent of patients.[33] The achievement of successful reperfusion (especially TIMI 3 flow) in the infarct artery after thrombolytic therapy is the most important determinant of 30-day mortality and recovery of left ventricular function.[33] Rescue angioplasty, the mechanical reopening of an occluded infarct artery after failed thrombolysis, has been used as adjunctive therapy in an attempt to improve outcomes in patients with failed thrombolysis. Despite the intuitive benefit of this approach, the value of rescue angioplasty remains controversial, especially given the disappointing results of the TAMI, TIMI-2a, and European Cooperative studies.

Numerous observational studies have documented that rescue angioplasty can achieve successful reperfusion in 82 to 92 percent of patients with occluded infarct arteries after failed thrombolysis,[34-38] but reocclusion of the infarct artery has been common (18 percent in Ellis's meta-analysis),[39] and recovery of left ventricular function has been variable.[34,36,37] Mortality associated with unsuccessful rescue angioplasty has been very high, and mortality associated with all rescue angioplasties (successful and unsuccessful) has been no better than in patients with failed thrombolysis who do not undergo rescue angioplasty and has been higher than in patients with successful thrombolysis[3437] (Table 46-1). The lack of benefit in these observational studies with rescue angioplasty may be related to selection bias, since rescue angioplasty often is selected for higher-risk patients.[39] The relatively high mortality after rescue angioplasty compared with successful thrombolysis is not surprising because patients with failed thrombolysis are a high-risk subgroup who have demonstrated resistance to pharmacologic reperfusion, possibly due to hypotension, large thrombus burden, or extensive intimal disruption, all of which are unfavorable to the success of coronary angioplasty. Also, reperfusion after rescue angioplasty, by definition, occurs later than reperfusion by successful thrombolysis, and this inherent delay decreases the extent of myocardial salvage. It is not clear if the particularly high mortality in patients with failed rescue angioplasty is due to additional associated high-risk features or if there may be harmful effects from the rescue angioplasty procedure itself.

Table 46-1: Observational Data Comparing Mortality* in Patients Undergoing Rescue Angioplasty (PTCA) for Failed Thrombolysis versus No Rescue Angioplasty versus Successful Thrombolysis

Trial	Successful Rescue PTCA	Failed Rescue PTCA	All Rescue PTCA	No Rescue PTCA	Successful Thrombolysis
TAMI 1-5 Trials (*n* = 192)[35]	10/169 (5.9%)	9/23 (39%)	19/192 (9.9%)	3/43 (7.0%)	28/607 (4.6%)
TIMI I and II Trials (*n* = 33)[36]	2/27 (7.4%)	2/6 (33%)	4/33 (12%)	7/100 (7%)	
TIMI IV Trial (*n* = 58)[37]	5/52 (9.6%)	2/6 (33%)	7/58 (12%)	4/37 (11%)	9/307 (2.9%)

GUSTO-I Trial (n = 198)[34]	15/175 (8.6%)	7/23 (30%)	22/198 (11.1%)	21/266 (7.9%)	55/1058 (5.2%)
TOTAL	32/423 (7.6%)	20/58 (34%)	52/481 (10.8%)	35/446 (7.8%)	92/1972 (4.7%)

*Mortality is in-hospital mortality for TIMI-IV and TAMI 1-5, 21 days for TIMI-I and II, and 30 days for GUSTO-I.

Two moderately sized randomized trials have evaluated the efficacy of rescue angioplasty. The TAMI-5 trial[40] randomized 575 patients with AMI treated with tissue-type plasminogen activator (tPA) or urokinase or both to emergency angiography with rescue angioplasty for failed thrombolysis versus conservative care. Rescue angioplasty was performed in 18 percent of the emergency catheterization group with a success rate of 83 percent. At hospital discharge, the emergency catheterization group had a slightly higher infarct artery patency rate (94 versus 90 percent; p = 0.07), better regional wall motion, and less recurrent ischemia, but there were no differences in mortality, reinfarction, or global left ventricular ejection fraction.

The Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints (RESCUE) trial[41] randomized 151 patients who had their first anterior wall myocardial infarction treated with thrombolytic therapy and had an occluded infarct artery demonstrated within 8 h of the onset of chest pain to rescue angioplasty versus conservative care. There was no difference in left ventricular ejection fraction at 30 days (40 versus 39 percent; p = NS), but the rescue angioplasty group tended toward a lower mortality (5.1 versus 9.6 percent; p = 0.18), less congestive heart failure (1.3 versus 7.0 percent; p = 0.11), had a lower composite of death and congestive heart failure (6.4 versus 16.6 percent; p = 0.05), and better exercise left ventricular ejection fraction (43 versus 38 percent; p = 0.04). These benefits occurred despite what the authors felt was a strong investigator bias not to randomize patients presenting very early in the course of their infarction.

Rescue angioplasty, especially after tPA, is associated with lower angiographic success rates and higher reocclusion rates than primary angioplasty and this limits its effectiveness. This may occur because infarct artery occlusion refractory to thrombolysis may have more extensive intimal disruption. In addition, platelet and thrombin activation that occurs with thrombolytic therapy may adversely affect the efficacy of PTCA.[42-44] Recent studies using coronary stenting with rescue angioplasty have reported high procedural success rates and low reocclusion rates.[45-47] The largest of these studies reported a success rate of 98 percent in 167 patients, a reocclusion rate of only 1.2 percent, and a combined end point of death or reinfarction of 1.4 percent at 30 days in nonshock patients.[47] Glycoprotein IIb/IIIa platelet inhibitors also may enhance outcomes with rescue angioplasty, but this has not been well studied, and the risk of bleeding when aspirin, heparin, ticlopidine, or clopidogrel and glycoprotein IIb/IIIa platelet inhibitors are used in conjunction with thrombolytic therapy is not established.[46]

A major limitation of the rescue angioplasty approach is the lack of a reliable noninvasive method to detect reperfusion after thrombolytic therapy. The ECG is very specific in predicting patency of the infarct artery when there is complete (>70 percent) resolution of ST-segment elevation at 90 min after thrombolytic therapy.[48] This occurs in only a minority of patients, however; in most patients there is only partial or no resolution of ST-segment elevation, and the patency status of the infarct artery is uncertain.[49] Similarly, enzyme rise or enzyme curves lack sufficient, rapid diagnostic accuracy.[50] Consequently, acute angiography is usually required to determine infarct artery patency.

Based on the available data, acute angiography with rescue angioplasty should be considered in patients with anterior or large myocardial infarction who are thought to have failed thrombolysis, as evidenced by persistent chest pain, lack of resolution of ST-segment elevation, or hemodynamic compromise 90 min or more after treatment.

The recently reported PACT trial[50a] of bolus tPA and transfer to the catheterization laboratory for rescue angioplasty for those without TIMI 3 flow showed that angioplasty could be performed safely following administration of a short-acting thrombolytic agent. Since transfer to the catheterization laboratory was very fast in this trial, no improvement in left ventricular function could be shown in the thrombolyzed cohort. An important question is whether in real-life situations, where transfer to the catheterization laboratory takes longer, will upstream thrombolysis be helpful.

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Chapter 46: MECHANICAL INTERVENTIONS IN ACUTE MYOCARDIAL INFARCTION

PRIMARY ANGIOPLASTY

In the early 1990s, great controversy still existed about the routine use of angioplasty for treatment of AMI. Angioplasty after thrombolytic therapy was abandoned except for its use as a rescue after failed thrombolytic therapy. In centers where interventional programs existed, controversy existed about the use of immediate PTCA without antecedent thrombolytic therapy as an alternative to routine thrombolytic therapy. This controversy has now been largely settled based on a number of randomized trials of these reperfusion modalities.

Comparison of Outcomes with Thrombolytic Therapy

RANDOMIZED TRIALS

In 1997, Weaver et al. published a meta-analysis of 10 randomized trials[51-60] in a total of 2606 patients comparing thrombolytic therapy with primary angioplasty[61] (Fig. 46-1). The largest of these trials were the PAMI-1 trial,[52] the Zwolle trial,[53] and the GUSTO-IIb trial.[58] In this meta-analysis, primary angioplasty was associated with a lower in-hospital mortality (4.4 versus 6.5 percent; $p = 0.02$), a lower incidence of nonfatal reinfarction (2.9 versus 5.3 percent; $p = 0.002$), and a lower incidence of death or nonfatal reinfarction (7.2 versus 11.9 percent; $p = 0.001$). Primary angioplasty also was associated with a significantly lower incidence of stroke (0.7 versus 2.0 percent; $p = 0.007$) and hemorrhagic stroke (0.01 versus 1.1 percent; $p = 0.0005$). The survival benefit of primary angioplasty compared with thrombolytic therapy reported in this meta-analysis was substantial (21 lives saved per 1000 patients treated) and compared favorably with the survival benefit of thrombolytic therapy compared with placebo reported by the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group (19 lives saved per 1000 patients treated).[62]

OUTCOMES IN HIGH-RISK PATIENTS

Patients with AMI at highest risk for mortality include patients with cardiogenic shock, elderly patients, patients with anterior wall myocardial infarction, and women. Data from randomized trials indicate that the greatest mortality benefit with primary angioplasty is seen in these high-risk patients (Table 46-2). The PAMI-1 investigators found a significant mortality benefit with primary angioplasty compared with tPA in non-low-risk patients (patients older than 70 years, anterior infarction, or heart rate >100 beats per minute) but no difference in mortality in low-risk patients.[52] Likewise, elderly patients showed a substantial mortality benefit with primary angioplasty compared with tPA in both the PAMI-1 trial[63] and the GUSTO-IIb trial,[64] whereas younger patients showed no mortality difference. The PAMI-1 investigators also found a substantial mortality benefit with primary angioplasty versus thrombolytic therapy in patients with anterior wall myocardial infarction but no mortality benefit in non-anterior wall myocardial infarction.[65] Garcia et al.[60] also found mortality benefit with primary angioplasty in patients with anterior wall myocardial infarction, but the GUSTO-IIb trial did not.[66] The lack of benefit in the GUSTO-IIb trial may be related to the lower rates of achieving TIMI 3 flow in the GUSTO-IIb trial.[67] Women are also at high risk for mortality with AMI partly related to more baseline risk factors. In the PAMI-1 trial, mortality in women was lower with primary angioplasty compared with tPA[68] (see Table 46-2). Patients with cardiogenic shock are the highest-risk subgroup of patients with AMI and appear to benefit most from primary angioplasty. Unfortunately, thrombolytic therapy is not very effective in patients with cardiogenic shock. In the GISSI-1 trial,[20] there was no difference in mortality in patients with cardiogenic shock treated with intravenous streptokinase versus placebo (70 percent in each), and the International Study Group found that mortality was high with both streptokinase and tPA (65 and 78 percent, respectively).[69] In contrast, pooled data from 19 observational studies with primary angioplasty for cardiogenic shock showed an overall mortality of 44 percent.[70] Recently, the SHOCK trial,[71] which randomized patients with

cardiogenic shock to emergency revascularization versus medical stabilization, found a decreased mortality rate in favor of emergency revascularization at 6 months (50 versus 63 percent; $p = 0.03$). Survival benefit was especially pronounced in patients treated within 6 h of symptom onset and in patients under age 75 years. These data and previous observational data strongly support the use of primary angioplasty to provide survival benefit in patients with AMI complicated by cardiogenic shock, especially in young patients who present early after symptom onset.

OUTCOMES IN LOW-RISK PATIENTS

While the survival benefit with primary angioplasty versus thrombolytic therapy is limited to high-risk patients, low-risk patients benefit from a reduction in the incidence of reinfarction and recurrent ischemia. In a randomized comparison, the PAMI-1 trial[65] found a lower incidence of recurrent ischemia (9.7 versus 27.8 percent; $p = 0.0002$) and the Zwolle group[57] found a lower incidence of reinfarction (0 versus 16 percent; $p < 0.01$) in patients with non-anterior wall myocardial infarction treated with primary angioplasty. Similarly, Ribichini et al.,[59] in a randomized comparison of primary angioplasty versus thrombolytic therapy in patients with inferior infarction, found a lower incidence of reinfarction (1.8 versus 9.1 percent; $p = 0.10$) and recurrent ischemia (1.8 versus 20.0 percent; $p = 0.002$), higher infarct artery patency (100 versus 71 percent; $p = 0.0001$), and better left ventricular ejection fraction (55.2 versus 48.2 percent; $p = 0.001$) at hospital discharge in patients treated with primary angioplasty.

Thus, while low-risk patients have no survival benefit with primary angioplasty, they do benefit from less reinfarction, less recurrent ischemia, higher infarct artery patency rates, and better left ventricular function without the risk of intracranial hemorrhage.

IMPORTANCE OF TIMI FLOW

The importance of achieving timely restoration of normal blood flow in the infarct artery in patients with AMI was convincingly demonstrated in the GUSTO trial.[72] Patients with normal (TIMI 3) antegrade flow in the infarct artery at 90 min after treatment had the highest left ventricular ejection fraction at follow-up catheterization and the lowest 30-day mortality (Table 46-3). Patients with slow (TIMI 2) flow had a left ventricular ejection fraction and 30-day mortality that was significantly worse than patients with TIMI 3 flow and similar to patients with no flow (TIMI 0-1). A similar relationship between TIMI flow and mortality has been found with primary angioplasty[73] (see Table 46-3). These data indicate that only restoration of TIMI 3 flow is associated with optimal outcomes and that only TIMI 3 flow should be regarded as "true patency." A comparison of the rates of TIMI 3 flow with various reperfusion strategies in the GUSTO trial and with primary angioplasty from the PAMI-1 and PAMI-2 trials are shown in Fig. 46-1.[72,73] The ability of primary angioplasty to achieve significantly higher TIMI 3 flow rates than thrombolytic therapy probably explains most of the mortality advantage seen with primary angioplasty. Indeed, there appears to be a tight inverse relationship between short-term mortality and the ability to achieve TIMI 3 flow with various thrombolytic regimens and with primary angioplasty (Fig. 46-2). Newer thrombolytic strategies combining low-dose thrombolytics with platelet glycoprotein IIb/IIIa receptor inhib-itors have shown improved TIMI 3 flow rates[74] (see Chap. 42), but these rates are still well below the TIMI 3 flow rates achieved with primary angioplasty, and these strategies remain to be tested in large clinical trials.

Table 46-3: Relationship Between TIMI Flow and 30-Day Mortality after Reperfusion Therapy for AMI

	30-Day Mortality	
TIMI Flow	GUSTO-I[72] (Lytic Therapy)	PAMI-1 and PAMI-2[73] (Primary PTCA)
TIMI 0-1	8.9%	17.2%
TIMI 2	7.4%	7.6%
TIMI 3	4.4%	2.1%

LATE CLINICAL AND ANGIOGRAPHIC OUTCOMES

A comparison of late clinical outcomes of patients with AMI treated with primary angioplasty versus thrombolytic therapy has been provided by the PAMI investigators.[75] The initial benefit of primary angioplasty in reducing death and reinfarction was maintained out to 2 years with event-free survival curves that remain nearly parallel after hospital discharge (Fig. 46-3). Primary angioplasty also was associated with lower hospital readmission rates (59 versus 69 percent; $p = 0.035$) and lower rates of target-vessel revascularization with either angioplasty or bypass surgery (33 versus 54 percent; $p = 0.001$) compared with tPA. More recently, the Zwolle group has demonstrated that the early mortality and reinfarction benefit is maintained over 5-year follow-up.[76]

Reocclusion of the infarct artery at follow-up angiography occurs frequently after thrombolytic therapy when adjunctive percutaneous coronary intervention is not employed. The Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT) study performed follow-up angiography at 3 months in patients with AMI treated with intravenous streptokinase who had a patent infarct artery at catheterization at 24 to 48 h and found a late reocclusion rate of 28 percent.[77] Similarly, White et al. found that 25 percent of patients with an initially patent infarct artery after thrombolytic therapy at 4 weeks had an occluded artery at 1 year.[78] In contrast, reocclusion rates at 6-month follow-up angiography after primary angioplasty have ranged from 5 to 13 percent[29,77,79-81] (Table 46-4). In a randomized comparison of primary angioplasty with streptokinase from the Zwolle group, reocclusion rates were significantly lower with primary angioplasty (9 versus 32 percent; $p = 0.001$).[53] With the use of coronary stenting, reocclusion rates at 6-month angiography have been reduced to about 5 percent.[81] The lower rates of reocclusion with primary angioplasty are likely related to the reduction in residual stenosis, since residual stenosis after thrombolytic therapy is highly correlated with late reocclusion.[77]

Infarct artery patency is important for recovery of left ventricular function[79] and may be important for late survival. Several observational studies with thrombolytic therapy and primary angioplasty have found that both left ventricular function and infarct artery patency are strong independent predictors of late cardiac survival.[82,83] This suggests that the late angiographic outcomes after primary angioplasty may translate into better long-term clinical outcomes.

The restenosis rate at 6-month follow-up angiography after primary angioplasty is similar to that after elective angioplasty and occurs in 24 to 46 percent of patients.[29,7779-81] While this remains a significant clinical and economic problem with primary angioplasty, only about one-half of patients with restenosis require repeat target-vessel revascularization, and restenosis does not interfere with recovery of left ventricular function as long as the infarct artery remains patent.[79] The use of stents with primary angioplasty, like elective angioplasty, has significantly reduced restenosis rates. The Stent PAMI trial showed a reduction in restenosis rates from 34 percent with angioplasty to 20 percent with stenting.[81] In comparison with primary angioplasty, the frequency of significant residual stenosis (>50 percent diameter narrowing) at 3-month follow-up angiography after thrombolytic therapy remains quite high[77] (Table 46-4).

Role of Cardiac Surgery in the Primary Angioplasty Approach

Not all patients with AMI brought to the cardiac catheterization laboratory undergo percutaneous coronary intervention.[52,84] Approximately 10 percent of patients are triaged to either medical treatment or are treated with coronary bypass surgery as the primary reperfusion strategy, i.e., primary coronary artery bypass grafting (CABG). Patients may be selected for primary CABG when there is severe left main coronary artery disease or severe three-vessel coronary artery disease with preserved (TIMI 3) flow in the infarct artery that allows time for transfer to the operating room. These patients frequently undergo operation emergently and comprise a little less than half the patients not undergoing percutaneous coronary intervention. The remaining patients not treated with percutaneous coronary intervention are treated medically. These include patients with no myocardial infarction (mistaken diagnosis), patients with no significant stenosis in the infarct artery (resolution of spasm or thrombus), patients in whom the infarct artery cannot be identified, and occasionally patients with unsuitable anatomy or a very small infarct-related artery.

Bypass surgery is also performed emergently after failed angioplasty, urgently for reinfarction or recurrent ischemia, and electively for definitive treatment of left main or severe multivessel disease. With recent experience and with the availability of stents, emergency bypass surgery is rare (~0.4 percent), and the need for urgent bypass surgery for reinfarction or recurrent ischemia that cannot be managed with repeat percutaneous coronary intervention is very infrequent (<1 percent).[81] Elective bypass surgery for treatment of residual coronary artery disease after initial successful primary angioplasty has been used in about 4 to 5 percent of patients. Altogether, bypass surgery is performed in about 7 to 10 percent of patients with the primary angioplasty approach.[84,85] Considering the severity of illness of these patients, surgical mortality has been relatively low (6.4 percent with emergency or urgent bypass surgery and 2.0 percent with elective bypass surgery in the PAMI-2 trial).[85]

Cardiac surgery is also used in patients with mechanical complications of AMI. Patients with ventricular septal rupture and acute mitral regurgitation from papillary muscle rupture usually develop cardiogenic shock and have a very poor outcome without surgical intervention and are candidates for emergency surgery. Patients with cardiogenic shock with severe left main disease (without mechanical complications) also may be candidates for emergency bypass surgery.[71]

Although cardiac surgery is an integral part of the primary angioplasty approach, it has been demonstrated that primary angioplasty can be performed safely and effectively at some community hospitals without on-site cardiac surgery when rigorous program criteria are established.[86,87] These criteria include the availability of experienced interventionists, a well-stocked and well-equipped catheterization laboratory, an experienced catheterization laboratory team, rigorous case-selection criteria, the establishment of good lines of communication between the interventional cardiologist and the cardiovascular surgeon at the referring institute, and an efficient emergency transport system. In many hospitals, transfer to an angioplasty/surgical center for those requiring an intervention may be a preferable approach.

Primary Angioplasty in Thrombolytic-Ineligible Patients

In most U.S. thrombolytic trials, 70 to 85 percent of patients with AMI screened have been considered ineligible for thrombolytic therapy because of advanced age, late presentation, prior bypass surgery, cardiogenic shock, or bleeding predisposition.[88] These patients constitute a high-risk subset with a significantly increased in-hospital mortality. Despite recommendations to broaden thrombolytic therapy to patients of any age and to patients presenting up to 12 h after the onset of symptoms, data from the National Registry of Myocardial Infarction (NRMI-2) have found that only 31 percent of patients with AMI are considered eligible for thrombolytic therapy, and only 75 percent of these patients are currently receiving thrombolytic therapy[89] (Fig. 46-4).

One of the major advantages of primary angioplasty compared with thrombolytic therapy is that primary angioplasty can be applied to a majority of patients with AMI.[90] The only contraindications to primary angioplasty are lack of vascular access, renal insufficiency, and active hemorrhage. Among patients who are usually not considered candidates for thrombolytic therapy but who may benefit greatly from reperfusion therapy with primary angioplasty are patients with cardiogenic shock, elderly patients, and

patients with a predisposition to bleeding. Elderly patients are frequently excluded from thrombolytic trials, but those who have been enrolled in trials comparing thrombolytic therapy with primary angioplasty have had a substantial mortality benefit with primary angioplasty.[63,64] Patients with AMI and contraindications to thrombolytic therapy due to bleeding risk have a high mortality, and observational data suggest that mortality may be reduced by reperfusion with primary angioplasty.[91]

There are very little data supporting benefit of reperfusion therapy in patients who present more than 12 h after the onset of symptoms. One exception to this is patients who present late but have persistent ischemic chest pain. These patients frequently have collateral flow to the infarct zone and show substantial recovery of left ventricular function following reperfusion with primary angioplasty.[92] It is also possible that late restoration of patency of the infarct artery could enhance late survival independent of myocardial salvage by preventing left ventricular dilatation, promoting electrical stability, and serving as a source for collateral flow,[93,94] but this remains to be tested in prospective studies. Patients with AMI who do not have electrocardiographic ST-segment elevation or left bundle-branch block have shown no benefit with thrombolytic therapy in randomized trials[62] and appropriately are not considered candidates for thrombolytic therapy. There are little data regarding benefit from primary angioplasty in this group of patients. McCullough et al.[95] demonstrated that patients with acute ischemic syndromes, including non-ST-segment elevation infarction, randomized to triage angiography with angioplasty when appropriate versus conservative care have less recurrent ischemia but have no mortality or reinfarction benefit.

Although prior bypass surgery is not a contraindication to thrombolytic therapy, these patients frequently have been excluded from thrombolytic trials. Reperfusion rates with thrombolytic therapy in patients with AMI due to saphenous vein graft occlusion are significantly less than with native vessel occlusion (TIMI 2-3 flow in the GUSTO trial: 48 versus 69 percent, respectively; $p < 0.01$).[96] Reperfusion rates with primary angioplasty in patients with saphenous vein graft occlusion are better than with thrombolytic therapy but are not as good as with primary angioplasty in native vessel occlusion. The PAMI-2 trial achieved TIMI 3 flow in 70 percent of patients with saphenous vein graft occlusion compared with 94 percent of patients with native coronary artery occlusion.[97] Patients with prior bypass surgery also had higher in-hospital mortality compared with patients without prior bypass surgery (6.9 versus 2.6 percent; $p = 0.05$).[97] While primary angioplasty appears to have an advantage over thrombolytic therapy in treating patients with AMI due to saphenous vein graft occlusion, new approaches are still needed to improve outcomes.

Cost Issues

RANDOMIZED COMPARISONS WITH THROMBOLYTIC THERAPY

There has been the perception that a strategy of primary angioplasty is more expensive than thrombolytic therapy in the treatment of AMI because of the initial cost of cardiac catheterization and coronary intervention. There are now data from several randomized trials that provide direct cost and length-of-stay comparisons between primary angioplasty and thrombolytic therapy.[98-100] The Mayo Clinic trial,[98] the PAMI-1 trial,[99] and the GUSTO-IIb trial[100] all showed a shorter length of hospital stay with primary angioplasty, which is likely due to a less complicated hospital course with less reinfarction and less recurrent ischemia (Table 46-5). The same randomized trials have shown comparable or lower hospital costs (charges) with primary angioplasty compared with thrombolytic therapy (see Table 46-5). A breakdown of the hospital charges from the PAMI-1 trial comparing primary angioplasty with tPA is shown in Fig. 46-5).[99] As expected, catheterization laboratory charges are higher with primary angioplasty, but the differences are not as great as expected because of the high use of catheterization and angioplasty in tPA-treated patients (63 and 36 percent, respectively). Initial catheterization laboratory charges with primary angioplasty are offset by higher drug charges in tPA patients due primarily to the charge for tPA. Other charges are slightly less with primary angioplasty, reflecting a shorter, less complicated hospital course. The cost advantages are not confined to hospital stay or American centers. The Zwolle group has shown similar decreases in cost during a 5-year follow-up.[76]

Table 46-5: Hospital Length of Stay and Hospital Charges/Costs Comparing Primary Angioplasty versus Lytic Therapy with tPA

	PTCA	tPA	*p* Value
Mayo Clinic trial[98]			
Length of stay (days)	8.1	10.5	0.08
Hospital charges ($)	21,000	26,700	0.09
PAMI-1 trial[99]			
Length of stay (days)	7.6	8.4	0.04
Hospital charges* ($)	23,468	26,904	0.04
GUSTO-IIb trial[100]			
Length of stay (days)	7.0	7.7	0.0009
Hospital costs* ($)	13,337	14,236	0.004

*PAMI-1 and GUSTO-IIb do not include professional charges.

EARLY-DISCHARGE STRATEGIES

A strategy of early discharge with primary angioplasty may reduce costs further. Primary angioplasty appears to have two advantages over thrombolytic therapy in allowing a strategy for early discharge. First, the incidence of recurrent ischemic events and reinfarction is substantially less with primary angioplasty, and unlike thrombolytic therapy, ischemic events are usually confined to the first 2 days.[101] Second, angiographic data obtained at cardiac catheterization with primary angioplasty provide powerful information for risk stratification. These data include left ventricular ejection fraction, number of diseased vessels, and the reperfusion status or TIMI flow in the infarct artery after intervention. The PAMI-2 trial has documented the safety and cost savings of early discharge in low-risk patients treated with primary angioplasty.[102] Patients were classified as low risk if they met all the following clinical and angiographic criteria: age less than 70 years, ejection fraction greater than 45 percent, one- or two-vessel coronary artery disease, successful angioplasty, no saphenous vein graft occlusion, no persistent arrhythmias, and no congestive heart failure. Using these criteria, an extremely low risk group of patients was identified comprising about one-half the study population with an in-hospital mortality of 0.4 percent. The study documented that a strategy of targeting early discharge on day 3 in these low-risk patients was safe and reduced length of stay from 7.0 to 4.2 days and hospital costs from $11,604 to $9658.

COST-EFFECTIVENESS OF ADJUNCTIVE THERAPY

The impact of adjunctive treatment with coronary stents and platelet inhibitors on costs with primary angioplasty is evolving. Initial data from the Stent PAMI trial[103] suggest that the initial increased costs of stenting versus angioplasty alone ($2185) are partially recovered by decreased posthospital costs due to less target-vessel revascularization (-$974). This makes the total 1-year costs $1211 higher with stenting compared with angioplasty alone. The costs and effectiveness of stenting patients with AMI appear comparable with those of elective stenting. The incremental costs and effectiveness of glycoprotein IIb/IIIa platelet receptor inhibitors in the setting of primary angioplasty is currently being evaluated.

Importance of Time to Reperfusion

Data from a number of randomized trials have shown that the mortality benefit of thrombolytic therapy is strongly dependent on the time from symptom onset until treatment up to 12 h.[62,72,104] Recent observations suggest that time to treatment may be less important with primary angioplasty.[105-107] The PAMI-2 trial found that mortality was lowest when patients were treated very early (<2 h) but that mortality was relatively independent of time to treatment after 2 h[105] (Fig. 46-6). Brodie et al.[107] also found that mortality was significantly lower when patients were reperfused at less than 2 h with primary angioplasty but that mortality was relatively constant after 2 h regardless of further increases in time to treatment[107] (see Fig. 46-6). (One exception to this is in patients with cardiogenic shock, who continue to have increasing mortality with increasing time to reperfusion.[71]) There are several possible explanations for this. First, data from several trials suggest that TIMI 3 flow is achieved in a smaller proportion of patients with increasing time to treatment with thrombolytic therapy.[108,109] In contrast, TIMI 3 flow is achieved with primary angioplasty in more than 90 percent of patients regardless of time to treatment.[105-107] Since achieving TIMI 3 flow in the infarct artery is the strongest predictor of survival, this may partially explain why mortality continues to rise with increasing time to treatment with thrombolytic therapy but remains fairly constant after 2 h with primary angioplasty. Second, cardiac rupture occurs more frequently with increasing time to treatment with thrombolytic therapy.[110,111] In the GISSI trial, mortality due to cardiac rupture increased from 0.7 percent at 0 to 3 h to 2.0 percent at 8 to 12 h.[111] With primary angioplasty, cardiac rupture is uncommon.[112] Finally, for reasons that are not clear, the incidence of intracranial hemorrhage also increases with increasing time to treatment with thrombolytic therapy from 0.5 percent at less than 2 h to 1.0 percent at more than 6 h.[113] These data may have important implications regarding the mechanism of benefit of reperfusion therapy. The traditional paradigm regarding the mechanism of benefit of reperfusion therapy is that early reperfusion results in myocardial salvage, which results in improved left ventricular function and better survival. This paradigm has been expanded to include benefit of late reperfusion when myocardial salvage is no longer expected. An open infarct artery, even if opened too late for myocardial salvage, may result in survival benefit by preventing ventricular dilatation, promoting electrical stability, and providing a source of collateral flow.[93,94] The survival benefit due to myocardial salvage is felt to be strongly time-dependent, whereas the survival benefit due to late reperfusion not related to myocardial salvage is felt to be relatively independent of time to reperfusion. The data with primary angioplasty are consistent with this expanded paradigm, but studies with primary angioplasty suggest that the time period for significant myocardial salvage and recovery of left ventricular function is relatively short (<2 h).[107,114,115]

These data also may have important implications regarding the triage of patients for primary angioplasty. Unless patients present very early (<2 h), when substantial myocardial salvage is possible (and this occurs in only about 12 percent of patients),[107] the time delay in transferring patients from community hospitals to tertiary centers for primary angioplasty may not be prohibitive. This concept is currently being evaluated in prospective randomized trials.

Technical Aspects of Primary Angioplasty

TREATMENT IN THE EMERGENCY DEPARTMENT

When primary angioplasty is planned for patients with known or suspected AMI, only a limited history and physical examination should be performed to avoid delays in initiating the catheterization procedure. Patients are given 325 mg of soluble chewable aspirin, 5000 to 10,000 units of intravenous heparin, sublingual nitroglycerin, intravenous beta blockers unless contraindicated, and supplemental oxygen and are transported promptly from the emergency department to the catheterization laboratory. A lower weight-adjusted dose of heparin should be given if the use of a glycoprotein IIb/IIIa receptor blocker is considered.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Femoral access is usually preferred because this allows for the use of larger devices if necessary and facilitates the use of adjunctive therapy with intraaortic balloon pumping or transvenous pacing when indicated. Low-osmolar ionic contrast material (ioxaglate) has been recommended to minimize the risk of hemodynamic and arrhythmic disturbances, as well as thromboembolic complications.[116,117] Recent studies

also have shown that the isomolar nonionic dimer iodixanol has been associated with a very low incidence of adverse events in high-risk patients undergoing percutaneous coronary intervention.[118]

After arterial access is obtained, an activated clotting time (ACT) is measured, and additional heparin is given to prolong the ACT to more than 350 s prior to balloon inflation (200- 300 s if use of a glycoprotein IIb/IIIa receptor blocker is planned). Left ventriculography is clinically useful when performed prior to intervention, even in patients who are hemodynamically unstable, to assess the severity of ventricular and valvular dysfunction, to help in identification of the infarct artery (if this is uncertain), and to aid in making decisions regarding the need for adjunctive therapy, such as intraaortic balloon pumping and pulmonary artery catheter insertion. Occasionally, papillary muscle rupture, ventricular septal defect, or rarely even frank free wall rupture will be demonstrated, prompting urgent surgery. Alternatively, demonstration of normal left ventricular function may raise early concerns of nonischemic diagnoses such as aortic dissection or pericarditis. A femoral venous sheath may be helpful in patients with occlusion of the right coronary artery to allow access for temporary transvenous pacing if necessary. In patients with hypotension or hemodynamic instability, placement of a pulmonary artery catheter is important to define and monitor hemodynamics. The use of a pulse oximeter to monitor oxygen saturation is also useful. Following diagnostic coronary and left ventricular angiography, patients are triaged to the most appropriate therapy.

PRIMARY ANGIOPLASTY PROCEDURE

Primary angioplasty is generally performed with 7 French standard guiding catheters and soft or floppy-tipped 0.014-in. steerable guidewires. The soft tip almost always can cross the soft fresh thrombus (in contrast to chronic total occlusions) and is less traumatic than stiffer wires. If the infarct lesion cannot be crossed with a soft wire, a stiffer wire is used. The guidewire is advanced well down the infarct artery to ensure that it is in the true lumen and not in the small side branch or under an intimal dissection, since navigation is usually done blindly distal to the occlusion. If the infarct-related artery is totally occluded initially, reperfusion often will be established after the occlusion is crossed with a guidewire. If reperfusion is not established with the wire, it may be preferable to cross the occlusion with the balloon and then withdraw the balloon without inflating it ("Dottering" the lesion) to establish reperfusion. The more gradual reperfusion provided with the wire or Dottering technique may result in fewer reperfusion arrhythmias than rapidly inflating the balloon immediately after crossing. Once reperfusion is established, balloon angioplasty of the infarct lesion is performed with similar technique to conventional angioplasty. Infarct lesions usually are soft and do not require high balloon pressures. The operator should strive for an optimal result with less than 30 percent residual luminal narrowing and TIMI 3 flow. If a significant residual stenosis remains, or if there is a dissection, coronary stenting is indicated because these features are predictive of recurrent ischemia or reocclusion.[119] As soon as the decision to perform coronary stenting is made, 500 mg ticlopidine or 150 to 300 mg clopidogrel should be given as a loading dose. As an alternative to stenting for suboptimal results, or if there is large residual thrombus, a glycoprotein IIb/IIIa platelet receptor inhibitor may be used (although if glycoprotein IIb/IIIa receptor blocker use is likely, it is preferable to use this agent prior to balloon inflation). The use of intracoronary thrombolytic therapy is not recommended because this results in increased rates of infarct artery occlusion when used as an adjunct to angioplasty in acute ischemic syndromes.[120] No flow (TIMI 0-1 flow) or slow flow (TIMI 2 flow) may occur after successful opening of the epicardial infarct artery obstruction. This is generally due to microvascular dysfunction from spasm, distal emboli, or endothelial injury and should be treated with intracoronary nitroglycerin, verapamil, and/or adenosine, which often helps to improve flow. Glycoprotein IIb/IIIa receptor blocking agents also may help with no reflow. With rare exceptions (such as refractory cardiogenic shock), a cardinal rule with primary angioplasty is to dilate only the infarct artery. Tandem lesions in the infarct vessel can be dilated, but dilating a noninfarct artery places too much myocardium acutely in jeopardy.

ACUTE CATHETERIZATION LABORATORY COMPLICATIONS

With increasing operator experience, improved equipment and patient selection, and the availability of stents, major catheterization laboratory complications with primary angioplasty have become infrequent. Acute catheterization laboratory complications from the Stent PAMI trial[121] in nonshock patients are shown in Table 46-6. Laboratory death and emergency bypass surgery for failed angioplasty are rare. Ventricular tachycardia or fibrillation requiring cardioversion, asystole and bradycardia including second- and third-degree atrioventricular (AV) block, and hypotension are the most common complications and

usually occur immediately after reperfusion. These complications, which occur more often with right coronary artery infarction, historically were a problem with primary angioplasty, but with increased experience, they occur less frequently and are manageable.[84]

Table 46-6: Acute Catheterization Laboratory Complications with Primary Angioplasty (PTCA) and Primary Stenting in Nonshock Patients

Complication	Stent (*n* = 451) (%)	PTCA (*n* = 448) (%)	Combined (*n* = 899) (%)
Laboratory death	0.2	0	0.1
Emergency bypass surgery	0.2	0.2	0.2
Cardiac arrest			
Ventricular tachycardia/fibrillation*	3.1	4.7	3.9
Cardiopulmonary resusitation†	0.9	0.4	0.7
Intubation	0.2	0.7	0.4
Asystole/bradycardia‡	9.3	8.5	8.9
Sustained hypotension§	7.8	8.3	8.0

*Requiring electric cardioversion.†Requiring chest compression.‡Requiring atropine or temporary pacing.§Requiring vasopressors or intraaortic balloon counterpulsation.
SOURCE: From the Stent PAMI trial.[76]

POSTANGIOPLASTY CARE

Following the interventional procedure, heparin should be held for 2 to 4 h until the ACT is less than 170 s, at which time the sheath should be removed. Heparin is resumed 2 h after sheath removal with a bolus at 15 units/kg per hour and titrated to maintain the activated partial thromboplastin time (aPTT) at 60 to 80 s. Full-dose heparin is continued until 48 h after the intervention, then is decreased to one-half dose for 12 h to prevent a rebound hypercoagulable state, and then is discontinued. In patients who receive abciximab, no postprocedural heparin is given. When tirofiban or eptifibatide is used, low-dose heparin is recommended. Low-risk patients (as defined earlier) can be transferred from the catheterization laboratory directly to the subacute unit (rather than the coronary care unit) and can be targeted for discharge on day 3 (day 0 = day of admission).[102] Aspirin should be given routinely. Ticlopidine 250 mg orally twice daily or clopidogrel 75 mg orally daily should be given in stented patients and continued for 2 to 4 weeks. If no contraindications are present, angiotensin-converting enzyme (ACE) inhibitors should be used in patients with congestive heart failure, hypertension, or low ejection fraction (<40 percent). Oral beta blockade also should be administered routinely in the absence of contraindications. Patients who develop symptoms or electrocardiographic changes suggestive of recurrent ischemia or reinfarction should undergo emergency repeat catheterization and intervention as indicated.

Adjunctive Therapy

STENTS

The use of stenting with percutaneous coronary intervention in AMI initially was thought to be contraindicated due to the presence of thrombus in the infarct artery and concern regarding the risks of subacute thrombosis. The use of platelet inhibition with aspirin plus ticlopidine or clopidogrel and high-pressure balloon deployment have greatly reduced the incidence of subacute thrombosis, and numerous

studies have now documented the safety of stent deployment in the setting of AMI.[81,122,123] Several studies with first-generation stents have documented superior outcomes with stenting compared with angioplasty alone, with lower composite end points due primarily to less target-vessel revascularization or less recurrent ischemia[123-125] (Table 46-7). The largest randomized trial, the Stent PAMI trial[121] with 900 patients, has documented lower restenosis rates (20 versus 34 percent; $p = 0.001$), including less reocclusion (5 versus 9 percent; $p = 0.04$) and less ischemia-driven target-vessel revascularization (8 versus 17 percent; $p = 0.0001$) with stenting versus angioplasty alone but no difference in mortality or reinfarction (see Table 46-7). Currently, stenting cannot be recommended for routine use with primary angioplasty but should be used in selected patients, especially when there are suboptimal results or dissection following angioplasty. The results of large ongoing trials with newer stents may provide data that will extend these indications.

PLATELET INHIBITORS

Several trials have documented the efficacy of glycoprotein IIb/IIIa platelet receptor inhibition during elective coronary intervention.[126-128] The RAPPORT trial evaluated platelet inhibition with abciximab in patients with AMI undergoing primary angioplasty and found a significant reduction in the 30-day composite end point[129] (Table 46-8). However, by 6 months, there was no difference in outcomes (see Table 46-8). Also, the use of high-dose heparin in concert with prolonged sheath dwell times resulted in an excess of major bleeding episodes. Two European trials, the ADMIRAL trial[130] and the Munich trial,[131] have evaluated abciximab in patients with AMI undergoing primary stenting, and both have found a significant reduction in composite end points with abciximab compared with placebo (see Table 46-8). The CADILLAC trial has evaluated the efficacy of abciximab in 2000 patients with AMI undergoing either primary angioplasty or primary stenting. This study should provide efficacy as well as cost data that will help to define the role of platelet inhibition with primary angioplasty for AMI.[132]

INTRAAORTIC BALLOON COUNTERPULSATION

Clinical studies have shown that the use of intraaortic balloon counterpulsation results in augmentation of systemic pressure, reduction in preload and afterload, and an increase in coronary blood flow velocity.[133,134] This has given hope that intraaortic balloon counterpulsation may improve outcomes in patients with AMI. Unfortunately, randomized trials in high-risk patients with AMI have shown little or no benefit when intraaortic balloon counterpulsation is used alone without concomitant reperfusion or revascularization.[135,136] Several studies have evaluated the prophylactic use of intraaortic balloon counterpulsation after reperfusion with primary or rescue angioplasty in high-risk patients[137,138] (Table 46-9). Initial studies[137] suggested benefit in terms of less infarct artery reocclusion and less recurrent ischemia, but larger, more recent studies including the large PAMI-2 trial have shown little or no benefit.[138,139] The results of these trials and the advent of coronary stenting, which has reduced the incidence of reocclusion and recurrent ischemia, have diminished the role of intraaortic balloon counterpulsation after primary angioplasty in hemodynamically stable patients. Intraaortic balloon counterpulsation still has a role in hemodynamically unstable patients with congestive heart failure or shock prior to primary angioplasty and in patients with mechanical complications of AMI or anatomy that is unsuitable for percutaneous coronary intervention as a bridge to surgery. There also may be a role for prophylactic intraaortic balloon pumping before primary angioplasty in selected high-risk patients to prevent hemodynamic deterioration.[140]

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FUTURE RESEARCH DIRECTIONS: BEYOND TIMI 3 FLOW

The superior TIMI 3 flow rates achieved by mechanical reperfusion largely explain the mortality advantage of this strategy. Today, TIMI 3 flow rates of 90 percent or more are expected for optimal clinical benefit. It must be emphasized, however, that TIMI flow is a subjective, qualitative assessment of relative contrast velocity in major epicardial coronary vessels. Observations using myocardial contrast echocardiography suggest that effective myocardial perfusion may occur in only 70 percent of patients with TIMI 3 flow.[141] Similarly, the Zwolle group has shown that myocardial contrast blush grade is impaired in a large number of patients with normal TIMI flow.[142] Finally, Tsunoda et al.[143] have shown that up to one-third of patients with TIMI 2 flow have abnormal Doppler wave flows with a systolic flow reversal and diminished diastolic flow pattern. The reason for concern is that each of these techniques measures myocardial perfusion, and each has shown that ventricular function is only improved in those patients with normal myocardial perfusion.

The cause for abnormal perfusion after PTCA is unknown. Most myocardium is stunned after prolonged ischemia, but lack of demand alone does not explain the abnormal flow. Distal embolization of macroscopic thrombotic and plaque debris and reperfusion injury after reperfusion may be contributory. Extensive myocardial edema with capillary constriction and leukoaggregation or platelet macroemboli may prevent capillary perfusion.

Exciting new research modalities will test each of these potential mechanisms. The goal is to normalize myocardial perfusion and thus optimize salvage after reperfusion. Agents such as adenosine will be tested to decrease reperfusion injury.[144] Filtered leukocytes and complement-depleted blood have been used to reperfuse patients.[145] Supersaturated oxygen is being employed to limit myocardial injury during reperfusion.[146] Mechanical traps[147] will be employed to prevent macroembolization of debris during angioplasty and stent placement. Even glucose-insulin-potassium solutions may be of value.[148] Finally, glycoprotein receptor blockade may prevent platelet-rich thrombi from impairing microcirculatory function. Two trials have demonstrated significant improvement in ejection fraction when abciximab is added to stent therapy of AMI.[130,131] Mechanical reperfusion not only has demonstrated improvement in clinical outcome but also will contribute to an understanding of mechanisms involved in myocardial injury.

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CONCLUSION

Mechanical reperfusion therapy of AMI has developed as an alternative to thrombolytic therapy. Reperfusion rates are significantly higher, rates of death and reinfarction are significantly lower, rates of intracranial hemorrhage are dramatically lower, and long-term survival is significantly greater compared with thrombolytic therapy. This treatment thus may be the preferred therapy for patients presenting to institutions equipped to perform it. Ongoing clinical trials will further elucidate the role of mechanical reperfusion after failed thrombolytic therapy and the role of transport of high-risk patients to referral institutions. The potential for mechanical reperfusion therapy is great. The major challenge for clinicians will be to find methods to apply this treatment to larger segments of the population.

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Part 6: CORONARY HEART DISEASE
Chapter 47:

CORONARY INTRAVASCULAR ULTRASOUND IMAGING

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Although angiography continues to serve as the primary imaging modality used to assess the anatomy of coronary artery disease, intravascular ultrasound has matured into an important alternative method for examination of the coronaries during diagnostic or interventional catheterization.[1-8] Studies comparing angiography and intravascular ultrasound have demonstrated important differences in quantitative and qualitative findings.[7-11] Unlike angiography, which portrays the vessel as a silhouette of the lumen, intravascular ultrasound provides tomographic images that portray not only the lumen but also the deeper intramural structures within the vessel wall. The ability of ultrasound to penetrate and image soft tissue enables direct visualization of the atheroma, providing insights into the pathophysiology of coronary disease not obtainable by any other technique. Accordingly, intraluminal ultrasound imaging is now commonly utilized to confirm, refute, or supplement angiographic data in patients with coronary disease.[8]

RATIONALE FOR INTRAVASCULAR ULTRASOUND

Limitations of Angiography

Visual interpretation of angiograms exhibits significant observer variability, and necropsy examination is often discordant with the apparent angiographic severity of lesions.[12-18] In comparison to postmortem evaluation, angiography often significantly underestimates the extent of atherosclerosis.[13,18] Angiographic assessment of lesion severity is strikingly discordant with measurements of the physiologic effects of stenoses.[19] Angiography depicts coronary anatomy from a planar two-dimensional silhouette of the contrast-filled lumen. However, coronary lesions are often complex, with markedly distorted or eccentric luminal shapes, and mechanical interventions (other than stenting) exaggerate luminal eccentricity by fracturing or dissecting the atheroma.[9,20,21] The angiographic appearance of the postintervention vessel often reveals an enlarged but "hazy" lumen. This indistinct, broadened angiographic silhouette may overestimate actual vessel diameter and misrepresent the gain in lumen size.[21]

The traditional method for characterizing angiographic lesion severity depends upon visual or computer measurements of the percentage stenosis. This process requires comparison of luminal dimensions within both the lesion and an adjacent, uninvolved "normal" reference segment. However, necropsy studies demonstrate that coronary disease is frequently diffuse and contains no truly normal reference segment.[18] In the presence of diffuse disease, calculation of percent stenosis will predictably underestimate disease severity. Diffuse, concentric, and symmetrical disease affecting the entire vessel may result in the angiographic appearance of a small but normal artery.[21] Angiography is also confounded by the phenomenon of coronary "remodeling," observed histologically as the outward displacement of the external vessel wall in segments with atherosclerosis.[22] This adventitial enlargement attenuates lumen encroachment, thereby concealing the presence of the atheroma on angiography. Although such lesions do not restrict blood flow, clinical studies have demonstrated that these minimal, nonobstructive lesions represent an important cause of acute coronary syndromes.[23] Angiographically unrecognized

disease virtually always underlies an ergonovine-positive response in symptomatic patients with a "normal" coronary angiogram.[24]

Theoretical Advantages of Ultrasound

Intravascular ultrasound has several unique properties of theoretical value in the detection and quantitation of coronary disease.[25,26] The cross-sectional perspective of ultrasound permits visualization of the full 360-degree circumference of the vessel wall. Accordingly, measurement of lumen area can be determined by planimetry independent of the radiographic projection or magnification.[7,21,25,26] The tomographic perspective of ultrasound enables evaluation of vessels difficult to assess by angiographic techniques, including diffusely diseased segments and bifurcation or ostial lesions. The ability to directly image the atheroma represents a truly unique capability not possible using any other commonly available imaging modality.

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Chapter 47: CORONARY INTRAVASCULAR ULTRASOUND IMAGING

IMAGING TECHNOLOGY

Catheter Design

Intracoronary ultrasound equipment consists of two major components: a catheter incorporating a miniaturized transducer and a console containing the electronics necessary to reconstruct the image. High frequencies (20 to 50 MHz) are employed, resulting in excellent theoretical resolution (axially <100 μm and laterally <250 μm). Two dissimilar technical approaches to transducer design exist: mechanically rotated devices and multielement electronic arrays[1-5] (Fig. 47-1). Each design has yielded small intravascular devices suitable for coronary imaging, typically ranging in size from 2.6 to 3.5 Fr (diameter of 0.86 to 1.17 mm). To facilitate subselective coronary cannulation and catheter exchanges, ultrasound catheters provide a lumen for a movable guidewire. Most systems generate images at a temporal frequency of 30 frames per second for recording on videotape.

Limitations and Artifacts

Intravascular ultrasound devices generate artifacts that may adversely affect image quality, alter interpretation, or reduce quantitative accuracy.[27] Ring-down artifact arises from acoustic oscillations in the piezoelectric transducer, resulting in high-amplitude signals that preclude imaging close to the transducer surface. Accordingly, the "acoustic" size of catheters is slightly larger than their physical size. Since the minimum size of current devices is approximately 0.9 mm, some severe stenoses cannot be imaged prior to intervention. Geometric distortion can result from imaging in an oblique plane (not perpendicular to the long axis of the vessel), resulting in an elliptical rather than circular imaging plane.[28]

Mechanical, but not electronic, transducers may exhibit cyclical oscillations in rotational speed, resulting in an artifact known as nonuniform rotational distortion (NURD).[27] This artifact arises from mechanical friction within the catheter drive shaft during the portions of its rotational cycle. This speed variation produces readily visible distortion often observed as circumferential stretching of a portion of the image with compression of the contralateral vessel wall. NURD is most evident when the drive shaft is bent into a small radius of curvature by a tortuous vessel. Improvements in the mechanical precision of ultrasound devices have reduced the impact of the artifact, but it still remains troublesome during some examinations.

Chapter 47: CORONARY INTRAVASCULAR ULTRASOUND IMAGING

CORONARY IMAGING

Examination Technique

Standard interventional techniques for intracoronary catheter delivery are used for intraluminal ultrasound examination. Intravenous heparin [to maintain activated clotting time (ACT) >200 to 250 s] and intracoronary nitroglycerin (100 to 300 μg) are routinely administered, although there are no controlled studies documenting the necessity for anticoagulation. Using a 7- or 8-Fr guiding catheter, the operator advances a steerable guidewire to subselectively cannulate the vessel. A stable guiding catheter position with good support is desirable, since current ultrasound catheters have less trackability and a larger profile than modern balloon angioplasty catheters. The operator carefully advances or retracts the imaging catheter over the wire to examine the vessel in real time, recording images on videotape for subsequent quantitative or qualitative analysis.

Some centers use a motorized pullback device to withdraw the catheter at a constant speed (between 0.25 and 1 mm/s, most frequently 0.5 mm/s). However, a single pullback, even when controlled by a precise motor, may be insufficient for a complete diagnostic ultrasound examination. Accordingly, motorized pullback is most often used to "survey" the coronary prior to more prolonged and thorough examination of sites of interest. Side branches, visualized with both angiography and ultrasound, are often used as landmarks to facilitate interpretation. Some practitioners advocate use of a uniform format, electronically rotating the ultrasound image so that branches appear in a standardized orientation. For example, imaging of the left anterior descending is often performed with the septal branches at 6 o'clock and the left circumflex appearing at about 9 o'clock.

Safety of Coronary Ultrasound

Although intravascular ultrasound requires intracoronary instrumentation, studies have demonstrated few serious untoward effects.[29-31] The most frequently encountered complication is focal coronary spasm, which usually responds rapidly to intracoronary nitroglycerin. Data from European centers reported a 1.1 percent complication rate in 718 ultrasound examinations.[30] Another report from 28 centers (2207 studies) documented spasm in 2.9 percent and major complications such as occlusion or dissection judged to have a "certain relation" to instrumentation in 0.4 percent.[29] In both studies, complications (spasm, vessel dissection, or guidewire entrapment) occurred in patients undergoing angioplasty rather than diagnostic imaging.[44] In 170 cardiac transplant recipients (240 studies), there was no morbidity, but spasm occurred in 20 patients (8.3 percent) despite pretreatment with nitroglycerin.[31] Any intracoronary instrumentation carries the potential risk of intimal injury or vessel dissection. Accordingly, most laboratories limit credentialing for this procedure to personnel with interventional training.

Normal Coronary Anatomy

Studies performed either in vivo or using excised, pressure-distended vessels have characterized the appearance of normal coronaries by intravascular ultrasound.[32-36] Important determinants of vessel wall appearance include both the normal arterial structure and the inherent properties of ultrasound. An ultrasound reflection occurs at a tissue boundary whenever there is an abrupt change in acoustic impedance. Normally, two strong acoustic interfaces are visualized by

ultrasound-the leading edge of the intima (at the interface between the blood-filled lumen and the endothelium) and the outer border of the media (at the junction of media and external elastic membrane). Underlying the trailing edge of the intima, a middle sonolucent layer is usually evident, which is composed principally of the tunica media. The echodense intima and adventitia with a sonolucent medial layer often give the wall a trilaminar appearance. However, this pattern is not a universal finding; in 30 to 50 percent of normal segments, a thin intimal layer reflects ultrasound poorly, which results in a monolayer appearance[35] (Fig. 47-2).

In a necropsy study, the ultrasound-derived intimal thickness in segments with three layers was significantly greater than for monolayered sites (0.24 ± 0.1 versus 0.11 ± 0.06 mm, $p < 0.001$). The mean age in the three-layered group was greater, 42.8 ± 9.8 versus 27.1 ± 8.5 years ($p < 0.001$).[37] Other studies demonstrate that a trilaminar appearance is dependent not only on the age but also on the histologic characteristics of the vessel. A three-layered appearance is consistently observed if an internal elastic membrane state is present.[38] However, if an internal elastic membrane is absent, a trilaminar appearance is observed only when the collagen content of the media is low. In older "normal" subjects, intimal thickening usually results in a pattern of two distinct echogenic layers sandwiching a sonolucent intermediate layer. In nearly all cases, the deepest arterial layers exhibit a characteristic "onionskin" pattern, representing the adventitia and periadventitial tissues with an indistinct outer vessel border.

In both normal and abnormal arteries, the lumen exhibits faint, finely textured, swirling echoes that arise from acoustic reflections from circulating blood elements. This blood "speckle" may assist image interpretation by providing a means to confirm the communication between dissection planes and the lumen. The pattern of blood speckle is dependent on the velocity of flow, showing increased intensity and a more coarse appearance when flow is reduced. In some cases, the coarse blood speckle can mimic the appearance of tissue, complicating image interpretation.

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Chapter 47: CORONARY INTRAVASCULAR ULTRASOUND IMAGING

CHARACTERIZATION OF ATHEROSCLEROSIS

Atheroma Composition

The subtle changes that occur early in the development of atherosclerosis, such as fatty streaks, are not visible using current ultrasound devices. Atherosclerotic arteries exhibit a variety of features that reflect the distribution, severity, and composition of the atheroma.[32-34] Sites with limited disease exhibit generalized or focal thickening of the intimal leading edge, while advanced lesions appear as large echogenic masses encroaching upon the lumen. A comparative study of ultrasound and histology in 1100 fresh necropsy sections demonstrated that lipid-laden lesions are usually hypoechoic.[32] Soft, low-intensity echoes most often represent fibromuscular lesions and very bright echoes are observed within dense fibrous or calcified tissues (Fig. 47-3). In highly echogenic plaques, foci of calcification are recognized by attenuation of ultrasound penetration, which obscures deeper layers, a phenomenon known as "acoustic shadowing." In lipid-laden or fibromuscular lesions, a prominent echogenic overlying fibrous "cap" may be observed.

The echogenicity of the plaque components is dependent not only on the acoustic properties of tissue but also on the acquisition settings (gain, compression, etc.). Accordingly, most classification schemes compare the echogenicity of the plaque to the surrounding adventitia to correct for differences in ultrasound technique. However, in plaques containing a zone of reduced echogenicity, it is not possible to determine whether these represent areas of lipid deposition, thrombus, or necrotic degeneration, all of which can appear as zones of low density. Plaque composition was accurately predicted by ultrasound imaging in 96 percent of 112 quadrants from 21 freshly explanted human coronary arteries.[29] Fibrous and calcified plaque quadrants were correctly identified in almost all incidences (100 of 103, or 97 percent), but only 7 of 9 quadrants (78 percent) with predominantly lipid deposits were correctly identified.

Accordingly, some caution is warranted in the intravascular ultrasound classification of atheroma composition. Although currently available devices produce detailed views of the vessel wall, interpretation employs visual inspection of acoustic reflections to determine morphology. Different histologic features may exhibit comparable acoustic properties, and methods do not yet exist for objective or automated classification of atheromatous lesions. Thus, intravascular ultrasound can delineate the thickness and echogenicity of vessel wall structures but does not provide actual histology. Despite these limitations, the classification of coronary plaques into the categories of soft, fibromuscular, and calcified has important clinical implications.

Detection of Calcification

Ultrasound imaging has shown superiority over fluoroscopy or angiography in the detection of coronary calcification. In a series of 110 patients undergoing intervention, target lesion calcification was detected by ultrasound and fluoroscopy in 84 and 50 patients, respectively (76 versus 14 percent, $p < 0.001$).[39] Another retrospective study analyzed calcification by angiography and ultrasound in 183 interventional patients.[40] Assessment by the two techniques was concordant in 92 and discordant in 91 cases. Calcification was detected in 138 patients by ultrasound and 63 by fluoroscopy, showing a sensitivity and specificity for angiography of 46 and 82 percent, respectively. When calcium was detected angiographically, calcification by ultrasound

often subtended >90 degrees and was superficial to the lumen in location. If no calcification could be visualized on the angiogram, the chance of detecting a large superficial arc of calcium by ultrasound was low (12 percent).

Ultrasound calcification is a major determinant of the arterial response to intervention, portending a greater risk of dissection following balloon angioplasty, less tissue retrieval with directional atherectomy, and greater benefit with the use of rotational atherectomy.[41,42] Because of the importance of calcium in the selection of interventional devices, most classification schemes quantify calcification, usually by measuring the circumferential angle subtended by calcified plaque.[39] Commonly, the axial length of the calcified portion of the lesion is also reported and the depth of calcification assessed, described as superficial when the calcium remains in contact with the luminal surface and deep if no portion of the calcium deposit is superficial.

Arterial Remodeling

This term refers to a change in arterial dimensions associated with the development of atherosclerosis. In a necropsy study of 136 human left main coronary arteries, Glagov et al. originally described focal arterial enlargement at atherosclerotic sites, reporting a positive correlation between external elastic membrane (EEM) area and the area occupied by atheroma ($r = 0.44$, $p < 0.001$).[22] At sites with area stenosis less than 40 percent, the increase in arterial size "overcompensated" for the plaque deposition, leading to an increase in absolute lumen area. With more advanced lesions (area stenosis >40 percent), the degree of arterial enlargement or remodeling was blunted, resulting in a smaller lumen area. The authors hypothesized that this phenomenon represented a compensatory mechanism to preserve lumen size.

The findings of Glagov et al. were later confirmed in vivo by intravascular ultrasound imaging[43,44] (Fig. 47-4). In 80 ultrasound cross sections obtained from 44 patients undergoing coronary interventions, EEM area correlated closely with plaque area ($r = 0.79$, $p = 0.0001$). In this study, lumen area increased with early atherosclerosis, confirming the phenomenon of overcompensation in early stages of the disease. With more advanced atherosclerosis, there was a correlation between increasing area stenosis and decreasing lumen area ($r = 0.58$, $p = 0.0001$).[43] Compensatory enlargement has also been demonstrated by ultrasound in superficial femoral arteries; however, there was no difference between lesions less than and greater than 40 percent stenosis.[45]

In recent years, ultrasound studies have demonstrated a new dimension to arterial remodeling: negative remodeling.[46,47] At diseased sites, the EEM area may actually be reduced in size, contributing to luminal narrowing rather than compensating for it. In 51 femoral arteries, EEM area was smaller at lesions than adjacent reference sites, with a negative correlation between stenosis severity and EEM area reduction ($r = 0.62$ by histology and 0.66 by ultrasound, $p < 0.001$ for both).[46] "Inadequate" remodeling, defined as an EEM area within the lesion less than 78 percent of a proximal reference site, has also been described in the coronaries of patients with stable angina.[47] Although 91 of 603 lesions (15 percent) fit this definition, there was a highly variable response among lesions within the same patient. However, when remodeling is defined in this fashion, there is an assumption that the reference EEM area represents the original vessel size, which may not be correct, since angiographic reference sites are invariably diseased according to ultrasound.

Although the exact mechanisms of compensatory or negative remodeling remain unclear, these phenomena have important clinical implications. Compensatory remodeling represents an important factor in the underestimation of the severity of atherosclerosis by angiography. Remodeling may influence the estimation of the vessel size during coronary interventions. Recently, negative remodeling has been implicated in restenosis following debulking and balloon

angioplasty.[48]

Unstable Plaque and Thrombi

An emerging application of intracoronary ultrasound is the characterization of the atheroma associated with acute coronary syndromes (Fig. 47-5). The typical angiographic appearance of a ruptured plaque is a stenosis with an eccentric or ulcerated lumen, often with overhanging edges (Ambrose type II lesion).[49-54] However, retrospective reviews of angiograms of patients performed before an episode of unstable angina usually reveal minimal disease within the culprit lesion segment.[51] These studies highlight the inability of angiography to identify "rupture-prone" lesions. Histologic examination of unstable plaques after rupture usually reveals a lipid-laden plaque with a thin fibrous cap.[49] Based on these observations, it has been postulated that the size of the lipid pool and the thickness of the fibrous cap are more important than severity of stenosis in predicting plaque rupture.[52]

Some intravascular ultrasound studies have confirmed the presence of an echolucent atheroma within culprit lesions in patients with acute coronary syndromes. In a small study of 22 stable and 43 unstable angina patients, type II eccentric lesions were detected on the angiograms in 18 percent of stable and 40 percent of unstable angina patients. Echolucent plaques were more frequently observed in patients with unstable than in those with stable angina syndromes (74 versus 41 percent, $p < 0.01$).[11] Recent and intriguing intravascular ultrasound studies have examined the relationship between remodeling and the type of clinical presentation. The culprit lesions in 76 patients with acute coronary syndromes were compared with lesions in 40 patients with stable angina. In the unstable patients, both EEM and plaque areas were significantly larger than the corresponding measurements in the stable patients ($p = 0.02$ for both). Positive remodeling was more prevalent in the unstable group (51 versus 18 percent, $p = 0.002$) and negative remodeling more prevalent in the stable group (58 versus 33 percent, $p = 0.002$).[55]

The formation of intraluminal thrombi at a ruptured or fissured plaque is considered to be the hallmark of acute coronary syndromes.[56] Angiographic criteria for diagnosis of a coronary thrombus, the presence of haziness, an intraluminal filling defect, and/or irregular lumen contour are not sensitive.[54] Small observational studies have attempted to differentiate the ultrasound appearance of thrombus, defined as hypoechoic material projecting into the lumen with a slight synchronous pulsation and a distinct acoustic interface, from more echogenic plaque[57,58] (Fig. 47-6). However, in vitro studies have revealed limitations in the reliability of intravascular ultrasound diagnosis of thrombi (sensitivity of 57 percent and specificity of 91 percent), considerably inferior to angioscopy (sensitivity and specificity of 100 percent).[56] Radiofrequency analysis of ultrasound signals has shown some promise in differentiating between thrombus and plaque, although the clinical application is not yet feasible.[59,60]

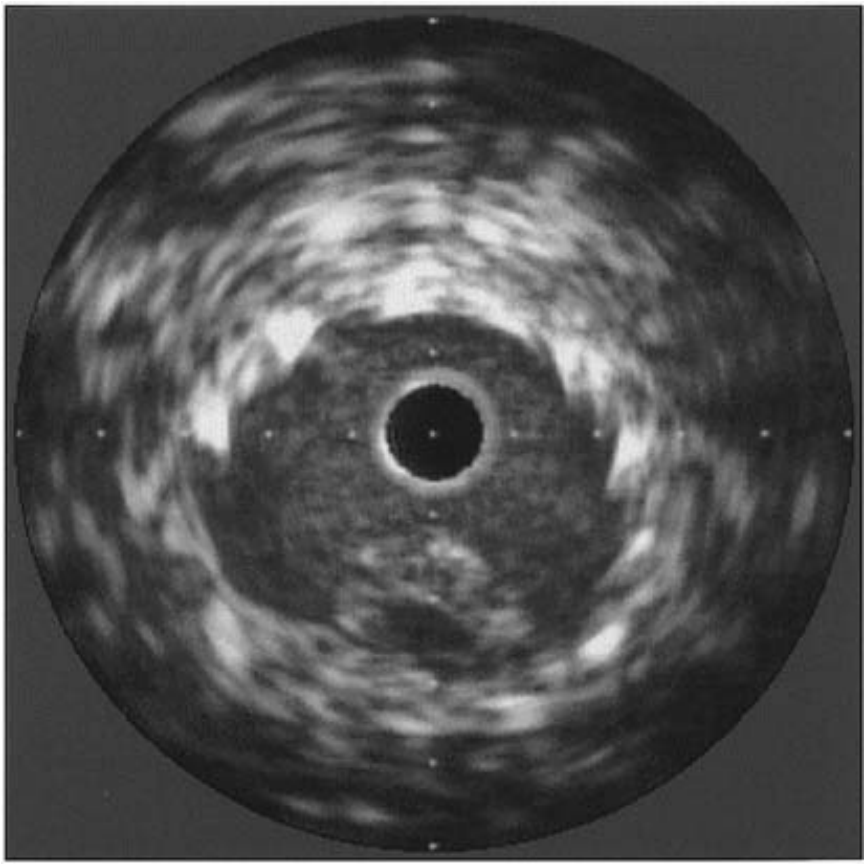

Figure 47-6: Thrombus within a coronary stent. In this intravascular ultrasound image, a stent is well visualized. There is a globular mass projecting into the lumen at 6 o'clock; it probably represents a large thrombus.

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Chapter 47: CORONARY INTRAVASCULAR ULTRASOUND IMAGING

DIAGNOSTIC CLINICAL APPLICATIONS

Quantitative Luminal Measurements

A broad spectrum of therapeutic decisions hinge upon assessment of coronary luminal dimensions. Accordingly, in diagnostic and interventional practice, quantitation of vascular dimensions represents an important clinical application of intravascular ultrasound. Several studies have compared luminal measurements by intravascular ultrasound and quantitative angiography.[6,7] For vessels without atherosclerosis, most studies document a close correlation between angiographic and ultrasonic coronary dimensions, although a few studies suggest slightly larger measurements by ultrasound.[7] However, in patients with atherosclerotic arteries, most investigators report only a moderate correlation between ultrasonic and angiographic dimensions, with the greatest disparities in vessel segments with a noncircular lumen shape.[5,7,10] This reduced correlation is probably explained by the irregular, noncircular cross-sectional profile of diseased vessels, which cannot be adequately measured using angiography.[10]

Quantitation of Atherosclerosis

Analysis of intravascular ultrasound images permits quantitative measurements of the extent and severity of coronary atherosclerosis[26] (Fig. 47-7). However, the inherent properties of ultrasound require utilization of different anatomic landmarks than those serving classic histology. In all ultrasound imaging, reflections at the leading edge of any interface are located precisely at the boundary where acoustic impedance abruptly changes. However, the position of the trailing edge of any anatomic structure is determined by multiple nonanatomic factors, including ultrasound beam properties, particularly the wavelength (frequency). Thus, leading-edge measurements accurately describe the location of a boundary, whereas trailing-edge measurements are unreliable. As previously noted, strong reflections are generally produced at two locations, the leading edge of the intima and the border between the media and the external elastic membrane. The position of the trailing edge of the intima is not accurately localized in intravascular ultrasound images. Accordingly, quantitative measurements must calculate the atheroma's cross-sectional area by subtracting the area bounded by the intimal leading edge from the area enclosed by the external elastic membrane. This approach results in a slight overestimation of atheroma volume (in comparison to histology) by including the area of the media within the calculation.

NORMAL INTIMAL THICKNESS

The threshold for abnormal intimal thickness by intravascular ultrasound is controversial, particularly since the categorical classification of a continuous variable, intimal thickness, as normal and abnormal is inherently arbitrary. In various histologic and ultrasound studies, normal intimal thickness ranges between 0.10 and 0.35 mm and the normal medial thickness ranges from 0.15 to 0.25 mm. In a necropsy study, normal intimal thickness not including media was age-dependent, averaging 0.21 mm in 21- to 25-year-olds, 0.22 mm in 26- to 30-year-olds, and 0.25 mm in 36- to 40-year-olds.[37] In a comparative study, intravascular ultrasound measurements of the intima plus media averaged 20 percent greater than histological measurements.[61,62] Considering the histologic and ultrasound data, most clinical studies have defined the ultrasound measurement threshold for coronary disease as an intimal thickness ≥0.5 mm.[63-67] Currently, there

is no well-defined threshold for normal values for other measures, like intimal cross-sectional area.

The tomographic orientation of intravascular ultrasound represents an additional problem in quantifying atherosclerosis. Since each image contains information from only a thin "slice" of the vessel, global measures of atheroma burden require the integration of multiple cross sections. One successful approach to this conundrum employs a motorized device to steadily and progressively withdraw the ultrasound catheter through the interrogated vessel, typically at 0.5 to 1.0 mm/s. Since motor speed is kept constant, the operator can obtain a series of cross sections separated by a constant, recurring time interval; these are individually measured and then summated to approximate total atheroma burden using Simpson's rule. A second approach to atheroma quantitation employs three-dimensional (3D) reconstruction of the vessel from the two-dimensional ultrasound tomograms.[68] Unfortunately 3D methods are exceedingly complex, have many unresolved confounding variables, and remain largely unvalidated.

Atheroma Distribution

The circumferential distribution of the atheroma varies from nearly symmetrical plaques to very eccentric lesions in which the entire atheroma is located on one side of the artery. Assessed by ultrasound, the majority of plaques are eccentric, with a maximum atheroma thickness more than twice the minimum plaque thickness.[69] Studies have demonstrated a poor correlation between the apparent circumferential pattern by angiography and the actual plaque distribution revealed by ultrasound examination.[69] Such studies demonstrate the inaccuracy inherent in determining plaque distribution from the projected two-dimensional silhouette of the lumen (angiography). This observation has important implications for guidance of coronary interventions, particularly techniques for selective plaque removal, such as directional atherectomy.

Angiographically Unrecognized Disease

In patients undergoing angiography for clinically suspected coronary artery disease, no angiographic evidence of narrowing is present in 10 to 15 percent of cases. In these patients, intravascular ultrasound commonly detects atherosclerosis at angiographically normal sites.[21,25,26,70,71] Using intravascular ultrasound, atherosclerotic abnormalities were documented in 21 of 44 patients (48 percent) with suspected coronary artery disease and normal coronary angiograms.[70] Combining ultrasound and functional assessment (coronary flow reserve and endothelium-mediated vasodilator response), only 36 percent of patients in this cohort were completely normal. Other studies demonstrate that, if any luminal irregularity is present by angiography, ultrasound will usually demonstrate atherosclerosis at nearly all other examined sites.[21] The prevalence of atherosclerosis at angiographically normal sites confirms the finding, previously reported from necropsy studies, that coronary involvement is frequently underestimated using angiographic evaluation methods[12,13] (Fig. 47-8).

There are several mechanisms by which angiography may underestimate the presence, extent, or severity of atherosclerosis.[21] First, to detect focal narrowing, angiography relies upon comparison of the interrogated site to an adjacent uninvolved segment. However, the involved vessel is often reduced in caliber along its entire length, containing no truly normal segment for comparison. The angiographer may erroneously conclude that the vessel is simply "small in caliber." Overlapping structures and mechanical limits in x-ray positioning may prevent the angiographer from obtaining optimal radiographic projections (orthogonal to the lesion). Accordingly, eccentric plaques that occupy only a portion of the vessel circumference represent an important source of false-negative angiography. At atherosclerotic sites, compensatory enlargement of the vessel wall overlying the plaque often preserves lumen diameter, resulting in false-negative angiography because the lumen size in the involved segment is identical to that of adjacent, uninvolved segments. Finally, radiographic foreshortening can conceal short "napkin-ring" lesions.

For each of these mechanisms of false-negative angiography, intravascular ultrasound has been employed to confirm the presence and estimate the extent of atherosclerosis.[21] However, the long-term clinical implications of angiographically unrecognized atherosclerosis remain uncertain since no outcomes-based research has demonstrated a worse prognosis for patients with atherosclerosis detected only by ultrasound. However, several investigators have demonstrated that plaques with minimal to moderate angiographic narrowing are the most likely lead to acute coronary syndromes. Accordingly, the presence of angiographically occult coronary disease may have prognostic significance. Studies are currently under way to determine the value of ultrasound in predicting the clinical outcome in patients with angiographically unrecognized coronary disease.

Lesions of Uncertain Severity

Angiographers commonly encounter lesions that elude accurate characterization despite thorough examination using multiple radiographic projections. Difficult-to-assess sites include ostial or bifurcation lesions and moderate stenoses (angiographic severity ranging from 40 to 75 percent) in patients whose symptomatic status is difficult to evaluate. For ambiguous lesions, ultrasound provides a tomographic perspective, independent of the radiographic projection, that may permit quantification of the lesion. In two prospective series, intracoronary ultrasound changed the management strategy in approximately 20 percent of the examinations performed immediately prior to coronary intervention.[72,73] In both studies, however, operator selection of patients for ultrasound examination may have resulted in an overestimation of the true impact of ultrasound imaging on clinical decision making.

Angiographic assessment of left main coronary artery (LMCA) obstruction represents a particularly vexing clinical problem.[14] Radiographic contrast in the aortic cusp can obscure the ostium, and "streaming" of contrast from the injection vortex can result in a false impression of luminal narrowing. The LMCA is often short in length, leaving no normal "reference" segment. The bifurcation or trifurcation of the LMCA into daughter branches may produce vessel overlap, thereby concealing a stenosis. Intravascular ultrasound is commonly used to quantify LMCA lesions when angiographic interpretation is uncertain.[74] The technique for examination consists of subselective placement of the ultrasound transducer in the circumflex or anterior descending, followed by slow pullback to the aorta with the guiding catheter disengaged. There is no consensus regarding the threshold for critical LMCA obstruction. However, an area stenosis >50 percent or an absolute area <9 mm^2 has been proposed as a threshold.[74]

Cardiac Allograft Disease

Transplant coronary artery disease is the leading cause of death beyond the first year after cardiac transplantation, with a reported incidence of 15 to 20 percent per year.[75] Although most transplant centers perform arteriograms annually for screening, these surveillance studies often fail to detect atherosclerosis prior to a clinical event.[76,77] Necropsy studies have demonstrated that angiography systematically underestimates coronary atherosclerosis in transplant recipients.[77] Patients may have diffuse vessel involvement that, for reasons already enumerated, conceals the atherosclerosis from the angiographer. Many active transplant centers now routinely perform intravascular ultrasound at the time of annual catheterization in all recipients. Investigations using ultrasound to detect transplant vasculopathy report a very high incidence of abnormal intimal thickening in 80 percent of patients at 1 year and in more than 92 percent studied 4 or more years after transplantation.[65-67,79-83]

Recent studies have revealed two pathways to transplant-associated atherosclerosis. Some patients receive atherosclerotic plaques transmitted via the donor heart, while others develop an immune-mediated vasculopathy.[67,81] Despite a young donor age, lesions of conventional atherosclerosis

are frequently present in donor hearts. At a mean donor age of only 32 years, atherosclerosis, defined as a maximal intimal thickness ≥0.5 mm, was evident in 56 percent of patients.[67] Multivariate analysis demonstrated donor age ($p = 0.0001$) and male donor gender ($p = 0.0006$) to be important predictors of atherosclerosis. Ultrasound imaging was a necessity for accurate detection of donor lesions, since the sensitivity of angiography was only 43 percent. The natural history of donor lesions after transplantation is largely unknown. Since angiography is relatively insensitive, ultrasound remains the most important method used to study the early atherosclerotic lesion. In the first year after transplantation, progression occurred in 42 percent of patients.[82]

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Chapter 47: CORONARY INTRAVASCULAR ULTRASOUND IMAGING

INTERVENTIONAL CLINICAL APPLICATIONS

Preinterventional Imaging

Several studies have demonstrated that ultrasound imaging of interventional target lesions may influence the approach to therapy. In one study (313 lesions), the intended revascularization strategy before ultrasound imaging was compared with the treatment actually performed.[42] In 40 percent of cases, the intended strategy was altered based on the ultrasound findings, most often ultrasound assessment of lesion composition or eccentricity (26 percent). Although there was a relatively close correlation between angiographic and ultrasonic lumen diameter ($r = 0.83$), a disagreement between the two methods was cited as the reason for altering the procedure in 13 percent of lesions. In another small, nonrandomized study ($n = 56$) of ultrasound guidance of balloon angioplasty or directional atherectomy, operators reclassified lesion characteristics after ultrasound in 68 percent of patients and the therapeutic approach was modified in 48 percent. Ultrasound measurements revealed a smaller lumen diameter than expected from angiography, leading to balloon upsizing in 34 percent of angioplasty cases.[84]

Several studies have purported to show benefits of ultrasound imaging prior to implantation of coronary stents.[85,86] The preliminary results of one prospective study identified vessel calcification as one of the predictors of "inadequate" stent expansion.[85] For ostial lesions, ultrasound imaging is sometimes used to determine whether the lesion involves the "true" ostium or spares the most proximal few millimeters, which may assist optimal stent positioning. When stents are used to treat dissections, ultrasound may reveal involvement of a longer segment than can be appreciated by angiography. This may be particularly relevant in "bailout" stenting for threatened abrupt closure, where it may be preferred to cover the full length of the dissection.[86] Despite promising data, reports on preinterventional imaging must be interpreted with caution. There are no prospective, controlled trials demonstrating a superior outcome using an ultrasound-guided approach. Study patients were not randomized, allowing for bias in selection of more complex cases for ultrasound guidance, which would likely emphasize the contributions of imaging. Furthermore, cases in which the operators were unable to advance the ultrasound catheter through the lesion were systematically excluded.

Imaging during Specific Interventions

BALLOON ANGIOPLASTY

Ultrasound guidance of balloon sizing has been proposed as a means to improve procedural result and late clinical outcome for percutaneous transluminal coronary angioplasty (PTCA).[87] In a study of 104 lesions, ultrasound was performed after obtaining a "satisfactory" angiographic result and revealed remodeling at the lesion or extensive plaque within the reference segment in 73 percent of the cases. In this subset, the balloon-to-artery ratio was increased from 1.12 ± 0.15 to 1.30 ± 0.17 ($p < 0.0001$) and the resulting angiographic minimal lumen diameter increased from 1.95 ± 0.5 to 2.21 ± 0.5 mm. Ultrasound lumen area improved from 3.16 ± 1.0 to 4.52 ± 1.1 mm^2 ($p > 0.0001$). Following ultrasound-guided balloon upsizing, the incidence of angiographic dissection was not increased (37 versus 40 percent, $p = 0.67$). However, the study was too small to demonstrate any effect upon intermediate or long-term clinical restenosis rates.

Intravascular ultrasound studies have evaluated the mechanisms of luminal enlargement following balloon angioplasty. Prior necropsy studies in patients who expired shortly after balloon angioplasty have described plaque fracture or disruption as the most common mechanism of dilatation.[20] Most ultrasound studies have confirmed that dissection is the most important mechanism of luminal enlargement, occurring in 40 to 80 percent of patients.[9,41,88-92] Identification of dissection or fracture is based on the visualization of blood flow in the newly created lumen, sometimes aided by injection of saline or iodinated contrast to opacify the lumen via microbubbles. Wall disruptions can be further defined by measuring the circumferential extent, length, and/or maximal depth of the dissection. One small study reported that calcified lesions had a higher incidence of dissection (67 versus 25 percent, $p = 0.03$) with a trend toward restenosis in lesions with no dissection.[41] Following iliac artery angioplasty, ultrasound evidence of dissection was noted in all 40 cases, accounting for 72 percent of the total lumen gain.[89]

Several alternative mechanisms for luminal enlargement not discernible by angiography have been identified using ultrasound, including arterial wall stretching and plaque compression, or "axial redistribution."[93-95] The contribution of vessel stretch to lumen gain following balloon angioplasty has been validated in experimental and clinical investigations. A peripheral angioplasty study reported that plaque area was reduced by 33 percent, accounting for only 20 percent of lumen gain.[89] However, studies using automatic pullback devices have shown that "compression" actually represents redistribution of plaque along the long axis of the vessel.[95] The prognostic significance of different mechanisms of luminal enlargement remains under investigation.

DIRECTIONAL ATHERECTOMY

Directional coronary atherectomy (DCA) is currently performed relatively uncommonly. DCA devices incorporate a rotating circular blade to remove atherosclerotic plaque from the luminal surface. This process requires the inflation of a balloon within the housing of the cutter, leading to invagination of the plaque into the open window on the cutting surface.[96] Because angiographic and/or ultrasound calcification is a well-documented predictor of failure of directional atherectomy, ultrasound imaging has been advocated for guidance of atherectomy, particularly for preintervention lesion selection.[97,98] Ultrasound imaging can differentiate between superficial calcium, which predicts poor tissue retrieval, and deep calcium, which does not appear detrimental to favorable results. In 70 atherectomy patients, lesion calcification was detected by ultrasound in 63 percent, compared with 22 percent by angiography. Ultrasound-detected calcification resulted in reduced lumen gain and a smaller final lumen area.[97]

The additional spatial perspective provided by ultrasound may assist in the orientation of atherectomy cuts. However, successful application is complex because precise orientation of the ultrasound image remains difficult, relying primarily upon anatomic features such as side branches to orient the image. Repeated ultrasound examinations are sometimes performed between passes of the DCA device to determine the extent of plaque removal and the need for additional cuts. Ultrasound studies before and after directional atherectomy confirm that plaque removal is the primary mechanism of luminal enlargement[91,97] (Fig. 47-9). In 25 treated lesions, plaque reduction accounted for 78 percent of total lumen gain. Plaque area was reduced from 14.3 ± 0.8 to 10.5 ± 0.7 mm^2, whereas EEM area increased only slightly, from 16.7 ± 0.8 to 17.5 ± 0.8 mm^2, $p < 0.02$. Ultrasound studies show that despite a successful angiographic result, 40 to 60 percent of the target site is still occupied by atheroma.

Some investigators have proposed that achieving a larger lumen after atherectomy using ultrasound guidance would result in a lower restenosis rate. This hypothesis was tested in a multicenter registry (the Optimal Atherectomy Restenosis Study [OARS]) in which residual stenosis was reduced from 64 to 7 percent with ultrasound guidance.[98] The angiographic

restenosis rate at 6 months was 28.9 percent and the 1-year target lesion revascularization rate was 17.8 percent. In the CAVEAT trial, DCA failed to reduce late events as compared with PTCA with or without ultrasound guidance.[99] Moreover, most atherectomy trials were performed without adjuvant therapy with GPIIb/IIIa inhibitors. It remains untested whether a larger postprocedure lumen and lower restenosis rate can be achieved using ultrasound guidance without a concomitant increase in complications.

ROTATIONAL ABLATION

Rotational ablation employs a high-speed (up to 200,000 rpm) diamond-coated burr to debulk atheroma. Theoretically, this device minimizes injury to the normal arterial wall by "differential cutting," in which normal elastic tissue is deflected away from the burr while relatively inelastic atheroma is not displaced and is therefore abraded by rotation of the burr. Clinical indications for rotational ablation include calcified segments or lesions that resist balloon dilatation. Rotational ablation is also sometimes used in long lesions, ostial lesions, and in-stent restenosis.[100-104] Demonstration of a heavily calcified vessel by angiography or ultrasound is often cited by operators as an indication for rotational ablation. However, there is a poor correlation between ultrasound and fluoroscopy in assessing the presence or extent of calcification. Accordingly, ultrasound is sometimes employed prior to rotational ablation to confirm or refute the presence of calcification. Vessels revascularized using rotational ablation are often diffusely diseased, and the "normal" dimension can be difficult to determine by angiography. Therefore, ultrasound is sometimes used to size the vessel and determine the largest burr that can be safely employed.

Intravascular ultrasound studies have confirmed the principle of selective plaque removal or differential cutting. In 48 lesions treated with rotational ablation, atheroma area decreased from 15.7 ± 4 to 13.0 ± 5 mm^2 and the arc of calcium decreased slightly from 227 ± 107 to 209 ± 107 degrees, $p < 0.05$.[104] Vessel expansion or dissection was noted in a minority of cases and did not contribute significantly to lumen gain. The residual narrowing of the cross-sectional area measured by ultrasound averaged 74 percent. Following rotational ablation, the residual lumen is usually round or ellipsoid and may have a 15 to 20 percent greater area than the largest burr used, presumably due to lateral movement of the burr during the procedure.

Luminal Measurements Postintervention

A poor correlation has been reported for comparisons of ultrasound and angiography in assessment of residual stenosis following balloon angioplasty, with measurements that are usually smaller by ultrasound than by angiography.[9,41,88-92] Two factors probably influence the overly optimistic tendency of angiographic imaging.[21] At the reference site, angiography tends to underestimate the diameter of the normal "reference" vessel because of the frequent presence of unrecognized atherosclerosis. At the target site, angiography tends to overestimate the actual gain in luminal diameter because contrast material penetrates into complex cracks and fissures produced by the intervention, giving the appearance of an enlarged lumen. To calculate a postprocedure percent diameter stenosis, the diameter at the target site (an overestimate) is divided by the reference diameter (an underestimate), resulting in a more favorable impression of the actual gain in luminal dimensions. Quantitative angiography showing a residual stenosis of 10 to 15 percent is commonly associated with a 60 to 80 percent atheroma burden.

Coronary Stent Deployment

INITIAL STUDIES OF ULTRASOUND GUIDANCE

The use of stents in percutaneous revascularization has increased exponentially over the last few years. Intravascular ultrasound imaging has played a pivotal role in understanding and optimizing the benefits of stent therapy.[105-107] In initial trials leading to FDA approval, articulated slotted-

tube stents were deployed using moderate balloon pressures (6 to 10 atm).[108,109] To reduce subacute thrombosis, patients received aggressive anticoagulation with both antiplatelet and antithrombotic agents, including warfarin, for 3 to 6 months. Initial studies demonstrated a reduction in the restenosis rate compared with balloon angioplasty but reported a high incidence of hemorrhagic complications and longer hospital stays. A pioneering report detailing the intravascular ultrasound experience of Colombo et al. in Milan, Italy, significantly altered the understanding of optimal stent deployment and prevention of subacute thrombosis.[107] Ultrasound examination revealed a mean residual stenosis of 51 percent following angiographically guided stent deployment, with frequent incomplete stent apposition (Fig. 47-10).

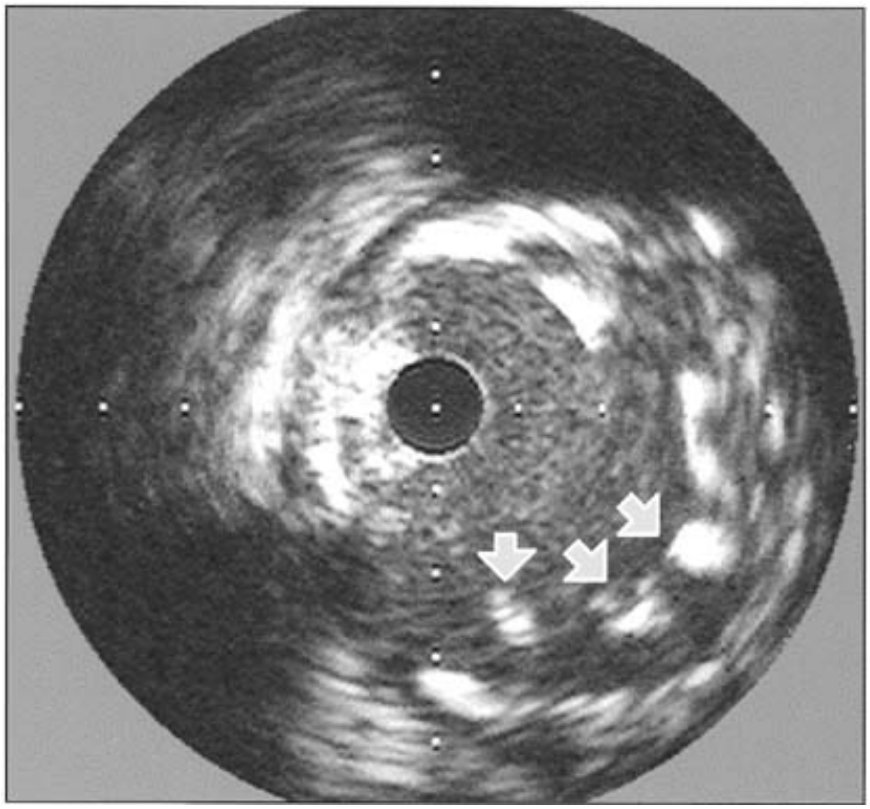

Figure 47-10: Underdeployed coronary stent. In this example, intravascular ultrasound images show several stent struts (*arrows*) that are not in full contact with the underlying vessel wall. This process is referred to as incomplete stent apposition.

Because stents are porous structures, angiographic contrast can flow outside of a partially deployed stent, resulting in the angiographic appearance of full deployment, despite the presence of incomplete apposition. In the Milan study, the operators performed additional balloon inflations at higher pressures (typically 18 to 20 atm) or used a larger balloon (or both), reducing final ultrasound residual stenosis to 34 percent and reporting a subacute thrombosis rate of only 0.3 percent with the use of no systemic antithrombotic agents (antiplatelet therapy only). It is now widely accepted that high-pressure deployment of the stents dramatically reduces the incidence of subacute thrombosis and obviates the need for acute and chronic administration of antithrombotic agents.[110,111] Subsequently, routine high-pressure deployment without ultrasound imaging became the standard of therapy.

ROUTINE VERSUS NONROUTINE ULTRASOUND

Following the widespread acceptance of high-pressure postdilatation with antiplatelet rather than

anticoagulation regimens, the further benefit of ultrasound imaging has been debated.[86,110-114] Some investigators have suggested that despite routine use of high-pressure postdilatation, ultrasound-guided therapy can improve procedural results.[86,114] In a retrospective analysis of 315 lesions treated by high-pressure stenting, ultrasound was defined as "beneficial" if imaging resulted in further interventions that increased stent area by >25 percent or identified other lesions that required treatment.[115] Prior to ultrasound, the mean inflation pressure was 14.7 ± 3.2 atm, but only 47 percent of stents were considered "optimally" deployed. Additional ultrasound-triggered inflations improved in-stent lumen area by more than 25 percent in 83 lesions (26 percent of patients), and additional procedures were performed in lesions identified by ultrasound in 51 (16 percent). Final in-stent area improved from 6.9 ± 2.2 to 8.0 ± 1.93 mm^2 ($p < 0.001$). Procedural results were "improved" in 39 percent of the cases following ultrasound imaging.[115] It is now generally accepted that after high-pressure coronary stenting, ultrasound imaging results in additional procedures in approximately 20 to 40 percent of cases.

Since in-stent restenosis is predominantly determined by the degree of intimal hyperplasia, a larger lumen can theoretically accommodate more tissue growth without flow-limiting obstruction.[116] However, it remains uncertain whether ultrasound-guided "optimal" expansion translates into better clinical outcome. A randomized trial in 164 patients of ultrasound-guided stenting demonstrated a 6.3 percent absolute reduction in restenosis rate, which was not statistically significant because the study was powered to detect a 50 percent reduction of the restenosis rate.[117] A nonrandomized substudy of 538 patients from the Stent Anticoagulation Regimen Study (STARS) compared the outcome of ultrasound and angiographically guided stenting. The ultrasound arm achieved a significantly larger lumen area and a 39 percent relative reduction in clinical restenosis.[118] However, the impact of the more aggressive dilatation on restenosis rates has not been adequately examined by prospective trials. It remains conceivable that increased vessel wall injury from a larger high-pressure balloon will yield less favorable long-term results.

ULTRASOUND IMAGING OF PERISTENT SEGMENTS

Ultrasound imaging of "reference" segments following stenting may be useful in identifying reference segment disease or dissections that require additional interventions. The presence of significant peristent flow-limiting lesions or dissections has been linked to higher likelihood of stent thrombosis.[119] These findings are often angiographically occult or appear as areas of indistinct vessel border "haziness." In 201 stent patients, 31 segments with peristent angiographic haziness were detected. Ultrasound imaging revealed an angiographically inapparent obstructive lesion in 15, a peristent wall injury in 14, and mild intimal thickening in the remaining 2 segments.[120] The extent of neointimal hyperplasia at the stent margins has been linked to preexisting reference-segment disease.[121] In stenting as a "bailout" for dissection, intravascular ultrasound is more sensitive in detecting the extent of dissection, often revealing a greater true length than is evident from angiography, which may be helpful in guiding vessel salvage.

OPTIMAL PROCEDURAL GOALS OF ULTRASOUND GUIDED STENTING

Although ultrasound guidance of stenting has been practiced for several years, there is no consensus regarding optimal procedural end points. Colombo initially recommended achieving ≥60 percent of the average proximal and distal reference areas but later altered the definition to ≥100 percent of the distal reference lumen area.[105-107] Other definitions of optimal expansion include ≥90 percent of the distal reference area, ≥80 percent or ≥90 percent of the average reference area, a "lumen symmetry index" >0.7, and/or full coverage of reference-segment disease or dissections.[122,123] In most clinical trials, procedural end points are not achieved in the majority of cases. In the Optimal Stent Implantation Trial, the target of >90 percent of the average reference or >100 percent of the smaller reference area were not achieved in half the patients at an inflation pressure of 15 atm and only 60 percent of patients at 18 atm.[122] In the Angiography

Versus Intravascular Ultrasound Directed Stent Placement (AVID) trial, the target end point of ≥90 percent of the distal reference area was not achieved in >70 percent of 225 patients.[124]

Recent reports have questioned the clinical relevance of using the stent-to-reference ratios as target for ultrasound-guided stenting. In 165 patients, target vessel revascularization was predicted by final in-stent lumen area (OR 1.4, 95 percent CI 1.1-1.9) and not the ratio of stent-to-reference area (OR 1.1, 95 percent CI 0.85-1.6).[112] Repeat revascularization was required in 30 percent of patients with a minimum in-stent lumen area <5 mm^2 but only 3 percent of cases with an area exceeding 9 mm^2. In another large cohort undergoing ultrasound-guided stenting, restenosis was inversely related to the minimum in-stent area.[125] An area of 9 mm^2 was achieved in 23 percent, but the incidence of restenosis in this subgroup was only 8 percent, compared with 29 percent in the remaining patients, $p < 0.0001$. Thus, commonly employed ultrasound end points based upon a predefined stent-to-reference ratio are both difficult to achieve and correlate weakly with clinical outcome.[125-127] Ultrasound studies have demonstrated that the degree of in-stent neointimal hyperplasia is independent of final lumen size, which may explain the higher restenosis rates in smaller vessels and poorly expanded stents.[116] If acute lumen gain is not adequate to accommodate subsequent tissue proliferation, there is significant late loss and restenosis.

Intravascular Ultrasound and Restenosis

A more complete understanding of restenosis has evolved from serial ultrasound measurements of plaque and lumen areas following balloon angioplasty and directional atherectomy.[128,129] In some studies, serial ultrasound examinations have shown that a late reduction in total vessel area (chronic negative remodeling) is an important mechanism of restenosis after interventional procedures.[129] These observations suggest that mechanical interventions to prevent chronic recoil (such as stenting) may be more important in preventing restenosis than interventions designed to prevent intimal hyperplasia. If further validated, this concept may explain the lower restenosis rate observed in randomized multicenter studies comparing balloon angioplasty and stent implantation.[108,109]

In 212 native coronary lesions in 209 patients following intervention, the ultrasound cross-sectional area with the smallest lumen area at late follow-up was compared with the matching site obtained immediately following the intervention.[129] At follow-up examination, there was a significant decrease in EEM area and an increase in plaque area ($p < 0.0001$ for both) that combined to reduce lumen area. More than 70 percent of lumen loss was attributable to the decrease in EEM area, whereas the neointimal area accounted for only 23 percent of the decrease in lumen area. The change in lumen area correlated more strongly with the change in EEM area ($r = 0.75$, $p < 0.0001$) than with the change in plaque area ($r = 0.28$, $p < 0.0001$). At lesions that demonstrated an increase in EEM area at follow-up (47 percent), there was no change or an actual gain in lumen area and a reduction in angiographic restenosis (26 versus 62 percent for lesions with a decrease in EEM area at follow-up, $p < 0.0001$).

Other investigators have suggested a bidirectional remodeling response following percutaneous coronary interventions: early adaptive enlargement and late shrinkage of the vessel. In a unique study, 61 lesions in 57 patients who underwent balloon angioplasty or atherectomy were examined by intravascular ultrasound in a serial manner-before and immediately after the intervention and after 24 h, 1 month, and 6 months.[48] The lumen area significantly improved during the first month following the intervention but significantly decreased at 6 months. Simultaneously, the EEM area increased in the first month but later decreased at 6 months. However, plaque area steadily increased from immediately postintervention to the 6-month follow-up. Thus the changes in lumen size closely tracked the changes in EEM area ($r = 0.72$, $p = 0.0001$). Although the increase in plaque area correlated with lumen loss, the correlation was not as strong ($r = 0.34$, $p = 0.0008$). The lumen gain observed during the first month was solely due to the compensatory vessel

enlargement, whereas the late lumen loss was mostly caused by vessel shrinkage but also by progressive neointimal hyperplasia.

Investigations employing quantitative angiography have demonstrated that late lumen loss is significantly greater with stents than with balloon angioplasty. This, however, is offset by the much larger acute lumen gain, such that the net gain at follow-up is significantly greater with stenting.[108,109] Intravascular ultrasound has been employed to examine the mechanism of stent restenosis. Unlike the restenotic response to other percutaneous devices, which is a mixture of arterial remodeling and neointimal growth, stent restenosis is almost exclusively due to the neointimal proliferation.[129] In a serial study using intravascular ultrasound of stented coronary segments, there was no significant change in the area bound by stent struts, indicating that stents can withstand and resist the arterial remodeling process.[130] In some cases, restenosis develops at the margins of the stent. Predictors of stent restenosis have been identified by multivariate analysis, including the smaller reference vessel and lumen size, the larger plaque burden at the reference segments, and the smaller achieved in-stent lumen area at the stent margins.[121]

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Chapter 47: CORONARY INTRAVASCULAR ULTRASOUND IMAGING

FUTURE DIRECTIONS

The technology and clinical role for intravascular ultrasound examination of the coronaries continues to evolve. Technological advances in intravascular imaging are anticipated, including further reductions in the size of imaging catheters and higher-frequency ultrasound catheters, yielding significantly better spatial resolution.[131,132] Although high-frequency probes enable better axial and lateral resolution, there are significant trade-offs in moving beyond the current 30-MHz frequency. For example, penetration is likely to be impaired in comparison with more conventional devices, and greater backscatter from blood cells at high frequencies may interfere with discrimination of the interface between lumen and vessel wall. However, if catheter miniaturization continues, a shorter wavelength will be important in preserving near-field image quality. It remains apparent that the physical limits of intravascular imaging technology have not been reached. Accordingly, further improvements in the performance of these devices are anticipated.

Analysis of backscattered ultrasound signals has been used by several investigators to perform "tissue characterization" of coronary plaques. Intrinsic characteristics of the backscattered ultrasound signals-including the amplitude distribution, frequency response, and power spectrum of the signal-convey specific information about tissue types.[133] Soft plaque consists of an amorphous collection of lipid substances, fibrosis, cholesterol clefts, and a variable amount of collagen and elastin. Thrombus, on the other hand, consists of a fairly organized layering of fibrous strands packed with a dense collection of red blood cells. The ability of computer-based analysis of the unprocessed radiofrequency backscatter to differentiate the histologic layers of the normal vessel wall remains investigational.

Three-dimensional reconstruction of intravascular ultrasound has been proposed as a means to facilitate understanding of the spatial relationship between the structures within different tomographic cross sections.[134] Despite the promise of these methods, many unresolved problems remain. The algorithms applied for 3D reconstruction do not consider the presence of curvatures of the vessel and assume that the catheter passes in a straight line through the center of consecutive cross sections. The systolic expansion of the coronary vessel and the movements of the catheter within the vessel during the cardiac cycle also generate artifacts. Accordingly, the reconstructed images should not be considered faithful representations of the vessel and should not be used for volumetric plaque determination. Simultaneous digitization of biplane fluoroscopic tracking of the radiopaque transducer and catheter tip has the potential to overcome some of these limitations, but is practical only for small-scale research purposes.[135]

Chapter 47: CORONARY INTRAVASCULAR ULTRASOUND IMAGING

SUMMARY

The equipment, technique, and applications for intravascular ultrasound imaging continue to evolve, finding increasingly common usage in clinical practice and research. The insights provided by the unique ability of intravascular ultrasound to directly image coronary plaques have contributed greatly to our understanding of the nature of atherosclerosis and the effects of interventional devices.

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Part 6: CORONARY HEART DISEASE
Chapter 48:

CORONARY BYPASS SURGERY

Author: Bruce W. Lytle

Coronary bypass surgery as a planned consistent approach for the treatment of patients with angiographically documented coronary atherosclerosis was begun by Sones, Favaloro, and colleagues in 1967. Many previous schemes for surgical myocardial revascularization, direct and indirect, had been attempted, including pericardial pouderage, mammary artery implantation (Vineberg operation), coronary endarterectomy, and "blind" bypass grafting without the angiographic definition of coronary lesions.[1,2] The concept behind the concerted effort undertaken by cardiologists and cardiac surgeons at The Cleveland Clinic Foundation in 1967 was that the symptoms and clinical events associated with coronary artery disease (CAD) were related to stenotic coronary artery lesions that could be specifically identified by coronary angiography, and if those lesions could be treated with bypass grafting, unfavorable symptoms and events would be less common. Experience has shown that concept to be correct but also has shown that atherosclerosis is a progressive disease.

In the early years of coronary bypass grafting, the vast majority of grafts were reversed segments of saphenous vein anastomosed to the aorta and to the coronary arteries distal to coronary stenoses (Fig. 48-1*A*). It was rapidly obvious that effective bypass surgery relieved symptoms of angina, and during the decade 1970-1980, the practice of coronary artery surgery exploded. Improvements in instrumentation, technology, and surgical training were rapid, and by 1980, bypass surgery had evolved into a microsurgical procedure usually performed with optical assistance at many hundreds of medical centers around the world.

EARLY RANDOMIZED TRIALS OF BYPASS SURGERY VERSUS MEDICAL TREATMENT

During the 1970s, multiple investigations were initiated to examine the long-term outcomes of patients receiving initial bypass grafting compared with those treated initially with medical management. The most influential were multicenter, randomized trials of patients with chronic stable angina: the Veteran's Administration study of patients with chronic stable angina (VA study),[3] the European Coronary Surgery Study (ECSS),[4] and the Coronary Artery Surgery Study (CASS).[5,6] These trials randomized patients with angiographically documented coronary stenoses to either initial medical management or initial treatment with bypass surgery, and their primary emphasis was survival. In the two largest trials (ECSS and CASS), severely symptomatic patients were excluded from randomization, and in all these trials, patients who experienced the onset or persistence of severe symptoms were allowed to change from medical to surgical treatment, a phenomenon called *crossover*. Analyses of outcomes were performed on an "intention to treat" basis. That is, patients who were randomized to the medical treatment group but who later decided to have surgery were still considered part of the medically treated group, and patients randomized to surgery who did not actually receive surgery were still considered part of the surgically treated group.

All these trials showed there were some patient subsets that experienced a higher survival rate if they received initial surgical management rather than initial medical treatment, although those subsets varied among the trials. Not surprisingly, the patients who benefited the most from surgery

in terms of survival were patients at the highest risk of death without operation. Individual trials noted improved survival rates for patients with significant left main stenosis, three-vessel disease with abnormal left ventricular (LV) function, and two- or three-vessel disease with a more than 75 percent stenosis in the proximal left anterior descending (LAD) coronary artery. The clinical descriptors of an abnormal baseline electrocardiogram (ECG) or a strongly positive exercise test helped to define patient subsets with improved survival rates with surgery. Recently, a metaanalysis that included the three major trials and some smaller ones confirmed the observations of the individual trials but also seemed to show a significant survival benefit for patients with triple-, double-, or even single-vessel disease that included a proximal LAD stenosis regardless of whether they had normal or abnormal LV function. For patients without a proximal LAD stenosis, surgery improved the survival rate for only patients with left main stenosis or triple-vessel disease. In addition, the surgically treated patients had fewer symptoms at 5 postoperative years and took fewer antianginal medications.

The degree of benefit achieved with initial bypass surgery diminished with time both in terms of survival and with regard to symptom status.[8] There were multiple reasons for this. First, the status of the surgically treated patients deteriorated based on late graft failure and the progression of native vessel atherosclerosis. Very few patients in these early trials received internal thoracic artery (ITA) grafts or were treated with platelet inhibitors or lipid-lowering agents, strategies we now know significantly improved long-term outcomes after surgery. Second, the status of the "medically treated" patients actually improved slightly because a large proportion of those patients "crossed over" and underwent bypass surgery, although they were still analyzed as part of the medically treated group. In the three major studies, 40 to 44 percent of the total medically treated patient population had undergone bypass surgery by 10 postoperative years, including 65 percent of patients with left main disease and 48 percent of patients with three-vessel disease.[7] Finally, when all-cause mortality is the end point, any two survival curves eventually will meet at zero.

Randomized clinical trials as described earlier have the advantage that they lessen the influence of bias in the selection of treatment once patients are entered into the study, but they have the disadvantage that bias may be exerted at the point of inclusion into the trial. In all these trials, a minority of patients presenting for evaluation met the criteria for entry into the trial, and of those who met the criteria for entry, a minority actually were randomized. In the case of CASS, however, patients who were not randomized were followed prospectively in a registry, and that registry has produced observational studies that continue to provide useful information.

Among the important conclusions from the CASS Registry are that asymptomatic patients with 50 percent or more of left main stenosis and patients with left main equivalent (70 percent or more stenosis of the proximal LAD and circumflex vessels) have improved survival with surgery.[9,10] For severely symptomatic patients, bypass surgery improved the survival rates of those with three-vessel disease regardless of whether they had normal or abnormal LV function, even if those patients did not have severe proximal coronary artery stenoses.[11] Also, surgically treated patients who were completely revascularized fared better than incompletely revascularized patients, particularly if they had abnormal LV function.[12]

Outcomes for patients with unstable angina based on either progressive symptoms or rest angina with electrocardiographic changes were tested in the Veterans Administration Cooperative Study. Patients with rest angina and abnormal LV function had greatly improved survival with initial surgery. Patients with progressive angina did not appear to have a worse survival rate if they were treated initially with medical therapy, but 19 percent of this group crossed over to surgery within 30 days of randomization, and by 96 months, 45 percent had crossed over to surgery.[13]

Although these trials were undertaken relatively early in the history of coronary bypass surgery and today we can expect lower operative mortality rates and improved long-term outcomes after

operation based on the use of arterial grafts, platelet inhibitors, and lipid-lowering agents, the observations from these studies provide the fundamental basis for the development of indications for bypass surgery even today.[2,14]

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Chapter 48: CORONARY BYPASS SURGERY

EVOLUTION OF THE OPERATION AND PATIENT POPULATION

In the early years of bypass surgery, surgical candidates usually were relatively young, had limited coronary artery disease, good LV function, and few comorbid conditions. The operation was almost always performed through a median sternotomy with the use of cardiopulmonary bypass. To achieve a surgical field and allow operations to be done on a still heart, either cold fibrillation or intermittent ischemic arrest was a common strategy. The operation involved bypass grafts of reversed segments of greater saphenous vein from the aorta to the distal coronary arteries (see Fig. 48-1*A*). In a small number of centers, the left ITA was used as a bypass graft, usually as a graft to the LAD artery (see Fig. 48-1*B*), but this strategy was not common.

Throughout the 1970s and 1980s, operations for bypass surgery became progressively safer for multiple reasons. Surgeons became better trained, and surgical experience increased. Optical assistance became routine, and microsurgical instrumentation improved. Cardiac anesthesia developed as a subspecialty, and postoperative care protocols became more routinized. Intraoperative myocardial protection improved with the use of cardioplegia, a strategy whereby a combination of cardiac standstill and effective myocardial protection was achieved by injecting cardioplegic solution (usually containing high potassium concentrations) into the coronary circulation. The use of this strategy allowed extensive coronary reconstructions to be achieved consistent with effective myocardial protection and made surgical treatment of extensive and severe coronary atherosclerosis possible with safety.

In addition, the population of patients undergoing bypass surgery changed to an older population with more extensive coronary stenoses, a higher incidence of left main stenoses, abnormal LV function, and more frequent comorbid conditions. Table 48-1 shows the changes in preoperative descriptors for patients undergoing primary coronary surgery at The Cleveland Clinic Foundation for selected years from 1967 to 1996, and Table 48-2 shows similar changes between 1980 and 1990 in a countrywide population as recorded by the Society of Thoracic Surgeons National Database.[15] The bypass surgery population changed for multiple reasons. Improved technology and experience made it possible to operate on more complex and sicker patients with reasonable risk. Also, the randomized trials demonstrated that the patients who have the most to gain from surgery were patients with left main or multivessel disease and abnormal LV function. Furthermore, the U.S. population has been aging, and older patients have high expectations for their activity level. Finally, in the early 1980s, the advent of percutaneous anatomic treatments for coronary stenoses (i.e., PCTA) provided an alternative treatment for patients with limited coronary lesions, removing many of those patients from the surgical population.

Table 48-1: Preoperative Clinical Characteristics for the First 1000 Patients per Year Undergoing Elective Primary Isolated Coronary Bypass Grafting (The Cleveland Clinic Foundation)

Clinical Variable	1967-1970	1973	1976	1979	1982	1985	1988	1990	1994	1996
Age (yr, median)	50	53	55	56	59	62	64	65	64	65
Men (%)	85	89	89	88	84	80	78	76	75	71
Severe angina (T)	19	21	24	20	17	23	26	34	30	34
Diabetes (%)	7	7	6	7	9	13	19	24	24	27
Age ≥70 yr (%)	0.2	0.5	3	4	10	17	26	32	28	34
Single-vessel disease* (%)	56	17	15	10	8	5	3	5	9	9

Double-vessel disease* (%)	31	33	28	28	25	25	19	25	29	26
Triple-vessel disease* (%)	13	50	57	62	67	71	78	70	60	63
Left main coronary stenosis (≥50%) (%)	9	8	12	12	13	13	16	17	19	19
Left ventricular asynergy (%)	41	41	45	54	55	56	57	51	48	39

The terms *single, double-,* and *triple-vessel disease* refer to the number of the three main coronary vessels (left anterior descending, circumflex, and right coronary arteries) that have stenoses ≥50%.

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Chapter 48: CORONARY BYPASS SURGERY

TYPES OF BYPASS GRAFTS AND THEIR OUTCOMES

Saphenous Vein Grafts

The most important technical change in coronary surgery has been in the types of grafts that are used. By 1980, angiographic studies at multiple centers had shown that early vein graft patency rates were favorable (80-90 percent within the first postoperative year). Early patency rates were influenced by surgical technique, gender (men experienced better patency rates), the coronary artery grafted (LAD artery patency rates were better than circumflex and right coronary artery rates), the size of the vessel grafted, and the indications for repeat study (routine studies demonstrating better patency rates than studies performed because of symptoms). Coronary risk factors did not appear to influence early patency rates.[1,16-20] However, sequential studies of patent vein grafts demonstrated substantial late attrition. Fitzgibbon et al.[17] studied 590 vein grafts that were patent at 1 postoperative year and found that when studied late (>5 years after operation) 30 percent of patent grafts had become occluded, and 76 percent had angiographic evidence of pathologic changes. Fitzgibbon et al.[17] and Bourassa et al.[16] found a 2.1 percent yearly rate of occlusion of vein grafts up to 5 years after operation, but Bourassa et al.[20] noted a 5.3 percent yearly occlusion rate between 6 and 11 years after operation. Data from sequential The Cleveland Clinic Foundation studies (Fig. 48-2) showed that of vein grafts patent without stenosis 1 to 5 years after operation, only 55 percent remained angiographically perfect 6 to 12 years after surgery.[19] In addition, the attrition rate of patent grafts was not related to the coronary vessel grafted but was related to coronary risk factors such as diabetes and hyperlipidemia.[18,19]

The pathologic changes found in stenotic or occluded vein grafts are different at different postoperative intervals.[21-25] Grafts occluded within 1 or 2 months of surgery exhibit thrombosis, often associated with endothelial disruption. Grafts examined more than a few months after surgery consistently exhibit a hypercellular, proliferative hyperplasia involving the intima-intimal fibroplasia. Intimal fibroplasia is a concentric lesion that evolves into a more fibrotic lesion. It may cause fixed stenoses and may be associated with occlusion but usually is not. However, it appears to be the substrate for the development of vein graft atherosclerosis (VGA), the process that leads to many late graft stenoses or occlusions.

VGA is different from native coronary atherosclerosis. Native coronary artery atherosclerosis is a proximal, eccentric, and intermittent lesion that usually is covered by a fibrous cap. VGA is distributed throughout the length of vein grafts, it is circumferential, it is not encapsulated, and it is extremely friable. With time, the early circumferential lesion often progresses to eccentric lesions causing severe stenoses (Fig. 48-3). Because of its friability and nonencapsulated nature, VGA is a dangerous lesion. Embolization of atherosclerotic debris is a major risk during percutaneous interventions on vein grafts and during reoperations, and it is probable that spontaneous embolization may occur.[20,26] VGA usually is not recognized before 2 to 3 years after operation and does not appear to cause much graft attrition before 5 postoperative years. However, grafts that become occluded more than 5 years after operation usually exhibit thrombosis superimposed on VGA, and the increased rate of graft attrition seen more than 5 years after operation appears to be due in large part to VGA.

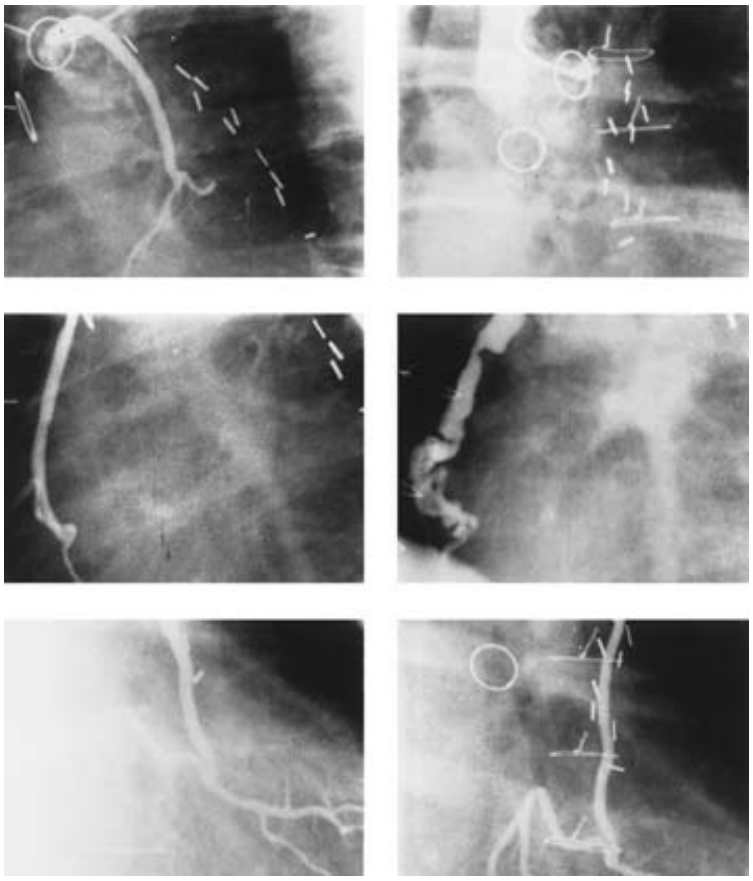

Figure 48-3: Angiographic anatomy 1 year after operation (*left*) showing patent vein grafts to the LAD artery and RCA and an ITA graft to the circumflex artery. Seven years later, the LAD artery vein graft is occluded, the RCA graft exhibits diffuse irregular stenoses characteristic of VGA, and the ITA graft is unchanged. (Used with permission from Lytle BW, Loop FD, Cosgrove DM, et al. Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. *Thoracic Cardiovasc Surg* 1985; 89:250.)

Since the early studies of vein grafts cited earlier, substantial progress has been made in the prevention of vein graft attrition. First, multiple randomized, prospective trials have shown that the perioperative and long-term treatment of patients who received vein grafts with platelet inhibitors have significantly decreased the occlusion rate of saphenous vein grafts at 1 year after operation to 6 to 11 percent.[27,28] Second, lipid-lowering trials using a cholesterol-niacin combination or using an aggressive regimen of Pravastatin to lower low-density lipoprotein cholesterol levels have been shown to decrease the progression of angiographic lesions in vein grafts, including a decrease in the rate of occlusion 5 to 15 years after operation.[29,30] Importantly, a clinical trial (CARE trial) of 1091 patients who survived a myocardial infarction (MI), had average cholesterol levels, and underwent bypass surgery showed that treatment with Pravastatin decreased the risk of death and nonfatal MI over a 5-year follow-up.[31] Thus multiple studies appear to show that outcomes for patients receiving vein grafts today can be expected to be better than those noted in studies from the 1970s. Furthermore, some vein grafts provide very long-term benefit. For patients studied 16 to 20 years after operation Lawrie et al.[32] noted 46 percent vein graft patency and Fitzgibbon et al.[20] noted a 50 percent patency rate 15 years or more after operation. However, although progress has been made in decreasing the *rate* of VGA, these strategies do not eliminate VGA, and vein graft attrition remains the biggest problem associated with bypass surgery. Fortunately, other grafts are available-arterial bypass grafts.

ITA Grafts

Early in the bypass surgery era, ITA (internal mammary artery) grafts were used in a few centers, usually as a graft to the LAD artery. As the late attrition rate of vein grafts began to surface, it also became apparent that the early patency rates of ITA grafts were slightly better than the early patency rates of vein grafts, but more important, the late attrition rate of patent ITA grafts was extremely low[1,19] (Fig. 48-4). Early occlusion of ITA grafts is usually technically related, since these grafts can remain functioning even when used to graft very small coronary arteries. ITA graft stenosis or occlusion beyond 6 months after operation is usually related to competition in blood flow through a native coronary artery that is not severely stenotic and becomes manifest as a "string sign" or diffuse spasm. Atherosclerosis may involve the ITA, but it is rare, and the late development of atherosclerotic lesions in an ITA graft known to be patent is extremely rare. Patency rates of left ITA to LAD artery grafts are greater than 90 percent even 10 to 20 years after operation.[1,19] The most contemporary prospective graft patency data come from the Bypass Surgery Angioplasty Revascularization Investigation (BARI) trial angiographic studies (135 patients) that documented 1-year patency (<50 percent stenosis) of 98 percent for ITA grafts and 87 percent for vein grafts.[33]

The success of the left ITA to LAD artery graft has led to the use of the right ITA as a bypass graft, usually simultaneously with the left ITA (bilateral ITA grafting). The right ITA has been used as an in situ graft and as a "free" graft with the proximal anastomosis constructed either to the left ITA (Fig. 48-5*A*) or to the aorta (see Fig. 48-5*B*). Although patency rates of ITA grafts have been highest when used to graft the LAD artery-diagonal system, Dion et al.[34] restudied 135 pedicled ITA to circumflex artery grafts 13 months after operation and noted a 95 percent patency rate. Longer-term studies of ITA to circumflex artery grafts also have showed favorable outcomes.[1] ITA grafts to the right coronary artery (RCA) have been less frequent and prospective postoperative studies are rare, but long-term patency of ITA grafts to the RCA is possible.

Studies of aorta to coronary ITA grafts have tended to show patency rates not quite as good as those of pedicled grafts. However, these types of grafts can exhibit 20-year patency, and once they are patent, they appear to remain free from graft atherosclerosis.[1,34]

A relatively new strategy is composite arterial grafting with the right ITA used as a free graft anastomosed to the left ITA[35,36] (see Fig. 48-4*B*). This strategy allows more flexibility in the use of the right ITA, and early data show patency rates of 91 to 95 percent within a year of operation for this type of free ITA graft. Long-term data are not available, but this strategy may make the use of free ITA grafts more effective. Once experience with composite grafting is gained, the right ITA may be used to graft the circumflex and right coronary systems in selected patients, achieving total arterial revascularization with the two ITAs.

Clinical Impact of ITA Grafts

The high and stable patency rate of the left ITA to LAD artery graft also produces improved clinical outcomes. No large randomized studies have compared ITA and vein grafts, but in a large observational study published in 1986, Loop et al.[37] showed that patients who received a left ITA to LAD artery graft (with or without vein grafts to the circumflex and RCA branches) had better 10-year survival rates when compared with patients who received only vein grafts (Fig. 48-6). This observation was true for patients with single-, double-, or triple-vessel disease. In addition, the ITA graft patients underwent fewer reoperations (4 versus 8 percent) and had fewer cardiac-related hospitalizations. Data from CASS have extended the observed benefits of ITA grafting to 15 to 18 years after operation.[38]

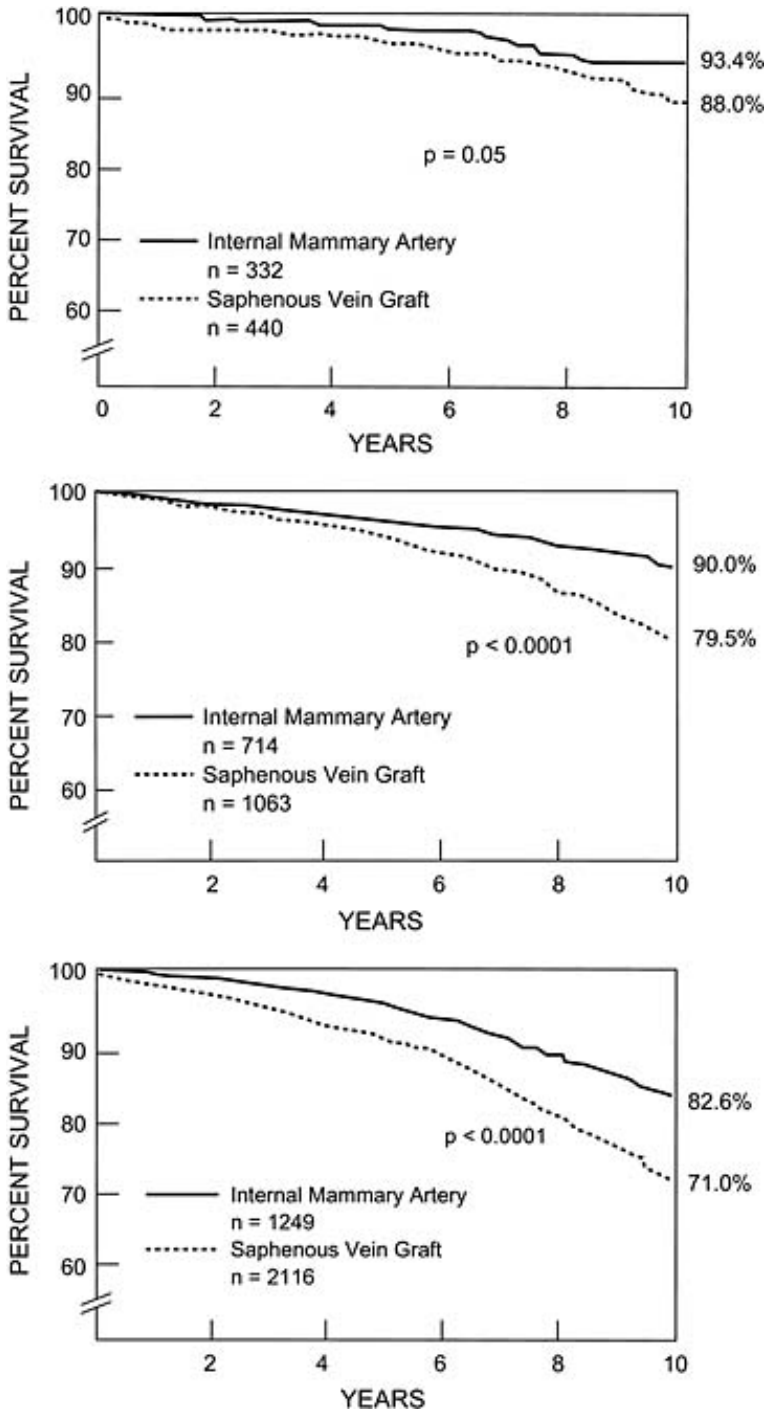

Figure 48-6: Survival for patients with an ITA to LAD artery graft with and without vein grafts to other coronary vessels compared with survival for patients with only vein grafts. An ITA to LAD artery graft was associated with significantly better survival for patients with single- (*top*), double- (*middle*), or triple-vessel (*bottom*) disease. (Used with permission from Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med* 1986; 314:106.)

Logic seems to dictate that if one ITA graft is good, two ITA grafts may improve outcomes further. However, the strategy of bilateral ITA grafting has not become widespread. Bilateral ITA grafting makes the bypass operation more difficult, some studies have shown an increase in the risk of wound complications, and the outcomes for patients receiving a single ITA to LAD artery

graft are very good, particularly over the first postoperative decade. Furthermore, because of the importance of the LAD coronary artery in many patients, improved results may be difficult to show if LAD artery revascularization is secure. And indeed, a number of retrospective studies have shown either no benefit or relatively little incremental benefit of bilateral ITA grafting over single ITA grafting. These studies involved either small patient numbers or relatively short follow-up intervals. Recently, we retrospectively reviewed a large series of patients receiving single or bilateral ITA grafts and found an improved 12-year survival rate for the patients receiving bilateral ITA grafts, as well as a decreased risk of reoperation or percutaneous intervention over that same time frame[39] (Fig. 48-7). Another recent study that confirmed these observations also involves relatively large patient numbers.[40] It is probable that the incremental benefit of bilateral ITA grafting over single ITA grafting may be less than the benefit of a left ITA to LAD artery graft over only vein grafts. Nonetheless, it does appear that bilateral ITA grafting does offer incremental benefit.

Other Arterial Bypass Grafts

The gastroepiploic artery (GEA) was used for Vineberg-type myocardial implantation prior to the bypass grafting era, and its use as a coronary bypass graft was begun by Suma and Pym in 1986. Suma reported a 94 percent (253 of 268) patency rate within 2 months of operation and 47 of 50 GEA grafts (94 percent) patent at 2 to 5 postoperative years.[41] In situ GEA grafts have had better patency rates than free grafts. When late attrition has occurred, it has appeared to be related to native coronary artery competitive flow. Anecdotal angiographic studies have documented the patency of GEA grafts 9 to 10 years after operation and have not shown evidence of the occurrence of graft atherosclerosis. The GEA is prone to spasm, and intraluminal vasodilators have been used by many of its proponents. In situ GEA grafts function well as a graft to the posterior descending branch of the RCA or circumflex system, although in selected circumstances the distal LAD artery may be grafted. Despite good long-term patency rates, the GEA has not become a popular graft because it is more difficult to use than most other conduits.

The inferior epigastric artery (IEA) also has been used as a bypass graft. Buche et al.[42] reported on patients receiving IEA grafts and noted patency of 132 of 135 grafts studied 11 days after operation, 44 of 48 grafts at 8 months (although 8 showed a string sign), and 25 of 29 grafts studied an average of 25 months after operation. They also noted that grafts exhibiting diffuse spasm at one postoperative study may show resolution at a second. Califiore[36] reported on use of the IEA as a composite graft and noted patency in 34 of 34 grafts studied within 2 weeks of operation and 20 of 21 grafts 6 to 14 months later. Because of its relatively short length, we have most commonly used the IEA as a composite arterial graft.

The long-term usefulness of the radial artery as a coronary bypass graft is an important question that is as yet incompletely answered. The radial artery is a long graft that is easily procured and has very favorable size and handling characteristics. However, it is a thicker, more muscular artery than the ITA, and when it was used by Carpentier[44] and others[43] in the early 1970s, patency rates were not favorable. Recently, its use has been revisited along with the use of calcium-channel blocking agents to prevent postoperative spasm, and Broadman et al.[45] and Acar et al.[46] have reported early (<6 months) patency rates of greater than 90 percent. Acar et al.[46] reported 75 radial grafts studied within 2 weeks of operation with 1 occluded graft and 4 with spasm. At 1 year, 61 grafts were restudied, with 4 occluded and 2 stenotic. At 4 to 7 years after operation, 50 patients underwent repeat study, and of 64 radial artery grafts, 10 were occluded, 1 had a string sign, and 53 (83 percent) looked perfect. In the same patients, 91 percent of left ITA grafts were patent. Possati et al.[47] performed serial studies after radial artery grafting and documented an 87 percent perfect patency at 5 postoperative years, compared with 98 percent left ITA patency and 69 percent vein graft patency in the same patients. Early diffuse radial artery graft abnormalities in

7 patients disappeared by the 5-year angiogram.[47] At this point the jury is still out on radial artery grafts. They are not as reliable in terms of patency as left ITA grafts are but may be superior to vein grafts over the long term if they are resistant to late graft atherosclerosis.

Total arterial revascularization is an appealing concept, but its clinical importance is not yet certain. For some patients, total arterial revascularization can be achieved solely with the use of ITA grafts, but for many others, other arterial grafts are needed. Bergsma et al.[48] reported on a group of 256 selected patients with triple-vessel disease revascularized with two ITA grafts and a GEA graft. These relatively good-risk patients experienced an expected good survival rate, but it was also noted that over a mean follow-up period of 51 months, 85.7 percent experienced no angina, an impressive figure. Much longer-term follow-up is needed. Realistically, it is unlikely that most coronary surgeons will use GEA grafts routinely, but if the long-term patency rates of radial artery grafts are superior to vein grafts, total arterial revascularization will become common.

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Chapter 48: CORONARY BYPASS SURGERY

CURRENT OPERATIVE STRATEGIES AND RISKS

Standard Operative Strategies

Currently, most operations for primary isolated coronary revascularization are still performed through a median sternotomy with the aid of cardiopulmonary bypass. Aortic occlusion and cold potassium-based cardioplegia (delivered antegrade through the aortic root or retrograde through a catheter in the coronary sinus) are used to achieve an immobile surgical field consistent with intraoperative myocardial protection. Standard revascularization techniques involve the use of an in situ left ITA to graft the coronary artery, and in most centers, vein grafts are then employed to graft the other vessels.

Hospital Mortality

Overall hospital mortality rates for primary bypass surgery vary between 1 and 4 percent. Mortality rates in the voluntary countrywide Society of Thoracic Surgeons Database ranged from 3.46 to 3.78 percent (including reoperations) from 1990 to 1994.[49] The unadjusted mortality rate for patients undergoing primary operations in New York State (a compulsory registry with subsequent public disclosure) from 1993 to 1995 was 1.9 percent,[50] and single-institution reviews have noted overall mortality rates of 1 percent or less for elective patients.[1] Multiple database analyses have been devoted to the identification of variables that can be used to predict in-hospital outcomes and adjust for patient selection. A recent review of the seven largest data sets available in the literature found that 7 variables were predictive of in-hospital death in all data sets: acuteness of operation, age, prior cardiac surgery, gender, LV ejection fraction, left main coronary artery percent stenosis, and number of coronary systems with more than 70 percent stenosis.[51] Acuteness of operation, age, and previous surgery had the greatest predictive value. Also identified were 13 variables that added some predictive value to the core variables: percutaneous transluminal angioplasty (PCTA) during the same admission, MI less than 1 week prior to operation, angina, ventricular arrhythmia, congestive heart failure, mitral regurgitation, diabetes, cerebral vascular disease, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), and serum creatinine.

In the spectrum of clinical settings ranging from stable angina, to unstable angina with electrocardiographic changes, to recent subendocardial infarction, to recent Q-wave MI, and to cardiogenic shock, there has been an increased operative risk associated with increasing degrees of ischemia and decreasing degrees of LV function. Modern methods of myocardial protection have diminished the impact of unstable angina. However, operations for postinfarction ischemia and shock still generate substantial risk, and the mortality rate of bypass surgery after MI decreases with increasing post-MI interval. Thus the usual strategy for patients after MI is to control acute ischemia with medical treatment and undertake operation more electively.

The risk-stratification process has value for both doctor and patient. However, the process contains some inherent inaccuracies. First, variables are measured differently in different institutions, particularly variables related to the acuteness of operation. Second, databases record and analyze variables that can be measured. Some variables, such as the diffuse nature of distal CAD, are difficult to measure and are rarely contained in databases. Third, a variable must be able

to be measured in large numbers of patients. The presence of severe ascending aortic atherosclerosis as defined by echocardiography is a risk factor not routinely measured in most large series. Were it to be measured, it would be important, but most institutions do not have the facilities to examine this variable in all patients. Fourth, for a variable to be predictive of risk, it must be measured and recorded with enough frequency to have a statistical impact. Examples of uncommon variables that have a strong impact on operative mortality include hepatic cirrhosis, congenital clotting disorders, severe protamine allergies, and previous mediastinal radiation therapy.

Coronary bypass surgery is a very scrutinized treatment. Overall mortality rates tend to be maintained in a narrow range in part because that scrutiny engenders careful patient selection if overall mortality rates begin to rise. Burack et al.[52] studied the New York State Department of Health Cardiac Surgery Reporting System (CSRS) and found evidence that high-risk patients were being denied bypass surgery. Certainly, not all institutions should perform all operations, and it probably is of benefit for high-risk patients to undergo surgery in selected institutions. However, in a milieu of medical economics where patient mobility may be limited, care must be exerted such that high-risk patients are not denied potentially lifesaving operations.

One operation-related variable that has been associated with decreased in-hospital risk is the use of ITA grafts. At one time there was concern that ITA use would increase risk. However, multiple retrospective studies from different data sets and during different surgical periods have shown that use of the ITA graft is associated with a decrease in hospital mortality rather than an increase.[53,54]

One advantage of identifying characteristics that predict high risk is that patients who are at extremely low risk also may be identified. For example, during the years 1995-1998, the STS Database recorded 25,776 patients who underwent a primary elective bypass operation, had a LV ejection fraction of greater than 50 percent, and did not have peripheral vascular disease, carotid disease, renal failure, a prior MI, or an intraaortic balloon pump. For these good-risk patients, 98 deaths occurred for a 0.38 percent mortality rate.[55]

Hospital Morbidity

PERIOPERATIVE MI

Since the early years of bypass surgery, improved strategies for myocardial protection have evolved, and significant perioperative MI has become less frequent. Today most surgeons employ aortic occlusion combined with some type of cardioplegia injected into the cardiac vascular system to produce a still heart. Originally, cardioplegic solutions were asanguineous, cold, high in potassium, and injected into the aortic root. Modifications of this basic strategy have included addition of blood, addition of metabolic substrates, warming some or all of the cardioplegic solution, and delivery of cardioplegia retrograde through the coronary sinus into the cardiac venous system.

The definition of what constitutes a perioperative MI varies among studies but with the use of cardioplegia, the risk of hemodynamically significant perioperative MI in elective patients is very low, and it has become difficult in such patients to show incremental benefit of any of the cardioplegia modifications. For example, a trial of warm blood cardioplegia versus cold crystalloid cardioplegia in primary elective bypass operations showed that rates of MI (1.4 versus 0.8 percent), intraaortic balloon pump use (1.4 versus 2.0 percent), and death (1.0 versus 1.6 percent) were equivalent.[56] For patients undergoing operation in the face of acute ischemia based either on failed PCTA or unstable angina, blood cardioplegia does appear to provide incremental benefit.[57,58] Retrograde delivery through the coronary sinus and coronary venous system provides more effective delivery during reoperations, in the setting of acute coronary ischemia, or if the

aortic valve is insufficient.[59]

For the period of time needed to complete even extensive coronary revascularization operations using standard techniques, the metabolic environment created by these cardioplegic strategies appears to be sufficient for protection. Significant perioperative MI, when it occurs, appears to be based on anatomic causes, acute coronary occlusion, graft failure, or incomplete revascularization.

NEUROLOGIC COMPLICATIONS

Adverse neurologic events after coronary bypass surgery may negatively affect overall outcomes, and at a period in time where myocardial protection has diminished the impact of perioperative MI, the perioperative risk of cerebral complications is still under intense investigation. A recent multicenter study authored by Roach et al.[60] separated postoperative neurologic abnormalities into focal strokes (type I) and diffuse encephalopathies (type II). In this study, the total number of adverse outcomes was 6.1 percent, divided between type I (3.1 percent) and type II (3.0 percent). Advanced age and hypertension predicted an increased risk for both types of deficits.

Focal strokes (type I) appear to have multiple causes, including carotid or intracranial vascular disease, embolic phenomena based on interventricular or atrial thrombi or postoperative atrial fibrillation, and atheroembolization from the aorta, probably the most common cause. In fact, in the study by Roach et al.,[60] the greatest predictor of a type I deficit was proximal aortic atherosclerosis as noted by the surgeon. Hartman et al.[61] have associated the risk of stroke with the severity of aortic atherosclerosis as defined by transesophageal echocardiography, and Blauth et al.[62] associated the presence of ascending aortic atherosclerosis with evidence of atherosclerotic emboli to multiple organ systems. There are multiple techniques available to diminish the impact of aortic atherosclerosis, including alternative arterial cannulation sites, single aortic cross-clamping, circulatory arrest and aortic replacement, and surgery without cardiopulmonary bypass. Which strategy will produce the best outcomes will vary according to the particular pathology involved, but the most important point is recognition by the surgeon of the existence of the problem. Other predictors of type I deficit have included a history of stroke, diabetes, unstable angina, peripheral vascular disease, and a total carotid occlusion.

Variables that were predictive of type II deficits in the Roach et al. study included a history of alcohol abuse, atrial fibrillation, prior coronary artery bypass grafting (CABG), peripheral vascular disease, and congestive heart failure. The anatomic basis of type II deficits is not known, but many authors have noted some evidence of gaseous or particulate embolization associated with cardiopulmonary bypass. Strategies designed to minimize microembolization associated with cardiopulmonary bypass includes the use of membrane oxygenators, arterial filters, alpha-stat extracorporeal circulation acid-base management, and avoidance of cerebral hyperthermia. Another appealing concept is the performance of bypass surgery without the use of cardiopulmonary bypass, and logic would seem to dictate that this strategy would decrease the incidence of both types of neurologic complications. This issue is currently being intensively investigated.

The presence of carotid stenoses, symptomatic or asymptomatic, in a patient undergoing bypass surgery creates both a short- and a long-term risk of stroke. Studies of patients over age 65 with carotid Duplex scans have defined the predictors of 80 percent or more carotid stenoses as female gender, peripheral vascular disease, previous transient ischemic attack (TIA) or stroke, smoking history, and left main stenoses.[63] The majority of patients aged 65 or older had one of these characteristics, and it may be logical to screen all patients in that age group undergoing bypass surgery. Regardless of age, patients with a previous stroke, TIA, or carotid bruit should undergo Duplex screening, and any patients evidencing symptoms characteristic of vertebrobasilar insufficiency should have further studies.

The patient with simultaneous carotid and coronary disease is at higher risk than the patient with only CAD regardless of which therapeutic approach is used. Staged operations with carotid endarterectomy performed first has been shown to be safe but has been applied in very selected patients with less severe CAD. Patients undergoing bypass surgery in the face of a severe uncorrected carotid stenosis are at increased risk of stroke, and patients with bilateral stenoses are at a greatly increased risk of stroke.[64,65] Many experienced centers recommend combined carotid endarterectomy and coronary surgery for patients with carotid stenoses who are undergoing primary bypass operations, although even with this approach stroke and mortality rates are slightly worse than those for patients with isolated CAD.[66]

WOUND COMPLICATIONS

Deep sternal wound complications represent a serious adverse outcome and occur in 0.5 to 4 percent of cases depending on patient selection. Obesity and diabetes have been implicated in multiple studies as factors increasing the risk of sternal complications. There is some evidence that aggressive treatment of blood glucose levels with intravenous insulin may decrease the risk of infection in diabetic patients. No studies have shown that the use of a single ITA graft increases the risk of sternal wound complications, but some authors have implicated bilateral ITA grafting, particularly for diabetic patients.[67] Dissection of the ITA as a skeletonized artery rather than as a pedicle may leave collateral circulation to the sternum intact and diminish the impact of ITA use.

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DIFFERENTLY INVASIVE BYPASS SURGERY

New concepts in how bypass surgery is being performed are now under exploration: operations done through small incisions (minimally invasive bypass surgery) and operations performed without the use of cardiopulmonary bypass (beating-heart or off-pump surgery). Stimuli for these changes include the maturation of small incision or endoscopic technology for the performance of thoracic and general surgery and the desire to decrease incision-related and cardiopulmonary bypass-related morbidity (and perhaps mortality) related to coronary surgery.

Small-incision and beating-heart concepts have been combined in an operation during which a small left anterior thoracotomy is used to prepare a left ITA graft that is then anastomosed to the LAD coronary artery under direct vision (MIDCAB or LAST operation) (Fig. 48-8). Endoscopic technologies sometimes have been used for the ITA preparation but usually not for creation of the anastomosis. Early studies showed that this approach was possible but also noted an increased risk of ITA graft failure associated with this strategy. However, with increased surgical experience, results clearly have improved.[68,69] Because the left ITA-LAD operation using standard techniques (median sternotomy and cardiopulmonary bypass) is extremely safe and produces excellent 20-year outcomes, the only major risks of bypass surgery that are likely to be diminished with the MIDCAB approach are wound complications. However, it is the hope that this less invasive approach may have cosmetic, hospital stay, time loss from work, and cost advantages. The disadvantage of a limited-access, off-pump operation is that a limited number of coronary vessels can be grafted through any one incision. To approach this issue, three directions are being pursued: small-incision surgery with cardiopulmonary bypass (CPB), large-incision surgery without CPB, and robotics surgery.

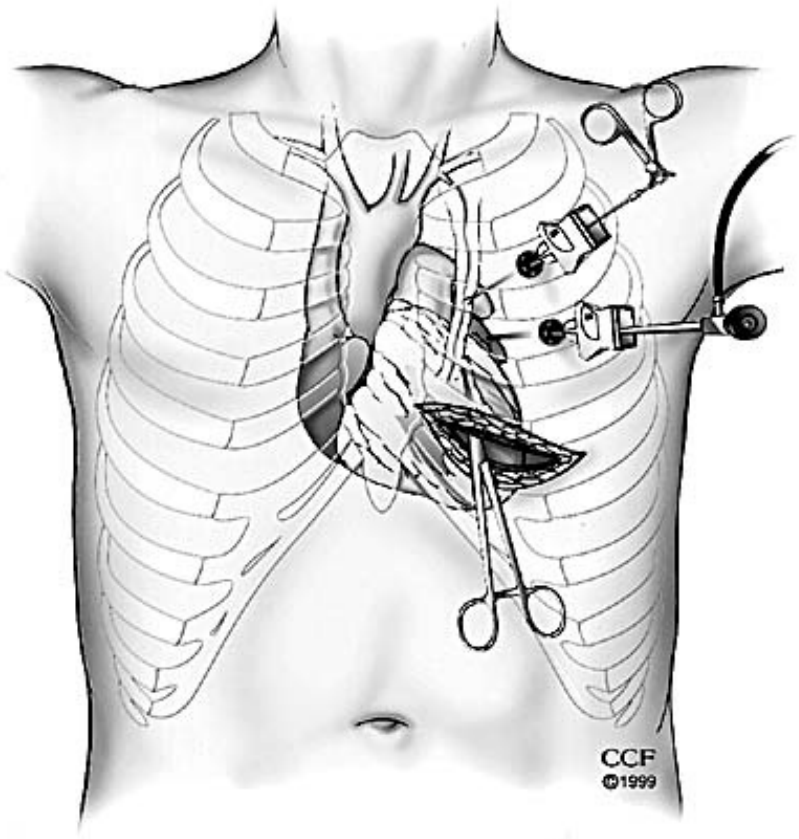

Figure 48-8: A small left anterior thoracotomy may be used to construct a limited anastomosis without the use of CPB, or with the use of percutaneous CPB, more vessels are accessible through this small incision. Endoscopic preparation of the left ITA graft may be employed.

A percutaneous CPB system has been developed that involves femoral arterial and venous cannulation and percutaneous cannulas that allow balloon occlusion of the ascending aorta and the delivery of antegrade and retrograde cardioplegia. This approach allows aortic occlusion, cardiac arrest, and decompression, making the coronary vessels more accessible through a small left thoracotomy. The disadvantages of this approach are that coronary exposure may not be ideal, the right ITA and GEA arteries are difficult to use as grafts, the patient undergoes the risks of CPB, and the patient is exposed to vascular-related risks of catheter placement such as aortic dissection and atherosclerotic embolization. Industry sources appear to show that an early increased risk of aortic dissection has lessened with experience and that the risks of death and stroke are not obviously out of line.[70] The possible benefits of this approach are a decrease in wound complications and a faster return to full activity. In carefully selected patients, these goals seem achievable.

A more common differently invasive strategy is to use a median sternotomy incision to improve coronary artery access but avoid the use of CPB, bypass surgery being performed on the beating heart. Beating-heart surgery was employed in the early years of bypass surgery, and although poor angiographic outcomes led to its decline, it never disappeared completely. Many surgeons continued to perform small numbers of off-pump operations for patients at particularly high risk for CPB, and some large series of elective off-pump operations were accumulated outside the United States.[71,72]

Differently invasive bypass operations have different risks. The disadvantages of off-pump surgery or any small-incision surgery is that coronary access and stabilization are not as optimal as is possible through a large incision with the use of CPB and cardiac arrest. However, progress

in stabilization devices and intracoronary shunts and increased surgeon experience have greatly enhanced the effectiveness of off-pump surgery, and it is a strategy that is here to stay. Current early angiographic evaluation indicates that for selected patients, favorable early graft patency rates can be achieved. Avoidance of CPB-related complications is the upside of off-pump surgery. So far, large comparative, but nonrandomized series show small differences in measurable early morbidity despite the avoidance of CPB.[73] Subgroups of patients at increased risk of a neurologic or renal complication would seem to be a group that would derive maximum benefit from off-pump surgery. However, avoiding CPB does not eliminate the risk of stroke, particularly if aortic clamps are used in the construction of aortic anastomoses. Composite grafts using the left ITA as inflow avoid aortic manipulation and are often used during off-pump surgery (see Fig. 48-5*A*, *B*).

The use of robotics-type visualization and manipulative technology is in its infancy but offers the possibility of expanding the extent of operations that can be performed through small incisions with or without CPB. The development of effective anastomotic stapling devices will greatly expand the possibilities for robotics bypass surgery.

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LONG-TERM OUTCOMES AFTER BYPASS SURGERY

Late survival after bypass surgery is related to the patient's cardiac status at the time of operation, the bypass operation, progression of atherosclerosis, noncardiac comorbidity, and fate. Recent follow-up of 8221 surgical patients from the CASS Registry documented overall survival of 96, 90, 74, 56, and 45 percent at 1, 5, 10, 15, and 18 postoperative years, respectively.[74] These figures are inferior to those for the age-sex-matched U.S. population. Noted in other follow-up studies is that 55 percent of deaths over the first postoperative decade were cardiac in nature.[75]

Age is a major determinant of survival. In the CASS review, very young and very elderly patients had a decreased survival rate. The lack of ITA grafting in the CASS population almost certainly had a detrimental effect on the survival of young patients, but no studies of patients 40 years of age or under have ever shown survival rates equivalent to age-matched controls. However, elderly patients, while having a diminished survival when compared with younger patients, actually have survival rates better than those for age-matched controls, an effect that begins to be observed around age 60.[74]

LV function is the cardiac-related variable most closely related to long-term survival. In addition, left main stenosis, a proximal LAD artery stenosis, and the number of significantly stenotic coronary arteries all have influenced survival in most studies. The late survival of patients treated medically is dramatically influenced by these cardiac variables, but bypass surgery at least partially ameliorates their impact.[74] In our study analyzing the impact of arterial revascularization, a proximal LAD artery stenosis had no effect on late survival, and left main disease and the number of systems diseased had minor influence.[39] In no long-term study has bypass surgery completely obliterated the impact of abnormal LV function on late survival.

Risk factors for atherosclerosis also decrease late survival, most particularly cigarette smoking, hypercholesterolemia, hypertension, and diabetes. Smoking decreases the survival rate, and stopping smoking returns the patient to a nonsmoker's prognosis.[76] High elevations in total cholesterol are related to a decreased survival in some studies,[77] and there is suggestive evidence that pharmacologic treatment may improve the survival rate for these patients. Diabetes severe enough to require treatment is associated with a decreased late survival rate, but it is not yet clear whether or not glycemic control will improve the late survival rate of surgically treated patients. However, it has been shown that close control of diabetes does improve long-term outcomes for medically treated patients, and logic would dictate the importance of this approach despite bypass surgery.

As discussed previously, the surgical strategies of the left ITA-LAD artery graft and bilateral ITA grafting incrementally improve the late survival.

The impact of incomplete revascularization on long-term outcome is of increasing importance with the emergence of PCTA and minimally invasive bypass operations, strategies that may involve less complete revascularization than can be achieved with standard bypass surgical techniques. Definitions of what *incomplete revascularization* is have varied, and it is difficult to separate incomplete revascularization as a surgical strategy from incomplete revascularization as a marker of bad coronary and noncoronary atherosclerosis. Retrospective multivariate analyses of

The Cleveland Clinic Foundation data identified incomplete revascularization as a risk factor for late death, but not a strong one.[77] A CASS Registry study by Bell et al.[12] noted a strong negative effect of incomplete revascularization on the late survival of patients with abnormal LV function who underwent bypass surgery, and Jones and Weintraub[78] observed a negative effect on patients with normal LV function.

Incomplete revascularization as a surgical strategy was examined in a study by Tasdemir et al.[72] that reviewed patients having off-pump bypass surgery. In this study, incomplete revascularization (usually of the circumflex system) was sometimes accepted in order to be able to perform bypass surgery without CPB. Failure to revascularize the circumflex system was a risk factor for early death and cardiac events, but late follow-up was not available.

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REOPERATION

Atherosclerosis is a progressive disease, and some patients eventually will undergo repeat bypass surgery. A study reviewing patients undergoing primary bypass surgery in the 1970s noted a cumulative incidence of reoperation of 2.7, 11.4, and 17.3 percent at 5, 10, and 12 years after bypass, respectively.[79] Young age, normal LV function, single- or double-vessel disease, severe symptoms, incomplete revascularization, and not having an ITA graft were all factors increasing the likelihood of a reoperation. Today, the availability of PCTA, use of arterial grafts, and possibly risk factor control will diminish the rate of reoperation. However, recurrent ischemic syndromes will develop in some patients with previous surgery, and reoperation will sometimes be required.

Patients who are candidates for reoperation are different from those having primary surgery. Today, the typical candidate for reoperation underwent primary surgery more than 10 years ago, had triple-vessel disease at that time, and needs reoperation at least in part because of graft failure. The atherosclerotic process is advanced, and such patients have a high incidence of noncardiac atherosclerosis. Their cardiac atherosclerosis is severe, and they have a higher prevalence of aortic atherosclerosis, left main stenosis, severe distal CAD, and abnormal LV function than patients undergoing primary surgery. They usually have the unique characteristics of having their myocardial blood supply dependent on ITA grafts, being at risk for injury, or having atherosclerotic vein grafts that create the possibility of coronary atheroembolism. In addition, few data are available that help to define the indications for reoperation, particularly for patients who are not severely symptomatic. None of the randomized trials included patients with previous bypass surgery, and since their myocardium is usually jeopardized at least in part by vascular pathology different from native coronary artery atherosclerosis, generalization from the randomized studies is unwise.

To examine outcomes for patients with prior surgery who developed recurrent ischemic syndromes, we performed two retrospective, nonrandomized studies of patients who underwent repeat angiography after primary bypass surgery. The first involved patients who did not undergo prompt reoperation and compared outcomes with patients with vein graft stenoses with patients without vein graft stenoses.[80] This study showed that late (≥5 years) stenoses in vein grafts are more dangerous lesions than are native coronary lesions. For example, patients 5 years or more after operation with a 50 percent or greater stenosis in the LAD artery vein graft had survival of 70 and 50 percent 2 and 5 years after angiography compared with survival rates of 97 and 70 percent for patients whose LAD coronary artery was jeopardized by a 50 percent or greater native vessel stenosis.

The second study involved patients with stenotic vein grafts and compared outcomes for those who underwent repeat surgery with those who were treated without initial reoperation.[81] Treatment was not randomized, and the patients who underwent repeat surgery were more symptomatic. Patients with late (≥5 years) stenoses in vein grafts had better survival rates with surgery, and the patients who particularly benefited were those with an atherosclerotic vein graft to the LAD coronary artery. The patients with a 50 percent or greater LAD artery graft stenosis had immediate and obvious benefit, but even those with a 20 to 50 percent stenosis had an improved survival rate with surgery when followed for 5 years (Fig. 48-9). Patients with late stenoses in non-LAD artery grafts also appeared to have improved late survival unless they

had a patent ITA to LAD artery graft. Patients with early vein graft stenoses did not have an improved late survival rate with surgery, although patients who underwent reoperation had fewer symptoms at late follow-up.

All studies that have examined large numbers of patients undergoing reoperation have noted an increased in-hospital risk when compared with patients undergoing primary surgery. The STS National Database noted an overall risk of 7.14 percent for reoperations from 1980 to 1990,[15] and The Cleveland Clinic Foundation studies have documented a risk of 3 to 4 percent for a first reoperation from 1967 through the present.[82-84]

The increased risk of reoperation is related in large part to an increased risk of perioperative MI. Graft injury, atherosclerotic embolization from vein grafts or the aorta, incomplete revascularization due to diffuse disease or lack of bypass conduit, and technical difficulty with severely atherosclerotic coronary vessels are anatomic causes of perioperative MI that are either unique to reoperation or more common in that setting. The use of retrograde cardioplegia has been of major benefit in the management of atherosclerotic vein grafts and patent ITA grafts, but avoiding perioperative MI during reoperation still represents a challenge.

In the reoperative setting, emergency operation produces a large increase in risk. Definitions of *emergency* vary among studies, but the lesson is the same. For example, in the STS National Database, primary operation had a risk of 2.24 percent for elective operation versus 5.7 percent for emergencies, whereas elective reoperations had a 5.33 percent risk compared with 12.69 percent for emergencies.[15] Left main stenosis, advanced age, congestive heart failure, female gender, and numbers of stenotic vein grafts have been other factors associated with increased risk.

In general, the long-term outcomes after reoperation are slightly inferior to those after primary surgery. Loop et al.[83] noted a 69 percent 10-year survival for 2429 hospital survivors of a first reoperation. LV function was the variable having the strongest impact on survival. Reoperations tend to achieve less perfect revascularization than primary procedures, and by 5 to 6 postoperative years, about 50 percent of reoperative patients have some angina, although in few patients is it severe.[82]

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PCTA VERSUS CABG

The advent of PCTA brought another invasive treatment for coronary atherosclerosis into the arena. Observational studies have identified many of the benefits (low procedure-related morbidity, early return to full activity, feasibility of multiple procedures) and disadvantages (not feasible for many patients, incomplete revascularization, restenosis, acute coronary occlusion) of PCTA. To compare PCTA and surgery for selected patient subgroups, multiple randomized trials have been undertaken.

A three-armed trial [The Medicine, Angioplasty or Surgery Study (MASS)] randomized 214 patients with severe (>80 percent) proximal LAD artery stenoses to medical treatment, PCTA, or bypass surgery (CABG).[85] During a 5-year follow-up, the primary end points of MI, death, and refractory angina occurred for 6 CABG patients, 29 PCTA patients, and 17 medically treated patients ($p = 0.001$). Considering repeat revascularization, death, and MI as events, event-free survival at 5 years was 98.6 percent after CABG, 93.9 percent after PCTA, and 88.9 percent for medically treated patients. The percentage of patients free of angina were CABG, 72.7 percent; PCTA, 64.7 percent; and medically treated, 25.8 percent. There was no difference, however, among the groups in the likelihood of death.

Multiple randomized, prospective trials have compared PCTA versus CABG for the treatment of multivessel CAD. The design of these trials has been to test the question of whether or not an initial strategy of PCTA compromises patient survival. The multicenter Bypass Angioplasty Revascularization Investigation (BARI) trial is the largest such trial (1792 patients randomized in 18 centers), and the single-center Emory Angioplasty Surgery Trial (EAST) is the other U.S. study.[86,87] Included in these trials were patients with stable or unstable angina who were good angiographic candidates for PCTA.

Of the spectrum of patients with coronary atherosclerosis who are considered for revascularization, a minority were included in these trials. Patients with left main stenosis of 50 percent or more were purposely excluded. In the BARI trial, more than half the patients who were potentially randomizable were excluded because of anatomy unfavorable for PCTA, and of the patients judged suitable, only half were randomized. A majority of BARI patients had two-vessel disease (59 percent) and normal LV function, and a minority (37 percent) had a proximal LAD artery lesion. Thus the BARI trial (and EAST patients had similar baseline characteristics) included very few patients who had been shown to have improved survival with CABG in the medicine versus surgery trials of the 1970s. In particular, the PCTA versus CABG trials are underpowered to detect a difference in survival for patients with multivessel disease and abnormal LV function because very few of such patients were randomized.

At approximately a 5-year follow-up interval, overall survival rates have been equivalent for the PCTA and CABG groups in both BARI and EAST. In the BARI trial, the subgroup of patients with treated diabetes had much worse survival with PCTA (Fig. 48-10). The survival advantage of the CABG group was present only if an ITA graft was used. Nondiabetic patients had equivalent survival.[88]

There were large differences between the PCTA and CABG groups in the need for repeat revascularization. Repeat revascularization was required in 54 percent of PCTA patients in both BARI and EAST versus 8 percent in the BARI CABG group and 13 percent in the EAST CABG group. There were smaller differences in symptom status and the need to take antianginal medications in favor of CABG. Detailed discussion of the limitation of these trials and the limitations in the conclusions that can be drawn from these trials have been described in detail by American College of Cardiology/American Heart Association task forces.[2,14] However, among the limitations of these trials in terms of current recommendations for the treatment of a broad spectrum of patients with multivessel CAD are the following: (1) The benefit of PCTA for high-risk patients (those subsets for whom surgery prolongs survival) has not been established because of the small number of such patients included in these randomized trials. (2) Only good angiographic candidates for PCTA were included, and the results of these trials cannot be extended to patients with more marginal suitability for PCTA. (3) Few PCTA patients received intracoronary stents. (4) Few surgical patients had extensive arterial revascularization. (5) None of the protocols included lipid-lowering therapy.

Observational studies have the disadvantage of bias in treatment selection but may have an advantage of being more inclusive. A recent large study from the New York State Cardiac Procedure Registries detailed a 3-year outcome of 29,646 CABG patients and 29,930 PCTA patients.[50] This study found a survival advantage for CABG for all patients with a proximal LAD artery lesion regardless of whether they had single-, double-, or triple-vessel disease.

Comparative trials of PCTA and CABG have involved patients with stable or unstable angina but not "beat the clock" treatment of acute MI. Currently, thrombolysis, PCTA, or both are the strategies employed for the vast majority of patients with acute MI.

There are no randomized studies of PCTA versus CABG for patients with previous bypass surgery. The percutaneous treatment of VGA usually has not been effective. Despite the use of stents, there is a high rate of restenosis and cardiac events.[89] Furthermore, it appears that these cardiac events are often serious ones, MI and/or death. Pathologies that are not based on VGA may be treated effectively with PCTA, including graft anastomotic stenoses, early vein graft stenoses, and native vessel stenoses. Patients with large amounts of myocardium jeopardized by atherosclerotic vein grafts usually should be treated with reoperation. However, generalizations are difficult for these complex patients, and therapeutic decisions are best made by interventional cardiologists, cardiac surgeons, and clinical cardiologists working in concert.

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INDICATIONS FOR BYPASS SURGERY

In the individual case, recommendations concerning bypass surgery may be influenced by comorbid conditions that greatly increase operative risk or that limit the patient's ultimate life span. However, some generalizations can be made.[2,14] Patients with 50 percent or greater left main stenosis or multivessel disease with a proximal LAD artery stenosis and abnormal LV function should have a recommendation of surgery regardless of their symptom status. Individual randomized trials and metaanalyses have shown clearly a survival benefit for these patients, and there is no evidence that PCTA is safe in these subgroups.

Diabetic patients with multilesion, multivessel disease including a proximal LAD artery lesion should have surgery regardless of LV function and symptom status. Survival is better with CABG than with medical treatment, and PCTA is clearly not an equivalent intervention in terms of survival.

Patients with multivessel disease that include a proximal LAD artery lesion and demonstrable ischemia should have a recommendation for revascularization. If these patients are nondiabetic with normal LV function and are good angiographic candidates for PCTA, it appears that PCTA does not compromise 5-year survival, and the options of PCTA and CABG should be discussed with the patient.

For patients with single-vessel disease based on a proximal LAD artery lesion, survival appears equivalent with medical therapy, PCTA, and CABG, and all options are reasonable, although CABG patients have had fewer events and symptoms over 5 years.

For other subsets of patients with multivessel disease, surgery may be a reasonable choice for the treatment of symptoms in the face of demonstrable ischemia. The choice between PCTA and CABG for these patients should be based on coronary vascular anatomy and patient preference.

For patients with previous bypass surgery and a significant (≥50 percent) late stenosis in a vein graft to the LAD coronary artery, surgery should be recommended regardless of symptoms. For patients in other anatomic subgroups, the risk-benefit situation is complex. Usually reoperation is undertaken to treat severe symptoms and/or large areas of ischemic jeopardy.

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TRANSMYOCARDIAL LASER REVASCULARIZATION

The concept of achieving myocardial revascularization by the creation of channels in the myocardium to allow perfusion of blood directly from the LV cavity to coronary sinusoids has been investigated since the 1950s. Early experiments involved mechanically created channels, but more recently, lasers of various wavelengths have been used. The increasing population of patients with severe distal native vessel atherosclerosis (usually occurring years after previous bypass surgery) who may not be well treated with either bypass surgery or PCTA has provided impetus to the search for such alternative revascularization strategies, and transmyocardial laser revascularization (TMLR) may be of value.

Recently, randomized studies of TMLR versus medical management have been conducted involving patients with angina and severe CAD judged untreatable by conventional invasive means. Both CO_2 and holmium lasers were tested, and in both studies, over 70 percent of TMLR patients noted improvement in angina at 1 year postoperatively compared with 13 to 32 percent improvement in the medically treated group ($p < 0.001$).[90,91] Survivals of the TMLR and medically treated groups were the same in both studies. In the CO_2 laser study, 20 percent of patients had improved myocardial perfusion as judged by pharmacologic stress testing with thallium-201 single-photon-emission computed tomography (versus 27 percent of the medically treated group with worse perfusion; $p = 0.002$). The holmium laser study did not show a significant improvement in perfusion.

Although there is some apparent benefit from TMLR, the mechanism of improvement is not clear. Autopsy studies have noted granulation tissue occluding the myocardial channels within a few days of operation, and angina relief may not be immediate. Denervation and microcollateral stimulation have been suggested as possible mechanisms of angina relief. TMLR appears to have a role in revascularization but currently does not appear to produce the degree or the consistency of improved myocardial perfusion that can be achieved when bypass surgery or PCTA is possible. The indications for TMLR are still in evolution.

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Figure 48-9: Patients with late (>5 years after operation) stenoses in venous grafts to the LAD coronary artery have better survival with reoperation than with medical treatment. (Used with permission from Lytle BW, Loop FD, Taylor PC, et al. The effect of coronary reoperation on the survival of patients with stenoses in saphenous vein bypass grafts to coronary arteries. *J Thorac Cardiovasc Surg* 1993; 605-14.)

Figure 48-10: BARI trial patients with treated diabetes had worse survival following PCTA than following CABG ($p = 0.003$). Patients without diabetes had equivalent survival. (Used with permission from BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease. *Circulation* 1997; 96:1761-1769.)

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Part 6: CORONARY HEART DISEASE
Chapter 49:

MANAGEMENT OF THE PATIENT AFTER CARDIAC SURGERY

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The initial management of the patient following cardiac surgery is primarily focused in specialized intensive care units. The unique pathophysiologic alterations associated with hypothermia and cardiopulmonary bypass (CPB)[1] mandated that a specialized environment, including intensive monitoring and offering sophisticated electrophysiologic, hemodynamic, and mechanical intervention supervised by specially trained critical care nurses, be available. While CPB is no longer universally applied in cardiac surgery, the multiple management problems posed by cardiac patients as a consequence of their preoperative status, effects of residual anesthetic drugs, success of the operative procedure, and intraoperative complications continue to demand specialized treatment. When direct coronary artery bypass grafting is done without CPB, the primary concerns are bleeding (residual heparin, surgical hemostasis), hypothermia, myocardial ischemia, and injury. The use of CPB accentuates these concerns and adds those of a generalized inflammatory response.

ROLE OF VASCULAR CANNULAE, LIFE SUPPORT, AND MONITORING IN THE IMMEDIATE POSTOPERATIVE PERIOD

On arrival in the ICU, the patient is still under the effects of anesthesia and hypothermia, often receiving one or more drugs affecting the systemic circulation, and, in most cases, mechanically ventilated. The patient typically arrives from the operating room with the necessary apparatus for monitoring the following parameters: heart rate and rhythm; arterial, central venous, pulmonary artery, and pulmonary artery occlusion pressures (PAOP); cardiac output; urinary output; mediastinal drainage; body temperature; and arterial oxygen saturation (SpO_2) and end-tidal carbon dioxide tension ($ETCO_2$). Immediately upon arrival in the ICU, reliable monitoring of the previously mentioned variables should be instituted. Once the patient is satisfactorily connected to the bedside monitors and ventilator, all the hemodynamic measurements should be recorded, the patient's level of consciousness and comfort should be assessed, a portable supine chest x-ray should be acquired, and a 12-lead electrocardiogram obtained.

Most of the apparatus attached to the patient upon arrival in the ICU serves a dual purpose. A pulmonary artery catheter not only allows monitoring of pulmonary artery pressures but can also be used to estimate the filling pressure of the left ventricle, cardiac output, and body core temperature. The peripheral arterial cannula provides a continuous pulse-wave tracing of systemic blood pressure and ready access to arterial blood sampling for laboratory analysis. *Regular periodic assessments of arterial blood gases, especially after a major change in ventilator settings, are essential unless continuous $ETCO_2$ and SpO_2 by pulse oximetry are being monitored.* $ETCO_2$ and SpO_2 are reliable in guiding the weaning of mechanical ventilation and tracheal extubation. Monitoring of these parameters has been used very effectively in "fast-track" protocols. Assessment of volume loss is based on chest and mediastinal tube drainage plus urine output. The endotracheal tube secured in the correct position with an appropriately inflated cuff is essential for positive-pressure ventilation of the lungs. Confirmation of bilateral breath sounds and absence of tracheal air leak versus cuff inflation should be made upon arrival in the ICU and after suctioning secretions from the oropharynx. The endotracheal tube's position should be ascertained

on the initial chest x-ray. The endotracheal tube also allows for suctioning of bronchial secretions and reduces (but does not eliminate) the risk of oropharyngeal and gastric reflux secretions entering the trachea and bronchi. The endotracheal tube can often be removed the evening of surgery if the patient is conscious, is able to protect the airway, has good ventilatory mechanics and muscle strength, and is able to take on the work of breathing. Most patients can have the pulmonary artery catheter removed within 12 to 24 h if cardiovascular drug therapy is at minimum levels. The peripheral arterial cannula can be removed once cardiovascular function is satisfactory and the need for blood sampling is at a routine daily level. The urinary catheter is usually removed when the patient is ambulatory unless there is a vigorous diuresis or an increased risk of urinary retention. Chest tubes are generally removed when the total drainage is less than 100 mL per tube over 8 h.

The primary factor that differentiates cardiac surgery from other forms of surgery is CPB. With such improvements in extracorporeal technology as membrane oxygenation, arterial blood filtration, and blood sparing techniques, the noncardiac complications have been significantly reduced. Major improvements in myocardial protection technology coupled with changes in anesthetic and CPB techniques now frequently allow extubation within several hours of surgery.[2] Intraoperative management has now evolved to the point of minimizing the need for cardiopulmonary support after surgery, thereby allowing the patient to recover satisfactory vital function more rapidly than before. As a consequence, mechanical ventilation and other measures can be discontinued much earlier, and the patient can be safely and comfortably transferred from the ICU within the first 6 to 24 h, a process that has been termed *fast-tracking*.[3]

Individuals undergoing "off pump" procedures also have the potential for rapid recovery and early extubation and removal of catheters and chest tubes, and can be sitting up in the chair the next morning ready for transfer.

Fast-tracking describes efforts to minimize the duration of the patient's stay in the ICU or postanesthesia care unit and to allow the early, safe transfer of the cardiac surgical patient to a so-called step-down level of monitored care. Early extubation and transfer should require that the patient's status is characterized as follows: awake or easily aroused, neurologically intact, cooperative, and comfortable; stable, satisfactory hemodynamics; normothermia; satisfactory spontaneous ventilation; normal coagulation with minimal chest tube drainage; satisfactory urine output, electrolyte, and acid-base balance.[4]

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Chapter 49: MANAGEMENT OF THE PATIENT AFTER CARDIAC SURGERY

EARLY POSTOPERATIVE MANAGEMENT

Pathophysiologic Consequences of Cardiopulmonary Bypass

The basic pathophysiology during the early postoperative period revolves around the following variables: transient left ventricular dysfunction, capillary leak, warming from hypothermia, mediastinal bleeding, and emergence from anesthesia.

The likely presence of left ventricular dysfunction during the first 24 h postoperatively with a gradual recovery to preoperative levels is suggested by studies based upon hemodynamic data, nuclear scanning, and metabolic techniques. While improvements in surgical techniques, cardioplegia delivery, and other myocardial protection measures achieved in the past decade would have been expected to lessen this complication, the reported prevalence of early ventricular dysfunction (90 percent) did not change between 1979 and 1990.[5] This transient myocardial depression has been attributed by some authors to inadequate myocardial protection or the effects of cold cardioplegia,[6,7] but the bulk of the evidence incriminates the inflammatory state induced by CPB as the primary causative factor.[1]

The inflammatory state induced by CPB involves platelet-endothelial cell interactions and vasospastic responses that result in low-flow states in the coronary circulation.[8] The inflammatory reaction causes vascular endothelial adhesion molecules to attract inflammatory cells that subsequently adhere to the vascular endothelium. These inflammatory cells mediate much of the subsequent injury by the release of oxygen radicals or proteolytic enzymes.[9] This release of oxygen-free radicals in response to reperfusion injury is now generally accepted as the explanation for the transient postoperative ventricular dysfunction.[10-12] Depressed myocardial function seems to be unrelated to CPB time, number of coronary artery grafts, preoperative medications, or postoperative core temperature. Ventricular function is generally depressed by 2 h and is at its worse at 4 to 5 h after CPB. Significant recovery of function usually occurs by 8 to 10 h, and full recovery is reached by 24 to 48 h.[13] Systemic vascular resistance, while not rising immediately after surgery, increases as ventricular function worsens. This rise in systemic vascular resistance is likely secondary to reduced ventricular function and the need to maintain systemic blood pressure and, per se, is not a major causative factor of depressed cardiac contractility. The confounding effect of vasopressor drugs used in an attempt to increase systemic blood pressure must be recognized.

The inflammation-mediated production of oxygen-free radicals and release of proteolytic enzymes by neutrophils also damages the endothelial cells. The "gatekeeper" function of the endothelium is disturbed and capillary permeability increases, resulting in edema.[9] The capillary leak syndrome may last from a few hours up to 1 to 2 days, depending to a large degree on the duration of CPB. When the capillary leak ceases and interstitial edema fluid is mobilized, intravascular volume overload is a threat. At this time, diuretics are beneficial to eliminate excessive fluid.

Hypothermia predisposes the patient to cardiac dysrhythmias, increases systemic vascular resistance, precipitates shivering (which increases O_2 consumption and CO_2 production), and impairs coagulation.[13] Hypothermia with the patient's core temperature below 35°C frequently recurs after rewarming to 37°C (98.6°F) at the end of CPB. This fall in core temperature reflects

the loss of heat from the surgical field after CPB, exposure of the patient to ambient temperature, and incomplete rewarming of peripheral tissues, especially fat and muscle. If the patient is hypothermic upon arrival in the ICU, monitoring the temperature of noncore body sites such as a finger or toe can assure complete assessment of rewarming. Hypothermia causes peripheral vasoconstriction and contributes to the hypertension frequently seen after cardiac surgery. Furthermore, hypothermia causes a decrease in cardiac output by producing bradycardia along with the increase in vascular resistance. As the patient is rewarmed, large increases in O_2 consumption, and CO_2 production can occur, with a consequent increase in demand on cardiovascular and pulmonary functions.[14]

Hypercarbia will cause catecholamine release, tachycardia, and pulmonary hypertension. If the patient cannot increase the cardiac output and O_2 delivery, venous hemoglobin desaturation and metabolic acidosis will result. Most believe that the patient should be passively rewarmed by warm air (e.g., Bear Hugger) and that shivering should be eliminated by the administration of meperidine (25 to 50 mg) and muscle relaxants.[15] As body temperature increases, the vasoconstriction and hypertension associated with hypothermia are replaced by vasodilatation, tachycardia, and hypotension. Volume loading during the rewarming process helps reduce the rapid swings in blood pressure. Vasopressors (e.g., norepinephrine) may be required to maintain an adequate systemic blood pressure.

The commonly reported prevalence of severe postoperative bleeding (more than 10 U of blood transfused) following cardiac surgery is between 3 and 5 percent. In some hospitals, 25 percent of all blood products are dedicated to cardiac surgery.[16] While approximately one-half of the patients who undergo reoperation for excessive bleeding exhibit incomplete surgical hemostasis, the remainder bleed because of various acquired hemostatic defects, most often related to acquired platelet dysfunction.[17] The factors that predispose to bleeding following CPB are residual heparin effect, platelet dysfunction (which may be intensified by preoperative drug therapy, e.g., aspirin and $GPII_bIII_a$ inhibitors), clotting-factor depletion, inadequate surgical hemostasis, hypothermia, and postoperative hypertension. CPB decreases both platelet count and function. Hemodilution causes platelet counts to fall rapidly to about 50 percent of preoperative values. Within minutes after instituting CPB, the bleeding time is prolonged and platelet aggregation is impaired. The bleeding time usually normalizes by 2 to 4 h after CPB. The platelet count usually requires several days to return to normal levels. While the exact mechanism responsible for the transient platelet dysfunction remains undefined, it appears to be related to contact of platelets with the synthetic surfaces of the extracorporeal oxygenator and to hypothermia. Reductions in the plasma concentrations of coagulation factors II, V, VII, IX, X, and XIII due to hemodilution occur during CPB, but these coagulation factors remain well above levels considered adequate for hemostasis and generally normalize within the first 12 h after surgery. Moreover, while bleeding after CPB is often attributed to excessive fibrinolysis, the decrease in both plasminogen and fibrinogen levels during CPB is due to hemodilution and not consumption.[17] Upon returning from the operating room after exploration for bleeding, a common report is that no localized site of bleeding occurred and only diffuse oozing was found. Less frequently, a specific site such as an internal mammary pedicle will be identified.

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Chapter 49: MANAGEMENT OF THE PATIENT AFTER CARDIAC SURGERY

MANAGEMENT OF COMMON POSTOPERATIVE SYNDROMES

Vasoconstriction with Hypertension and Borderline Cardiac Output

Increased arteriolar resistance as a consequence of hypothermia and increased levels of circulating catecholamines, plasma renin, or angiotensin II is present in most postoperative cardiac patients. The usual criterion for pharmacologic lowering of blood pressure in postoperative patients is a mean arterial blood pressure 10 percent above the upper level of normal (>90 mmHg). Patients with a friable aorta or friable suture lines might be subjected to a lower mean arterial pressure to prevent dehiscence. The mean arterial blood pressure is monitored because it is most reflective of systemic vascular resistance. As the hypothermic patient is rewarmed, a short-acting vasodilator (nitroprusside, nitroglycerin, or nicardipine) can be infused intravenously to maintain mean arterial pressure at 80 to 90 mmHg. Intravascular volume should be maintained at a relatively high level (PAOP of 14 to 16 mmHg) in anticipation of vasodilation upon rewarming and to enhance cardiac output and peripheral perfusion. If the cardiac index is marginal (2.0 to 2.2 L/min/m^2), an inotropic drug should be administered in addition to the vasodilator.

Vasodilatation and Hypotension

This condition, which generally appears during rewarming, is most effectively prevented and best treated by fluid administration. The specific volume expander selected should be based upon a determination of the predominant factor leading to the hypovolemia. If the predominant factor is a capillary leak syndrome with generalized edema, the use of colloids could aggravate the situation as the oncotic elements pass into the interstitium and exacerbate tissue edema. If vasodilatation with increased venous capacitance is the major problem, colloids will provide longer-lasting augmentation of intravascular volume. Hetastarch (administered in 250- to 500-mL increments) provides sustained volume expansion equal to 5 percent albumin, at a significant reduction in cost. It does, however, have a tendency to increase bleeding. If fluid administration has increased PAOP appropriately (e.g., 14 to 16 mmHg for a normal ventricle or 18 to 22 mmHg for a noncompliant ventricle) and systemic blood pressure remains marginal, vasopressor or inotropic drugs should be administered. Generally, a PAOP above 15 mmHg in the postoperative period is of little benefit due to a "flattening" of the diastolic function curve, which accompanies the decline in systolic function.[18] An inotropic vasopressor should be infused if more than 1 or 2 L of fluid have been administered and the PAOP is not rising. In some patients after cardiac surgery, fluid administration produces a substantial increase in left ventricular end-diastolic volume without changing PAOP. Whether this is due to an open pericardium with overdistension of the left ventricle or some other factor is unclear.[19] If the blood pressure is marginal and the cardiac index is over 2.0 L/min/m^2, norepinephrine or dopamine is the preferable agent. If the cardiac index is less than 2.0 L/min/m^2, an inotropic agent should be administered initially.

Normal Ventricular Systolic Function and Low Cardiac Output

This set of circumstances is often noted in small women with systemic hypertension and in patients undergoing aortic valve replacement for aortic stenosis. The likely explanation is diastolic dysfunction. The problem should be managed by volume expansion with the intent to elevate PAOP to levels as high as 20 to 25 mmHg if necessary. Sinus rhythm and atrioventricular synchrony are essential and, if not present, should be restored. In the absence of other reasons for

diastolic dysfunction, the possibility of cardiac compression from clots in the mediastinum and pericardial space should be considered. If volume expansion does not lead to hemodynamic improvement, transesophageal echocardiography (TEE) should be used to establish or exclude the presence of clots or other causes of low output. If the information derived from TEE does not permit explanation and/or resolution of the problem, the patient should return to the operating room for exploration.

A rather characteristic presentation of cardiac compression is the patient who initially has significant mediastinal bleeding that ceases rather abruptly. The patient then becomes hypotensive, with high PAOP and central venous pressure and progressively increasing inotropic drug requirements. Cardiac compression from clots in the pericardial space should be suspected and, if time allows, confirmed by TEE. Rapid clinical deterioration demands immediate exploration of the pericardial space.

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Chapter 49: MANAGEMENT OF THE PATIENT AFTER CARDIAC SURGERY

APPROACH TO POSTOPERATIVE CARDIOVASCULAR PROBLEMS

Low Cardiac Output Syndrome

Satisfactory cardiac performance following cardiac surgery is usually indicated by a cardiac index greater than 2.2, L/min/m^2 with a heart rate below 100 beats per minute. Marginal cardiac function is present with a cardiac index between 2.0 and 2.2 L/min/m^2. A cardiac index below 2.0 L/min/m^2 is unacceptably low, and therapeutic intervention is indicated. Clinical signs of the adequacy or inadequacy of organ perfusion must be incorporated into any assessment of cardiac performance.

ASSESSMENT

The most common causes of low cardiac output postoperatively are related to a decreased left ventricular preload. The decreased preload, in turn, can likely be attributed to hypovolemia (due to bleeding or to vasodilatation as a consequence of warming or of drugs), cardiac tamponade, or right ventricular dysfunction. Alternative explanations for low cardiac output include decreased contractility due to a preexisting low ejection fraction or to intra- or postoperative ischemia or infarction. Perioperative myocardial ischemia or infarction is usually due to poor intraoperative myocardial protection, incomplete myocardial revascularization, coronary artery spasm, coronary embolism of atherosclerotic debris or air, prolonged systemic hypotension, or severe acute anemia. Tachy- or bradyarrhythmias decrease cardiac output by reducing ventricular preload (e.g., decreased diastolic filling time, loss of atrial contraction or atrioventricular synchrony) or by reducing the number of effective ventricular contractions per minute. Substantial increases in systemic vascular resistance (i.e., vasoconstriction) impede ventricular ejection and lower cardiac output. Vasodilatation from sepsis or anaphylaxis resulting in systemic hypotension could lead to reduced coronary blood flow and myocardial ischemia. Sepsis (an unlikely occurrence in the immediate postoperative period) is also associated with the production of myocardial depressant factors. Anemia may result in reduced blood viscosity (a major determinant of total peripheral resistance) leading to hypotension and decreased oxygen delivery to the heart. The hypotension in anemia, however, is most often due to changes in effective blood volume rather than to the changes in viscosity.

ETIOLOGY AND MANAGEMENT

The multiple variables constantly monitored usually provide sufficient clues as to the cause of low cardiac output. If there is no obvious noncardiac cause such as anaphylaxis or anaphylactoid reaction, acidosis, severe anemia, or marked alterations in body temperature, then the first step is to optimize the preload (PAOP of 15 to 18 mmHg). The next step is to optimize the heart rate by either cardiac pacing or antiarrhythmic drugs. Postoperative myocardial performance is usually best at a rate of 90 to 100 beats per minute. If these measures prove unsuccessful, pharmacologic intervention with inotropic agents, vasodilators, vasopressors, or a combination of these drugs must be considered. The selection of drugs should be based upon the balance of their effects on heart rate, contractility, ventricular preload, and systemic vasculature resistance (Table 49-1). The presence of elevated left- and right-sided filling pressures, a recent cessation of mediastinal drainage, and progressively increasing inotropic drug-dosage requirements suggests tamponade, which should be relieved emergently. TEE has been very helpful in clarifying these situations.

The final therapeutic step, if the preceding measures have proved inadequate, is the use of aortic counterpulsation (i.e., intraaortic balloon pump) or another type of cardiac assist device.

Table 49-1: Medications Used in Low Cardiac Output Syndrome

Medication	Hemodynamic Properties	Dosage Range
Dopamine	Low dose-dopaminergic effect	2-20 μg/kg/min
	Moderate dose-inotropic effect	
	High dose-vasopressor effect	
Dobutamine	Positive inotropic agent	2-20 μg/kg/min
Epinephrine	Positive inotropic agent	1-4 μg/min
Amrinone	Positive inotropic agent	10-15 μg/kg/min
Isoproterenol	Potent inotropic agent	0.5-10 μg/min
	Pronounced chronotropic effect	
Norepinephrine	Potent vasopressor effect; inotropic effect	1-100 μg/min
Phenylephrine	Potent vasopressor agent	10-500 μg/min

Hypertension

MANAGEMENT

A variety of medications are available for control of hypertension, and the drug selected should depend on the hemodynamic status of the patient, the cardiovascular effects of the drug, and the patient's other medical problems. Systemic hypertension in the presence of a high left ventricular filling pressure and marginal cardiac output is most appropriately treated by an arterial vasodilator. Nitroprusside relaxes vascular smooth muscle in arterial resistance vessels (both systemic and pulmonary) and in venous capacitance vessels. The potential exists with nitroprusside for dilation of the coronary resistance vessels and production of a coronary steal syndrome by shunting blood away from any ischemic areas. The advantages of the drug are its very rapid onset and the rapid dissipation of its effects. The risks with this agent are rapid and excessive hypotension and the potential for either acute cyanide toxicity or thiocyanate toxicity with prolonged use.[19]

Nitroglycerin is primarily a venous dilator, although it produces varying degrees of arterial vasodilatation, especially at high doses. Its major role in treating systemic hypertension is in the patient with high filling pressures and active myocardial ischemia.[20] Nicardipine is a potent systemic and coronary vasodilator without the risk of coronary steal, and it has no significant effect on the venous system. It can, therefore, effectively control postoperative hypertension without reducing the filling pressures or causing a coronary steal. While its onset of action is rapid (1 to 2 min), its elimination half-life is about 40 min. Unlike some calcium channel blockers, this agent lacks a negative inotropic effect and has no effect on atrioventricular conduction.[21] Hydralazine is a direct arterial vasodilator, which is usually administered in intermittent intravenous or intramuscular doses. Hydralazine-induced arterial vasodilation may produce a compensatory tachycardia. This drug is frequently resorted to in patients who are

hemodynamically stable but remain hypertensive several days after surgery and cannot yet take or absorb oral medications.

When the hypertension is associated with a normal cardiac output and a relatively rapid sinus heart rate or a propensity toward dysrhythmias, a drug with negative inotropic and chronotropic properties is desirable. Esmolol is a cardioselective, ultrashort-acting beta blocker, which also produces a rapid and titratable control of the blood pressure accompanied by a decrease in heart rate. The drug is usually tolerated satisfactorily by patients with a history of bronchospasm because of its relatively high selectivity for $beta_1$-type adrenergic receptors. It is not ideal for patients with impaired cardiac contractility, particularly in the presence of elevated filling pressures.[22] Diltiazem is an arterial vasodilator that has a mild negative inotropic effect and a more potent negative chronotropic effect. Verapamil is a less potent vasodilator but with more potent negative inotropic, chronotropic, and dromotropic effects. It can be administered intravenously by either boluses or continuous infusion. Labetalol has both alpha- and beta-blocking properties as well as a direct vasodilatory effect. Its predominant effect is as a beta blocker, especially in the intravenous form. The angiotensin-converting enzyme inhibitor enalaprilat, which is the active form of enalapril, can be administered intermittently by the intravenous route. This agent is usually reserved for the patient who is hemodynamically stable with either a normal or reduced cardiac output but with hypertension expected to persist (Table 49-2).

Table 49-2: Intravenous Antihypertensive Agents

Drug	Peak Effect	Duration	Dosage
Nitroprusside	Immediate	2-5 min	0.3-1.0 μg/kg/min
Nitroglycerine	Immediate	2-5 min	5-100 μg/min infusion
Nicardipine	5-60 min	20-40 min	2.5 mg over 5 min; may repeat times 4 at 10-min intervals; infusion 2-15 mg/h
Esmolol	2-5 min	8-10 min	1-min loading infusion of 0.25-0.5 mg/kg; sustained infusion of 50-200 μg/kg/min
Enalaprilat	15-30 min	6 h or more	0.625-1.25 mg slowly over 5 min every 6 h
Hydralazine	15-20 min	3-4 h	5- to 10-mg bolus may be repeated every 15 min; up to total of 40 mg
Diltiazem	3-30 min	3 h	20- to 25-mg bolus may repeat; infusion of 10-20 mg/h
Verapamil	2-3 min	20-40 min	5- to 10-mg bolus; may repeat in 10 min; infusion of 3-25 mg/h
Labetalol	5-15 min	2-6 h	20-mg bolus over 2 min; then 40- to 80-mg boluses every 15 min until effect achieved (to total dose of 300 mg)

Arrhythmias

GENERAL CONSIDERATIONS AND SINUS TACHYCARDIA

The most common rhythm disturbance immediately after cardiac surgery is sinus tachycardia.

This condition is appropriately treated by searching for and correcting the underlying cause (pain, anxiety, low cardiac output, anemia, fever, or beta-blocker withdrawal). The second most common arrhythmia is ventricular ectopy. Again, an underlying cause such as myocardial ischemia, hypokalemia, hypomagnesemia, hypoxia, or administration of sympathomimetic drugs must be sought and corrected if possible. It is also important to review the patient's preoperative record to determine if the patient had preexisting ectopy. Patients with chronic ventricular ectopy frequently have their ectopy exaggerated postoperatively.[23] In the presence of active myocardial ischemia, pharmacologic suppression is advisable for complex ventricular ectopy. In the first 12 h after coronary bypass surgery, myocardial ischemia must be suspected and is difficult to exclude; accordingly, the preceding policy for ectopy suppression should be adhered to with the possible exception of those with known chronic ectopy. Lidocaine is the drug of choice in most instances. The loading dose of lidocaine is approximately 3 mg per kilogram of ideal body weight given over 20 min. One approach is to give an initial bolus of 75 mg, following by 50 mg every 5 min to a total dose of 225 mg. An alternative is to give a priming dose of 75 mg, followed by a loading infusion of 150 mg over 20 min. The usual initial maintenance infusion is 1.5 to 2.5 mg/min. If the arrhythmia is uncontrolled, one can give another bolus of 25 to 50 mg and increase the infusion rate. The chances of toxicity rise significantly at infusion rates above 4 mg/min, especially in individuals greater than 65 years of age. If the ectopy does not respond to lidocaine, the option is to not use an antiarrhythmic agent unless ventricular tachycardia occurs *or* to use intravenous amiodarone. Pacing the heart at a faster rate may prove successful in suppressing the ectopy.

VENTRICULAR TACHYCARDIA AND FIBRILLATION

After cardiac surgery, a few patients develop sustained ventricular tachycardia (either monomorphic or polymorphic) or ventricular fibrillation. These profound rhythm disturbances may develop in the absence of evidence of acute myocardial ischemia or infarction or electrolyte imbalance. In most cases the patients have had previous myocardial infarction and have undergone "complete" revascularization, including regions likely to be nonviable. Reperfusion of these areas that probably include viable as well as nonviable myofibrils embedded in the healed infarct may lead to altered dispersion of repolarization. These changes support development of reentry arrhythmias.[23] The ventricular tachycardia in these patients uncommonly responds to lidocaine and usually requires amiodarone. In some instances, a combination of amiodarone and a beta blocker is required. In a rare circumstance, aortic counterpulsation has seemed to be of benefit.

Every encounter with a wide complex tachycardia requires careful consideration as to the possibility of supraventricular tachycardia with aberrant conduction. In the presence of atrial fibrillation with a rapid ventricular response, right bundle branch aberrant conduction often mimics ventricular tachycardia. Care must be given to avoid lidocaine in these situations, because it may result in an even more rapid ventricular rate.

Wide complex tachyarrhythmias in the range of 250 to 300 beats per minute should suggest the presence of an anomalous conduction pathway. The mechanism of this arrhythmia usually involves atrial flutter, with one-to-one conduction or atrial fibrillation with a very fast ventricular response involving an anomalous pathway. Once this is recognized, procainamide becomes the drug of choice, since it does have favorable therapeutic effects on the bypass track tissue. Lidocaine and verapamil should be avoided if the presence of an anomalous pathway is suspected (see also Chap. 24).

SUPRAVENTRICULAR ARRHYTHMIAS

The most common supraventricular dysrhythmias, with the exception of sinus tachycardia, are atrial fibrillation and atrial flutter. These rhythm disturbances occur in 10 to 30 percent of patients following cardiac surgery. The predominant predisposing factor in the development of atrial

fibrillation is the patient's age. The prevalence of atrial fibrillation in postoperative cardiac patients <40 years of age is as low as 3.7 percent, while the prevalence is at least 28 percent in patients >70 years. Atrial fibrillation is most likely to appear on the second postoperative day. Within 1 to 3 days, 80 percent of these patients will return to sinus rhythm with only digoxin or beta-blocker therapy.[24-26] The prophylactic use of beta blockers has a protective effect against the development of atrial fibrillation or flutter. This beneficial effect has been demonstrated with any one of several beta blockers, administered in low or high doses and started preoperatively or postoperatively. Neither digoxin nor verapamil has demonstrated effective prophylaxis against atrial fibrillation or flutter.[27]

Preoperative oral administration of amiodarone also reduces the prevalence of postoperative atrial fibrillation.[28] The major limitation to the widespread application of this prophylactic approach is the apparent need for a 7-day preoperative treatment period. An accelerated loading regimen over 1 to 2 days may be effective, but is unproved.[29]

Intravenous infusions of either esmolol or diltiazem can be used to control the ventricular rate with atrial fibrillation or flutter. Esmolol is given as a 1-min loading infusion of 0.25 to 0.5 mg/kg, followed by a sustained infusion of 50 to 200 μg/kg/min. Diltiazem is administered as a bolus of 20 to 25 mg (which may be repeated), followed by an infusion of 10 to 15 mg/h.

Atrial epicardial pacing wires provide the means of atrial pacing to convert some cases of atrial flutter to sinus rhythm.[25] Short bursts (15 to 30 s) of atrial pacing at rates of 300 to 600 per minute may be effective in converting atrial flutter. Approximately 10 percent of patients with atrial fibrillation require electrical cardioversion to restore sinus rhythm. If hemodynamic compromise is present and aggravated by a supraventricular tachyarrhythmia, cardioversion should be used immediately rather than later.

Intravenous ibutilide (1 mg infused over 10 min to be repeated once if necessary) is the most effective pharmacologic means of converting recent-onset atrial flutter. The drug is much less effective (in the range of 30 to 50 percent) for conversion of recent-onset atrial fibrillation. The disadvantage of ibutilide is the propensity for causing torsades de pointes in 2 to 4 percent of patients.[29]

CONDUCTION DEFECTS

The prevalence of intraventricular conduction abnormalities after coronary bypass surgery is reported to be from 1 to 45 percent, with approximately 10 percent being the most commonly reported frequency. The most common conduction defect is right bundle branch block, which may be due to selective sensitivity of the right bundle to the effects of hypothermia and the extracorporeal circulation process. Only about 5 percent of the patients are left with a permanent conduction abnormality, and the prognosis for these patients is no worse than it is for comparable patients with no conduction defect.[30,31] The development of high-degree (second- or third-degree) atrioventricular block is an indication for temporary pacing via epicardial pacing wires. Atrioventricular block is not as common as either bundle branch block or fascicular block, but it does occur, especially after aortic valve surgery.

Respiratory Management

EXPECTED RESPIRATORY CHANGES AFTER CARDIAC SURGERY

Pulmonary problems are the most significant cause of morbidity following cardiac surgery. The pain associated with sternotomy and, especially, with thoracotomy has a deleterious effect on the patient's willingness to breathe deeply and cough. Pain caused by the presence of chest tubes may also interfere with normal respiratory function. Phrenic nerve damage can result in diaphragmatic

dysfunction. More commonly, the diaphragm is passively displaced cephalad by abdominal contents (gastrointestinal intraluminal air and fluid and edematous bowel) in the anesthetized, paralyzed patient supported by mechanical ventilation. Elevated left side of the heart filling pressures may cause alveolar edema and, in some patients, increased capillary permeability may exist. Insertion of an oro- or nasogastric tube by the anesthesiologist while the patient is under general anesthesia is recommended.

Atelectasis is the most common pulmonary complication, occurring in about 70 percent of patients following cardiac surgery with CPB.[32] During CPB, the lungs are not perfused and are usually allowed to collapse. Once the lungs are reexpanded, a variable amount of atelectasis remains. While the atelectasis might be microscopic, intermediate degrees (subsegmental and segmental) are common. The preponderance of atelectasis occurs in the left lower lobe because of its compression during cardiac surgery, the tendency to suction more thoroughly the right mainstem bronchus during blind naso-orotracheal suctioning, and the frequent surgical practice of opening the left pleural space to facilitate dissection of the left internal mammary artery. Evidence for a depletion of surfactant after cardiopulmonary bypass is lacking.[33]

After thoracotomy, both lung and chest wall compliance decrease significantly. The maximum decrease occurs at approximately 3 days, but the decrease persists to a lesser degree 6 or more days after sternotomy. Alterations in chest wall mechanics lead to a decrease in the forced expiratory volume (FEV_1) and the functional residual capacity (FRC). The changes in the FEV_1 may persist for 6 weeks. In addition to these changes in flows and volumes, reduced inspiratory strength and uncoordinated rib cage expansion occur. These changes result in an increase in respiratory rate and a decrease in tidal volume, a decrease in respiratory efficiency, and an increase in oxygen cost of breathing. The atelectasis and decrease in lung volume result in ventilation:perfusion mismatch and shunting. The clinical manifestation is a decrease in arterial PO_2 and hemoglobin saturation.[33]

There is little evidence of a significant increase in lung water after routine CPB. When increased capillary permeability exists, it is usually related to elevated cardiac filling pressures.[33]

BASIC CONCEPTS OF OXYGENATION AND ALVEOLAR VENTILATION

The goals of mechanical ventilation are the maintenance of satisfactory arterial oxygenation and CO_2 removal. Direct measurement of PaO_2 is generally used to assess the overall adequacy of blood oxygenation, while pulse oximetry (SpO_2) is used to monitor peripheral arterial hemoglobin saturation on a continuous basis. An $SpO_2 > 90$ percent is considered to be acceptable, but it may be associated with a marginal PaO_2. The oxygen-hemoglobin dissociation curve portrays this relationship (Fig. 49-1). The shoulder of this sigmoid curve lies at a PaO_2 of approximately 65 mmHg. A PaO_2 below this level will result in a precipitous fall in the oxygen saturation of hemoglobin. With hypothermia or with profound respiratory alkalosis, the curve will shift to the left, resulting in more avid binding of oxygen to hemoglobin and less release of oxygen to the tissues. The patient will likely be receiving 100 percent oxygen during transfer from the operating room to the ICU or postanesthesia care unit. The FIO_2 should be gradually decreased to 0.4 as tolerated to minimize adsorption atelectasis and pulmonary O_2 toxicity. Mechanical ventilation is also used to maintain alveolar ventilation, which regulates the arterial blood CO_2 tension ($PaCO_2$). Alveolar ventilation is regulated by controlling the tidal volume and the respiratory rate. Generally, the ventilator should maintain an exhaled minute ventilation of 6 to 8 L/min. Decreasing the tidal volume below 8 to 10 mL/kg may result in alveolar hypoventilation and atelectasis. Mild hypocarbia ($PaCO_2$ of 30 to 35 mmHg) is satisfactory immediately after surgery, but more profound respiratory alkalosis should be avoided because it leads to hypokalemia and a leftward shift of the oxygen-hemoglobin dissociation curve (decreased oxygen release to the

tissues). Hypocarbia is best corrected by reducing the ventilator rate.

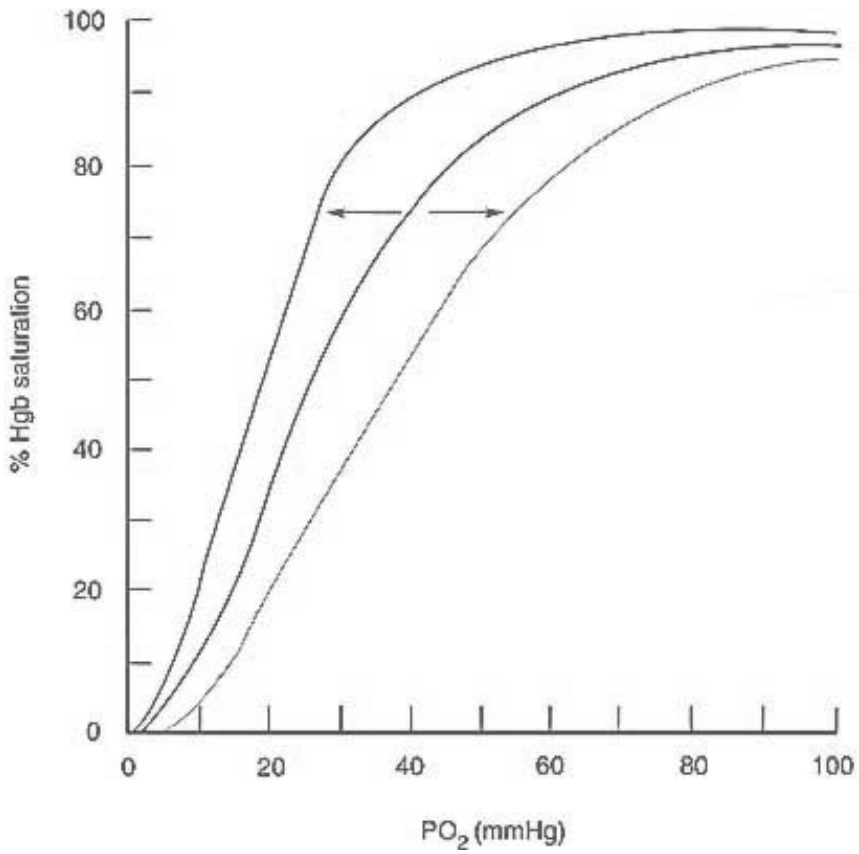

Figure 49-1: Oxygen-hemoglobin dissociation curve. The curve depicts the saturation of hemoglobin at increasing levels of PaO_2. A shift of the curve to the left increases the affinity of hemoglobin for oxygen and a shift to the right decreases the affinity.

Hypercarbia in the immediate postoperative period usually indicates that minute ventilation is inadequate. The problem can be rectified primarily by increasing the ventilator rate; in some cases it is appropriate to increase the tidal volume as well. Later, as the patient is weaned from the ventilator, hypercarbia may reflect opioid analgesia (a necessary side effect of satisfactory analgesia) or compensatory hypoventilation in response to a metabolic alkalosis, most likely due to excessive diuresis. Acetazolamide (Diamox), 250 to 500 mg intravenously every 6 h, is beneficial in correcting a primary metabolic alkalosis. Severe hypercarbia should raise a concern about mechanical problems such as ventilator malfunction, endotracheal tube malposition, or a pneumothorax.[5] Occasionally, hypoxemia and even hypotension may develop in the mechanically ventilated patient due to a tension pneumothorax or hemothorax. If the latter are suspected, assessment of breath sounds and a chest x-ray are indicated for confirmation.

VENTILATORY WEANING AND EXTUBATION

Ventilatory support should be reduced as tolerated when the cardiovascular system has become stable and the arterial oxygen tension is satisfactory [PaO_2 > 70 mmHg, with FIO_2 of 0.5 and PEEP (peak end-expiratory pressure) of 5 cm H_2O]. The patient should also be alert, normothermic, and have no active bleeding. Monitoring of SpO_2 and $ETCO_2$ is helpful and allows the weaning process to be done safely and expeditiously. Typically, the intermittent mandatory ventilation rate is decreased in a stepwise fashion to 0. Then PEEP and pressure support are reduced. Finally, a T-piece adapter is connected to the endotracheal tube and the patient is allowed

to breathe oxygenenriched air spontaneously. After 30 to 60 min, the arterial blood gases are analyzed. Weaning should be discontinued if any of the following signs appear: SpO_2 < 90; PaO_2 < 60 mmHg; $ETCO_2$ > 50 mmHg; $PaCO_2$ > 55 mmHg; pH < 7.30; 10-mmHg rise in pulmonary artery pressure; respiratory rate > 30; 20-mmHg rise in systemic blood pressure; or 20-beat rise in heart rate.[5]

Most patients require low to moderate doses of morphine or another opioid in order to tolerate the endotracheal tube. As long as the spontaneous ventilatory rate remains greater than 15 breaths per minute, the patient will almost certainly be able to maintain adequate ventilation after the endotracheal tube is removed. Common mistakes that contribute to patient discomfort and difficulty in achieving tracheal extubation are (1) trying to sedate the patient with benzodiazepines only, which have no antitussive effect and (2) avoiding opioids for fear of respiratory depression.

BRONCHOSPASM

Severe bronchospasm during CPB is an unusual event, but it can occur. A few patients cannot have their chest cavity closed at the end of surgery because of hyperinflated lungs. The most likely cause of this fulminant bronchospasm is activation of human C5a anaphylatoxin by the extracorporeal circulation. Other likely causes of bronchospasm in the postoperative period are cardiogenic pulmonary edema; simple exacerbation of preexisting bronchospastic disease triggered by instrumentation, secretions, or cold anesthetic gas; beta-adrenergic blockers in susceptible individuals; and allergic reaction to protamine.[32]

The initial therapy of bronchospasm in the postoperative patient, once a diagnosis of heart failure is excluded, should be inhaled $beta_2$-agonists (terbutaline, metaproterenol, albuterol) and/or inhaled cholinergic agents (ipratropium bromide or glycopyrrolate). In the inhaled form these rather potent bronchodilators have minimal cardiovascular effects. In addition to their bronchodilator effect, these agents may augment mucociliary transport and aid in clearing secretions. A combination of $beta_2$-agonists and cholinergic agents should be tried in the patient refractory to a single agent. Even more refractory bronchospasm requires either a short course of systemic steroids or intravenous aminophylline. In addition to being a bronchodilator, aminophylline is a mild diuretic, increases the central nervous system respiratory drive, improves respiratory muscle function, and may decrease pulmonary artery pressure. It is, however, arrhythmogenic and chronotropic.

Postoperative Oliguria and Renal Insufficiency

ETIOLOGY

The use of radiocontrast agents in the days immediately preceding cardiac surgery may embarrass renal function, as manifested by a rise in blood urea nitrogen and serum creatinine values. Following CPB, there is a substantial incidence of postoperative renal dysfunction (up to 30 percent) but a relatively low incidence of severe renal impairment requiring dialysis (1 to 5 percent). Renal blood flow and glomerular filtration rate are reduced by 25 to 75 percent during bypass, with partial but not complete recovery in the first day after CPB. This reduction in renal function is attributed to renal artery vasoconstriction, hypothermia, and loss of pulsatile perfusion during CPB. Angiotensin II levels are higher with nonpulsatile flow as compared to pulsatile flow. While renal dysfunction cannot be consistently related to the systemic blood pressure and pump flow rate during nonpulsatile bypass, there is a definite relation between the incidence of postbypass renal dysfunction and the duration of CPB. In addition to the duration of CPB, the risk of developing postbypass renal failure seems to be a function of the patient's underlying renal function (also affected by age) and the perioperative circulatory status. The histologic changes that accompany renal impairment after cardiopulmonary bypass are characteristic of tubular necrosis.

The tubular cells seem to be the most susceptible to acute reductions in renal perfusion.[33]

MANAGEMENT

There are three agents (so-called renoprotective drugs) that might be used during CPB to prevent an ischemic insult to the kidneys. Mannitol used in the CPB priming fluid may moderate ischemic insult, probably by volume expansion and hemodilution. It also initiates an osmotic diuresis, which prevents tubular obstruction and may serve as a free radical scavenger. Furosemide appears to improve renal blood flow when given during bypass. So-called renal dose dopamine (1 to 2.5 μg/kg/min based on ideal body weight) may maintain renal blood flow and urine output. Once renal failure has developed, none of these drugs is likely to offer any beneficial effect. A megadose of furosemide (200 to 300 mg) may be tried, but if there is no diuretic response, it should not be repeated. Similarly, a single dose of mannitol (12.5 to 25 mg) either with or without furosemide could be tried but not repeated if there is no effect. Whenever possible, it is advisable to avoid potentially nephrotoxic agents in the early postoperative period. Examples of such include radiologic contrast agents, aminoglycoside antibiotics, and angiotensin-converting enzyme inhibitors.

Postoperative Gastrointestinal Dysfunction

GASTROINTESTINAL CONSEQUENCES OF CARDIOPULMONARY BYPASS

The gastrointestinal consequences of CPB appear to be minimal. Reviews of the subject report a 1 percent prevalence.[32,33] Most patients eat within 24 to 48 h after an uncomplicated elective procedure. The limited investigations of the gastrointestinal tract after cardiac surgery have found a slight decrease in hepatic and pancreatic blood flow during cooling and rewarming on bypass and a decrease in gastric pH.[32,34] Transient elevations in liver function tests and hyperamylasemia may occur after cardiac surgery, and the risk factors include long CPB time, multiple transfusions, and multiple valve replacements. Appearance of jaundice portends a poor prognosis.[35] Severe gastrointestinal complications are usually ischemic in nature and are often associated with a low-output syndrome.[32] The use of opioids as part of general anesthesia and postoperative pain management contributes to gastrointestinal dysfunction (cramping, ileus, and constipation) and to postoperative nausea and vomiting. The nausea and vomiting can be minimized by use of a naso- or orogastric tube to maintain gastric decompression intraoperatively and early in the postoperative period, with the additional benefit of improving thoracoabdominal compliance to positive-pressure ventilation.

Postoperative Metabolic Disorders

POTASSIUM IMBALANCE

There are multiple factors that can produce large and rapid shifts in the serum potassium levels during and after CPB. These factors include the following: (1) high-potassium cardioplegia solution used during surgery; (2) renal dysfunction with associated oliguria and decreased clearance of potassium; (3) low cardiac output states accompanied by oliguria and acidosis; (4) hemolyzed red blood cells' release of potassium; (5) potassium lost by diuresis; and (6) diabetes mellitus interference with cellular uptake of potassium, unless insulin is infused intra- and postoperatively. The principal detrimental effects of these potassium shifts is on the electrical activity of the heart. The electrocardiographic signs of hyperkalemia and hypokalemia are described in Chap. 11. The electrocardiographic changes of hyperkalemia do not necessarily appear in the classic progressive manner; they are more related to the rate of rise in serum potassium rather than to the absolute serum concentration. The therapy of severe hyperkalemia should include counteracting the toxic cardiac effects of the elevated potassium with intravenous

calcium gluconate or calcium chloride and lowering the serum level of potassium with sodium bicarbonate and/or administration of regular insulin and glucose. Hypokalemia does not usually become clinically evident until the serum potassium concentration is <2.5 meq/L, and at these levels it can be associated with severe ventricular tachyarrhythmias. Another consequence of potassium depletion is metabolic alkalosis as the hydrogen ions replace potassium ions within the cells. Hypokalemia is treated with the intravenous administration of KCl at a rate of no more than 10 to 15 meq/h. The serum potassium rises approximately 0.1 meq/L for each 2 meq of KCl administered. Large doses of KCl should be administered by a central venous catheter because of the caustic effect of potassium on peripheral veins.

HYPOMAGNESEMIA

Hypomagnesemia is common following cardiac surgery using CPB. Magnesium mimics potassium in its effects on the electrical activity of the heart. The cause of the hypomagnesemia is unknown, but it is probably multifactorial. Many patients will be hypomagnesemic preoperatively due to the use of loop diuretics, thiazides, digoxin, or alcohol and to the effects of type I diabetes mellitus. Magnesium is usually lost in the urine during CPB. Patients with postoperative hypomagnesemia develop atrial and ventricular dysrhythmias more frequently and require more prolonged mechanical ventilatory support than do patients with normal magnesium levels.[36] Magnesium administration also seems to improve stroke volume and cardiac index in the early postoperative period.[37] Magnesium can be administered as magnesium sulfate (2 g in 100-mL solution) to raise serum levels to 2 meq/L.

HYPERGLYCEMIA

During CPB there is a rise in blood glucose levels. The elevation is modest during hypothermia and becomes more marked during rewarming. This rise in glucose is due in part to increased glucose mobilization related to dramatic increases in cortisol, catecholamine, and growth hormone levels during CPB. Also, there is an apparent failure of insulin secretion, particularly during hypothermia, probably related to inhibition of the insulin secretory response by the elevated catecholamines. This blunting of the insulin response persists for the first 24 h after surgery. These changes are exaggerated in the diabetic patient.[38] Insulin requirements are likely to be 7 times greater than the preoperative requirements during the first 4 h postoperatively. Furthermore, such insulin resistance is exacerbated by catecholamines, diuretics, and blood transfusions.[39] These multiple factors make the diabetic patient susceptible to hyperosmolar, hyperglycemia, nonketotic diabetic coma.[40]

Postoperative Fever

Fever is a common occurrence in the postoperative patient. It is generally a consequence of pleuropericarditis, atelectasis, or phlebitis. Since 70 percent of patients have atelectasis after cardiac surgery, it is the most likely etiology of postoperative fever.[32] A reasonable assumption in a patient with a core temperature <38°C (100.4°F) and no evidence of phlebitis or presence of a pericardial or pleural rub is that the source of the fever is atelectasis. The appropriate therapeutic approach is to encourage intensified efforts at incentive spirometry and coughing. Any fever >38.5°C (101.3°F) warrants blood, sputum, and urine cultures. A white blood cell count (total and differential) and a chest x-ray should also be obtained.

Sternal wound infections occur in 0.4 to 5 percent of patients after sternotomy.[41-43] Multiple factors have been identified as increasing the risk of developing sternal wound infection. These include pneumonia, prolonged mechanical ventilation (especially with tracheostomy), emergency operations, postoperative hemorrhage with mediastinal hematoma, early reexploration, obesity, diabetes mellitus, and use of bilateral internal mammary grafts. While some studies have not

found a higher prevalence of sternal wound infections with bilateral mammary grafts, the bulk of the evidence argues to the contrary. Perhaps some of the conflicting results can be explained by the fact that different degrees of devascularization of the sternum occur, depending on the particular technique used to harvest the internal mammary artery. The greatest risk for sternal infection seems to be in diabetic patients who receive bilateral internal mammary grafts.[43] Debate continues as to whether the most appropriate initial treatment is debridement and closure or open packing and subsequent plastic surgical closure with a muscle flap.

Approximately 1 percent of patients who have had coronary artery bypass surgery experience leg wound infections that necessitate extra care. Leg infections seem to occur more frequently in obese women, especially if the thigh veins are harvested.[44]

Neurologic and Neurophysiologic Dysfunction

MECHANISM

The mechanisms thought to account for most cerebral injury during cardiac surgery are macroembolization of air, debris from aortic atheroma, or left ventricular thrombus; microembolization of aggregates of granulocytes, platelets, and fibrin; and cerebral hypoperfusion. Death or disabling stroke occurs in about 2 percent of patients, with another 3 percent experiencing transient or minor functional disability secondary to cerebral infarction.[45] Focal neurologic deficits resulting from intraoperative events are usually noted within the first 24 to 48 h after surgery.

ENCEPHALOPATHY AND DELIRIUM

Alteration of mental status (encephalopathy and delirium) will be seen in approximately 30 percent of patients after cardiopulmonary bypass.[45] While the appearance of these encephalopathic symptoms likely reflects cerebral injury, other causes must be excluded, including drugs, sepsis, fever, hypoxemia, ethanol withdrawal, renal failure, and hyperosmolar state. Postoperative encephalopathic changes, varying from mild confusion and disorientation to protracted somnolence or agitation and hallucinations, may appear at any time during the hospital stay.[46] In fact, some physicians will not accept a diagnosis of postcardiotomy delirium unless the delirium develops following a lucid interval of 2 to 5 days after surgery. Studies of this condition have not identified any consistent risk factors, but advancing age, duration of CPB, and sleep deprivation have been frequently associated. The prevalence of this condition has remained rather constant since the early days of cardiac surgery involving CPB, but there has been a shift in the clinical presentation. Currently, the condition seems to present with disorientation rather than with hallucinations, paranoid ideation, and agitation noted earlier.[46] Recognition of this entity is important because the family can be assured that the patient's mental status is likely to recover. Agitation and acute psychosis in these patients usually respond to intravenous haloperidol, 2 to 10 mg, repeated as needed to produce adequate sedation.

BRACHIAL PLEXOPATHY AND ULNAR NERVE DYSFUNCTION

Another serious neurologic complication of cardiac surgery is brachial plexopathy. This neurologic dysfunction, involving C8 and T1, usually results from mechanical trauma secondary to sternal retraction but may be due to penetration by a posterior fractured segment of the first rib or injury during internal jugular cannulation. There is no specific therapy for this condition, and recovery can take as long as 6 months, with a few cases being permanent.[47] Ulnar nerve dysfunction may result from malpositioning of the upper extremities during surgery, which results in pressure being exerted on the ulnar nerve at the elbow.

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Part 6: CORONARY HEART DISEASE
Chapter 50:

REHABILITATION OF THE PATIENT WITH CORONARY HEART DISEASE

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Cardiac rehabilitation, an essential component of the long-term comprehensive management strategy for coronary patients, includes an individualized regimen of physical activity and health education and counseling appropriate for the individual patient's needs and specific cardiac problem.[1] *Cardiac rehabilitation* is described by the American College of Cardiology as "those exercise and counseling services which reduce symptoms or improve cardiac function"[2] and by the U.S. Public Health Service as "comprehensive, long-term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling." Initially, these services were recommended for patients following myocardial infarction (MI); subsequently, they were applied after coronary artery bypass graft (CABG) surgery or for patients with chronic stable angina pectoris. More recently, the U.S. Health Care Financing Administration concluded[3] that heart transplant patients and patients who had undergone percutaneous transluminal coronary angioplasty (PTCA) could benefit from prescribed cardiac rehabilitation. The Clinical Practice Guideline *Cardiac Rehabilitation*[4] documented the benefits of rehabilitative services for patients with heart failure and left ventricular (LV) systolic dysfunction and recommended their application.

The current short hospital stay for uncomplicated MI necessitates early ambulation and an accelerated educational regimen, with deferral of most teaching and counseling to the outpatient setting. Early discharge from the hospital is characteristic for patients after successful myocardial reperfusion by coronary thrombolysis or acute primary angioplasty. Patients recovering from CABG surgery typically undergo rapid ambulation, have a short hospital stay, and constitute an increasing percentage of patients referred for cardiac rehabilitation.[5] Such patients without prior MI characteristically have good ventricular function and favorable survival and are at low risk for proximate coronary events. Many require protracted guidance for coronary risk reduction; early counseling appears to aid in averting physiologic and psychological disability. Most patients following successful PTCA have brief hospital stays, good functional status, and early resumption of employment and other activities.[6,7] Patients with stable angina without recent MI constitute almost one-fourth of the total coronary population but are undeserved in terms of rehabilitative care. They are frequently not referred for formal rehabilitative services, often due to lack of insurance reimbursement. This population often has substantial loss of productivity and reduction in the quality of life and requires comprehensive medical management, with needs that may exceed those of patients after uncomplicated MI. With the aging of the U.S. population, coronary rehabilitative care is now provided to many elderly patients,[8,9] as well as to many patients with severe and complicated coronary illness. There is increasing contemporary emphasis on education and counseling as additional cornerstones of rehabilitative care, using the behavioral approach to assist patients in coronary risk reduction and other cardiovascular health-related goals[10-12]; on psychosocial assessment and interventions; and on occupational assessment and vocational counseling.

Each year almost 1 million survivors of MI are candidates for cardiac rehabilitation services in the United States, in addition to more than 7 million patients with stable angina pectoris and patients following revascularization with CABG surgery (367,000 patients in 1996, 44 percent under age

65) or PTCA and other transcatheter interventional procedures (482,000 in 1996, 51 percent younger than age 65). Of these several million patients with coronary heart disease for whom benefits can be anticipated from cardiac rehabilitation, only 11 to 20 percent participated in formal rehabilitation programs.[4,13] Among patients with acute MI enrolled in the Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO) trial, 38 percent of U.S. patients and 32 percent of Canadian patients attended cardiac rehabilitation programs.[14] A U.S. national survey of 500 cardiac rehabilitation programs highlighted the underrepresentation of women, nonwhites, and those older than age 65.[15] Heart failure is the most common discharge diagnosis for hospitalized Medicare patients in the United States and the fourth most common discharge diagnosis for all hospitalized patients. Although coronary heart disease (CHD) is not etiologic in all these patients, it is a substantial contributor to heart failure. Application of cardiac rehabilitation services to patients with heart failure (as well as after cardiac transplantation) has gained increasing acceptance as its benefits and safety have been documented. An estimated 4.7 million patients with heart failure are potential candidates for cardiac rehabilitation.[4]

Nonetheless, this component of cardiac care is underutilized despite its efficacy and cost-effectiveness.[16,17]

EXERCISE TRAINING

Although no single randomized trial of exercise training demonstrated a reduction in mortality and morbidity in patients following MI, in part owing to inadequate sample size and/or duration of follow-up, to high dropout rates, etc., favorable trends occurred in several. Metaanalysis[16,18] of pooled data from large prospective, randomized exercise trials suggest as much as a 25 percent survival advantage for exercising subjects at 3-year follow-up following MI. This benefit cannot be attributed solely to exercise training, since many studies included coronary risk reduction as well as exercise. The reduction in mortality approaches that resulting from pharmacologic management of patients following MI with beta-blocking drugs and of patients with LV systolic dysfunction with angiotensin-converting enzyme (ACE) inhibitor therapy. The reduction in cardiovascular mortality was 26 percent in multifactorial randomized trials of cardiac rehabilitation as compared with 15 percent in trials that involved solely exercise training. There is no evidence that cardiac rehabilitation exercise training changes the rates of nonfatal reinfarction.[4,11]

The evidence-based Clinical Practice Guideline *Cardiac Rehabilitation* of the U.S. Department of Health and Human Services[4] highlights the beneficial effect of cardiac rehabilitation exercise training on exercise tolerance as one of the most clearly established favorable outcomes for coronary patients with angina pectoris, MI, CABG surgery, and PTCA and for patients with compensated heart failure or a decreased LV ejection fraction. This approach particularly benefits patients with decreased exercise tolerance.[19] Improved exercise tolerance was evident for both women and men and also occurred in elderly patients. The most consistent benefit resulted from exercise training at least three times weekly for 12 or more weeks' duration. The duration of aerobic exercise sessions varied from 20 to 40 min, at an intensity approximating 70 to 85 percent of the baseline exercise test heart rate. Improvement in exercise tolerance occurred with lower-intensity exercise as well.[20-22] Maintenance of exercise training is required to sustain improvement in exercise tolerance.

No significant increase in cardiovascular complications or other serious adverse outcomes was reported in any randomized, controlled trial of exercise training in coronary patients. These randomized, controlled trials involved 3932 patients following MI, 745 patients with catheterization-documented coronary disease, 215 patients following CABG surgery, and 139 following PTCA. No deterioration in measures of exercise tolerance was reported in any patients undergoing exercise training, nor did any controlled study document significantly greater

improvement in exercise tolerance in control patient groups compared with exercising patients.

The improvement in functional capacity with exercise training, averaging 20 percent after recovery from MI, is associated with a reduction in activity-related symptoms: angina, dyspnea, fatigue, and at times claudication. Exercise training results in (1) an improvement in oxygen transport, evident as an increase in maximal cardiac output and oxygen consumption, (2) a reduction in heart rate, systolic blood pressure, and thereby myocardial oxygen requirement at rest and at submaximal work levels, and (3) and more rapid return to normal of the exercise heart rate.

The improvement in functional capacity and decrease in activity-related symptoms following usual moderate-intensity exercise training appear to be related primarily to peripheral adaptations. These include an increase in oxygen extraction and use by trained skeletal muscle, with a decrease in myocardial oxygen demand and requirement for coronary blood flow at submaximal exercise. The redistribution of cardiac output, decrease in systemic vascular resistance, and autonomic nervous system adaptations (particularly lowering of the heart rate) result in a decreased rate-pressure product at submaximal levels of exertion. High-intensity, long-term endurance exercise may effect cardiac (central) adaptations, possibly including improved ventricular contractility and increased maximal stroke volume in selected coronary patients[23]; such intensive exercise training is feasible for only a small subset of coronary patients. There is no evidence that exercise training as a sole intervention alters the angiographic characteristics of coronary lesions, increases coronary blood flow or myocardial oxygen supply, or stimulates the formation of a coronary collateral circulation in humans. No consistent improvement in cardiac hemodynamic measurements or ventricular systolic function has resulted from exercise training.[24,25] Exercise training, however, may improve skeletal muscle functioning in patients with heart failure.[26] Exercise training can decrease evidence of myocardial ischemia, as measured by exercise electrocardiogram (ECG) testing, ambulatory ECG recording, and radionuclide perfusion imaging.[27,28] In several randomized clinical trials, apparently spontaneous improvement in resting ejection fraction after MI occurred in both exercising and control populations, rendering suspect the improvements in ejection fraction described in observational studies of exercise training. There were no consistent changes in ventricular arrhythmia related to exercise rehabilitation.

Clinical benefits of exercise training include a decrease in the symptoms of angina pectoris in patients with coronary disease[27] and the symptoms of heart failure in patients with LV systolic dysfunction.[29,30] The improvement in electrocardiographic and nuclear cardiology measures of myocardial ischemia provides objective support for the symptomatic improvement. Exercise training of patients with LV systolic dysfunction provided added symptomatic improvement to that achieved by appropriate medication.[30]

The decrease in symptoms and improvement in functional status that result from exercise training can enable a return to remunerative employment as well as to leisure and recreational activities.[31] For more impaired coronary patients, including many elderly ones, even a modest increase in functional capacity can help maintain independence.[8,9,32-35]

Guidelines for Prescriptive Exercise Training

Individualized medically prescribed physical activity is the hallmark of rehabilitative exercise training. Standards and guidelines have been promulgated by a number of professional organizations.[2,37-43] The prescriptive components of exercise training include its "dosage," determined by the intensity, frequency, and duration of exercise; the types of exercise; and the rate of progression of exercise intensity. Coronary patients should not exercise at a level higher than that documented to produce an appropriate cardiovascular response during testing. The predischarge (or early posthospitalization) exercise test, typically performed for risk stratification, can serve as the basis for initial exercise recommendations. It is inappropriate to use age-predicted

target heart rates for coronary patients; disease, therapies, and prior levels of training or fitness may influence the heart rate response to exercise.

Prescription of target heart rate range is based on the results of exercise testing. Although in prior years patients were advised to exercise to a target heart rate range between 70 and 85 percent of the highest level safely achieved at exercise testing,[44] exercise intensities in the 50 to 70 percent heart rate range have produced comparable improvement in functional capacity and endurance and may provide greater safety because of the lower risk of cardiovascular complications with unsupervised exercise.[21,22,45] These lower rates are less likely to produce discomfort that may deter long-term exercise adherence. The documented efficacy of lower-intensity exercise training to improve aerobic capacity has increased both its applicability and acceptance.[1,21,22] Particularly for unfit patients or those with lower exercise capacities, the increased comfort of lower-intensity exercise may encourage adherence, although increased duration of training may be required. Comparable favorable effects on quality of life occurred with low- and high-intensity exercise.[46] An alternative method for calculating target heart rate involves 70 to 85 percent of the difference between peak exercise test heart rate and resting heart rate, added to resting rate. This method may be advantageous in patients whose heart rate is attenuated by beta-blocking or other drugs.

The basic design of an exercise session involves an initial 5 to 10 min of warm-up exercise, i.e., stretching and range-of-motion activities that enable musculoskeletal and circulatory readiness for exercise. This is followed by a 20- to 40-min endurance component that initially involves walk-run sequences or exercise on a stationary bicycle or treadmill; for these activities, skill is a minimal component of the intensity of work demand.

When space for exercise is limited, "station" training may be preferable, with participants serially using bicycle ergometry, arm ergometry, rowing machines, and treadmills. When more space is available, gymnasium-type programs can accommodate larger numbers of patients for walk-jog activities and floor exercises; some facilities have indoor or outdoor tracks. A final 5- to 10-min cool-down period entails a gradual decrease in intensity that allows the heart rate to slow and averts postexercise hypotension. Three exercise sessions weekly appear adequate, and a greater frequency does not significantly improve aerobic capacity. Aerobic games, as a recreational component, add variety to an exercise program and improve adherence; they also provide upper body exercise. Because the oxygen cost of these activities varies with each patient's skills and competitiveness, they should be limited early in exercise training.

As the level of training increases, recreational activities in which skill often influences the intensity of work may add variety to the exercise regimen. Enjoyable, effective endurance activities include rope skipping, bicycling, skating, swimming, rowing, and aerobic dancing; both rope-skipping and swimming (for unskilled swimmers) impose higher workloads and should be undertaken carefully.

Characteristics of Aerobic (Dynamic) and Strength (Isometric) Exercise Training

Aerobic (dynamic) exercise, rhythmic repetitive movements of large muscle groups, traditionally is prescribed for coronary patients. The physiologic response, an increase in heart rate, parallels the intensity of activity, and an increase in stroke volume occurs in young and middle-aged patients. In most elderly patients, the increase in heart rate predominates, with little increase in stroke volume. Systolic blood pressure increases progressively with exercise intensity, with maintenance of or slight decrease in diastolic blood pressure and widening of the pulse pressure.

By contrast, with strength (isometric) training, the increase in heart rate is modest, and the increase in cardiac output is slight. There is a substantial increase in systolic blood pressure with high-intensity isometric activity, particularly in unfit individuals; this may provoke angina, ventricular dysfunction, and/or arrhythmias and is the basis for limiting isometric activity in

coronary patients with a low exercise capacity. Once a reasonable aerobic capacity is achieved, combined aerobic and strength training exercises in coronary patients may produce substantial training effects and improve muscle strength,[47] with resulting improvement in endurance and the ability to return to active occupational and recreational lifestyles.[48] Studies document the effectiveness of mild to moderate resistive exercise training in selected patients with coronary heart disease.[49-52] The absence of signs or symptoms of myocardial ischemia, abnormal hemodynamic changes, and cardiovascular complications suggests that resistance exercise training is safe for coronary patients who have previously participated in aerobic exercise training. A major change in contemporary exercise programs is the inclusion of strength training for appropriately selected coronary patients. Most reported studies have involved small numbers of low-risk male patients, 70 years or younger, with minimal functional aerobic impairment and with normal or near-normal LV function. The extent to which the safety and effectiveness of resistance training demonstrated by these studies can be extrapolated to other populations of coronary patients (e.g., women, older patients of both genders with low aerobic fitness, or patients at moderate to high cardiovascular risk) is not known.[4]

Arm versus Leg Exercise Training

Because exercise training is predominantly muscle-specific, both arm and leg exercises should be included in exercise rehabilitation.[53] The heart rate and blood pressure responses to leg work decrease following leg training, with only modest improvement in the response to arm work. Following arm training, the most prominent decreases in heart rate and blood pressure response occur with arm work. In one study, improvement in exercise response of the untrained limb was only 50 to 75 percent of the trained limb, suggesting that about half the increase in trained-limb performance is due to a generalized training effect; the remainder reflects predominantly improved oxygen extraction by trained skeletal muscle.

Since walk-run sequences or exercise on a stationary bicycle or treadmill train primarily leg muscles, supplementary arm exercise training is accomplished by selected repetitive calisthenics, shoulder wheels, rowing machines, and arm ergometers. When data from leg exercise testing are used to prescribe arm exercise, a reduction of about 10 beats per minute in target heart rate range is appropriate. The workload for arm training is about half that for leg training.[53] Since most occupational and recreational activities entail both arm and leg work (and often predominantly arm work), arm exercise training should be included in rehabilitative exercise.

The Effect of Cardiovascular Drugs on Exercise Training

Exercise training can occur in patients receiving antianginal drugs, which may lessen symptoms and improve the ability to exercise.[54] Although beta-blocking drugs decrease the heart rate and blood pressure response to exercise, they do not attenuate the improvement in physical work capacity that results from exercise training. Exercise testing undertaken to prescribe exercise should be performed with patients receiving medications that are planned for their training.

The Role of Exercise Testing in Coronary Rehabilitation

Graded exercise testing, using either a treadmill or a bicycle protocol, is safely performed within the initial weeks following MI.[55] Most centers currently test patients to a sign- or symptom-limited end point because heart rate limits are often inaccurate as a result of antianginal therapy effects on heart rate. Treadmill testing typically entails serial 3-min stages of walking, beginning at slow speed, initially on the level, and then at increasing speed and elevations; comparable test protocols are available for a bicycle ergometer (see Chap. 14). Arm testing may be undertaken in patients with claudication or musculoskeletal problems that make leg testing not feasible.[56]

The results of predischarge exercise tests, performed with or without radionuclide studies, contribute independent prognostic information for risk stratification.[55] High-risk patients are characterized by having a low exercise capacity [peak workload below 4 to 6 metabolic equivalents (METs)]; the occurrence of angina, ischemic ST-segment abnormalities, and/or exercise-induced hypotension at low levels of exercise; and the development of ventricular arrhythmias at low levels of exercise. Radionuclide evidence of myocardial ischemia or LV dysfunction with exercise also indicates an adverse prognosis. Predischarge exercise testing also identifies low-risk patients with a favorable prognosis who do not require additional diagnostic testing, are well-suited for accelerated rehabilitation, and for whom early discharge home and prompt resumption of preinfarction activities, including return to work, can be recommended.[55,57] The exercise test can help define safe levels of activity and guide the surveillance necessary during exercise rehabilitation. This permits simple, effective, accelerated, and less costly rehabilitation for low-risk coronary patients, reserving financial and personnel resources for high-risk patients who may derive substantial benefit from supervised exercise training. Satisfactory performance of an exercise test, coupled with explanation of its relationship to activities to be undertaken at home, may lessen the common fear of postinfarction patients that physical activity may result in reinfarction or death.[58] Such counseling also has been associated with an early return to work.[31]

Safety of Rehabilitative Exercise Training

The Clinical Practice Guideline *Cardiac Rehabilitation*[4] highlights the safety of cardiac rehabilitation exercise training in that randomized, controlled trials involving over 4500 coronary patients showed no increase in morbidity or mortality. A questionnaire survey of 142 U.S. cardiac rehabilitation programs, involving patients participating in exercise rehabilitation between 1980 and 1984, reported a low rate of nonfatal MI of 1 per 294,000 patient-hours and a cardiac mortality rate of 1 per 784,000 patient-hours.[59] Twenty-one episodes of cardiac arrest occurred, with successful resuscitation of 17 patients. A 1978 report[44] also described a low rate of fatal cardiac events during or immediately following exercise training: 1 per 116,400 patient-hours of participation. Definitive information is not available regarding the effect of levels of supervision and of ECG monitoring of exercise training on safety.

NEXT

Chapter 50: REHABILITATION OF THE PATIENT WITH CORONARY HEART DISEASE

IMPLEMENTATION OF CARDIAC REHABILITATIVE CARE

Inpatient, or Hospital, Phase

The major components of rehabilitative care for patients hospitalized for a coronary event include progressive resumption of physical activity (early ambulation) and education and counseling of both patient and family (see also Chap. 42).

EARLY AMBULATION

Early ambulation is designed to limit the detrimental effects of deconditioning: reduced physical work capacity and maximal oxygen uptake; orthostatic intolerance, characterized by orthostatic hypotension and tachycardia (due both to hypovolemia and to a lessened cardiovascular reflex response); increase in blood viscosity owing to a decrease in plasma volume disproportionate to the decrease in red blood cell mass; and decrease in pulmonary ventilation. The decrease in muscle mass and muscular contractile strength renders muscular contraction inefficient, with more oxygen required for comparable work.

Guidelines[60] for physical activity in the coronary or surgical intensive care unit are for initial low-intensity exercise (1-2 METs), with gradual progression in work demand; supervision of progressive ambulation permits detection of inappropriate responses. Patients are encouraged to feed themselves, perform personal care, use a bedside commode, and sit in a bedside chair. Cardiac work is less in the seated than in the supine position. Sitting in a chair two or three times daily limits the hypovolemia of immobilization and resulting orthostatic hypotension. Exposure to gravitational stress, rather than physical activity intensity, appears to be the determinant in limiting hypovolemia, cardiac underfilling, and deterioration of oxygen transport capacity with effort intolerance.[61] Patients perform selected arm and leg exercises designed to maintain muscle tone and increase flexibility and joint mobility. Incentive spirometry is important for postoperative patients.

Disproportionate responses[60] to low-level activity include chest discomfort, dyspnea, or palpitations; a heart rate in excess of 100 beats per minute or lower than 50 beats per minute; ST-segment displacement on the electrocardiographic monitor; appearance of arrhythmias; or a decrease of more than 10 to 15 mmHg in systolic blood pressure. Although the latter usually indicates ischemic ventricular dysfunction, the vasodilator effect of nitrate, calcium channel blocking drugs, or ACE inhibitor therapy also must be considered. A systolic blood pressure response during low-level activity of more than 180 mmHg or a diastolic pressure response of more than 110 mmHg is an indication for antihypertensive therapy. Appropriate responses to ambulation indicate that the patient can progress to higher-intensity activity; disproportionate responses require activity restriction and clinical reassessment for unrecognized cardiac ischemia or ventricular dysfunction.

The major prescriptive hospital activity is walking, with stepwise increases in pace and distance. Patients who must climb steps at home should practice this in the hospital. Most household tasks require a work intensity of 2 to 3 METs. Electrocardiographic telemetry monitoring during ambulation is indicated for selected patients, e.g., those with serious ventricular arrhythmias or asymptomatic myocardial ischemia. A protocol for early ambulation and concomitant educational activities for patients with MI is applicable, with minor modifications, to postoperative coronary patients (Table 50-1).

Table 50-1: Inpatient Rehabilitation: Five-Step Myocardial Infarction Program (Revised 1996: Grady Memorial Hospital/Emory University School of Medicine)

Step	Date	M.D. Initials	Nurse/Exer Specialist Notes	Supervised Exercise	CCU/Step Down Unit Activity	Educational Activity
				CCU		
1	-			Active and passive ROM all extremities in bed	Partial self-care	Orientation to CCU
					Feed self	Personal emergencies, social service aid as needed
				Teach patient ankle plantar and dorsiflexion-repeat hourly when awake	Dangle legs on side of bed	
					Use bedside commode	
					Sit in chair 15 min, 1-2 times/day	Bedside teaching (CCU staff)
2	-			Active ROM all extremi-ties, sitting on side of bed or bedside chair	Sit in chair 15-30 min, 2-3 times/day	Orientation to rehabilitation team, program
					Complete self-care	Smoking cessation
						Educational literature if requested
						Planning transfer from CCU
				Step Down Unit		
3	-			Warm-up exercises, 2-2.5 METs:	Sit in chair ad lib	Normal cardiac anatomy and function
					Walk in room	
				Stretching ROM	Walk to class with supervision	Development of atherosclerosis
				Calisthenics		
				Walk in hall 50-75 ft and back at slow pace	Out of bed as tolerated	What happens when myocardial infarction occurs
						Coronary risk factors and their control
						Diet
4	-			Teach pulse counting, Borg Scale	Tepid shower or tub bath, with supervision	Heart attack management:

				Medications
		ROM and calisthenics, 3 METs	Walk in corridor prn	Exercise
				Surgery
		Practice walking few stairsteps		Response to symptoms
				Family, community adjustments on return home
		Walk 300-500 ft bid		
		Instruct on home exercise		
				Work simplification techniques (as needed)
5	-	Continue above activities	Continue all previous activities	Discharge planning
		Check pulse counting		Medications, diet, activity
		Walk up flight of steps	Predischarge exercise test (as appropriate)	
		Walk 500 ft bid		Return appointments
		Continue home exercise instruction; present information regarding outpatient exercise program		Schedules tests
				Return to work
				Community resources
				Educational literature
				Medication cards

NOTE: 1 foot = 0.30 meter.
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Neither early ambulation nor early hospital discharge adversely affects the short- or long-term morbidity or mortality of appropriately selected coronary patients.[60,62] Benefits include prevention of deconditioning, decrease in pulmonary atelectasis and thromboembolic complications, lessened anxiety and depression, and an enhanced sense of well-being, related to improved functional status. Improved functional status of

patients at hospital discharge has been associated with an earlier and more complete return to work.

EDUCATION AND COUNSELING OF HOSPITALIZED PATIENTS AND THEIR FAMILIES

The current abbreviated hospital stay limits the ability of health professionals to address the informational and learning needs of the patient, spouse, and family; to assist them through recovery; and to prepare them adequately for convalescence. Answering the questions or concerns of patients in a coronary or surgical intensive care unit (or during the preprocedure phase for elective coronary angioplasty or bypass surgery) can provide reassurance. Education includes a brief explanation of the medical or surgical problem(s), tests anticipated in subsequent days, and familiarization with procedures and equipment; this information helps patients adjust to a situation perceived as life-threatening. The temporary nature of most restrictions should be emphasized, citing that improved coronary status with recovery lessens the intensity of surveillance and care.

During the remainder of the hospitalization, providing more information and planning for discharge are appropriate. Increased knowledge can lessen anxiety and improve adherence to recommendations. Patients should be instructed about medications-the purpose, dosage, desired effects, and potential adverse responses of each. Many patients have not taken medications prior to a coronary event and may be unfamiliar with the problems of taking medications. Patients and family members should be taught the appropriate response to new or recurrent symptoms and how to gain access to emergency medical care.

Outpatient, or Ambulatory, Phase

About 70 percent of contemporary survivors of MI are younger than 70 years of age[10] and many patients following successful myocardial revascularization procedures are at low risk for proximate coronary events. Exercise rehabilitation for most low-risk coronary patients, particularly following myocardial revascularization, begins shortly after discharge from the hospital; these patients usually progress rapidly in increasing their intensity and duration of exercise, often without supervision. Coronary patients who are elderly; those with significant comorbidity, myocardial ischemia, heart failure, or serious arrhythmias; those with complications of MI or CABG surgery; or those with severe angina may require exercise surveillance of variable duration.[2,37,39,55] Outpatient exercise rehabilitation is best described by the characteristics of the exercise training and the requirements, duration, and complexity of surveillance, based on the patient's clinical and risk factor status, rather than by traditional phases of earlier years that typically had fixed durations and composition. This is concordant with responding to an individual patient's needs for exercise training rather than requiring a patient to conform to program phases or requirements.

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THERAPEUTIC EXERCISE TRAINING

Therapeutic exercise training typically lasts for 8 to 12 weeks. Initial home exercise may involve progressive walking and walk-jog sequences or serial increases in the intensity and duration of use of a stationary bicycle. Videotapes may help guide and pace home exercise and are available for varying intensities of exercise training. Home-based exercise rehabilitation optimally includes planned communication and management by rehabilitation nurses and other specially trained personnel.[10,11]

In the early years of outpatient exercise rehabilitation, few patients had continuous ECG monitoring because ECG telemetry was not widely available. In subsequent years, complication rates were described as being lower in exercise programs with continuous ECG monitoring.[44] It remains unknown, however, whether ECG monitoring, closer medical supervision, and/or differences in exercise intensity were the safety determinants. More recently, continuous ECG monitoring has not been shown to provide added safety for low-risk patients during supervised exercise[59]; as a result, ECG monitoring is currently recommended only for high-risk patients and other selected patients with problems in exercising,[1,2,4,39] although some recommend more extensive ECG monitoring. Often, ECG monitoring is undertaken solely owing to its requirement for insurance reimbursement rather than based on medical need. Many patients in supervised exercise programs without continuous ECG monitoring or patients exercising independently can be taught either to check their heart rate response intermittently to ensure that it remains in the prescribed target heart rate range or to estimate exercise intensity by the rating of perceived exertion, as described by Borg.[64] In supervised settings, heart rate response can be documented by intermittent use of defibrillator paddles as ECG leads. A technique of value in maintaining appropriate exercise intensity in unsupervised settings is the "talk test," wherein patients exercise only to the level that permits continued conversation with an exercising companion, a level generally below the anaerobic threshold at which respiratory rate accelerates.

High-risk coronary patients may require supervised and often ECG-monitored exercise. These patients are characterized by having a markedly reduced exercise capacity, severely depressed ventricular function, complex ventricular arrhythmias, exercise-induced angina, ischemia, or hypotension at low exercise intensities, and/or the inability to self-monitor exercise heart rate. Because of their increased risk for adverse events, exercise training should occur, at least initially, in a medically supervised and probably ECG-monitored setting.[65] Because exercise-related cardiac complications may be increased not only in proximity to an acute coronary event, the need and duration of ECG surveillance of exercise for these high-risk patients remain uncertain. The uniform success of resuscitation with supervised exercise, despite the rarity of its application, suggests that exercise supervision may be beneficial for selected patients.[59]

Although recent studies document the efficacy of home-based exercise training and risk reduction guided by a specialized cardiac nurse manager, data are not available as to the efficacy of long-term risk reduction or long-term compliance with unsupervised exercise in the absence of management and supervision strategies. Several studies showed that all training regimens appeared to increase functional capacity more rapidly than occurred spontaneously.[11,29,30,47] Supervision of exercise may not entail an "all or nothing" approach; intermittent supervision may be feasible in a community facility, there may be periodic telephone transmission of the exercise

ECG of patients who exercise at home, patients may use inexpensive heart rate monitors during home exercise, or a combination of these techniques may be used. It is not known whether any of these approaches improves adherence to exercise or exercise safety; several studies of independent exercise showed a lack of coronary risk reduction.

The Clinical Practice Guideline *Cardiac Rehabilitation*[4] highlights alternative approaches to the delivery of cardiac rehabilitation services, other than traditional supervised group interventions, as effective and safe for carefully selected clinically stable patients. Transtelephonic and other means of monitoring and surveillance of patients can extend cardiac rehabilitation beyond the setting of supervised, structured, group-based rehabilitation. The feasibility, safety, and efficacy of these alternative strategies for exercise rehabilitation must be assessed in more diverse populations of patients with stable coronary heart disease, particularly elderly patients, those with ventricular dysfunction, and other patients of higher risk status.

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MAINTENANCE EXERCISE TRAINING

Once patients attain their initial exercise goals, maintenance training can be undertaken or continued in community recreational facilities or at home. Because lifetime regular physical activity is necessary to maintain physical fitness, patients must achieve reasonable independence in exercising and remain involved in an exercise regimen that is social, enjoyable, convenient, and appropriate. Most coronary patients with prior exercise restrictions who can safely attain a 7- to 8-MET level of performance can safely progress to unsupervised exercise. Patients leaving supervised exercise programs may require counseling regarding the selection and initiation of long-term exercise in the community or at home.

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EDUCATION AND COUNSELING OF AMBULATORY CORONARY PATIENTS

The behavioral approach to coronary risk reduction encourages and enables coronary patients to manage their illness, adopt and maintain healthy lifestyles, and improve adherence to medications and other recommended regimens.[66,67] Metaanalysis of 28 controlled trials of patient education showed that "education programs have demonstrated a measurable impact on blood pressure, mortality, exercise, [and] diet" and that other parameters are positively affected, although less consistently.[68] A combination of education, counseling, and behavioral intervention strategies seems most effective in promoting health, reducing risk, and favorably altering lifestyle.[4,10,66] Whether the same interventions are equally effective for men and women and across the life span remains unanswered because few studies have enrolled patients over 70 years of age or included women.

Patients with diagnosed coronary disease are at the highest risk for disability and death and thus constitute patients for whom untreated risk factors are most damaging.[69] Cardiac rehabilitation services provide an integrating structure for the multiple risk-reduction components of secondary prevention.

There is no evidence that the performance of CABG surgery per se encourages favorable modification of coronary risk status postoperatively.[70,71] Postoperative recurrence of coronary symptoms or deterioration of function following saphenous vein CABG surgery relates predominantly to progression of the underlying atherosclerosis both in the graft vessels and in the native circulation. Control of hypertension, diabetes, hyperlipidemia, and obesity and cessation of cigarette smoking,[72,73] with adoption of a physically active lifestyle, even at advanced age, may slow progression or induce regression of atherosclerosis and decrease the occurrence of subsequent coronary events.

Community resources that may be helpful in rehabilitation should be identified: counseling and guidance services, home-care agencies, vocational rehabilitation facilities and services for job training and placement, services for financial aid, outpatient coronary rehabilitation programs, and postcoronary groups or clubs. Participation in community heart clubs or educational groups may further facilitate rehabilitation; coronary risk reduction and other skills learned and practiced in these settings may encourage health-related behaviors and aid in reinforcing maintenance of these changes. Acquisition of knowledge appears to affect favorably both behaviors involving implementing recommendations for care and coping behaviors.[63]

Chapter 50: REHABILITATION OF THE PATIENT WITH CORONARY HEART DISEASE

CORONARY POPULATIONS WITH SPECIAL REHABILITATION NEEDS

Elderly Coronary Patients

Elderly patients constitute a high percentage of those with MI, CABG surgery, and PTCA and other transcatheter revascularization procedures. Complications of MI and myocardial revascularization are more frequent in the elderly, with prolongation of both immobilization and hospitalization predisposing to deconditioning; early ambulation can limit functional deterioration and decrease depression. In both medical and surgical coronary intensive care settings, the major educational strategy involves concise and repeated explanations, reassurance, and time and place orientation to help avert confusion and delirium. Teaching energy-conserving techniques for self-care and performance of household tasks helps maintain independent living, an outcome valued by elderly patients. Modification of conventional coronary risk factors is feasible and warranted, given the greater prevalence and severity of coronary disease at elderly age.

Elderly patients are also at high risk of disability following a coronary event. Recent trials of exercise rehabilitation have begun to include patients over 65 years of age and to evaluate outcomes in the elderly coronary population specifically. Although few studies and no randomized, controlled trials have addressed the efficacy and safety of exercise training and multifactorial rehabilitation in the elderly, the available studies provide important new information for clinical practice.

Elderly coronary patients in posthospital exercise regimens have exercise trainability comparable with that of younger patients participating in similar exercise rehabilitation,[35,74] with elderly women and men showing comparable improvement. One report found that exercise testing before hospital discharge was feasible in about half of patients aged 70 years or older with MI, enabling accurate risk stratification and exercise prescription.[75] No complications or adverse outcomes of exercise training in elderly patients were described in any cardiac rehabilitation study. Nonetheless, rates of entry referral to and participation in exercise rehabilitation were substantially lower among elderly than among younger patients,[9,33] and older women were even less likely to be referred than were older men.[34] Elderly patients are less fit after a coronary event, in part because of decreased fitness prior to the event. Adherence to exercise training was high (90 percent) in the reported studies,[35] and significant reduction in coronary risk factors occurred in elderly patients who participated in multifactorial cardiac rehabilitation.[9]

For elderly patients who exercise independently, emphasis should be placed on the importance of warm-up and cool-down activities because of the delayed return of the exercise heart rate to normal at elderly age. Walking provides an adequate training stimulus for many elderly patients because it constitutes a significant percentage of the decreased aerobic capacity of aging.[76] Running, jumping, and other high-impact activities should be limited to avoid musculoskeletal complications. Walking, bicycle ergometry, and/or walking in a pool in shallow water can favorably modify the decreased joint mobility of aging; enhance neuromuscular coordination, balance, and stability and thereby lessen propensity for falls; and improve endurance. Elderly individuals who exercise independently should be cautioned to decrease their exercise intensity in hot and humid environments.

Coronary Patients with Heart Failure

Impairment of exercise capacity with heart failure appears in part due to inadequate nutritive blood flow to skeletal muscle; factors other than lack of increase in cardiac output with exercise seem important, including the ability to decrease peripheral vascular resistance and possibly the adequacy of right ventricular function (see also Chap. 20). Patients with heart failure and normal cardiac output responses to exercise frequently improve their functional capacity with exercise training, whereas those with severe hemodynamic dysfunction with exercise often do not.[77] A combination of LV systolic dysfunction and residual myocardial ischemia may limit trainability. The ventricular ejection fraction predicts poorly both exercise capacity and the potential for improvement of exercise performance with training; some patients with substantial ventricular dysfunction have a normal exercise capacity and no symptoms or impairment of lifestyle.[78]

Most studies of exercise training of patients with heart failure and moderate to severe LV systolic dysfunction do not demonstrate deterioration in LV volume, wall thickness, or function.[79,80] Randomized, controlled clinical trial data of exercise training in postinfarction patients with an ejection fraction less than 40 percent showed that long-term home-based exercise may attenuate the unfavorable remodeling response and even improve ventricular function over time.[79] Peripheral (skeletal muscle) adaptations appear to mediate the improvement in exercise tolerance; exercise training can substantially correct the impaired oxidative capacity of skeletal muscle in chronic heart failure.[81] Exercise training also may improve peripheral artery endothelial function in patients with chronic heart failure.[82] Exercise training can augment both the symptomatic and functional benefits of ACE inhibitor therapy.[30] Even small improvements in symptomatic status and functional capacity can exert a substantial favorable impact on quality of life. Improved clinical outcomes are also described.[83] In both the supervised and at-home settings, low- to moderate-intensity exercise regimens provide benefit, although adverse events may occur in this high-risk patient group.[4]

Although the initial exercise training programs of patients with ventricular systolic dysfunction were predominantly supervised, typically with continuous ECG monitoring, other studies have described moderate-intensity, unsupervised exercise as safe and effective.[84,85] The optimal duration of exercise supervision and the duration and need for ECG monitoring of these patients remain uncertain but should be guided by clinical evidence of exercise-related ischemia and/or arrhythmia.[29] In a study of 105 ambulatory cardiac transplant candidates, nonsupervised prescribed walking at a target heart rate range close to baseline exercise test-determined anaerobic threshold produced significant improvement in peak maximal oxygen consumption and peak exercise tolerance in 38 of 68 clinically stable patients without adverse effects. After an average of 6 months of such exercise, 31 of these 38 patients improved sufficiently to be removed from the transplant list, with improvement persisting to 2 years.[86]

Additional important components of rehabilitative care for patients with significant activity limitations include teaching work simplification, particularly the pacing of daily living activities; working in a seated rather than a standing position; and taking frequent rest periods between activities.

Patients with Implanted Pacemakers and Cardioverter-Defibrillators

Exercise prescription is determined by the characteristics of the implanted pacemaker. Because most patients likely to exercise currently receive rate-responsive pacemakers, exercise testing can ascertain the appropriateness of the sensor response to the exercise intensity,[87] and reprogramming can be undertaken as needed.

The exercise target heart rate range for patients with implanted cardioverter-defibrillators should be set at 20 to 30 beats per minute below the threshold rate of the device to fire. This also enables

appropriate work-related activities.[88] Coparticipants in the exercise setting must be reassured that they cannot be harmed by physical contact with a patient whose cardioverter-defibrillator discharges.

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PSYCHOLOGICAL ASPECTS OF CORONARY REHABILITATION

The importance of psychosocial variables in the prognosis of patients with established coronary disease has received increasing attention during the past decade. Although the type A behavior pattern previously received emphasis, currently the hostility component of type A behavior is regarded as its most adverse feature. High levels of anger and hostility appear associated with increased cardiac morbidity and mortality.[89,90]

Other major psychological problems in coronary patients involve anxiety, depression, denial, and dependence.[91] Denial of presenting symptoms may limit or delay access to care, often with adverse outcomes. "Appropriate" denial, characterized by confidence in a favorable outcome, often an effective coping strategy of patients with a coronary event, is associated with a favorable prognosis. Anxiety, which is often the initial psychological manifestation at hospitalization, is related to a fear of dying and may progress to depression as patients contemplate their potential inability to resume former family, occupational, and community roles. Anxiety and depression, the most common psychological complications of infarction, contribute to the failure to make satisfactory life adjustments, to return to work, to return to sexual function, and to engage in social activities subsequent to hospital discharge. Depression is reported to precede MI in 30 to 50 percent of patients. Depression is associated with increased morbidity and mortality following MI and CABG surgery[92,93]; patients with depression were five times more likely to die during the initial 6 months following MI than nondepressed patients.[94] Depression may be associated with social isolation, which may serve as an independent risk factor. The 6-month mortality of patients living alone was double that of patients living with others (16 versus 8 percent), and follow-up study of patients with angiographically documented coronary disease showed a 50 percent 5-year mortality rate among those most socially isolated, compared with 17 percent among those without these characteristics. The impact of social isolation on prognosis appeared independent of ventricular ejection fraction and other physiologic prognostic factors. Interventions against depression and social isolation following MI are currently being evaluated.

Many patients with successful physical recovery following MI or myocardial revascularization often have residual psychological impairment.[91] Two major strategies that appear to limit this complication are education and counseling and the initiation of a physical activity regimen. Many patients remain psychologically disabled because, inappropriately, they perceive an excessive severity of infarction and vulnerability to sudden death; safe resumption of physical activity provides reassurance and restores self-confidence.[58] In randomized exercise trials, exercising patients returned to sexual activity, to work, and to a near-normal lifestyle more rapidly and had greater improvements in work capacity, income, and job responsibility.[95] Both physical and psychosocial benefits occurred even with low-intensity exercise, particularly among older and sicker coronary patients. Despite the paucity of controlled studies, consistent moderate psychosocial benefit appears to result from combinations of structured exercise, education, and counseling.[63,96] Although the contribution of peer support in a group program has not been ascertained, it may be helpful given the predictive power of social isolation for coronary mortality.[97]

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VOCATIONAL ASPECTS OF CORONARY REHABILITATION

A major goal of rehabilitative care for nonelderly patients recovered from MI or myocardial revascularization is resumption of gainful employment, a change in occupation if needed, and the resulting economic and psychological benefits. In the 1980s, about 80 percent of patients who recovered from uncomplicated MI and who were younger than 65 years of age and employed at the time of infarction returned to work within 2 to 3 months, typically resuming former jobs.[98] Despite this favorable early return to work, subsequent cessation of employment was high, with as much as a 20 percent decrement in continued employment between 6 months and 1 year. Comparable data are not available for patients with complications of MI or residual functional impairment, although their return to work is estimated at 25 to 33 percent.

These data contrast markedly with work resumption following CABG surgery. Despite a substantial decrease in symptoms, improvement in functional capacity, and reported enhancement of life quality and participation in leisure activities, return to work following coronary bypass surgery has been much less favorable than anticipated.[99,100] No difference in 10-year employment status was described between patients randomized to medical and surgical treatment in the Coronary Artery Surgery Study (CASS).[101] Return to work following PTCA is comparable with that following CABG surgery, although PTCA patients are reported to return to work more promptly.[100] Other reports described lack of confidence in the ability to return to work following PTCA, even when patients were physically able to do so.[102]

Most studies of the return to work have involved predominantly or exclusively men; recent examination of working women with coronary disease showed them to have a longer convalescence and even lesser return to work; whether this is a gender issue or reflects older age or greater occurrence of depression among women warrants study.[103]

For patients younger than 65 years of age following MI or myocardial revascularization, the indirect health care costs of disability, including lessened productivity, loss of income, welfare payments, and unemployment insurance costs, must be considered when the cost-effectiveness of rehabilitation is determined.[57,104-106] Coronary heart disease is the leading problem in the United States for which adults receive premature disability benefits under the Social Security system; almost one-fourth of men and women receiving Social Security disability allowances have permanent disability due to coronary disease. Following both MI and myocardial revascularization, symptomatic and functional improvement correlates poorly with the return to work and resumption of preillness lifestyle, with psychosocial status appearing as a more important determinant.[99] Since only about 15 percent of the U.S. labor force currently performs manual labor and this percentage decreases with older age, the severity of angina or heart failure in coronary patients only rarely precludes or delays return to work. Many nonmedical factors negatively influence resumption of employment: older age, adequate nonwork income, anxiety or depression, activity-induced symptoms, lower social class and less education, jobs involving high-level physical activity (more common among blue-collar workers), and perception of the coronary illness as job-related. Patients who fail to resume employment within 6 months after a coronary event are unlikely ever to do so.[107]

Among the medical reasons for failure to return to work are unwarranted medical restrictions or,

even more commonly, lack of professional assurance of the safety of so doing.[107] Exercise testing performed for risk stratification also can be used for work evaluation; it permits a relatively precise assessment of function that may help allay the apprehensions of the patient,[58] family,[108] physician, and employer about the capability and safety of return to work.[109] One randomized, controlled trial of occupational work assessment in a health maintenance organization population early following MI, identifying low-risk patients and counseling them about the appropriateness of prompt return to work, effected a 32 percent reduction in the duration of convalescence.[31] Extrapolation of exercise test data to job requirements should include an analysis of the job to be performed and differences in temperature, environment, intellectual demands, relation to meals, travel requirements, and emotional stress, among others. Nonetheless, patients without evidence of ischemia or arrhythmia during a symptom-limited standard exercise test typically are free of these problems when occupational static and dynamic work are combined.[110] Arm ergometry may be preferable for occupational assessment of patients who perform predominantly arm work.[53]

Furthermore, since most occupational work is intermittent, with brief periods of strenuous activity and longer intervals of low-level activity or rest, occupational myocardial work demand is lower than for the same level of steady-state exercise; cardiac output, blood pressure, and oxygen uptake do not approach steady state until about 2 min after the onset of work, explaining the tolerance of patients with modest cardiac impairment and limitation of cardiac output for significant workloads of short duration, when adequate rest periods are interspersed. Recommendations for full-time work should be for work levels approximating 30 percent of measured physical work capacity. Guidelines are available to assist physicians in assessing and establishing the employment of patients with coronary heart disease.[111]

Other nonmedical considerations also influence postinfarction or postrevascularization employment, particularly the financial, social, disability, and compensation benefits of not returning to work. Although appropriate physician and employer attitudes may facilitate reemployment, the viewpoint of the patient appears the major determinant. In a number of studies, the patient's preoperative perception about ability to return to work appeared to be the most important determinant.

Benefits to employers of cardiac rehabilitative care for their employees include earlier return to work, less disability, less absenteeism, reduced financial expenditures for sickness and disability payments, reduced training costs for replacement of personnel, and greater productivity.[1] Employers thus should encourage coronary rehabilitative care as a component of their managed care plans.

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Part 7: SYSTEMIC ARTERIAL HYPERTENSION
Chapter 51:

HYPERTENSION: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

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INTRODUCTION

Hypertension is the most common disease-specific reason for which Americans visit a physician. It is currently among the leading causes of morbidity and mortality in the world and is expected to have an even greater impact on the health of the public as more of the world becomes developed.[1] In addition to the morbidity and mortality directly attributable to hypertension, high blood pressure (BP) is a powerful risk factor (a condition or characteristic of an individual or a population) that in this case increases the likelihood that an individual or population will develop a wide variety of cardiovascular (CV) diseases (Table 51-1).[2-5] Hypertension even has been associated with an increased risk of certain cancers.[6-8] Some authors have failed to appreciate this relationship when attributing certain cancers to particular antihypertensive treatments.[9]

Table 51-1: Risks Associated with Hypertension

Cerebrovascular disease	Renal insufficiency
Coronary artery disease	Peripheral vascular disease
Heart failure	Premature mortality

All health care providers routinely encounter patients whose BP is elevated. In patients with definite hypertension (see below), the paramount consideration is the choice of treatment, but in an increasing number of individuals, lowering BP may be beneficial even if definite hypertension cannot be diagnosed. In the next decade, it is expected that more and more patients will become candidates for antihypertensive therapy, especially as trials demonstrate the benefits of treatment and pharmacologic approaches become safer and more effective. Furthermore, many citizens, perhaps of the majority of those over 40 years of age, who do not yet meet the criteria for pharmacologic treatment for hypertension will benefit from lifestyle modification, a presumably safe and cost-effective public health approach to reducing BP. Many of the lifestyle habits that lower BP or slow the rate of rise of BP probably should be incorporated into everyone's lifestyle very early.

This chapter reviews the risks imparted by elevated BP, discusses the pathophysiology of hypertension, and analyzes currently available and recommended tools to measure BP and evaluate patients with hypertension. Treatment both with and without drugs is discussed in light of the explosion of information furnished by clinical trials and the newer approaches to lowering BP created by an enhanced understanding of the mechanisms responsible for raising it. The techniques of molecular biology and the contribution of genetics to hypertension have dramatically increased physicians' appreciation of the complexity of the problem.

Hypertension is a disorder of circulatory regulation. The now-classic mosaic theory of the etiology of hypertension, which first was proposed in 1949 by Page, can be endorsed even more enthusiastically in light of current knowledge.[10] No longer can one expect a simple explanation of why BP is elevated in an individual patient or expect that a single approach to therapy will be successful in the majority of those who are treated.

However, with all the progress that has been made in identifying the risks associated with elevated BP and all the efforts to develop ways to lower BP and prove that they work, the situation in the United States leaves much to be accomplished.[11,12] Only 27.4 percent of hypertensive Americans ages 18 to 74 in the period 1991 to 1994 had a BP of <140/90 mmHg, the current goal.[11] The data are still worse for those ≥75 years of age, and the goal may well be too high in some subpopulations of hypertensives, particularly those with diabetes mellitus (DM) and/or renal disease with proteinuria. The record in the rest of the world is much worse.[13-17] Although the United States does better than other countries, much still needs to be done here and elsewhere. One must understand hypertension better to give optimal care to the 1.2 billion hypertensives estimated to be living by the year 2010. Physicians must strive to prevent as much of the enormous morbidity and premature mortality that one can predict will result.

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Chapter 51: HYPERTENSION: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

DEFINITION

Blood pressure is a continuous variable, and whatever number is used to define hypertension will be arbitrary. In the past several decades, the levels at which definite hypertension is defined as beginning have changed from >160/95 mmHg to >140/90 mmHg. Although there is still some disagreement, most authorities now agree on several important principles:

- Hypertension should be defined by both systolic and diastolic BP levels.
- Simply defining and consequently categorizing individuals as hypertensive or not only on the basis of their BP levels neglects the value of using the presence or absence of other risk factors, comorbidity, and target organ damage (TOD) to assess prognosis and ultimately to guide therapy. Thus, the Sixth Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI), the World Health Organization/International Society of Hypertension (WHO/ISH), and the British Hypertension Society (BHS) use a more comprehensive system to define hypertension (Table 51-2). These definitions are based on properly measured office readings (see below). The definitions of hypertension for home and ambulatory measurements are different. Blood pressure >135/85 mmHg for 24-h ambulatory monitoring or home monitoring is the usual level considered to be where hypertension starts. Although home or ambulatory measurements are useful, it is not appropriate routinely to use those values to diagnose most individuals. Office readings remain the standard. In certain situations, especially when an individual claims to have multiple "normal" readings outside the physician's office (see below), it may be reasonable to rely more on out-of-office measurements.
- The treatment approach to individuals with elevated BP should not focus simply on the BP level, which assesses the relative risk that is imparted by that BP, but also on the remainder of the CV risk profile, which estimates the absolute risk of events that an individual with that particular BP and risk profile will face. In the JNC VI classification and stratification of hypertension, for example, the stages (optimal to normal to high normal through stages 1 to 3) represent increasing relative risk as BP rises, while risk group A-C denotes increasing absolute risk as other risk factors and TOD are superimposed on the level of BP (Table 51-3).

It is not of major significance whether hypertensives are classified as being in a stage as recommended by JNC VI or a class per WHO/ISH.[11,18] What is important is that one base the evaluation and care of hypertensive patients on more than the BP number. Black and Yi have suggested that reimbursement for care of a hypertensive patient be based on the stage and risk group into which that patient falls, but to date such a system has not been implemented.[22]

Table 51-2: Threshold Values for 'Normal' versus 'Abnormal' BP (in mmHg)

Source	Office Readings	Home Readings	ABPM Readings
JNC VI	140/90		
Ohasama	140/90	137/84	
French	140/90	127/83	
ASH	140/90	135/85	135/85
Staessen	140/90		133/82

SOURCE: Adapted from JNC VI: The sixth report on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997; 157:2413-2443. Ohasama: Tsuji I, Imai Y, Nagai K, et al. Proposal of reference values for home blood pressure measurement: Prognostic criteria based on a prospective observation of the general population in Ohasama, Japan. *Am J Hypertens* 1997; 10:409-418. French Society of Hypertension: De Gaudemaris R, Chau NP, Maillion JM. Home blood pressure variability, comparison with office readings and proposal for reference values: Groupe de la Mesure, French Society of Hypertension. *J Hypertens* 1994; 12:831-838. ASH: Pickering T. Recommendations for use of home (self) and ambulatory blood pressure monitoring: American Society of Hypertension Ad Hoc Panel. *Am J Hypertens* 1996; 9:1-11. Staessen: Staessen JA, O'Brien ET, Atkins N, Amery AK. Short report: Ambulatory blood pressure in normotensive compared with hypertensive subjects: The Ad-Hoc Working Group. *J Hypertens* 1993; 11:1289-1297.

Table 51-3: JNC VI Stratification of Cardiovascular Risk and Links to Initial Treatment Strategy

		RISK GROUP		
		A	B	C
	No. of Risk Factors	0	1 (not DM[a])	≥2 (or DM)
	Target organ damage	Absent	Absent	Present
BP stage	Cardiovascular disease	Absent	Absent	Present
High normal (130-139/85-89)		LM[b] only	LM only	LM plus drug therapy
Stage 1 (140-159/90-99)		LM for 12 months	LM for 6 months	LM plus drug therapy
Stage 2 (160-179/100-109)		LM plus drug therapy	LM plus drug therapy	LM plus drug therapy
Stage 3 (≥180/≥110)		LM plus drug therapy	LM plus drug therapy	LM plus drug therapy

[a]DM = diabetes mellitus.[b]LM = lifestyle modifications.

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EPIDEMIOLOGY AND RISK

Physicians generally do not concern themselves with reducing BP when it is elevated because of the specific clinical problems they can attribute to that elevation. Instead, hypertension is treated because of the increased risk of mortality and CV disease that results from having an elevated BP (Table 51-1).

These risks have been well documented in numerous epidemiologic studies, beginning with the Framingham Heart Study and many others in the 1950s and 1960s and extending to the present.[23-29] More recently, meta-analyses of pooled data have confirmed the robust, continuous relationship between BP level and cerebrovascular disease and coronary artery disease (CAD) in both western and eastern populations.[30,31] In addition, BP is directly related to left ventricular hypertrophy (LVH) and heart failure (HF), peripheral vascular disease (PVD), carotid atherosclerosis, renal disease, and "subclinical disease."[4,5,32,33] Kannel and colleagues in the Framingham Heart Study have documented the fact that CV risk factors tend to cluster in hypertensives.[34] Hypertensives are more likely to have dyslipidemias, especially elevated serum triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C), and type 2 DM. The common denominator may be insulin resistance, perhaps as a result of the frequent association of hypertension and obesity.[35]

In the last several years, it has become increasingly clear that the risks attributed to hypertension are much more strongly related to the level of systolic BP than to diastolic BP, especially in those over age 50 or 60 years.[36,37] The observation that systolic BP predicts events and TOD better than diastolic BP was persuasively argued in the early 1970s, but it took until 1993, in the Fifth Report of the Joint National Committee on the Detection, Evaluation and Treatment of Hypertension, before systolic BP was given even equal weight to diastolic BP in classification systems.[36,38]

Some have argued that one should not measure diastolic BP other than perhaps to calculate pulse pressure (PP).[39,40] Pulse pressure, the difference between systolic and diastolic BP, is an even better predictor of risk than is systolic BP in most of the epidemiologic studies done to date.[41-46] A wide PP, unless it is a result of aortic insufficiency or an arteriovenous malformation, is a simple clinical indicator of stiffer and less compliant large central arteries and significant arterial damage. Franklin and colleagues, again using data from the Framingham Heart Study cohort, showed that at all levels of systolic BP (even as low as 110 to 130 mmHg), risk is less with higher diastolic BPs.[46] More recent analyses by this group have suggested that these findings may be relevant only in those over age 60, and so it is not appropriate to ignore those with elevated diastolic BP level if their systolic readings are not above normal. The classification systems cited above have been careful not to include PP either in defining the risks of hypertension or in recommending treatment. A recently published position paper from the National High Blood Pressure Education Program has cautioned physicians not to rely on PP measurements until more support is gathered for this position.[47]

With the exception of hypertensive encephalopathy, it has long been felt that few, if any, clinical symptoms can be attributed to increased BP levels. This may have to be reevaluated, however, as newer and very well tolerated drugs are developed and as improved methods of assessing subtle

symptoms are perfected. Clinical trials with angiotensin receptor blockers (ARBs), for example, consistently show that the members of the actively treated group have fewer adverse reactions than do those given placebo.[48,49] Furthermore, in the Treatment of Mild Hypertension Study (TOMHS) and the Hypertension Optimum Treatment (HOT) trial, the group with the lowest BP had the fewest complaints.[50,51] These trials utilized a wide variety of drugs to reduce BP and clearly showed not only that lowering BP is safe but that hypertensives treated to lower levels feel better. Hypertension may not be the asymptomatic condition it has long been thought to be.

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ECONOMICS

Cost considerations are playing an increasingly important role in the pharmacologic management of hypertension in the United States, and they have always been a major consideration in the rest of the world. No regimen, no matter how carefully and appropriately selected, will be effective if the patient cannot afford it. Moreover, if antihypertensive agents do not appear on the national formulary or the formulary of the insurance company from which a patient gets medication, the cost will not be covered and the patient may not be willing or able to purchase them. Generic preparations are available for every class of antihypertensive agent except ARBs, and these generic preparations tend to be the least expensive options for initial therapy. In general, branded calcium antagonists (CAs) are the most expensive, with ARBs and angiotensin-converting enzyme inhibitors (ACE-Is) the next most expensive drugs. For many of the fixed-dose combinations now available, the cost is less than what would be paid for the individual components if they were purchased separately. It is also customary for fixed-dose combinations that include a thiazide diuretic to cost no more than does the nondiuretic component alone.

A careful analysis of the economics of hypertension treatment has to include more than what is spent on drugs, patient visits, or laboratory tests.[52,53] For many affected (and especially high-risk) patients, the extremely expensive complications of under- and/or untreated hypertension far outweigh the inconvenience and costs associated with effective treatment.[53] Current estimates are that in the United States in the year 2000, hypertension will cost approximately $37.2 billion.[54] Nearly half this total is spent on indirect costs (death benefits for the families of those who die from untreated hypertension, disability payments for stroke survivors, time away from work, and transportation costs, to name a few) and payments to hospitals and nursing homes.[54] Both of these expenses could be reduced if hypertension treatment were more effective in controlling BP and reducing the risk of the clinical sequelae of hypertension, including myocardial infarction (MI), HF, stroke, and end-stage renal disease (ESRD).[55]

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PATHOPHYSIOLOGY

Hypertension is a disorder of BP regulation and results from a multitude of causes. Control of BP involves a complex interaction among the kidneys, the central nervous system (CNS) and peripheral nervous system (PNS), and the vascular endothelium thoughout the body as well as a variety of the other organs, such as the adrenal and pituitary glands. The heart is the organ that responds to many of the changes mediated by these systems. It also secretes hormones locally and systemically that interact with substances produced elsewhere and help regulate BP levels. In those genetically predisposed to develop hypertension, an imbalance occurs among the various systems that modulate the level of BP. The sympathetic nervous system (SNS), the renin-angiotensin-aldosterone (RAA) system, vasopressin (VP), nitric oxide (NO), and a host of vasoactive peptides, including endothelin, adrenomedullin, and others produced by the heart and a host of different cells (endothelial and vascular smooth cells, for example), modulate the responses of these systems and help maintain BP over a range commensurate with optimum physical and mental activity. Additionally, these systems affect the ability of the kidney to handle sodium (Na^+) and volume, which Guyton and colleagues feel is the primary controller of BP.[56]

Sympathetic Nervous System and Renal Sodium Handling

Guyton and colleagues noted that while the SNS and the RAA system are important for short-term changes in BP, ultimately it is the kidney that is responsible for long-term blood volume and BP control.[56] High-pressure baroreceptors in the carotid sinus and aortic arch respond to acute elevations in systemic BP by causing a reflex vagal bradycardia that is mediated though the parasympathetic system and inhibition of sympathetic output from the CNS. Low-pressure cardiopulmonary receptors in the atria and ventricles likewise respond to increases in atrial filling by increasing heart rate (HR) through inhibition of the cardiac SNS, increasing atrial natriuretic peptide (ANP) release, and inhibiting VP release.[57-59] These reflexes are largely controlled centrally, particularly in the nucleus tractus solitarii of the dorsal medulla. This vasomotor center also receives input from the limbic system and hypothalamus in response to emotional or psychological stress.

The consequences of SNS stimulation are peripheral vasoconstriction, an increase in HR, release of norepinephrine from the adrenals, and a resultant rise in systemic BP. The increase in SNS activity also plays a role in mediating local vascular hypertrophy and stiffness. Renal efferent sympathetics also are activated and cause internal vasoconstriction with a fall in renal blood flow and an increase in renal vascular resistance.[60] The renal SNS also directly stimulates Na^+ reabsorption and renin release from the juxtaglomerular apparatus.[60-62] Thus, the SNS and CNS have effects on renal handling of Na^+.

Hyperactivity of the SNS has been described in patients with essential hypertension, particularly in the young and those with "high-normal" BP (130 to 139/80 to 89 mmHg).[63,64] Elevated plasma norepinephrine levels with increased HR and cardiac indexes have been described in people with newly diagnosed hypertension.[64] These individuals frequently show exaggerated BP responses to emotional (mental arthimetic) and physical stressors such as ice-water immersion. Additionally, a

subset of these patients exhibit elevated plasma renin levels that may reflect beta-adrenergic stimulation of renin secretion.

A defect in baroreceptor sensitivity has been postulated to be responsible for abnormal responsiveness of the SNS and thus may contribute to the increase in BP and HR variability noted in some hypertensive patients.[65] SNS activity also is increased in certain high-risk groups with hypertension, including African-Americans, those with obesity, those with insulin resistance, and those who ingest or inhale certain agents, such as nicotine, alcohol, cyclosporine, and cocaine.[66-68] A very small subset of patients may have hypertension caused by compression of the lateral medulla by cranial nerves and/or vessels.[60] This results in increased SNS activity. Selective decompression of these nerves may ameliorate the hypertension in rare instances. Activation of the CNS/SNS also may result from renal afferent sympathetics from the kidney in hypertensive patients. In experimental models of hypertension, renal sympathectomy resulted in a reduction in BP.[60,64]

The influence of the SNS on Na^+ handling in the kidney also has been examined in detail.[69] Several studies have linked SNS hyperactivity with greater than normal increases in BP in response to a given Na^+ load.[70-73] Indeed, Dahl and Heine were the first to show that hypertension can be transferred from a hypertensive Dahl salt-sensitive rat to a nonhypertensive Dahl salt-resistant rat by transplantation of the kidney.[70] Patients with essential hypertension and associated renal failure have been cured of the underlying hypertension by renal transplantation from a normotensive donor.[74]

Most authorities believe that the mechanism by which the kidney causes hypertension is impairment in the excretion of Na^+.[60,61,71,75-78] This impairment may be related to genetic changes in various Na^+ exchangers in the proximal and distal tubules that result in altered responses to stimulation by the SNS and the RAA system. Epidemiologic studies have linked the relative Na^+ content in the diet with the prevalence of hypertension in various populations, although the value of dietary Na^+ restriction in reducing BP remains controversial (see below).[79,80] Interventional studies with Na^+ restriction and/or loading have revealed that the BP responses in many hypertensive patients are "salt-sensitive": Their BP rises with a salt load.[81,82] In addition, several studies have shown that salt loading of patients with essential hypertension results in a net total body Na^+ accumulation. Three genetic diseases associated with hypertension in childhood (Liddle's syndrome, the syndrome of apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism) all are associated with increased reabsorption of Na^+ by the kidney.[83]

A genetically mediated defect in the ability of the kidney to excrete Na^+ does not readily explain certain observations:

- Young hypertensive subjects appear to excrete Na^+ normally or supernormally.
- Individuals with high-normal BP may have a low blood volume.
- As many as 40 percent of people with hypertension do not show a change in BP with Na^+ loading ("salt resistance").
- With aging, salt sensitivity increases both in frequency and in degree such that by age 70, the majority of hypertensive patients are salt-sensitive.

In fact, it has been argued from meta-analyses that salt restriction is not important either in normotensives or in patients with hypertension under age 40.[84,85] All these findings are consistent with the possibility that the defect in Na^+ excretion in hypertensive patients is acquired rather than genetically determined. It should be kept in mind, however, that abnormal Na^+ handling is a

mechanism that contributes to elevating BP in many but probably not all patients with hypertension.

The Renin-Angiotensin-Aldosterone System

The RAA system is one of the most important physiologic mediators that regulate blood volume and BP. Plasma angiotensinogen, which is released primarily from the liver, is acted on by renin from the kidney to generate angiotensin I, which is further degraded in the presence of angiotensin-converting enzyme to angiotensin II (AII). In addition to the systemic RAA system, there is now evidence that a local RAA system is present in blood vessels, the heart, the kidney, and elsewhere, where it may mediate local effects (such as tissue remodeling) independent of circulating renin or angiotensinogen levels.

Most of the actions of AII are mediated by the AT_1 receptor and include stimulating vascular smooth muscle contraction and hypertrophy, increasing cardiac contractility, stimulating the SNS in the CNS and PNS, increasing NO production, causing aldosterone and VP release, and increasing thirst (Table 51-4).[86] Within the kidney, stimulation of the AT_1 receptor by AII also causes renal vasoconstriction (especially of the efferent arteriole and vasa rectae), a fall in renal blood flow, and an increase in renal vascular resistance.[87] Angiotensin II also increases Na^+ reabsorption both by increasing aldosterone release and through direct effects on the proximal tubule. Additionally, AII increases the sensitivity of the tubuloglomerular (TG) feedback response.

Table 51-4: Characteristics and Functions of AT_1 and AT_2 Receptors

AT_1 Receptors
Always expressed
Mediate vasoconstriction
Mediate growth
Smooth muscle proliferation
Stimulate connective tissue deposit in media
Facilitate low-density lipoprotein cholesterol transport to media
Inhibit endothelial function
Mediate renal tubular sodium reabsorption
AT_2 Receptors
Increased expression during stress or injury
Mediate vasodilatation
Inhibit growth (antiproliferation)
Decreased renal absorption of sodium

Angiotensin subtype 2 (AT_2) receptors also are stimulated by angiotensin II. These receptors produce virtually opposite actions in some experimental systems and are clearly active during fetal development (Table 51-4). Their role in healthy adults and even in those with cardiac or vascular damage is still uncertain.

The role of the RAA system in essential hypertension is complex. Whereas plasma renin activity (PRA) is elevated in 20 percent of hypertensive patients, PRA is either normal (50 percent) or low (30 percent) in the majority. However, in many patients with normal plasma renin levels, PRA may be inappropriately high in relation to total body Na^+. This has been suggested by the observation that Na^+ depletion accentuates and Na^+ infusion blunts changes in PRA levels in patients with hypertension. Additional evidence to support this concept comes from the observation that BP in these patients frequently is reduced after the use of ACE-Is or ARBs.[88]

Sealey and colleagues have suggested that the reason for widely varying PRA levels may be nephron heterogeneity within individual kidneys, in which there are some ischemic nephrons that make excess renin and other hyperfiltering nephrons in which renin secretion is suppressed.[89] They postulated that the increased renin release from the ischemic nephrons enters the circulation and then leads to AII generation, which causes inappropriate vasoconstriction and Na^+ reabsorption in the other hyperfiltering nephrons. This results in Na^+ retention and the development of hypertension.

Unfortunately, this is only part of the explanation, since PRA is relatively low in African-Americans and the elderly, two populations with a high prevalence of hypertension and a high rate of complications from hypertension. Low PRA, however, does not necessarily mean that the RAA is not active, since tissue effects and local actions are not necessarily evident from PRA alone.

Vasopressin

While VP has been clearly shown *not* to play a role in the genesis of essential hypertension, it does play an important role in the maintenance of established hypertension, especially in African-Americans.[90] In African-Americans, studies have shown that selective inhibition of V_1A receptors reduces systolic BP by an additional 8 to 12 mmHg in the presence of a high-salt diet (suppression of the RAA system) and clonidine (suppression of SNS).[91,92] Interestingly, this is not observed in whites. In light of the interaction between arginine vasopressin (AVP), AII, and endothelin on cellular growth and vascular responsiveness, it appears that AVP may have a potentiating effect on one of these other hormones.[93]

Endothelin

Endothelin is known to be the most potent vasoconstrictor in humans.[94] Comparative studies with AII have demonstrated not only that the endothelin family of hormones has cellular actions similar to those of AII but that the two hormones work in concert to potentiate each other's vascular and cellular effects.[95] Given this, however, the specific role of endothelin in the etiology of essential hypertension is minimal.[96] It plays a far more important role in cyclosporine-induced hypertension and decreased renal function as well as in maintaining BP in people with HF.[97]

Endothelin is the major mechanism by which cyclosporine constricts the afferent arteriole of the kidney and reduces renal function. Calcium antagonists and endothelin receptor blockade prevent this reduction. Additionally, endothelin A receptors have been shown to play a major role in contributing to the maintenance of elevated renal perfusion pressure in patients with HF.[98]

Nitric Oxide

Nitric oxide is the vasodilator produced by the endothelium in response to vasoconstrictor hormones, and so the contribution of NO to the maintenance of normal BP is vitally important.[99,100] Defects in NO release or synthesis that are induced by atherosclerosis or that are genetically programmed are a major determinant in predisposing individuals to the development of atherosclerosis and hypertension.[101] NO serves as a major counterbalancing factor that maintains BP within the range necessary to maintain organ perfusion but avoid injury. It counterbalances vasoconstrictive hormones, cytokines such as AII, platelet-derived growth factor (PDGF), tumor necrosis factor-alpha, and other hormones that stimulate its release. Transgenic animal models that do not have the ability to synthesize NO have very high BP and die of CV causes earlier than do animals that can produce NO.

Additionally, NO plays a major role in the genesis of hypertension in people who are insulin-resistant. The underlying mechanisms and the factors that may govern the interaction between insulin and NO have been studied extensively in healthy people and insulin-resistant subjects. It appears that a genetic and/or acquired defect of NO synthesis could represent a central defect that triggers many of the metabolic, vascular, and sympathetic abnormalities characteristic of insulin-resistant states, all of which may predispose to CV.[102]

Ion Transport Abnormalities

A number of dietary factors affect the SNS, the CNS, and the RAA system in those genetically predisposed to develop hypertension. These dietary factors, such as high Na^+ intake and low potassium (K^+), Ca^{2+}, and/or magnesium (Mg^{2+}) intake, may produce, worsen, or attenuate changes in BP. Substantial evidence from animal models of hypertension as well as diabetic and nondiabetic hypertensive individuals supports an association between the hypertension and changes in intracellular pH as well as electrolyte composition.[103-121] These observations have led to various hypotheses regarding the importance of one ion relative to others.

Numerous investigators have documented increases in cytosolic free Na^+ concentrations in cells of hypertensive or diabetic patients compared with age- and sex-matched normotensive or nondiabetic controls.[103-105] These increases result from altered activity of the Na^+/H^+ antiporter and the Na^+/Li^+ countertransporter. These increases in intracellular Na^+ are highly correlated with the presence of an elevated diastolic BP.

The relationship between intracellular Mg^{2+} and BP is less clearly defined. Data from experimental models of hypertension as well as from patients with hypertension demonstrate an inverse relation between intracellular Mg^{2+} concentration and BP elevation.[106,107] The primary mechanism responsible for this relative reduction in intracellular Mg^{2+} relates to Na^+-dependent Mg^{2+} efflux through the plasmalemma membrane.[112]

Increases in the intracellular Ca^{2+} concentration are seen commonly in obese and essential hypertensive subjects.[105,110] Like Na^+, these changes reflect altered membrane ion transport activity. Early clinical studies demonstrated that oral Ca^{2+} ingestion reduces BP, but the results from clinical trials do not consistently show a reduction in BP after Ca^{2+} supplementation.[120,121]

Increased K^+ intake is well known to have effects on BP control through multiple mechanisms, including opening K^+ channels in the vasculature, altering sympathetic neuronal output, and increasing vasodilatory prostaglandins.[122-125] This is exemplified by the fact that hypokalemia in

patients will blunt reductions in blood pressure by antihypertensive medication, perhaps because it results in the closure of K^+ channels.

Potassium also plays a role in modulating vascular responsiveness in salt-sensitive individuals. In a recent clinical study, increasing dietary K^+ for 3 weeks in 16 predefined salt-sensitive subjects and 42 salt-resistant subjects resulted in the conversion of all salt-sensitive subjects from nocturnal nondipping to dipping status[126] (see below). These results suggest that a positive relationship between dietary K^+ intake and BP modulation can exist even when daytime BP is unchanged by a high-K^+ diet.[126]

Taken together, these data suggest that both univalent and divalent cations affect vascular responses to stimuli such as those mediated by the RAA and the SNS. Changes in vascular responses are linked to altered function of membrane ion transporters (Na^+/H^+ antiporter, Na^+/K^+/ATPase, Mg^{2+}/Na^+ exchanger, Ca^{2+}/H^+ exchanger, Ca^{2+} ATPase, and others). Both the Na^+/K^+/ATPase and the Ca^{2+}/ATPase pumps are important in maintaining the Ca^{2+} homeostasis of the cell.

Extracellular Volume Homeostasis

Whereas an acute infusion of saline administered to animals with experimentally induced hypertension will initially raise blood volume and cardiac output, the increase in cardiac output is transient and is replaced by a rise in systemic vascular resistance (SVR).[71,72]

There are several potential mechanisms for this observation. First, the normal response to a salt load is inhibition of the SNS. However, it is known that in salt-sensitive patients, the SNS is not inhibited and even may be activated with a salt load.[127,128] A possible explanation is that in the setting of renal dysfunction or intrarenal ischemia, salt loading triggers an intense tuboglomerular feedback signal that activates the renal afferent SNS. This renal response subsequently triggers a CNS response. Indeed, there is evidence that renal afferent nerves activate CNS sympathetic activity in both experimental hypertension and chronic renal disease.

Second, parabiotic experiments have suggested there may be circulating factors in salt-loaded animals with hypertension that are responsible for some of the increase in SVR. One class of factors is circulating Na^+/K^+/ATPase inhibitors, which have been documented in some patients with essential hypertension.[129-131] These substances, one of which is ouabain, are digitalis-like and adrenally derived. Blaustein has suggested that these substances, which presumably are secreted in an attempt to facilitate Na^+ excretion, may have the adverse consequence of increasing intracellular Na^+ and thus facilitating Na^+-Ca^{2+} exchange in vascular smooth muscle cells. This would lead to a rise in intracellular Ca^{2+} and stimulate vascular smooth muscle contraction, vasoconstriction, and a rise in SVR.[110]

A third mechanism is the loss of a vasodepressor substance. There is good evidence that a lipid-like vasodepressor factor termed adrenomedullin is expressed in some of the interstitial cells in the renal medulla and the juxtamedullary region. Release of this factor into the circulation appears to depend on medullary blood flow and can be inhibited if activation of renal SNS or inhibition of NO reduces blood flow.[60] Thus, one might expect to see lower circulating levels of this substance in the setting of tubulointerstitial (TI) injury and intrarenal ischemia.

Fourth, the increase in pressure associated with a saline load could cause increased tension in the peripheral vasculature, leading to microvascular rarefaction (which has been observed in the forearms and nail beds of patients with essential hypertension) that could raise the SVR. An increased pressure load on the vessels also could result in compensatory vascular hypertrophy

mediated by local growth factors and the local RAA system. Indeed, there is evidence that AII, PDGF, and basic fibroblast growth factor are involved in these processes.

Mechanisms of Na^+ Retention in Essential Hypertension

A rise in systemic BP normally is associated with brisk natriuresis. This is thought to be due to a transient rise in pressure in the peritubular capillaries in the juxtamedullary region, with a subsequent increase in interstitial pressure and a backflow of Na^+ through the paracellular space of the proximal tubule. Numerous studies have confirmed that most patients with essential hypertension have a defect in the pressure natriuresis curve, in which higher systemic pressures are required to excrete a Na^+ load.[132,133]

A second mechanism for decreased Na^+ excretion is an enhancement of TG feedback. Tubuloglomerular feedback is a reflex vasoconstriction that occurs with chloride delivery to the macula densa, and the vasoconstrictive response will reduce glomerular filtration and Na^+ excretion. TG feedback can be enhanced in the setting of increased local vasoconstrictors such as AII and adenosine or by a reduction in local vasodilators such as NO. TG feedback appears to be enhanced in models of experimental hypertension.[132,134]

Finally, alterations in intrarenal vasoactive mediators may be involved in the impairment of Na^+ excretion in patients with hypertension. In both experimental and human hypertension, there may be low levels of renal vasodilators, such as prostaglandins, dopamine, and NO as well as elevated levels of renal vasoconstrictors such as AII and adenosine and increased activity of the renal SNS. In addition to their effects of enhancing TG feedback, alterations in the levels of these agents could contribute to net Na^+ reabsorption because of their direct effects on tubular Na^+ transport.

Some studies have shown that TI injury can be induced in rats with either catecholamine (phenylephrine) or AII infusion and that subsequently these animals will develop hypertension when placed on a high-salt diet.[134] Evaluation of these biopsies demonstrated focal areas of peritubular capillary rarefaction. This also has been observed in kidney biopsies of patients with essential hypertension. The loss of peritubular capillaries could help explain the impairment of pressure natriuresis. The ischemia related to the vasoconstriction and capillary loss could lead to alterations in the various vasoactive mediators. Indeed, there is some evidence that NO levels fall and adenosine levels rise with TI injury and ischemia, and this could contribute to the enhanced TG feedback that has been observed.[135,136]

While this pathway links a hyperactive SNS or RAA system with TI injury and salt-dependent hypertension, it is likely that TI injury induced in other ways could result in salt-sensitive hypertension. Indeed, it is of interest that TI disease is associated with reflux nephropathy, chronic pyelonephritis, DM, cyclosporine, radiation, lead and analgesic nephropathy, hypercalcemia/nephrocalcinosis, and gout, all of which are strongly associated with hypertension. In addition, it is noteworthy that many high-risk groups associated with salt-dependent essential hypertension, such as aged persons, obese persons, and African-Americans, have a high prevalence of TI disease.

Insulin Resistance

Insulin resistance is a metabolic disorder that is manifested by a reduction in peripheral skeletal muscle utilization of glucose.[35] To fully understand the contribution of insulin resistance to the genesis of hypertension, one has to evaluate the effects of insulin resistance and hyperinsulinemia on factors that contribute to BP elevation. High levels of insulin cause sodium retention and other

vascular effects, such as cellular proliferation and matrix expansion.[137] In the presence of hyperinsulinemia, neurohumoral factors such as AII, endothelin, and VP also potentiate proliferation of endothelial and vascular smooth muscle cells.[138] Lastly, the effect of insulin on various growth factors contributes to the development of vascular injury through its potentiation of the atherosclerotic process.[139] These factors in a person genetically predisposed to develop nephropathy can potentiate injury to the vasculature and end organs.

It should be noted, however, that not all subjects with insulin resistance have all the associated components of insulin resistance syndrome or syndrome X, i.e., lipid abnormalities, hyperuricemia, type 2 DM, glucose intolerance, hypertension, microalbuminuria, left ventricular hypertrophy, salt sensitivity, and obesity, among others. Studies in the normotensive offspring of hypertensive nondiabetic parents demonstrate the presence of insulin resistance.[140,141] This is also true for nondiabetic first-degree relatives of patients with type 2 DM.[142] Thus, a genetic predisposition seems to be needed to develop this syndrome.

Genetic Factors

Commonly accepted candidate genes associated with the genesis of hypertension are summarized in Table 51-5. Insulin resistance is clearly associated with hypertension. A possible genetic link between the presence of insulin resistance and the development of hypertension has been proposed.[143-146] Recent studies also have identified insulin resistance in the normotensive offspring of parents with essential hypertension. Saad and coworkers evaluated the association between insulin resistance and the propensity to develop hypertension in different racial groups.[147] Those investigators examined Pima Indians, whites, and blacks who were normotensive and nondiabetic. They noted that Pima Indians had higher fasting plasma insulin concentrations than did whites or blacks and lower whole body glucose disposal. They also noted a strong correlation between fasting plasma insulin concentrations and the rate of glucose disposal in whites but not in Pima Indians or blacks. Thus, the development of hypertension does not necessarily correlate with the presence of either hyperinsulinemia or insulin resistance in certain racial groups.

Table 51-5: Candidate Genes Associated with Hypertension and Cardiovascular Risk

Monogenic forms
Glucocorticoid-remediable aldosteronism
Liddle's syndrome
Polygenic forms that affect
Angiotensinogen gene
Na^+-Li^+ countertransport
Epithelial amiloride-sensitive sodium channel
Nitric oxide generation
Alpha-adducin
G_3 beta subunit (intracellular signal transduction)
Insertion/deletion of ACE gene

Work by various investigators to isolate a "hypertensive gene" or group of genes has been ongoing for many years. Abnormalities in the angiotensinogen gene identified by Caufield and coworkers provide evidence to link mutations in the angiotensinogen gene to the pathogenesis of essential hypertension.[148] A study of 179 hypertensive sibpairs from 69 type 2 diabetic kindreds showed that specific changes in the linkage of the angiotensinogen gene were highly correlated with the presence of hypertension.[149]

The delineation of a gene profile that will predict who will develop hypertension is near. A number of federally funded studies to gather sib pairs and families to identify candidate genes that predispose individuals to the development of hypertension are under way. Data from these studies may lead to the identification of such genes within the next 5 to 10 years. Thus, until these genetic profiles are delineated, it will be necessary to rely on the data garnered from epidemiologic studies to identify subjects at risk for the development of hypertension and CV events.

These are several clear examples of genetic influences in hypertension.

GLUCOCORTICOID-REMEDIABLE ALDOSTERONISM

This is an inherited autosomal dominant disorder that mimics an aldosterone-producing adenoma.[150] An important clinical clue to diagnosing this disease is the age at onset of hypertension. Patients with glucocorticoid-remediable aldosteronism (GRA) typically are diagnosed with high BP as children, whereas patients with other mineralocorticoid excess states, such as aldosterone-producing adenomas (APA) and idiopathic adrenal hyperplasia, usually are diagnosed in the third through sixth decades of life. A strong family history of hypertension is the rule, often associated with early death of affected family members from cerebrovascular accidents, as is seen characteristically in some GRA families.

In GRA, the RAA system is suppressed and aldosterone secretion is regulated solely by ACTH. As a result, plasma aldosterone levels usually decline during the course of an upright posture study, similar to what is seen in patients with APA.[151-153] The administration of exogenous ACTH to patients with GRA is associated with aldosterone hyperresponsiveness compared with normal subjects.[153] Moreover, in contrast to normal subjects in whom continuous ACTH administration is associated with a rise and a subsequent fall in aldosterone to basal levels over days, patients with GRA exhibit an exuberant aldosterone response that is sustained as long as ACTH is infused.

GRA is caused by a genetic mutation that results in a hybrid or chimeric gene product fusing nucleotide sequences of the 11-hydroxylase and aldosterone synthase genes.[154,155] Characterization of this chimeric gene indicates that it arose from unequal crossing between 11-hydroxylase and aldosterone synthase genes.[155] These two genes are located in close proximity on human chromosome 8, are 95 percent homologous in nucleotide sequence, and have an identical intron-exon structure. The structure of the duplicated gene contains the 5′ regulatory sequences that confer the ACTH responsiveness of 11-hydroxylase fused to more distal coding sequences of the aldosterone synthase gene.[153,154] Therefore, this hybrid gene is expected to be regulated by ACTH and have aldosterone synthase activity. This hybrid gene allows ectopic expression of aldosterone synthase activity in the ACTH-regulated zona fasciculata, which normally produces cortisol.[156,157] This abnormal gene duplication can be detected readily by southern blotting, allowing for direct genetic screening for this disorder with a small blood sample.

GLUCOCORTICOID RESISTANCE

The structure, growth, and secretory activity of the adrenal cortical zona fasciculata are regulated largely by ACTH. Only cortisol can inhibit ACTH release. An increase in ACTH release raises the levels of cortisol, which then inhibits the release of ACTH. This continuous inhibitory feedback effect of cortisol on ACTH release is interrupted in patients with glucocorticoid resistance. In this disorder, although cortisol levels are exceedingly high, ACTH release is not inhibited, leading to uninhibited ACTH secretion, which in turn stimulates the adrenal cortex to produce 11-deoxycorticosterone (DOC).[157] If sufficient DOC is secreted, salt and water retention ensue, precipitating hypertension and hypokalemia. Animal studies indicate that the mechanism for this may in part be related to changes in hippocampal steroid receptor building.[158]

Animal studies also indicate that an expressional downregulation of endothelial cell nitric oxide synthase (NOS III) may contribute to the hypertension caused by glucocorticoids. Ingestion of dexamethasone by telemetrically instrumented rats increased BP progressively over 7 days. Plasma oxidation products of NO decreased to 40 percent, and the expression of endothelial NOS III was found to be downregulated in the aorta and several other tissues in glucocorticoid-treated rats. Dexamethasone treatment significantly attenuated the relaxation to the endothelium-dependent vasodilator acetylcholine but not to the endothelium-independent vasodilator S-nitroso-*N*-acetyl-D,L-penicillamine. Additionally, incubation of human umbilical vein endothelial cells or bovine aortic endothelial cells with several glucocorticoids reduced NOS III mRNA and protein expression to 60 to 70 percent of control, an effect that was prevented by the glucocorticoid receptor antagonist mifepristone.[159]

LIDDLE'S SYNDROME

Liddle's syndrome is an autosomal dominant disorder that mimics the signs and symptoms of mineralocorticoid excess.[160] The fault appears to lie with continuously avid Na^+ channels in the distal nephron, resulting in excessive salt absorption and K^+ wasting (despite negligible aldosterone production) and severe hypertension.[161,162] A prominent feature is premature death from stroke or HF. The clinical manifestations can be corrected by triamterene and amiloride but not by spironolactone. Triamterene and amiloride directly block the Na^+ channel, whereas spironolactone inhibits Na^+ absorption by binding the aldosterone receptor.

The cellular defect associated with this syndrome is located on the apical portion of the tubule where the epithelial Na^+ channel (EnaC) located on the apical membrane plays a critical role in Na^+ absorption. Mutations in this channel cause diseases of Na^+ homeostasis, including a genetic form of hypertension (Liddle's syndrome inhibits cAMP-mediated stimulation of EnaC). Thus, the apical Na^+ channels and transepithelial Na^+ current are inhibited. Experimental data indicate that cAMP-mediated translocation of EnaC to the cell surface is defective in patients with Liddle's syndrome.[163]

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Chapter 51: HYPERTENSION: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

DIAGNOSIS OF HYPERTENSION

Estimation of the pressure generated by the heart during its normal contractile cycle has been measured for more than 100 years. The value of such readings in predicting prognosis was recognized in the early 1930s by insurance companies, which probably have the best data correlating causal BP measurements and the risk of future disability and death.[164] Since the second half of the 1800s, palpation of the pulse and appreciation of the contour and pressure within a peripheral artery were skills learned only through extensive experience. Such subjective observations were supplanted by objective (albeit indirect) measurements after the introduction of the Riva-Rocci sphygmomanometer in the late nineteenth century.[165,166] This instrument was refined by Janeway and Korotkoff, who characterized the sounds heard when using a stethoscope placed over the compressed artery in 1906.[167-169] Even today, the terminology introduced by Korotkoff is still used: Systolic BP is recognized when clear and repetitive tapping sounds are heard; diastolic BP is recorded when the sounds disappear. Exceptions to these general rules are still recognized among patients who have audible sounds even down to zero mmHg and in obstetric patients: In both situations, the "muffling" of the sounds (Korotkoff phase IV) is recorded either in addition to the phase V measurement or as the diastolic BP, respectively.[170]

Techniques of Measuring Blood Pressure

The proper technique for accurate BP measurement typically is taught very early during medical training but then seldom is followed.[171-173] Many expert panels have made recommendations regarding the methodology of BP measurement, that frequently do not agree in all details, but several general principles can be extracted[174-177]:

- There are six sizes of commonly available BP cuffs (Table 51-6). Using a smaller than recommended cuff on a larger arm typically results in an overestimation of casual BP. In obese or muscular persons, the large adult-size cuff is required for all those with an arm circumference at the mid-humerus over 38 cm. In very large individuals, a "thigh" cuff is often necessary.
- In accurately measuring BP, the deflation rate of the column of mercury should be 2 to 3 mmHg/s. The lower rate of deflation should be used for persons with HRs less than 72 beats per minute (bpm); the more rapid deflation is appropriate only for those with resting tachycardia. If the precision of measurement is to be at least 2 mmHg, the observer should have the opportunity to hear at least one Korotkoff sound at each 2-mmHg gradation of the mercury column. Thus, the proper deflation rate depends on the HR of the subject and is unlikely to be more than 3 mmHg/s if a precise BP measurement is desired.
- It is unusual for a single BP measurement to be an accurate indicator of future CV risk; multiple measurements made on different occasions are more likely to be helpful in deciding whether a particular person ought to have his or her BP lowered. Although it is traditional to average the second and third of a series of BP measurements in a single position (e.g., supine, seated, or standing) and record this as the "average BP" at a given visit, recent "quality care guidelines" mandate instead the recording of individual BP measurements, with the lowest on a given date being the one of greatest interest to auditors. For these reasons, it is quickly becoming "standard practice" to record individual readings and is especially important to measure BP in several positions (including standing), since the auditors record only the lowest BP reading (in any position) as the "BP taken at that visit." The BP readings of many physicians participating in managed care audits are being judged as a "quality of care" indicator, and recording the largest number of BP measurements in several positions offers the greatest opportunity to have at least one which is deemed "acceptable."

- Most of the long-term data on hypertension and its treatment were derived from "casual" measurements made with a mercury sphygmomanometer and stethoscope in a health care provider's office. Physicians and patients often are more interested and impressed by BP readings taken in other settings (e.g., home monitors or ambulatory BP monitoring devices, both of which are discussed further below), but the great majority of data linking BP measurements to adverse clinical sequelae (including MI, stroke, and death) were made in the traditional fashion in the physician's office, and for now, office readings taken by a trained professional should be the BP used for diagnosing and treating hypertensives in all but a few special situations.

Blood pressure is subject to a large degree of intrinsic variability. Several steps can be taken to minimize this variability, including the following:

Table 51-6: Blood Pressure Cuff Names and Sizes

Cuff	Width, cm	Length, cm
Newborn	2.5-4.0	5.0-9.0
Infant	4.0-6.0	11.5-18.0
Child	7.5-9.0	17.0-19.0
Normal adult	11.5-13.0	22.0-26.0
Large adult	14.0-15.0	30.5-33.0
Thigh	18.0-19.0	36.0-38.0

- Taking multiple measurements, especially when the pulse is irregular (e.g., atrial fibrillation). This is necessary because ventricular filling pressures vary considerably as a result of variability of diastolic filling time. Blood pressure variability is especially pronounced in older persons with primarily or exclusively systolic BP evaluations.
- Centering the bladder of the cuff over the brachial artery with its lower edge within 2.5 cm of the antecubital fossa. This leaves enough space so that the stethoscope head can be applied inferiorly without touching the cuff (and generating background noise).
- Having the subject rest silently and comfortably (with back support if seated) for at least 5 min before the measurement.
- Abstaining from drinking caffeine or alcohol-containing beverages or tobacco use within 30 min before a BP measurement.
- Questioning the subject regarding the most recent meal or evacuation of bowels or bladder. Distended abdominal viscera not only are painful but routinely cause elevations in BP, presumably related to anxiety and pain. Older persons typically have a lower BP postprandially; thus, it is often necessary to inquire about and record when the last meal was eaten.
- Assuring that the arm is supported at the level of the heart. Both muscular work (of tensed muscles around the elbow) and hydrostatic pressure caused by a "dangling arm" increase the pressure necessary to obliterate the pulse and lead to overestimates of systolic BP.
- Listening over the brachial artery by using the bell of the stethoscope with minimal pressure exerted on the skin. At the conclusion of the BP measurement, there should be no lasting indentations in the area where the head of the stethoscope was placed. Otherwise the systolic BP is likely to be overestimated and the diastolic BP to be underestimated because too great a pressure was exerted directly over the artery.
- The "peak inflation level" of the mercury column should be determined by using palpation of the radial artery before the stethoscope is applied. For all subsequent BP measurements, the cuff typically should be inflated 20 mmHg higher than the pressure at which the palpable pulse at the radial artery disappears. Important prognostic information may be missed if the "auscultatory gap" is not detected; this risk is minimized by determining the peak inflation level by palpation before the

stethoscope is applied.

- Although mercury columns traditionally have been used in the measurement of BP, environmental concerns associated with elemental mercury are increasing. In Sweden and many other countries, elemental mercury is forbidden in the workplace. Nonetheless, sphygmomanometers used in the measurement of BP should be calibrated frequently and routinely against such standards (typically every 6 months) to assure accuracy.
- Attempting to avoid "terminal digit preference." Traditionally, BP measurements have been made to the nearest 2 mmHg (the typical markings on a mercury sphygmomanometer). Theoretically, in a large collection of systolic and diastolic BP measurements, there should be an equal number of readings ending in 0, 2, 4, 6, or 8 mmHg. It is often instructive to compare the actual distribution of terminal digits with the 20 percent expected for each one. This typically reveals a preference for 0 (in inpatient medical services, where BP readings are typically precise to ±10 mmHg) or 8 (for outpatients in a managed care organization being graded on how many people are <140/90 mmHg).
- Measurements of BP in both arms typically are obtained at the initial visit, and the arm with the higher BP is used thereafter if the difference is greater than 10/5 mmHg. In such situations, there is often concern about coarctation of the aorta or Takayasu's arteritis or moyamoya disease, but seldom is this seen on ultrasonography or other confirmatory testing. Blood pressure measurement in a leg should be commonplace in all young hypertensives at the first visit and may be useful in older people as a peripheral indicator of aortic insufficiency ("Hill's sign").
- Assuring that the equipment used to measure BP is in good working order. Many sphygmomanometers (even in hospitals) are in poor repair and should be cleaned, calibrated, and fitted with nonleaking tubing and properly sized cuffs. The interest in BP measurements recently demonstrated by agencies that certify health systems for quality has improved the chance that any given patient will be hospitalized in a bed with properly maintained BP-measuring equipment.

Home Blood Pressure Measurements

The technology for obtaining accurate and reproducible BP measurements outside the traditional medical environment has improved greatly in the last 20 years. Many types of machines now exist (Table 51-7) that are convenient, inexpensive, and relatively accurate. Even persons with hearing difficulties, problems with hand-eye coordination, and other disabilities can operate semiautomatic devices with digital readouts and printers to estimate BP. Some authorities feel that such devices should be provided to every person with elevated BP, but others are concerned about overinterpretation of the data, which generally have not been used commonly in clinical decision making in clinical trials and should not be used routinely in practice to make diagnostic or therapeutic decisions.

Table 51-7: Advantages and Disadvantages of Methods of BP Measurement Available to Patients in the Outpatient Setting

Attribute	Anaeroid with Stethoscope	Oscillometric with Stethoscope	Oscillometric with Digital Readout
Coordination necessary	Yes	Yes	Less so
Affected by presbyacusis	Yes	Yes	No
Affected by presbyopia	Yes	Less so	Less so
Widely available	Yes	Less so	Increasingly
Inexpensive	Yes	Less so	Increasingly
Good-quality results	Yes, with effort	Yes, with effort	Yes
Increases patients' interest in managing BP	Yes	Yes	Yes
Battery-powered	No	Yes	Yes

Affected by impaired grip strength	Yes	No	No
Independently validated by prospective studies	No	No	No

Home BP readings are typically lower (by an average of 12/7 mmHg) than measurements taken in the traditional medical environment, even in normotensive subjects.[21] Home readings tend to be better correlated with both the extent of TOD and the risk of future mortality than are readings taken in the physician's office.[182] Home readings can be helpful in evaluating symptoms suggestive of hypotension, especially if the symptoms are intermittent or infrequent. During treatment, reliable home readings can lower costs by substituting for multiple visits to health care providers.[183] Persons who routinely measure BP at home probably have a better prognosis than do those who do not because of both selection bias (they tend to be more interested in their BP than are those who refuse to purchase and use a home BP machine) and social support (when a friend or spouse becomes involved in measurement and overseeing pill-taking and appointment-keeping behaviors).

Home BP readings should be interpreted cautiously, carefully, and conservatively.[184] There are no data from long-term clinical studies that based all treatment decisions solely on home readings, but several preliminary reports show benefit from supplementing office BP measurements with home readings.[185-186] Several studies have shown that prognosis is better predicted by home readings than by one or two "casual" BP measurements.[187-189] Many of the factors that contribute to BP variability are more difficult to control in the home environment, including intrinsic circadian variation, food and alcohol ingestion, exercise, and stress. The possibility that home BP measurements will become an obsession is also a disadvantage. If home readings are to be taken, most authorities recommend that the instrument be calibrated against a mercury sphygmomanometer by using a Y-tube and that the technique of the measurer be checked. Home readings can be a useful adjunct to information obtained in the physician's office, especially when the two are widely disparate. One long-term study showed that people with much lower home BP readings (compared with those in the physician's office) suffer fewer major CV events than do people who have elevated readings both in the office and at home.[187,190] The authors recommend that patients who are interested in and capable of measuring their BP at home do it at a fixed time of the day and record all the readings obtained. The physician then can review them during the office visit and strive to educate the patients about the difficulties of interpretation of the readings.

Ambulatory Blood Pressure Monitoring

Extensive research has led to a better definition of the role of automatic recorders that measure BP frequently over a 24-h period during a person's usual daily activities (including sleep). Despite the acquisition and dissemination of excellent data, however, the use of these devices by practitioners in the United States has been extremely limited, mostly because of a lack of reimbursement by third-party payers. As a research tool, however, the advantages and disadvantages of ambulatory blood pressure monitoring (ABPM) have been well documented (Table 51-8), normal values have been defined (Table 51-2), and multiple publications correlating abnormal patterns of ABPM with adverse outcomes have appeared.[191,192] Several expert panels have defined the special situations in which ABPM is particularly useful (Table 51-9).

Table 51-8: Advantages and Disadvantages of Ambulatory Blood Pressure Monitoring

ADVANTAGES
Many BP and pulse measurements during 24-h period
Measures diurnal variation (including during sleep)
Measures BP and pulse during daily activities
Can identify 'white coat' hypertension
No 'alerting response'
No placebo effect
Better correlation with target organ damage than other methods
DISADVANTAGES
Cost
Limited availability of equipment
Disruption of daily activities from noise/discomfort (e.g., sleep quality, flaccid arm during measurement)
Limited 'normative' data
Limited guidelines (or consensus) for interpretation of data in individuals
Few long-term prospective studies demonstrating utility compared with traditional (and much less expensive) BP measurements

SOURCE: Adapted from Elliott WJ, Black HR. Special situations and special considerations. In: Hollenberg NK, ed. *Hypertension: Mechanism and Treatment.* Volume 1 of Braunwald EB, ed. *Atlas of Heart Disease.* Philadelphia: Current Medicine; 1995:12-1.

Table 51-9: Situations in Which ABPM is Useful

'High-normal' blood pressure without target organ damage
Office or 'white coat' hypertension
Refractory hypertension
Episodic hypertension
Symptoms consistent with hypotension associated with antihypertensive medication
Hypertension with autonomic dysfunction
Nocturnal hypertension
Evaluation of efficacy of antihypertensive drugs in clinical research

SOURCE: Adapted from the National High Blood Pressure Education Program's Working Group Report on Ambulatory Blood Pressure Monitoring. *Arch Intern Med* 1990; 150:2270-2280.

Several varieties of ABPM devices are currently available. In the United States, those which measure BP indirectly (i.e., without arterial cannulation) use either an auscultatory or an oscillometric technique. The former type uses a microphone placed over the artery to detect Korotkoff sounds in the traditional fashion.

The latter measures biophysical oscillations of the brachial artery, which are compared (using a standardized algorithm) with those observed with a mercury sphygmomanometer: Systolic BP is determined directly from the threshold oscillation, mean arterial pressure is estimated, and diastolic BP is calculated. Both types of monitors are small (<450 g), simple to apply and use, accurate, relatively quiet and tolerable, and powered by two to four small batteries. Data from 80 to 120 measurements of BP and pulse typically are stored in a small microprocessor and then downloaded into a desktop computer, which then edits the readings and prints the report.

None of the currently available ABPM devices is completely without problems. Devices that rely on direct measurements require 24 h of arterial cannulation, which is potentially dangerous, and rarely are used even for research. Indirect measurements of BP using auscultatory techniques can be confused by ambient noise levels even if R-wave gating is used (this requires the electrocardiographic leads to be attached to the chest). Oscillometric techniques require that the subject keep the arm straight and flaccid during the measurement and can be completely confused if the subject has a tremor. The interpretation of ABPM readings may be enhanced by a diary of the subject's activities, but such diaries are not always completed.

ABPM makes it possible to measure BP routinely during sleep and has reawakened interest in the circadian variation of HR and BP. Most normotensives and perhaps 80 percent of hypertensives have at least a 10 percent drop in BP during sleep compared with the daytime average. Although there may be some important demographic confounders (blacks and the elderly have less prominent "dips"[193,194]), several prospective studies have shown an increased risk of CV events among those with a "nondipping" BP or pulse pattern.[195-197] However, there is concern, based on several Japanese studies, that elderly persons with more than a 20 percent difference between nighttime and daytime average BPs ("excessive dippers") may suffer unrecognized ischemia in "watershed areas" (of the brain and other organs) during sleep if their BP declines below the autoregulatory threshold.[198]

During the last 15 years, research has demonstrated an important correlation between ABPM readings and the prevalence and extent of TOD in hypertensives. Compared with "casual" BP measurements (obtained in the health care provider's office), ABPM measurements clearly are a better predictor of LVH, cardiac function, and overall scores summing optic, carotid, cardiac, renal, and peripheral vascular damage resulting from elevated BP.[199-201] Ambulatory BP monitoring also may be useful in identifying the small minority of typically unrecognized patients [61 of 234 (26 percent) in New York City] with "white coat normotension" who have normal BP readings in the physician's office but elevated ABPM readings with LVH and carotid wall thickening similar to that usually seen in sustained hypertensives.[202]

Perhaps the most important data demonstrating the value of ABPM have come from recent end-point studies of CV events (death, MI, stroke). In the first published study of outcomes in central Italy, ABPM was the best predictor of future CV events; "nondipper hypertensives" had approximately three times the risk of hypertensives whose BP was ≥10 percent lower at night compared to daytime ("dippers").[195] A population-based study involving 1572 men and women of ABPM versus casual and home BPs has been ongoing since 1987 in Ohasama, Japan.[188] After an average of approximately 5 years of follow-up, there was no significant relationship between one casual BP measurement and future CV mortality. However, there was a highly significantly increased risk of CV death in the quintile with the highest ABPM, and the lowest risk was found in those in the lowest quintile of ABPM.[189] The value of ABPM in refractory hypertension was demonstrated in a study of 86 hypertensive people taking on average three antihypertensive medications daily.[203] Follow-up data were collected approximately 4 years after an ABPM was performed; the patients having ABPM results in the lowest tertile had significantly lower rates of CV complications: 2.2 versus 9.5 versus 13.5 events per 100 patient-years. These data suggest that ABPM may be helpful in sorting out which patients with elevated office BP measurements who already are taking multiple antihypertensive medications ought to have intensified treatment and which ones can be spared the additional expense and risk. A subsidy of the Systolic Hypertension in Europe (Syst-EUR) trial involved 808 patients who had ABPM in addition to the usual clinic BP measurements before randomization to placebo or active treatment.[197] In the group randomized to placebo, ABPM was clearly a better predictor of future CV events than was the office BP measurement. Active treatment reduced the difference in prognosis

among ambulatory and office measurements. Furthermore, the risk of a CV event was much higher in patients who did not display a nocturnal decline in BP. These data suggest (but do not prove) that the poor prognosis seen with nondipping hypertension can be mitigated by active antihypertensive treatment.

White Coat Hypertension

Since the advent of technology that allows accurate BP measurement outside the health care provider's office, it has been estimated by many but not all reports that 10 to 20 percent of American hypertensives have substantially lower BP measurements in other settings.[204] The name *white coat hypertension* has been given to the situation in which BP measurements outside the health care setting are considerably lower than those in it even though the "white coat" itself is unlikely to be the only factor that increases BP. Careful studies originally done in Italy and later corroborated in other countries show that BP rises in response to an approaching physician who is not previously known to the subject. This apparently does not happen if the subject is approached by a nurse even if she or he is wearing a white coat.

The clinical consequences and prognostic significance of white coat hypertension have been hotly debated in the medical literature for some years. One school of thought suggests that if a person has an acute rise in BP caused by stress related to an approaching physician, similar elevations in BP are likely whenever a stressful stimulus is encountered. Thus, some of the literature supports the concept that the white coat response is merely a precursor to "more substantial and more sustained hypertension."[205] This point of view is buttressed by the realization that in several clinical and population-based studies, white coat hypertension also is found in people with a greater prevalence of subclinical risk factors for CV, including LVH, a family history of hypertension and heart disease, hypertriglyceridemia, elevated fasting insulin levels, and lower HDL-C levels.[205-208]

A second school of thought, based on more careful and conservative definitions of the white coat effect, proposes that some individuals consistently show a similar and marked elevation in BP in response to the health care environment. Using somewhat more stringent criteria than the studies cited above, several long-term studies have shown a greatly reduced risk of either TOD or major CV sequelae among people with lower BPs measured either at home or by 24-h BP monitoring compared with measurements taken in the same person in the physician's office.[187,190,195] Whether the future risk of such individuals for CV events is similar (or even identical) to that of completely normotensive people is open to question. A third group has claimed that white coat hypertension simply represents regression to the mean in those with considerable BP variability.[204]

The best approach to the treatment of white coat hypertension is unresolved. Clearly, such individuals would benefit from lifestyle modification, which presumably would reduce the probability of progression to sustained hypertension. Completely abstaining from antihypertensive medication in "white coat hypertensives" appears unwise. Verdecchia and colleagues have published data indicating that in the long term, the risk of future CV events did not differ between white coat and sustained hypertensives when both were treated with antihypertensive medications.[209] Whether intensive treatment with continuous antihypertensive medication is warranted for only temporary increases in BP is debatable. Clearly, the treatment and repeated ABPM sessions required to monitor therapy would not be very cost-effective. The cost-effectiveness of ABPM to diagnose and monitor people with white coat hypertension has been estimated by several groups, primarily because 10 to 20 percent of hypertensives might be spared the cost of treatment and close follow-up.[210-212] One ABPM session annually has been set as the upper limit of what most American health plans could afford.[213] Several authoritative groups have recommended that ABPM be used sparingly in the general antihypertensive population but may be more widely used in managed care, veterans' hospitals, and other situations where minimal incremental direct costs are involved.[213,214]

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Chapter 51: HYPERTENSION: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

EVALUATION OF THE HYPERTENSIVE PATIENT

Six key issues must be addressed during the initial office evaluation of a person with elevated BP readings:

- Documenting an accurate diagnosis of hypertension (see above)
- Defining the presence or absence of TOD related to hypertension
- Screening for other CV risk factors that often accompany hypertension
- Stratifying risk for CVD (according to risk Group A, B, or C in JNC VI)
- Assessing whether the person is likely to have an identifiable cause of hypertension (secondary hypertension) and should have further diagnostic testing to confirm or exclude the diagnosis
- Obtaining data that may be helpful in the initial choice and subsequent choice of therapy

There are many diagnostic possibilities for explaining a single set of elevated BP readings (Tables 51-10 and 51-11). Aside from those who take one of several types of drugs known to elevate BP, many persons with only one elevated BP reading will have their BP decline and return to the normal range. This is the reason for recommending multiple encounters (at least two or three) before a diagnosis of hypertension is firmly established.

Table 51-11: Drugs Known to Elevate Blood Pressure

Nonsteroidal anti-inflammatory drugs
Sympathomimetic amines (e.g., phenylpropanolamines)
Estrogen and estrogen analogs (e.g., oral contraceptive pills and hormone replacement therapy)
Methylxanthines (e.g., theophylline, caffeine, theobromine)
Cyclosporine
Erythropoietin
Cocaine
Nicotine
Phencyclidine ('angel dust')
'Herbal ecstasy' (and other ephedra-containing substances)
Withdrawal from certain drugs (e.g., beta blockers, alpha agonists, opioids, ethanol, calcium antagonists)

Routine Evaluation in All Hypertensive Patients

The recommendations of JNC VI and other national and international expert panels limit the number of and the expense related to initial tests for the routine evaluation of a hypertensive patient[11,18,19] (Table 51-12). Those which are used in assessing the presence or absence of TOD include physical examination, blood urea nitrogen (BUN)/creatinine, electrolytes, urinalysis, and an electrocardiogram (ECG). Assessing the number of CV risk factors can be accomplished with the medical history, chemistry panel [glucose, total

cholesterol (TC), triglycerides], and urinalysis. The JNC VI suggests stratifying patients' risk for CV into three risk groups (Table 51-3). Other national expert panels have even more elaborate systems for linking the assessment of CV risk and the intensity of antihypertensive treatment.[19,215]

Table 51-12: Routine Tests Recommended by JNC VI for the Initial Evaluation of a Hypertensive Patient

Serum chemistry (glucose, potassium, creatinine)
Urinalysis
Electrocardiogram

Several elements of the evaluation of a hypertensive patient warrant further comment. The physical examination needs to be "directed" toward looking for clues that might indicate an identifiable secondary cause of hypertension such as an abdominal or flank bruit, which would be a sign of visceral atherosclerosis or perhaps renal artery fibromuscular disease, or an abdominal or flank mass that might be a pheochromocytoma or a polycystic kidney.

Proper examination of the optic fundus often is neglected even though it is a valuable tool for evaluating hypertensive patients. In the years before effective antihypertensive drug therapy became available, the most important predictor of future CV mortality and morbidity was not the level of BP but in the appearance of TOD in the optic fundi.[216] Although the prognosis of hypertensive patients has improved greatly since that time, the appreciation of hypertension-related changes in the optic fundus is still important in the assessment of both the severity and the duration of elevated BP. The optic fundus is the only site in the entire body where blood vessels can be examined directly. Very few patients with a recent onset of hypertension have Keith-Wagener-Barker (KWB) grade III or IV fundi (Table 51-13).

Table 51-13: Keith-Wagener-Barker Classification of Optic Fundi

Grade	Characteristic Finding
I	Arterial tortuosity, localized arterial spasm or narrowing (relative to neighboring vein), 'silver wiring'
II	Extensive or generalized arteriolar narrowing, resulting in arteriovenous crossing changes ('arterial nicking')
III	Hemorrhages or exudates
IV	Papilledema

Arteriosclerosis can be directly recognized, and the severity and duration of previous hypertension can be estimated through the appreciation of abnormalities of the retinal arteries.[217] The normal yellowish-white color of the retinal arteries gradually changes to a reddish-brown tone ("copper wire"), and the ratio of artery/vein diameters is reduced from the normal 2:3 to less than 1:3. Over time, the column of blood within the artery gradually diminishes and the artery is reduced to a whitish thread ("silver wire") despite a persistent (albeit reduced) flow of blood. "AV nicking" is perhaps the most easily recognized ocular abnormality in hypertension. When the thickened artery containing blood at elevated pressure compresses a low-pressure, thin-walled vein within the shared adventitial sheath, the vein disappears from view. Hypertension is therefore both epidemiologically and pathophysiologically a risk factor for retinal vein occlusion, although this is not a common occurrence.[218,219] When arterial blood flow is reduced sufficiently to cause infarction of underlying retinal tissue, round to oval white patches with fluffy borders are formed ("cytoid bodies" or "cotton-wool spots"). When there is breakdown in the blood-retinal barrier

(caused by a ruptured aneurysm, neovascularization-typically in diabetics-or "blowout" hemorrhages resulting from hypertension), intraretinal "flame-shaped" hemorrhages can be recognized on direct ophthalmoscopy. The leakage of plasma into the macular space often causes an acute reduction in vision and leaves behind the "macular star figure" for years thereafter. Grade IV retinopathy (papilledema), which is the hallmark of either retinal vein occlusion or a hypertensive emergency, usually is caused by ischemia in the optic nerve circulation resulting from increased intraocular or intracranial pressure and diminished axoplasmic flow in the optic nerve fibers. In some cases, particularly when BP is not exceedingly high and there is no other evidence of acute TOD from a hypertensive emergency, another cause should be sought. Papilledema without other evidence of hypertensive retinopathy generally is due to another etiology.

The impact of controlling hypertension on ophthalmic end points (e.g., vision loss, retinal hemorrhages, and laser photocoagulation procedures) has not received much attention in the general medical literature. There are nonetheless several reports of reduced risk of these end points in several clinical trials that assessed their incidence prospectively, particularly among diabetic hypertensives.[220-222]

Cardiac Evaluation

One of the most important elements of the physical examination of hypertensive patients is the cardiac examination. An atrial (S_4) gallop is an extremely common finding and may be a vital clue to the presence of hypertensive heart disease.

A key part of the laboratory evaluation is directed at determining whether LVH is present. The ECG is currently recommended by nearly all authorities as part of the initial evaluation of persons with hypertension. Not only is the ECG useful in documenting previously undetected MI, myocardial ischemia, and/or cardiac rhythm disturbances, it is the least expensive and possibly the most cost-effective way to diagnose and/or exclude LVH. Although several studies have suggested that compared with echocardiography, computed axial tomography (CAT), or magnetic resonance imaging (MRI) of the heart, the ECG is perhaps only 10 to 50 percent sensitive (depending on which criteria are used) and at best 80 percent specific, the expense of these more accurate methods of screening for LVH limits their use.[223-225] A "limited echocardiogram" that accurately calculates left ventricular (LV) size at a very affordable price and also provides information about ventricular geometry has been recommended by several authorities but has not been commonly endorsed by third-party or other payers.[226]

The prognostic significance of LVH among hypertensive patients is well established. Left ventricular hypertrophy often is thought of as the "hemoglobin A_{1c} of BP," since it is an objective measure of both the severity and the duration of elevations in BP. In the Framingham Heart Study, ECG evidence of LVH was associated with an approximately threefold increase in the incidence of CV events.[227] Echocardiographically detected LVH appears to predict an even greater incremental increase in the risk of future CV events, although the geometry of the ventricle also may play a role.[228,229] Hypertension typically is associated with concentric hypertrophy of the ventricle, perhaps as a result of concentric remodeling, which in one series carried a fourfold increased risk of cardiac morbidity and mortality (compared with nonhypertrophied hearts).[230] Eccentric hypertrophy, which is seen in response to exercise in athletes, imparted only a twofold increased risk of events in the same series.[229] In several reports from various locales, in both univariate and multivariate models, LVH was the most powerful of any of the traditional CV risk factors in predicting not only death or MI but also stroke, HF, and other CV end points.[228,229,231,232] Although research studies including thousands of people have demonstrated the importance of echocardiographically determined measurements of LV mass, there is concern that the intrinsic variability of a single echocardiogram is sufficiently high (perhaps 10 to 15 percent) that serial determinations in a usual hypertensive individual are unlikely to be cost-effective. The exception may be a person with stage 1 hypertension, in whom the presence of this form of LVH would lead to a reclassification of the patient and indicate the need for antihypertensive drug therapy earlier than it might have been given if the clinician had thought the patient was free of TOD.

LVH is associated both epidemiologically and pathophysiologically with intimal hyperplasia of the epicardial coronary arteries, increased coronary vascular resistance, increased severity and frequency of ventricular dysrhythmias, decreased flow reserve, and reduced diastolic relaxation. At the extreme, diastolic

dysfunction and restrictive cardiomyopathy result clinically in "flash pulmonary edema" despite a normal ejection fraction. Although this phenomenon is not well understood, some feel that hypertension plays the major role in the pathogenesis of this syndrome, which has been identified in up to 40 percent of patients presenting to the hospital with HF.[233] The important prognostic role of LVH was demonstrated and separated from possible subclinical coronary disease in a consecutive series of 785 patients who had cardiac catheterization.[234] After 4 years of follow-up in patients with echocardiographically documented LVH, the risk of dying was increased twofold if there was coronary artery disease (CAD) but more than fourfold if CAD was not present.[234] Echocardiographically defined LVH was the most powerful risk factor for death.

The most contentious aspect of LVH is the importance of its reversal and how to achieve it. While early data from several centers indicate a better prognosis among patients with echocardiographically determined LVH whose LV mass index is reduced (typically by pharmacologic treatment of hypertension) compared with those whose index increases over time, the large therapeutic trials directed primarily at this question are still ongoing. There are major controversies, supported by separate meta-analyses with differing conclusions, about whether certain classes of antihypertensive drug therapy are more effective at quickly reducing LV mass, but these changes have not been correlated with a reduced risk of CV events in large numbers of patients.[235-237] Most studies agree that LVH is unlikely to regress without reducing BP; most authorities therefore recommend spending resources on achieving BP control rather than on serial echocardiograms to see if the LV mass index is returning toward normal.

Renal Evaluation

Current recommendations for the evaluation of renal function include just a measure of BUN and serum creatinine and a dipstick to detect heavy proteinuria. A more extensive search for microalbuminuria (MA), as defined by the presence of albumin in the urine above the normal range of less than 30 mg/day but below the detectable range with the conventional dipstick methodology, i.e., 300 mg/day, is also warranted.[238] Data from several pioneering studies done over the last two decades have demonstrated that MA is not only a predictor of diabetic complications but also a powerful independent risk factor for CV disease.[238-240] Moreover, MA predicts the development of ischemic CV events related to the development of atherosclerosis. Numerous clinical studies in persons with either type 1 or type 2 DM as well as those with renal disease have demonstrated higher CV mortality in those with MA.[239-244]

The prevalence of MA in patients with type 2 DM is about 20 percent (range, 12 to 36 percent) and affects about 30 percent of people with type 2 DM older than 55 years of age.[242-244] The prevalence of MA ranges from 5 to 40 percent among nondiabetic persons with essential hypertension.[244] The reason for this high variability in MA prevalence among those with essential hypertension relates to both the duration of BP control and associated lipid abnormalities, especially low-density lipoprotein cholesterol (LDL-C) levels.[245] A second related predictor is the duration of hypertension.[246] In this way, MA may be a marker of BP control, since BP control with all agents, except dihydropyridine CA and central or peripheral sympathetic blockers, reduces albuminuria.[247] Subsequent chronic renal failure occurs at a rate of 1 percent per annum in those with type 2 DM; the risk for those with type 1 DM approaches 75 percent after 10 years, while for those with essential hypertension, it is less than 1 percent over 5 years.[247,248]

Some studies have shown that the amount of MA present in a person is proportional to the severity of systolic, diastolic, and mean BP elevation as measured by either clinic or 24-h ambulatory BP monitoring.[249,250] This observation has been corroborated by the results of a clinical study of 211 untreated men with MA and essential hypertension.[251] This study agreed with the findings of previous investigators and showed that patients with MA had higher BP levels.[249] Another Italian population study with 1567 participants revealed an 18-mmHg higher systolic BP in the group of nondiabetic people with MA.[252] Lastly, circadian abnormalities of BP seen in nondippers (see above), who are known to be at higher risk for CV, also have a higher prevalence of MA.[253,254]

The exact pathophysiology of how MA contributes to or accelerates the atherosclerotic process is uncertain. The current understanding, however, suggests that MA is an indicator of increased vascular permeability

and, hence, altered barrier function of the endothelium.[249,250,252-,255] People with MA have an elevated transcapillary escape rate of albumin regardless of whether they have preexisting DM. Moreover, it has been argued that when albumin leaks into the interstitial space, cellular injury occurs secondary to free radicals and cytokine production enhanced by the presence of albumin. More recently, some authors have suggested that MA is another element of the metabolic components of syndrome X[256-258] (see above).

Simply using a conventional dipstick that can detect only higher levels of urinary protein (>300 mg/24 h) means that the clinician will miss the opportunity to characterize a patients' prognosis more precisely at the initial visit. Dipsticks that detect MA are available and inexpensive. Perhaps all hypertensives with "trace" proteinuria (generally 300 to 500 mg/day) when measured by conventional dipsticks should have a spot urine measurement of the albumin/creatinine ratio.[238] Routine assessment of MA in diabetic patients is well advised, but in hypertensives without DM, its value is still debatable. In part, this is due to the relatively low prevalence of MA in the nondiabetic population and the uncertainty of the significance of its modification in these groups.

Studies found that subjects with MA and type 2 DM have approximated total mortality of 8 percent and CV mortality of 4 percent annually. These values are up to four times higher than those of patients without MA.[258] Similar increases in CV mortality also are present in people with MA and without diabetes. In several series, the CV event rate in nondiabetic people with MA and hypertensives was twofold to fourfold higher than it was in those without MA.[259]

In several studies, people with MA had larger LV mass and higher degrees of LVH.[260-262] This has been documented by both ECG and echocardiographic criteria. However, this finding was not consistent in other populations that were relatively young (age between 18 and 45) and had stage 1 hypertension. This association of MA with LVH may be related to a higher BP load.

Evaluation of the Vasculature

One of the hallmarks of the hypertensive circulation is decreased vascular compliance. Acutely, elevated BP affects the elastic behavior of both large and small arteries such that the muscular layers of the arterial wall are unable to relax as quickly and transmit pressure waves as easily and reproducibly as they can when BP is lower. This is a passive and reversible phenomenon that typically lasts minutes to hours. Over a prolonged period, however, there is a gradual infiltration of the internal elastic lamina of blood vessels with thinned, split, and frayed elastic fibers and a laying down of new intercellular matrix; in extreme cases, medial necrosis is found within the arterial wall. This process, which is attributed to aging, hypertension, or a combination of the two, often is described as "arteriosclerosis," since it leads to chronic and generally irreversible stiffening of the arterial tree.[263]

There are several methods of assessing arterial compliance (Table 51-14), but most are invasive, expensive, or not widely used in clinical medicine.[264] Several new methods for calculating total arterial compliance are based on pulse contour analysis but have not been tested in large population-based studies to prove their value in estimating CV risk.[265,266] Blacher and associates showed in 710 subjects from the Framingham Heart Study that pulse wave velocity is higher in subjects with known atherosclerotic CV.[267] Whether this measure will be used routinely to evaluate hypertensives remains to be seen.

Table 51-14: Methods for Determining Arterial Compliance

	Measured in	Invasive?	Drawbacks
Direct methods			
Angiography	Aorta	Yes	Expensive
Echocardiography	Aorta	No	Expensive
Echo tracking	Peripheral arteries	No	Not widely available
Intravascular ultrasound	Peripheral arteries	Yes	Expensive
Venous occlusion plethysmography	Peripheral arteries	No	Time- and operator-intensive
Indirect methods			
Stroke volume/pulse pressure ratio	Total arterial compliance	No	Reproducibility questionable
Pulse wave velocity	Segmental arteries	No	Limited to large arteries
Fourier pulse analysis	Peripheral arteries	No	Reproducibility questionable
Total compliance	Total arterial compliance	No	Expensive
Pulse contour analysis	Total arterial compliance	No	Time- and operator-intensive

Pseudohypertension is the name given to the rare circumstance in which BP measurements by the usual indirect sphygmomanometry are much higher than direct intraarterial measurements; these differences usually are attributed to very "stiff" and calcified arteries that are nearly impossible to compress with the bladder in the usual BP cuff. The "Osler maneuver" (palpating the walls of the brachial artery when blood flow has been interrupted by inflating the cuff higher than systolic pressure) has been recommended as a simple measure to diagnose this condition, but several reports have found it less sensitive and specific than was reported initially, and the authors do not recommend using it.[268] Because making the diagnosis of pseudohypertension requires a potentially dangerous and expensive intraarterial measurement (and perhaps an infusion of an intravenous antihypertensive agent to "calibrate" the difference between indirect and direct BP measurements), few clinicians routinely check for and diagnose pseudohypertension.

The benefits of lowering BP in older patients with "stiff" arteries, however, are well established. Three clinical trials specifically in isolated systolic hypertension [systolic blood pressure (SBP) ≥160 mmHg with diastolic blood pressure (DBP) <90 or <95 mmHg] proved that older individuals with BP elevations only in systolic BP (a typical finding in patients with reduced vascular compliance) have a reduced risk of CV events with pharmacologic treatment.[269-271] Whether arterial compliance should be measured as a predictor of CV risk and measured serially over time is controversial; perhaps it would not be as cost-effective as serial BP determinations during treatment.

Other Evaluation

Other blood tests such as PRA and serum insulin or newly appreciated markers of CV risk such as C-reactive protein have been abandoned for routine or even specialized evaluation or have not been proved to be sensitive or specific enough to warrant inclusion in the evaluation of all hypertensive patients.[272]

Evaluation for Identifiable Causes of Hypertension

There are many identifiable causes of hypertension (secondary hypertension). In patients with some of these causes, the elevation of BP can be eliminated with specific treatment such as angioplasty or surgery therapy or by removing the agent that caused the hypertension. By far the most common identifiable cause

is chronic renal failure. Although chronic renal disease almost never can be cured, the hypertension associated with it often can be controlled with adequate dialysis without the use of drugs. Renal artery stenosis, pheochromocytoma, and primary aldosteronism, however, are potentially curable. These conditions are encountered commonly enough that the clinician seeing a hypertensive patient must have a high index of suspicion in the appropriate clinical setting and should order the specialized tests necessary to screen for and confirm the diagnosis. Other etiologies, such as specific enzyme deficiencies, coarctation of the aorta, and Ask-Upmark kidney, are distinctly rare. This section will cover only the most common etiologies listed in Table 51-10. If a secondary cause of hypertension is suspected, a referral to a hypertension specialist may be appropriate.[11,19]

RENOVASCULAR HYPERTENSION

Patients with this form of secondary hypertension often have stage 3 hypertension and considerable TOD and are at risk of losing renal function. At least 90 percent of cases of renovascular hypertension now are due to renal artery atherosclerosis, with only 10 percent being due to fibromuscular dysplasia or unusual causes.[273,274] Atherosclerotic renal artery stenosis is a disease of older individuals. Characteristically, these patients develop hypertension after age 50 or have a history of hypertension that had been relatively easy to control and became refractory. A large proportion of these patients have evidence of vascular disease elsewhere (carotids, coronaries, and peripheral circulation, in particular), and the majority are cigarette smokers, often heavy smokers.[275] Although it is more common in whites, blacks also can develop atherosclerotic renovascular hypertension.[276,277] Fibromuscular dysplasia tends to affect young white women in whom BP tends to rise abruptly to stage 3 during the third decade of life. Abdominal or frank bruits are heard commonly, and renal function is usually normal when the diagnosis is entertained.

Laboratory Testing

The objective of laboratory testing in patients suspected of having renovascular hypertension is not only to verify that arterial lesions are present but also to determine that the lesion that is discovered is in fact the cause of the patient's hypertension.[273] The clinical situations in which renovascular disease should be suspected are listed in Table 51-15.

Table 51-15: Testing for Renovascular Hypertension: Clinical Index of Suspicion as a Guide to Selecting Patients for Workup

Low (should not be tested)
Stage 1 or 2 hypertension in the absence of clinical clues
Moderate (noninvasive test recommended)
Stage 3 hypertension
Hypertension refractory to standard therapy
Abrupt onset of sustained stages 2-3 hypertension at age <20 years
Hypertension with a suggestive abdominal bruit (long, high-pitched, and localized to the region of the renal artery)
Stages 2-3 hypertension (diastolic BP exceeding 105 mmHg) in a smoker, a patient with evidence of occlusive vascular disease (cerebrovascular, coronary, peripheral, vascular), or a patient with unexplained but stable elevation of serum creatinine
High (may consider proceeding directly to arteriography)
Stage 3 hypertension with either progressive renal insufficiency or refractoriness to aggressive treatment, particularly in a patient who has been a smoker or has other evidence of occlusive arterial disease

Accelerated or malignant hypertension (grade III or IV retinopathy)
Hypertension with recent elevation of serum creatinine, either unexplained or reversibly induced by an angiotensin-converting enzyme inhibitor
Moderate to severe hypertension with incidentally detected ansymmetry of renal size

SOURCE: Modified from Mann SL, Pickering TG. Detection of renovascular hypertension: State of the art: 1992. *Ann Intern Med* 1992; 117:845.

The tests used to confirm the clinical suspicion that a patient has renovascular hypertension are biochemical or depend on a variety of imaging techniques (Table 51-16).

Table 51-16: Detection of Renovascular Hypertension

Biochemical
Serum K^+
PRA
Renal vein renin activity
Split renal function tests
Imaging
Rapid-sequence intravenous pyelography
Renography
Captopril or enalaprilat renography
Intraarterial digital substraction angiography
Standard angiography
Duplex renal ultrasound
Magnetic resonance angiography

Biochemical

Measurement of serum K^+ (which, if low, may indicate hyperaldosteronism) or PRA (which, if high, may confirm activation of the RAA system) plays no role in the further case finding for renovascular hypertension because the sensitivity and specificity are too low.[278] Even measuring the PRA after captopril (the so-called captopril test) has a sensitivity of only 60 to 70 percent, although better results have been obtained in some series.[278] Measuring the concentration and activity of renin simultaneously from each renal vein and computing the renal vein renin ratio was a very popular approach at one time, but the sensitivity and specificity for detection of renovascular hypertension with this test are both approximately 75 percent, unacceptably low for an invasive procedure that requires special expertise and sophisticated measurements.[278] This ratio may still be useful to help prove that an anatomic lesion is also the cause of a patient's hypertension but should not be used as a screening tool.

Imaging

Rapid-sequence intravenous pyelography and standard renal scanning were the earliest noninvasive imaging studies used for diagnosing renovascular hypertension.[278] Even though in expert hands each has reasonable sensitivity (65 to 70 percent for scanning and 75 percent for pyelography), neither has a place in the diagnostic approach any longer. Renal duplex ultrasound has the advantage of being noninvasive and widely available. In some laboratories, the sensitivity of this test approaches 90 to 95 percent.[279] However, the presence of abdominal gas or fat may make it difficult to visualize the renal arteries, and the test is very operator-dependent. In specialized centers with special expertise and in selected patients, it may be a useful test. In most settings, however, little is gained by using this technique. Magnetic resonance angiography with gadolinium is a new approach to visualization of the renal arteries that is becoming widely available and is noninvasive.[280] However, until the quality of the images improves and the cost becomes lower, this technique is not likely to replace angiography when visualization of the renal arteries is felt to be necessary.

The two imaging modalities currently favored are isotopic renography with labeled dethylenetriamine pentaacetic acid (DTPA) (a measure of glomerular filtration) of MAG-3 (a measure of renal blood flow) with captopril and intraarterial digital subtraction angiography.[273] Isotopic renography with captopril is a minimally invasive test that detects a discrepancy between perfusion and function of the kidneys. The overall sensitivity and specificity are 90 percent when done carefully, especially in patients whose prior probability of having renovascular hypertension is judged to be high.[273,278] Only ACE-Is and ARBs need to be stopped before the test is performed, and adverse reactions from the single dose of captopril are rare. Isotopic renography with captopril also provides functional information. If the time to peak activity is initially normal and becomes abnormal after captopril ("captopril-induced changes"), the likelihood of cure or improvement after revascularization is high.[273]

Intraarterial digital subtraction angiography has become the invasive procedure of choice to demonstrate definitively the renal artery anatomy and determine whether an arterial lesion is present. Although an arterial puncture is required, the needle used is small and the dye load is modest. In addition, the type of lesion (ostial, nonostial, or branch) can be determined. In some centers, percutaneous renal angioplasty is done at the same time if it is felt to be indicated. The authors are not in favor of doing revascularization unless evidence has been obtained (a positive captopril renogram with captopril-induced changes or a renal vein renin ratio >1.5) that the lesion is functionally significant. The presence of anatomic renal artery stenosis does not mean that the lesion is responsible for the elevation in BP (functional renal artery stenosis).[273]

When considering whether to proceed with these studies, the clinician must consider how the data will be used. In a number of hypertensive patients with renovascular hypertension, BP is controlled adequately with medical therapy. If the risk of surgery or angioplasty is viewed as unacceptably high or if the patient will not consent to having a revascularization procedure if a remediable lesion is discovered, any specific further evaluation may not be appropriate.

PHEOCHROMOCYTOMA

Patients with pheochromocytoma are almost always symptomatic on presentation.[281] These patients usually have a characteristic cluster of complaints that occur in paroxysms or "spells." The description of the spell tends to be typical and is usually the same in each patient. The spells may occur many times a day or may be separated by weeks or months.[282] Often there is a characteristic trigger (change in position, certain foods, trauma, pain, or drugs) that if present should greatly increase the clinician's index of suspicion of pheochromocytoma. Hypertension is not usually paroxysmal, as has often been stated, with some BP readings elevated and some normal. Most measurements are in fact in the hypertensive range, although wide variability is the rule. The three most common symptoms of pheochromocytoma are headache, diaphoresis, and palpitations[282] (Table 51-17). Many other symptoms, particularly anxiety, weakness, and tremulousness, are also quite common. The pattern of symptoms can provide guidance about the predominant hormone secreted by the tumor. When norepinephrine is the primary hormone produced, pallor is usually the symptom. Flushing is more likely if substantial amounts of epinephrine are produced.

Laboratory Testing for Pheochromocytoma

Whereas it is possible and sometimes desirable to manage hypertensive patients with renovascular hypertension or mineralocorticoid-excess states with medical therapy, it is almost always imperative to remove a pheochromocytoma. As with renovascular hypertension, once the clinical presentation suggests that a pheochromocytoma may be the cause of a patient's hypertension, a variety of tests are available to confirm the diagnosis (Table 51-18). If a pheochromocytoma is suspected, the next step is to obtain biochemical confirmation of an increase in catecholamine production. The authors prefer to measure 24-h urinary excretion of total catecholamines (norepinephrine, epinephrine, or dopamine) or their metabolites (vanillylmandelic acid or metanephrine).[282] In some laboratories, 24-h urinary metanephrines are the most sensitive and specific in the diagnosis (both approximately 85 percent and 90 percent), but when done precisely, there is little to choose in regard to which should be measured. When the two or three of these compounds are quantitated and several samples are analyzed, both the sensitivity and the specificity of the tests improve. Attention must be paid to the conditions under which the sample is collected, and urinary creatinine also should be measured to verify that the collection represents the 24-h excretion. To reduce the number of false-positive results, the patient should be in a nonstressful situation when the sample is obtained.

Table 51-18: Diagnostic Tests for Pheochromocytoma

Biochemical
Urinary free catecholamines
Urinary vanilylmandelic acid
Urinary metanephrines
Plasma catecholamines (or metanephrines)
Clonidine suppression test
Imaging studies
Computed axial tomography
Magnetic resonance imaging
^{131}I-meta-iodobenzylguanidine
Abdominal ultrasound
Adrenal vein or vena caval drainage
Angiography

In the authors' view, only when the urinary assays are borderline can the measurement of plasma catecholamines be useful. If plasma catecholamines (norepinephrine plus epinephrine) levels exceed 2000 pg/mL in the basal state, the presence of a pheochromocytoma is highly likely. If the levels are less than 1000 pg/mL, the diagnosis is very unlikely, whereas in patients with plasma catecholamine levels between 1000 and 2000 pg/mL, the clonidine suppression test may be useful.[283] If plasma catecholamine levels do not suppress after the administration of 0.3 mg of oral clonidine in an appropriately prepared and monitored patient, a further aggressive search for a pheochromocytoma is warranted.

The choice of which initial imaging procedure to obtain is also somewhat controversial. CT scanning is a highly sensitive imaging modality that will locate nearly all pheochromocytomas, especially those in the adrenal gland or the abdomen. MRI has the advantage of not requiring contrast material (which is sometimes necessary with CT scanning) and is also helpful in localizing nonadrenal or nonabdominal pheochromocytomas. Enhancement of the T2-weighted images happens virtually only with pheochromocytomas and adrenal carcinomas, helping distinguish adrenal masses that are not biochemically

active (so-called incidentalomas) from metabolically active or malignant tumors.

The use of I-meta-iodobenzylguanidine scanning has been particularly helpful when a pheochromocytoma is suspected but is not clearly located with CT or MRI. This radiopharmaceutical is a guanethidine analog that is concentrated in pheochromocytomas and other neural crest tumors.[284] Using total-body scanning helps localize the tumor if the initial CT or MRI scans are negative or equivocal. The sensitivity of this test exceeds 90 percent, but it is not uniformly available.

PRIMARY ALDOSTERONISM

In a hypertensive patient receiving no treatment who demonstrates significant hypokalemia (serum $K^+ \leq 3.2$ meq/L) with renal K^+ wasting (24-h urinary $K^+ > 30$ meq), PRA below 1 ng/mL, and elevated plasma or urinary aldosterone values, the diagnosis is unequivocal. Often, however, the diagnosis is not obvious because the values are not as definitive; in such cases, multiple measurements are needed during salt loading.

The single best test in people with normal renal function for identifying patients with primary aldosteronism is the measurement of 24-h urinary aldosterone excretion during salt loading[285,286] (Table 51-19). An excretion rate of >14 μg of aldosterone in 24 h after 3 days of salt loading (greater than 200 meq/day) distinguishes most patients with primary aldosteronism from those with essential hypertension. Only 7 percent of patients with primary aldosteronism have values that fall within the range for essential hypertension. In contrast, a substantial number (about 39 percent) of patients with primary aldosteronism have plasma aldosterone values that fall within the range for essential hypertension.[287] The findings of hypokalemia and suppressed PRA provide corroborative evidence, but the absence of either or both does not preclude the diagnosis.

Table 51-19: Diagnostic Studies for Mineralocorticoid Excess States

Biochemical
Serum potassium
Plasma renin activity
Plasma aldosterone
Plasma aldosterone/renin ratio
24-h urinary aldosterone excretion
Plasma 18-hydroxycorticosterone
Plasma 18-oxocortisol
Plasma 18-hydroxycortisol
Adrenal vein sampling for aldosterone
Imaging studies
Abdominal ultrasound
Computed axial tomography
Iodocholesterol scanning
Adrenal venography

A substantial number of patients with primary aldosteronism, however, do not present with hypokalemia; serum K^+ concentration is normal in 7 to 38 percent of reported cases.[288,289] In addition, 10 to 12 percent of patients with proven tumors may not have hypokalemia during short-term salt loading. Plasma renin activity <1 ng/mL per hour or one that fails to rise above 2 ng/mL per hour after salt and water depletion and upright posture has been used as an additional test to exclude primary aldosteronism.[288] However, a significant number (about 35 percent) of patients with the disease have values that rise >2 ng/mL per hour when appropriately stimulated.[286] In addition, about 40 percent of subjects with essential hypertension have suppressed PRA, and 15 to 20 percent of these patients have values <2 ng/mL per hour under conditions of stimulation.

The plasma aldosterone/renin ratio has been used to define the appropriateness of PRA for the circulating concentrations of aldosterone.[286] It is assumed that the volume expansion associated with excessive aldosterone production inhibits the synthesis of renin without affecting the autonomous production of aldosterone. Both tests are subject to the same limitations: First, there is inherent variability of plasma levels of aldosterone even in the presence of a tumor, and this translates into variability in the absolute value of the ratio; second, the use of drugs that result in marked and prolonged stimulation of renin long after their discontinuation may alter the ratio.

The most common cause of primary aldosteronism is an aldosterone-producing adenoma (70 to 80 percent of all proven cases). Approximately 20 to 30 percent of cases are caused by hyperplasia of the zona glomerulosa layer of the adrenal cortex (bilateral adrenal hyperplasia). Some reports suggest the occurrence of a syndrome intermediate between adenoma and hyperplasia.[288] The distinction between these two processes is important because surgical intervention is likely to be curative in the majority of adenomas and fails to reduce BP in patients with bilateral adrenal hyperplasia.

An adenoma is likely in the presence of spontaneous hypokalemia <3.0 meq/L, plasma 18-hydroxycorticosterone values >100 ng/dL, and an anomalous postural decrease in plasma aldosterone concentration.[289,290] In addition, adenomas are largely unresponsive to changes in sodium balance and appear to be exquisitely sensitive to ACTH, unlike hyperplasias, which are more sensitive to angiotensin II infusions.[290] Plasma 18-hydroxycorticosterone values <100 ng/dL, a postural increase in aldosterone, or both, are findings usually associated with hyperplasia, but they do not completely rule out the presence of an adenoma.[291]

An adrenal CT scan should be considered the initial step in tumor localization. It is noninvasive, and all adenomas ≥1.5 cm in diameter can be located accurately. Only 60 percent of nodules measuring between 1 and 1.4 cm in diameter are detected by CT scanning. Nodules <1 cm in diameter are very difficult, if not impossible, to demonstrate. The overall sensitivity of localizing adenomas by high-resolution CT scanning exceeds 90 percent.[292] Adrenal venous aldosterone levels should be measured when the biochemical findings are highly suggestive of an adenoma, but the adrenal CT scan is ambiguous.[293]

Medical therapy is indicated in patients with adrenal hyperplasia, patients with adenoma who are poor surgical risks, and patients with bilateral adrenal adenomas that may require bilateral adrenalectomy. Total bilateral adrenalectomy has no place in the management of primary aldosteronism.

The long-standing experience has been that the hypertension associated with primary aldosteronism is salt- and water-dependent and is best treated with sustained salt and water depletion.[294] The usual doses of diuretic agents are hydrochlorothiazide 25 to 50 mg/day or furosemide 80 to 160 mg/day in combination with either spironolactone 100 to 200 mg/day or amiloride 10 to 20 mg/day. These combinations usually result in prompt correction of hypokalemia and normalization of BP within 2 to 4 weeks.

In the majority of these patients, surgical excision of an aldosterone-producing adenoma leads to normotension as well as reversal of the biochemical defects. One year postoperatively, about 70 percent of patients are normotensive, but 5 years postoperatively, only 53 percent remain normotensive. The restoration of normal K^+ homeostasis is permanent. Patients undergoing surgery should receive drug treatment for a least 8 to 10 weeks both to decrease BP and to correct metabolic abnormalities. These patients have a significant K^+ deficiency that must be corrected preoperatively because hypokalemia

increases the risk of cardiac arrhythmias during anesthesia.

After the removal of an aldosterone-producing adenoma, selective hypoaldosteronism usually occurs even in patients whose PRA had been stimulated with chronic diuretic therapy. Potassium supplementation therefore should be given cautiously, and serum K^+ values should be monitored closely. Sufficient residual mineralocorticoid activity often is left to prevent excessive renal retention of K^+ provided that Na^+ intake is adequate. Abnormalities in aldosterone production can persist for as long as 3 months after tumor removal.

OTHER FORMS OF IDENTIFIABLE SECONDARY HYPERTENSION

In addition to these three most common and potentially curable forms of identifiable secondary hypertension, there are a vast number of rare conditions in which the cause of the hypertension cannot be found (Table 51-10). These include enzyme deficiencies such as 17-β-hydroxylase deficiency and 17-α-hydroxylase deficiency, other congenital disorders such as the Ask-Upmark kidney, trauma such as the Page kidney, urologic causes such as hydronephrosis, endocrine abnormalities such as Cushing's syndrome and Cushing's disease, and even infectious etiologies such as renal tuberculosis.[274] Although the practicing clinician may never encounter a patient with any of these disorders, it is incumbent on him or her to know that these unusual conditions may present with hypertension and that the elevated BP may be the first clue to the diagnosis. Two causes of identifiable hypertension are not rare, and all clinicians will see patients with iatrogenic hypertension and those with sleep apnea (Table 51-11). Any of the drugs or other substances listed in the table should be stopped before one concludes that a patient has hypertension. The relation of sleep apnea to hypertension and obesity has long been recognized.[295,296] The typical clinical presentation of sleep apnea (daytime drowsiness, snoring) in an obese hypertensive should alert the clinician to this disorder.

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Chapter 51: HYPERTENSION: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

TREATMENT OF HYPERTENSION

Patients with JNC VI stage 2 or 3 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg) and those in risk group C (those with DM and those with clinical CV) should receive drug therapy once their hypertension has been diagnosed and confirmed.[11] Furthermore, the length of time the clinician should rely on lifestyle modifications before starting drug therapy has been clarified in JNC VI and is based on risk estimates, not just on the level of BP (Table 51-3). Those with stage 1 hypertension (SBP 140 to 159 mmHg and/or DBP 90 to 99 mmHg) who have no other risk factors or end-organ damage (so-called risk group A) can be treated only with lifestyle modification for up to 1 year even if goal BP is not reached before drug therapy should be considered necessary. Since male sex and age over 60 years are considered risk factors, only women under 60 years of age are in group A.

Patients with stage 1 hypertension who are in risk group B (other CV risk factors but no TOD or DM) should receive pharmacologic therapy after only a 6-month trial of lifestyle modification unless goal BP is achieved without drugs. Those in risk group C [TOD, clinical cardiovascular disease (CVD), and/or DM) should be treated with pharmacologic agents and lifestyle modification even if they have high-normal BP (SBP 130 to 139 mmHg and/or DBP 85 to 89 mmHg).

Lifestyle Modification

The JNC VI recommended weight loss for obese hypertensive patients, modification of dietary Na^+ intake to ≤100 mmol/day, and modification of alcohol intake to no more than two drinks per day.[11] It also recommended an increase in physical activity for all patients with hypertension who have no specific condition that would make such a recommendation not applicable or safe. However, for many of the authors' patients these suggestions are not practicable or already are being implemented. For such patients, drug therapy may be indicated even sooner in group A and group B hypertensive patients.

There is little doubt that lifestyle factors such as diet, exercise, and stress can affect BP. There is a strong positive correlation between the level of body weight and body mass index (weight/height) and the level of BP.[297] The relationship of dietary Na^+ and BP is equally clear, especially at low and modest intakes of Na^+ and in those deemed to be salt-sensitive. Other nutrients, such as K^+, the omega-3 fatty acids present in fish oil, and possibly Ca^{2+} and Mg^{2+}, are inversely related to BP level. Sedentary individuals who do little, if any, aerobic exercise usually have higher BPs than do appropriately matched controls even when one controls for other confounding variables.[298] The relationship of stress to BP is somewhat less clear. Physical or mental stress will raise BP temporarily, but the relationship of chronic anxiety and stress has been more difficult to demonstrate.

The appreciation of these relationships has naturally led to numerous attempts to lower BP by modifying lifestyle (Table 51-20). The most important trial that evaluated the benefits of lifestyle modification, including weight loss, was the Trial of Hypertension Prevention (TOHP-1).[299] This study was large (n = 2182) and randomized and compared the benefits of weight loss, Na^+ reduction, or stress reduction to usual care and also compared K^+ supplements at 60 meq/day or Ca^{2+} at 1.0 g/day or Mg^{2+} at 15 mmol/day or fish oil at 3.0 g of omega-3 fatty acid to placebos. The weight loss, Na^+ reduction, and stress management were given to 308, 327, and 240 participants, respectively, for 18 months. The group assigned to supplementation (Mg^{2+}, Ca^{2+}, or placebo) then was rerandomized to fish oil, K^+, or placebo. In addition, 589 participants received usual care, giving this trial the ability to judge the efficacy of these treatments more objectively than any prior studies could. The nutritional treatments were delivered by trained nutritionists using group and individual sessions to maximize the adherence to the regimen and presumably its efficacy. The long

period of treatment and observation in TOHP-1 also provided important information about the "natural history" of the efficacy of these therapies. TOHP-1 showed that weight loss was the most effective lifestyle modification, reducing BP by 2.9/2.3 mmHg in association with an average weight loss of 3.9 kg. Sodium reduction was the only other therapeutic modality that reduced BP a significant amount (1.7/0.9 mmHg) with a reduction of 44 meq/day of Na^+. All the other arms of the study (K^+, Ca^{2+}, Mg^{2+}, fish oil supplements, and stress management) failed to demonstrate any reduction in BP compared with placebo or usual care. Whereas there were physiologic markers that indicated that the nutritional approaches and weight loss did at least partially achieve their objectives, the stress management techniques used were not effective. Perhaps successful stress management might lower BP.

Table 51-20: Lifestyle Modifications That Lower Blood Pressure

PRIMARY LIFESTYLE MODIFICATIONS

1. Reduction of body weight (5-kg threshold; 10 kg reduces BP ~10/8 mmHg)
2. Reduction in dietary salt consumption (target 100 mmol/day; can lower BP ~12/10 mmHg, but individual responses vary)
3. Increase physical activity to 30-45 min, four times a week (can lower BP 8/4 mmHg and often helps control weight)
4. Increased consumption of fruits and vegetables (at least 4 servings/day; can lower BP ~6/3 mmHg and often helps reduce salt consumption)
5. Moderation of alcohol consumption (target 10-20 g ethanol for women, 20-30 g for men; can lower BP up to 8/4 mmHg in those who have more than 5 drinks/day)
6. Stress management (randomized clinical trials outside the workplace have been unconvincing, but many psychologists still recommend the approach despite a lack of detailed protocols that uniformly lower BP)

OTHER LIFESTYLE MODIFICATIONS THAT ARE ROUTINELY RECOMMENDED

1. Tobacco avoidance (lowers cardiovascular risk independently of any effect on BP)
2. Fish consumption (improves lipid profiles and cardiovascular risk more than expected if BP effect alone is operative)
3. Increasing dietary fiber (improves lipid profiles and cancer risk independently of effect on BP)

LIFESTYLE MODIFICATIONS THAT ARE NOT ROUTINELY RECOMMENDED

1. Biofeedback
2. Dietary calcium supplementation
3. Dietary magnesium supplementation
4. Micronutrient supplements

SOURCE: Whelton PK, Appel LJ, Espeland MA, et al., for the TONE Collaborative Research Group. Sodium restriction and weight loss in the treatment of hypertension in older persons: A randomized controlled trial of nonpharmacologic interventions in the Elderly (TONE). *JAMA* 1998; 279:839-846. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997; 336:1117-1124. Bao DG, Mori TA, Burke V, et al. Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. *Hypertension* 1998; 32:710-717. Arakawa K. Antihypertensive mechanism of exercise. *J Hypertens* 1993; 11:223-229. Beilin LJ. Stress, coping, lifestyle and hypertension: A paradigm for research, prevention and non-pharmacological management of hypertension. *Clin Exp Hypertens* 1997; 19:739-752.

TOMHS also evaluated the long-term benefit of lifestyle modification.[300] This study compared five classes of antihypertensives (diuretics, CAs, ACE-Is, alpha blockers, and beta blockers) to placebo in middle-aged

subjects with minimal elevations of BP (average BP of 140/91 mmHg when the study started) and superimposed these pharmacologic treatments on a comprehensive lifestyle regimen that included weight loss, Na^+ restriction, alcohol reduction, and exercise. A subgroup of the cohort got lifestyle modification with placebo. In TOMHS, the nutritional advice and the exercise program were presented to the participants and monitored by certified nutritionists and trained exercise physiologists. The subjects were seen frequently in group and individual sessions. The group given placebo reduced BP from 140/91 to 132/82 mmHg (a reduction of 9.1/8.6 mmHg) and sustained that level for the 4.4 years of study follow-up, even though the reduction of the Na^+ intake, amount of weight loss, and the increase in exercise did not reach study goals. Perhaps the most important finding in TOMHS was the statistically significantly fewer number of CV events (p <.03), in the group given pharmacologic treatment plus lifestyle modification. These patients achieved an average BP of 125/79 mmHg, a reduction of 16/12 mmHg. Even though the lifestyle modification was successful and sustained, the group given drugs had statistically significantly fewer CV events (p <.03), probably because their BP was lower.

The inevitable conclusion from this trial is that even successful lifestyle modification that brings BP to the current goals does not reduce morbidity and probably mortality as well as does the combination of drugs and lifestyle adjustments that brings BP down even further. The fact that the value of BP reduction in preventing CV complications with pharmacologic agents could be demonstrated in a group at such low risk calls into question the current emphasis on delaying treatment with drugs even in low-risk individuals while the patient and provider try to get BP to goal without them. In a subsequent paper, Grimm and colleagues also showed that quality of life, as assessed by a very extensive questionnaire delivered on multiple occasions during TOMHS, showed that subjects felt best in all the ways studied when their BP was lowest.[50] This result was seen whether they were on active pharmacologic treatment with lifestyle modification or on lifestyle modification alone. These data lead the authors to believe that physicians should strive to get the maximum BP reduction that can be achieved safely and do so by combining treatments and not restrict their approach to one modality or the other.

More recent studies have combined the two most successful lifestyle modifications (weight loss and Na^+ restriction) in prospective, randomized, and well-controlled long-term trials. The Trials of Hypertension Prevention-2 (TOHP-2) studied the value of weight loss and Na^+ restriction in a 2 × 2 factorial design against usual care.[301] The group assigned to both Na^+ reduction and weight loss did the best at 6 months [BP fell 4.0/2.8 mmHg (usual care subtracted)], while those receiving a single modality did not experience as much of a BP reduction (3.7/2.7 mmHg for the weight loss only group, 2.9/1.6 mmHg for the Na^+ reduction only group, also usual care subtracted). The disturbing finding here was that most of this reduction was gone by the 3-year follow-up, with the combined treatment having reduced BP by only 1.1/0.6 mmHg at that time. This finding highlights another difficulty with lifestyle modification: the high recidivism rate seen in virtually all long-term studies. While adherence to a drug regimen is notoriously poor, adherence to lifestyle modification is, if anything, even worse. As in TOHP-1, the regimen was delivered by highly trained nutritionists in group and individual sessions and is consequently not an inexpensive way to reduce BP.

The second long-term, randomized, and well-controlled study directly assessing the value of lifestyle modification was the Trial of Nonpharmacologic Interventions in the Elderly (TONE).[302] This study also evaluated the efficacy of weight loss and Na^+ reduction, but in a different population and with a somewhat different objective. Only hypertensives 60 to 80 years of age were enrolled, and all already were on single-drug pharmacologic treatment. The objective of TONE was to see whether the imposition of a formal lifestyle approach, again taught by highly trained professionals, would allow hypertensives to go off their medications. The results were equally disappointing. After 30 months, when the study ended, 44 percent of the actively treated subjects were able to stay off antihypertensives (they did not have a CV event or have BP rise to levels that were considered too high not to be given drugs: >150/90 mmHg) compared with 38 percent of those not getting active lifestyle modification. While this was statistically significant (p <.001), it means that 56 percent of successfully treated hypertensives needed to resume drug therapy even when given the best possible lifestyle regimen available administered by experts.

The value of alcohol reduction also has been addressed by a recently published clinical trial (PATHSI).[303] This study took 641 patients at seven Department of Veterans Affairs clinics who were actively employed

and completely functional but had at least six alcoholic drinks per day. The subjects reduced their alcohol intake nearly 20 percent once they entered into the study and before their randomization to intensive counseling or usual care was done. Those in the intensive counseling group were seen frequently and were able to reduce their average alcohol consumption to 2.0 drinks per day, which was significantly better than the usual care group (3.3 drinks per day). In spite of this, BP and events were not different at the end of this 2-year trial.

Appel and associates showed in the Dietary Approaches to Stop Hypertension (DASH) trial that a diet rich in fruit and vegetables lowered BP by 2.8/1.1 mmHg more than did the control diet.[304] The fruit and vegetable diet was designed to contain K^+ and Mg^{2+} at the 75th percentile of the usual American diet, while the control diet was at the 25th percentile. A "combination" diet that also contained foods rich in Ca^{2+} and was lower in total and saturated fat content lowered BP by 5.5/3.0 mmHg more than did the control diet. In the hypertensive subjects in DASH (*n* = 133 of 459), the BP reduction was impressive (11.4/5.5 mmHg). Although this study was short (only 8 weeks) and may not be generalizable to the population since it was carried out in four centers with special expertise, this approach offers great promise for using nutritional management to prevent hypertension in individuals with high-normal BP. The DASH diet provides high amounts of K^+, Mg^{2+}, and Ca^{2+} in the food eaten, not as supplements, and also limits the dietary fat and saturated fat intake in a diet only modestly low in Na^+ (3000 mg/24 h). Further studies done over longer periods in a less highly selected cohort will be needed to verify these results and determine whether the DASH diet will be a valuable therapeutic tool for the general population.

While treatment modalities such as K^+, Ca^{2+}, and/or Mg^{2+} supplements, fish oil, and garlic have advocates, careful and objective assessment of the data leads one to the conclusion that lifestyle modification should be primarily adjunctive to drug therapy in hypertensives, especially now that so many well-tolerated agents have been developed and it has been proved that lowering BP with drugs reduces morbidity and mortality.[305-309] No study of lifestyle modification in hypertensives has demonstrated that life is prolonged or CV events prevented.

The recommendations for lifestyle modification from JNC VI and other guideline committees also include smoking cessation.[11] The reason for the inclusion of this recommendation was to improve CV health rather than because of a proven direct relationship between smoking and hypertension. A direct relationship between smoking and BP, in fact, had not been demonstrated in epidemiologic studies, and often the opposite (BP lower in smokers) was observed.[310] It is now clear, however, that cigarette smoking increases BP and HR transiently (for about 15 min) and that the rise in both is gone by 30 min. The mechanism is the increase in catecholamine secretion induced by smoking. Since the authors recommend that office readings be taken no sooner than 30 min after smoking and caffeine ingestion (another substance that transiently raises BP), one may well miss the elevation of BP caused by smoking if it is measured when the patient has not smoked. Indeed, ABPM studies have shown that smokers have significantly higher BP on days when they smoke compared with days when they do not.[311] The recommendation not to smoke is clearly appropriate, and it is worthwhile not only because of enhanced CV health but also because smoking induces a rise in BP.

The lack of proof of efficacy or effectiveness when using lifestyle modification to treat or even prevent hypertension does not mean that physicians should abandon their efforts to encourage patients to lose weight; restrict their Na^+ intake; eat generous amounts of K^+, Mg^{2+}, Ca^{2+}, and fish; exercise regularly; drink only moderately if they wish to; stop smoking; and reduce stress. What one needs to realize is that the most important thing is to lower BP, perhaps to the lowest tolerable level, and to do so safely and without excessive personal or societal cost. The tension between advocates of lifestyle modification and those who consider it at best no more than an adjunct is not useful. The recommendations for modifying lifestyle are still very appropriate for the general population. If adopted, they will prevent or delay the virtually inevitable rise in BP that occurs with age and many hypertensives will be able to reduce BP further than might be achieved with drugs alone. Lifestyle modification is the primary public heath approach to trying to reduce the prevalence of hypertension and the average BP in the society. If successful, such modification is likely to save more lives and prevent more MIs, strokes, and episodes of HF than can be prevented by using drugs in those who are already hypertensive.

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Chapter 51: HYPERTENSION: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

PHARMACOLOGIC THERAPY

The primary goal of BP reduction is to achieve the recommended goal BP by using the least intrusive means possible.[11] *Intrusive* has several interpretations: economic, office visits, adverse effects, and convenience. The choice of the drug with which to begin therapy is probably the most important decision the clinician must make when treating hypertensive patients. Approximately half the patients physicians treat will respond to the first choice and can tolerate most rational options. If physicians choose wisely, the first choice will be successful in getting BP to goal, and that will be the drug on which the patient remains for what is usually an indefinite period of therapy. Since the remainder will need additional treatment, the choice of the first drug must be done with an eye toward what can be added to achieve that goal.

Classification of Antihypertensive Agents

Antihypertensive agents can be classified in a number of ways. Some are effective parentally and are indicated only for a hypertensive crisis, and others (the overwhelming majority) are used orally for chronic therapy. Antihypertensive agents are further classified by pharmacologic class and alleged primary mechanism of action (Table 51-21). There are more than 80 effective antihypertensive drugs and 40 fixed-dose combinations from which to choose. This provides physicians with many options but can make the choice seem more perplexing than it should be. All the drugs that are available lower BP safely and, in appropriate doses, essentially to the same degree. Some classes are more likely than others to reduce BP to goal with monotherapy and with acceptable tolerability. Those agents are appropriate choices for initial treatment.

Table 51-21: Pharmacologic Properties of Commonly Used Antihypertensive Agents

Drug	Dose, mg/day	Doses per Day	Mechanisms of Action	Special Considerations
Diuretics				
Thiazides and related drugs	12.5-25	1	Decreased body sodium and extracellular fluid volume	More effective antihypertensive agents than loop diuretics unless serum creatinine is ≥2.0 mL/min or creatinine clearance is ≤50 mL/min
Hydrochlorothiazide				
Loop diuretics				
Furosemide	20-320	2	Inhibit $2Cl^-Na^+$ pump	Effective even in patients with advanced renal or congestive heart failure
Bumetanide	0.5-5	2	Ascending loop of Henle	

Ethacrynic acid	25-100	2		
Torsemide	5-20	1		
Fixed-dose diuretics (potassium-sparing)			Increase K^+ reabsorption	Weak diuretics
Hydrochlorothiazide/amiloride				
HCTZ/triamterene				
Spironolactone	25-100	2-3	Aldosterone antagonist	May cause hyperkalemia in patients with serum creatinine >2.5 mg/dL, particularly when combined with ACE inhibitors, K^+ supplements, or NSAIDs
Triamterene	50-100	2		
Adrenergic inhibitors				
Beta blockers				
Cardioselective			Inhibit $beta_1$ receptors, decrease CO	In higher doses, also inhibit $beta_2$ receptors
Atenolol	25-100	1	Increase SVR, decrease plasma renin activity	
Metoprolol	50-200	1-2	(PRA)	
Noncardioselective			Inhibit $beta_1$ and $beta_2$ receptors	More likely to cause metabolic side effects
Nadolol	20-240	1		
Propranolol	40-240	1-2		
Timolol	20-40	2		
With intrinsic sympathomimetic activity (ISA)				
Acebutolol	200-1200	2	Partial agonist activity on beta-adrenergic receptors	No clear advantage except for less bradycardia and metabolic side effects than other beta blockers
Pindolol	10-60	2		
Antiadrenergic agents				
0x002003 *Centrally acting*				

α-Methyldopa	250-1500	2	Stimulate $alpha_2$-adrenergic receptors in the brainstem, resulting in inhibition of efferent sympathetic activity; decrease SVR	Sudden withdrawal may result in hypertensive crisis
Clonidine	0.1-0.6	2		
Clonidine TTS	0.1-0.3	Once a week		
Guanfacine	1-3	1		
Peripherally acting				
Guanethidine	10-100	1	Inhibit norepinephrine release from sympathetic nerve terminals	Frequently cause orthostatic hypotension and sexual dysfunction
			Decrease SVR	
Reserpine	0.05-0.25	1	Depletion of norepinephrine	Causes frequent neurologic symptoms; $alpha_1$-receptor blockers
Doxazosin	2-16	1	Inhibit $alpha_1$-adrenergic receptors.	First-dose effect; postural hypotension; useful for prostatic hypertrophy
Prazosin	2-20	1-2	Decrease SVR; CO same or increases	
Terazosin	1-20	1		
Alpha/beta blockers				
Labetalol	200-800	2-3	Blocks alpha- and beta-adrenergic receptors (7:1 beta:alpha blockade)	Same as beta blockers
Carvedilol	3.75-25	2	Blocks alpha- and beta-adrenergic receptors (3:1 beta:alpha blockade)	Same as beta blockers
ACE inhibitors				

Benazepril	10-40	1-2	Block conversion of angiotensin I to angiotensin II; decrease aldosterone; may increase bradykinin and vasodilatory prostaglandins; decrease SVR; no change in CO	When added to diuretics, may cause hypotension; may cause hyperkalemia in patients with renal failure, those with hypoaldosteronism, those receiving K-sparing diuretics or NSAIDs
Captopril	12.5-100	2-3		
Cilazapril	2.5-5	1-2		
Enalapril	2.5-40	1-2		
Fosinopril	10-40	1		
Lisinopril	5-40	1		
Perindopril	1-16	1-2		Can cause acute renal failure in patients with bilateral renal artery stenosis, renal artery stenosis of a solitary kidney, creatinine >3 mg/dL, or severe heart failure
Quinapril	5-80	1-2		
Ramipril	1.25-20	1		
Spirapril	12.5-50	1-2		
Trandolapril	1-4	1		
Calcium antagonists			Blocks entry of calcium into smooth muscle cells, resulting in vasodilation; decreases SVR; blunts increases in exercise heart rate	
Diltiazem	90-360	3-4		
Diltiazem CD	180-360	1		
Verapamil	80-480	2-3		May cause heart block, particularly when combined with beta blocker
Verapamil SR	120-480	1-2		
Verapamil-Covera HS	180-240	1 (at bedtime)		

Dihydropyridines				
Amlodipine	2.5-10	1	Same as diltiazem and verapamil	More potent vasodilators than diltiazem and verapamil; may cause dizziness, headache, tachycardia, flushing, edema
Felodipine	5-20	1	Do not blunt increase in exerise heart rate	
Isradipine	2.5-10	2		
Nicardipine	60-120	3		
Nifedipine	30-120	3		
Nifedipine (GITS)	30-120	1		
Nisoldipine	10-10	1-		
Direct vasodilators				
Hydralazine	50-200	2-4	Direct relaxation of smooth muscle cells, causing arteriolar vasodilation secondary to opening [K^+] channels	Limited efficacy if given alone due to fluid retention and reflex vasodilation; should be combined with a diuretic and a beta blocker to prevent edema and tachycardia
Minoxidil	2.5-80	1		

COMBINATION DRUGS FOR HYPERTENSION

Drug	Trade Name
Beta-adrenergic blockers and diuretics	
Atenolol 50 or 100 mg and chlorthalidone 25 mg	Tenoretic
Bisoprolol fumarate 2.5, 5, or 10 mg, and hydrochlorothiazide 6.25 mg	Ziac[a]
Metoprolol tartrate 50 or 100 mg and hydrochlorothiazide 25 or 50 mg	Lopressor HCT
Nadolol 40 or 80 mg and bendroflumethiazide 5 mg	Corzide
Propranolol hydrochloride 40 or 80 mg and hydrochlorothiazide 25 mg	Inderide
Propranolol hydrochloride (extended release) 80, 120, or 160 mg and hydrochlorothiazide 50 mg	Inderide LA

Timolol maleate 10 mg and hydrochlorothiazide 25 mg	Timolide
ACE inhibitors and diuretics	
Benazepril hydrochloride 5, 10, or 20 mg, and hydrochlorothiazide 6.25, 12.5, or 25 mg	Lotensin HCT
Captopril 25 or 50 mg and hydrochlorothiazide 15 or 25 mg	Capozide[a]
Enalapril maleate 5 or 10 mg and hydrochlorothiazide 12.5 or 25 mg	Vaseretic
Lisinopril 10 or 20 mg and hydrochlorothiazide 12.5 or 25 mg	Prinzide, Zestoretic
Angiotensin II receptor antagonists and diuretics	
Losartan potassium 50 mg and hydrochlorothiazide 12.5 mg	Hyzaar
Calcium antagonists and ACE inhibitors	
Amlodipine besylate 2.5 or 5 mg and benazepril hydrochloride 10 or 20 mg	Lotrel
Diltiazem hydrochloride 180 mg and enalapril maleate 5 mg	Teczem
Verapamil hydrochloride (extended release) 180 or 240 mg and trandolapril 1, 2, or 4 mg	Tarka
Felodipine 5 mg and enalapril maleate 5 mg	Lexxel
Other combinations	
Triamterene 37.5, 50, or 75 mg, and hydrochlorothiazide 25 or 50 mg	Dyazide, Maxide
Spironolactone 25 or 50 mg and hydrochlorothiazide 25 or 50 mg	Aldactazide
Amiloride hydrochloride 5 mg and hydrochlorothiazide 50 mg	Moduretic
Guanethidine monosulfate 10 mg and hydrochlorothiazide 25 mg	Esimil
Hydralazine hydrochloride 25, 50, or 100 mg, and hydrochlorothiazide 25 or 50 mg	Apresazide
Methyldopa 250 or 500 mg and hydrochlorothiazide 15, 25, 30, or 50 mg	Aldoril

Reserpine 0.125 mg and hydrochlorothiazide 25 or 50 mg	Hydropres
Reserpine 0.10 mg, hydralazine hydrochloride 25 mg, and hydrochlorothiazide 15 mg	Ser-Ap-Es
Clonidine hydrochloride 0.1, 0.2, or 0.3 mg, and chlorthalidone 15 mg	Combipres
Methyldopa 250 mg and chlorothiazide 150 or 250 mg	Aldochlor
Reserpine 0.125 or 0.25 mg and chlorthalidone 25 or 50 mg	Demi-Regroton
Reserpine 0.125 or 0.25 mg and chlorothiazide 250 or 500 mg	Diupres
Prazosin hydrochloride 1, 2, or 5 mg, and polythiazide 0.5 mg	Minizide

[a]Approved first-line medications.

Surrogate versus Clinical End Points

Physicians are no longer willing simply to look at the degree of BP reduction when making a choice of antihypertensive therapy. Clinical end points are the events that physicians are trying to prevent in treating hypertension. So-called surrogate (or intermediate) end points are factors that may contribute to clinical end points and can be affected favorably or unfavorably by treatment. Blood pressure reduction is a surrogate or intermediate end point, since the reason for treating hypertension is to reduce the morbidity and mortality associated with elevated BP, not simply to lower BP. Physicians now expect and demand proof that the selection made will prevent hypertension-related clinical end points. Data from large and prospective clinical trials that are designed to evaluate the ability of a drug to reduce hypertension-related CV events as well as or better than an otherwise reasonably alternative drug are the reliable means to use in choosing from among the otherwise bewildering number of options.

Before 1997, only diuretics and beta blockers had been shown to reduce the morbidity and mortality in clinical trials in hypertension. Dihydropyridine (DHP), CAs, and ACE-Is were added to the list after the Syst-EUR trial was completed.[270] This trial used the DHP CA nitrendipine, followed by enalapril and hydrochlorothiazide, if needed, to get BP to goal. It was only in 1999, when the Captopril Prevention Project (CAPPP) was published, that the ability of an ACE-I to reduce morbidity and mortality in a trial that enrolled subjects because they were hypertensive was demonstrated.[312] That project showed that a regimen starting with the ACE-I captopril achieved the same overall benefit in reducing morbidity and mortality as did one that began with diuretics or beta blockers (so-called conventional therapy).[312] Certain interesting findings need further study. For example, the group randomized to conventional therapy had statistically significantly fewer strokes, and the group given the ACE-I had a lower incidence of new DM and better outcomes in those with known type 2 DM. A more recent active comparison study, the second Swedish Trial of Hypertension in Older Persons (STOP-2), again confirmed that both ACE-Is and DHP CA reduce morbidity and mortality as well as but clearly not better than do diuretics and beta blockers.[313] In STOP-2, conventional treatment was not better than newer agents at preventing strokes, and the ACE-I group did not have less incident DM. This trial failed to confirm the intriguing findings from CAPPP.

Numerous studies have shown the value of ACE-Is in saving the lives of patients with HF, in those with an MI, and in those with type 1 DM with nephropathy and proteinuria.[314-317] Many of the subjects in these

trials had hypertension but were enrolled in the studies because they had these other conditions, and so one needs to be cautious about whether these data can be extrapolated to hypertensives who do not have these complications. A major new trial, the Heart Outcome Prevention Evaluation (HOPE) trial, was published in 2000.[318] This trial demonstrated that treatment with the ACE-I ramapril significantly reduced CV events compared with placebo in participants with multiple CV risk factors who had an average BP of 138/78 mmHg.[318] However, HOPE did not have an active comparator, and the group on ramapril did have a modestly lower BP (3/2 mmHg). Although the investigators claimed that this small difference in BP could not explain most of the benefit of ramapril, it is still possible that it was the reduction in BP rather than the ACE-I that was responsible for the dramatic reduction in events.

In the next few years, approximately 30 more events trials will be completed.[319] Table 51-22 lists some of the more important trials in progress. When some or all of these trials are published, it should be known with some degree of certainty whether lowering BP is all that matters or whether a particular drug or class of drugs should be selected because it or they prevent hypertension-related events more effectively. The largest of these trials (42,448 subjects), the Antihypertensive and Lipid Lowering Trial to Prevent Heart Attack (ALLHAT), is due to be completed in 2003.[320] ALLHAT compares diuretics to DHP CAs, ACE-Is, and alpha blockers. Acute MI in the primary end point. In February 2000, the alpha-blocker arm of the ALLHAT trial was stopped because of a 25 percent higher CV mortality and twofold increase in HF when doxazosin was compared to chlorthalidone.[321] The primary end point was not different between the two groups. Here too, there was a difference in BP control. The chlorthalidone group had a 3/0 mmHg lower BP almost from the start compared with those getting doxazosin. Thus, the question of the degree BP reduction versus how one chooses to achieve it remains open.

Table 51-22: Long-Term Outcome-Based Clinical Trials of Antihypertensive Agents in Progress

Acronym (Name)	First-Line Agent	Comparator	Patients	Comments
ALLHAT (Antihypertensive and Lipid Lowering Prevention of Heart Attack Trial)	Amlodipine, Doxazosin, Lisinopril	Chlorthalidone	42,448 in 625 centers in United States and Canada	Doxazosin arm stopped prematurely; 6-year follow-up planned
ANBP-2 (Australian National Blood Pressure Trial No. 2)	ACE inhibitor	Diuretic	6000 65-84-year-old Australians	5-year follow-up planned
ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)	Calcium antagonist or ACE inhibitor	Diuretic or beta blocker	18,000 residents of Scandinavia or United Kingdom	5-year follow-up planned
CONVINCE (Controlled-Onset Verapamil Investigation of Cardiovascular Endpoints)	COER-verapamil	HCTZ or atenolol	16,602 in 661 centers worldwide	5-year follow-up planned
ELSA (European Lacidipine Study of Atherosclerosis)	Lacidipine	Beta blocker	2251 European patients with known atherosclerosis	4-year follow-up planned
HYVET (Hypertension in the Very Elderly Trial)	ACE inhibitor (± diuretic)	Placebo	2100 patients >80 years old	5-year follow-up planned

INSIGHT (International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment)	Nifedipine GITS	HCTZ plus amiloride	6592 patients in nine European countries	3-year minimum follow-up planned
LIFE (Losartan Intervention for Endpoint Reduction)	Losartan	Atenolol	9194 patients in >300 centers worldwide	ECG LVH only; 4-year follow-up planned
NICS-EH (National Intervention Cooperative Study in Elderly Hypertensives)	Calcium antagonist	Diuretic	1000 Japanese >60 years old	5 year follow-up planned
NORDIL (Nordic Diltiazem Study)	Diltiazem	Diuretic or beta blocker	11,000 patients in 480 centers in Sweden and Norway	5-year follow-up planned
SHELL (Systolic Hypertension in the Elderly Long-Term Lacidipine Trial)	Lacidipine	Diuretic	4800 Europeans with isolated systolic hypertension	Compares 3.5-year incidence of cardiovascular morbidity/mortality
VALUE (Valsartan Amlodipine Long-Term Utilization Evaluation)	Valsartan (±HCTZ)	Amlodipine (±HCTZ)	14,400 patients in 1000 centers in 31 countries	6 years follow-up, 1450 primary end points expected

It is of great interest that the participants receiving the alpha blocker had lower TC, triglycerides, and serum glucose and higher serum K^+ than did those on the diuretic.[321] If metabolic surrogate end points are important, all these changes would predict that alpha-blocker-treated subjects should have fewer events than do those on chlorthalidone. The opposite was the case. Another trial, the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE), will be completed in 2002.[322] This study compares a nondihydropyridine CA (verapamil) to diuretics/beta blockers in 16,600 older hypertensives. This trial will indicate whether this class of CA will prevent mortality and morbidity as well as or better than conventional therapy does. It also will evaluate the importance of circadian variation in BP since the verapamil preparation used is designed to be given at night and released in concert with the morning rise in BP (see below). Event trials of ARBs in older high-risk hypertensives [Valsartan Amlodipine Long Term Use Evaluation (VALUE)] in hypertensives with ECG LVH (the Losartan Intervention for End Point Reduction-LIFE), and in those with diuretic nephropathy are in progress and will be finished in the next few years.[319,323]

Individualizing Therapy

In view of the many effective options available, the physician must pay very close attention to each patient's needs and plan his or her regimen accordingly. Each patient must be treated as an individual, not as a member of a population, and so the drug chosen must be compatible with that individual patient's preferences, lifestyle, and job requirements. Whatever is selected, it must be affordable. No amount of therapeutic wisdom will be effective if the patient does not have the funds to purchase the physician's choice.

Goal of Therapy

One must strive to reduce SBP to below 140 mmHg and to reduce DBP to below 90 mmHg, the goal currently articulated by several guidelines committees.[11,18,19] In diabetic patients, the recommended goal is lower (SBP <130 mmHg and DBP <85 mmHg). JNC VI recommended these more stringent goals for those with DM without proof from a clinical trial to support this aggressive approach. The subsequent publication of the HOT study and the United Kingdom Diabetes Prevention Study (UKDPS) provided the solid evidence that was needed to support this recommendation.[324,325] In patients with renal disease and at least 1 g of proteinuria per day, JNC VI recommended an even lower goal (SBP <125 mmHg and DBP <75 mmHg). This too was not an "evidence-based" recommendation but was based on the expectation that a still lower BP would be helpful in preventing morbidity and mortality in this population of hypertensives.[326] The African-American Study of Kidney Disease (AASK) will provide definitive evidence for or against this very stringent goal.[327] Whether this more aggressive goal should be extended to other subpopulations, such as those with prevalent CVD, remains to be proved.

One of the perceived limitations to achieving this lower level of BP control was the fear that lowering BP too far might be harmful, the concept of the "J" curve. Several investigators had pointed out that subjects treated to diastolic BP level below 85 mmHg had higher rates of MI than did those whose on-treatment diastolic BP was between 85 and 90 mmHg.[328,329] However, an increased risk for those with low diastolic BP is also evident in populations and in the placebo groups of several trials.[330,331] Furthermore, the Systolic Hypertension in the Elderly Program (SHEP) treated individuals down to an average diastolic BP of 67 mmHg and prevented MIs compared with those with an average of 71 mmHg.[269] Definite proof that aggressive treatment is not harmful has come from the HOT and UKPDS trials.[324,325] These studies showed no increase in the incidence of CV events in the groups randomized to the lowest levels of BP control, but HOT could not show that those treated to the lowest goal necessarily did the best. Both demonstrated reduced risk in hypertensives with DM and did not support the contention that hypertensives with known CAD would be at risk if treated aggressively. Both support the more aggressive BP treatment goals now recommended by guidelines committees (Table 51-23).

Table 51-23: Goal Blood Pressure

General population without diabetes or renal disease	<140/90 mmHg
Diabetes	<130/85 mmHg
Renal disease with >1 g proteinuria	<125/75 mmHg
Isolated systolic hypertension	<140 mmHg

While the benefits of this level of aggressive therapy have not been proved conclusively, clinical trial results suggest that more events would be prevented with these treatment goals than with higher levels, with little if any harm to the patient. Another aspect, that of cost, was addressed in an analysis by Elliott and colleagues.[332] They compared the putative cost/effectiveness ratio of treating to a goal of [140/90 mmHg (JNC V) compared with 130/85 mmHg (JNC VI)] in hypertensives with type 2 DM.[11,38] Their theoretical analysis suggested that the aggressive approach would save money. Even though more drugs would be needed, the reduction in both direct costs (hospitalization for the greater number of events that would occur in those with higher BP) and indirect costs (lost work) would more than balance the money spent for additional antihypertensives, any costs related to adverse reactions, and the extra visits to providers necessary to get BP to the lower goal.

Factors to Consider in Choosing an Initial Antihypertensive Agent

There are 10 factors that should always be considered when initial therapy is chosen and other drugs are added (if additional agents are needed to reduce BP to goal) (Table 51-24).

Table 51-24: Factors in the Choice of Agents for Antihypertensive Therapy

1. Efficacy
2. Comorbidity and other risk factors
3. Safety (adverse reactions and side effects)
4. Demographic considerations
5. Special situations
6. Dose schedule (dosage and chronotherapy)
7. Drug interactions
8. Adherence
9. Mechanism of action of drug and pathophysiology of patient's hypertension
10. Cost

EFFICACY

JNC VI made the distinction between surrogate and clinical end points when it provided guidelines for selecting treatment that were based on efficacy, defined as the reduction of morbidity and mortality. Now four classes of drugs (thiazide diuretics, beta blockers, long-acting DHP CAs, and ACE-Is) have been shown to reduce CV end points when used as the initial therapy for hypertension in appropriately designed and implemented clinical trials. Other agents, such as peripheral sympatholytics (reserpine and guanethidine), centrally acting alpha agonists (alpha-methyldopa), and vasodilators (hydralazine), also have been used in clinical trials as the second, third, or even fourth agent to be added to get BP under control. None is an option for initial therapy because they are relatively poorly tolerated compared with the agents that are recommended as initial therapy or need to be taken together with diuretics to lower BP effectively in the long term. Other drugs, such as alpha/beta blockers and ARBs, that are effective as monotherapy and are well tolerated, have not yet been shown to reduce clinical end points. Alpha blockers are valuable as adjunctive therapy, but the early data from ALLHAT have shown that this class should not be used as the initial treatment for hypertension unless symptomatic relief of benign prostatic hypertrophy (BPH) is needed.[321] Many would now recommend that a man with hypertension and BPH get another drug along with the alpha blocker as part of an antihypertensive regimen.

COMORBIDITY AND OTHER RISK FACTORS

JNC VI has recognized two other factors that may alter the correct choice of initial treatment in an individual hypertensive patient:

- Data from events trials that were conducted in subjects with other conditions (e.g., type 1 DM, acute MI, HF, and after HOPE, those considered to be at high risk for CV events) but in which many subjects with hypertension were enrolled. These trials were the basis for the JNC VI designation of a "compelling" indication (Table 51-25)
- Individual patients may have certain comorbid conditions for which a specific agent may be appropriate even though no trial has been completed in which that agent has been compared to drugs for which clinical trial data are currently available. This was the basis of the JNC VI recommendation for a drug to be indicated or contraindicated as a "specific" indication even though randomized clinical trials might not be available to support that decision (Table 51-26). A "specific" indication tries to codify clinical judgment, or that which any reasonable clinician would do to care for all the health needs of his or her patients. For the most part, these recommendations do not add classes of drugs to the list of those which are favored because of a reduction in clinical end points but instead alter the choice of which class should be selected for initial therapy. Good examples are osteoporosis and thiazide diuretics and angina pectoris and beta blockers.

The factors that influence the specific indications are generally the presence of other risk factors and active clinical problems. These conditions may and often should alter the initial and subsequent choice of antihypertensive therapy in an individual patient. An appreciation of the fact that the drugs prescribed to

reduce BP can improve or adversely affect other clinical conditions is the basis for the JNC VI recommendation that although diuretics and beta blockers should be used when a patient has "uncomplicated" hypertension, the presence of these comorbid conditions clearly affects that decision.

Table 51-25: Considerations in Individualizing Antihypertensive Drug Therapy

Indication[a]	Drug Therapy
DM (type 1) with proteinuria	ACE-I
HF (systolic)	ACE-I, diuretics, beta blockers, aldosterone receptor blockers
Isolated systolic hypertension (older patients)	Diuretics (preferred), DHP CAs
MI	Beta blockers (non-ISA), ACE-Is (systolic dysfunction)

[a]Compelling indications unless contraindicated.

SOURCE: Modified from JNC VI.

Table 51-26: Drugs That May Have Favorable or Unfavorable Effects on Comorbid Conditions

Favorable

- Angina
- Atrial tachycardia and fibrillation
- Cyclosporine-induced hypertension
- DM (types 1 and 2) with proteinuria
- HF
- Liver disease
- Peripheral vascular disease
- Pregnancy
- DM (type 2)
- Dyslipidemia
- Essential tremor
- Hyperthyroidism
- Migraine
- MI
- Osteoporosis
- Preoperative hypertension
- Prostatism (benign prostatic hyperplasia)
- Renal insufficiency (caution in renovascular disease)

Unfavorable

- Bronchospastic disease
- Depression
- DM (types 1 and 2)
- Dyslipidemia
- Gout
- Second- or third-degree heart block
- Renal insufficiency, renovascular disease
- Beta blockers, Ca^{2+} antagonists
- Beta blockers, CA nondihydropyridines
- Ca^{2+} antagonists (caution with the dose of cyclosporine)
- ACE-Is (preferred), CAs (nondihydropyridines), low-dose diuretics
- ACE-Is, losartan, K^{+}-sparing agents, beta-blockers
- Beta blockers
- Alpha-blockers, CAs
- Labetalol hydrochloride, methyldopa
- ACE-Is
- Alpha blockers
- Beta blockers
- Beta blockers
- Beta blockers (noncardioselective), Ca^{2+} antagonists (nondihydropyridine)
- Beta blockers (cardioselective)
- Thiazide diuretics
- Beta blockade
- Alpha blockers
- ACE-Is, ARBs, K^{+}-sparing agents for hypertension and creatinine >3 mg/dL
- Beta blockers
- Beta blockers, central alpha agonists, reserpine
- Beta blockers, high-dose diuretics
- Beta blockers (non-ISA), diuretics (high-dose)
- Diuretics
- Beta blockers, Ca^{2+} antagonists (nondihydropyridine)
- ACE-Is, ARBs

This approach was also used by the BHS.[19] In those guidelines, similar language to that in JNC VI was used, but the BHS considered the presence of some of these comorbid conditions to be a compelling reason rather than a specific one to choose a particular class of drugs even though a trial had not been completed proving the value of those agents in patients with these conditions. The lessons from the Evaluation of Losartan in the Elderly II trial (ELITE II), which failed to show any advantage of an ARB over an ACE-I (see below), and ALLHAT are that it is best to demand and wait for evidence that an agent prevents events before recommending to clinicians that they should feel "compelled" to prescribe that class.

Dyslipidemias

Hypertensive patients who have lipid abnormalities (which may be present in as many as 50 percent of those treated for hypertension) probably should not be treated with drugs that worsen their particular dyslipidemia. Although it has not been proved that the changes in serum lipids caused by certain classes of antihypertensive agents are harmful, it is certainly reasonable to choose an equally effective drug that is lipid-neutral or one that may improve the lipid profile.[333] In large doses (>25 mg/day), thiazide diuretics and related compounds such as chlorthalidone raise TC and LDL-C 5 to 10 percent at least transiently and may lower HDL-C 2 to 4 percent. Serum triglycerides are increased 15 to 30 percent.[334] With the doses that are currently recommended (using up to but no more than 25 mg of hydrochlorothiazide), there is little if any alterations in these parameters. The beta blockers that do not have intrinsic sympathomimetic activity lower HDL-C even more (10 percent) and also raise triglycerides (approximately 20 percent) without affecting TC or LDL.[335] Beta blockers that do have intrinsic sympathomimetic activity and alpha/beta

blockers are lipid-neutral.

Conversely, one could choose to add to therapy using a peripheral alpha blocker in patients with dyslipidemias who are already being treated with agents known to reduce CV events, such as beta blockers, ACE-Is, and diuretics.[333,336] These drugs reduce TC and LDL cholesterol approximately 8 to 10 percent, triglycerides 15 percent, and HDL-C 10 to 15 percent. The ALLHAT results mentioned above call into question the wisdom of this approach.[321] ACE-Is do not affect serum lipids, and in some studies benefits similar to those seen with alpha blockers have been observed. ARBs and CAs are lipid-neutral.[334,335]

Other sympatholytics do not affect the lipid profile, and direct vasodilators (e.g., hydralazine) raise HDL-C and lower triglycerides and TG even when used in combination with thiazide diuretics.

Glucose and Insulin and Diabetes Mellitus

Antihypertensive drugs may affect glucose metabolism and worsen or improve insulin sensitivity.[333] The magnitude and direction of the drug-induced changes seen in glucose and insulin are very similar to what occurs with lipids. Peripheral alpha blockers and some ACE-Is (captopril, enalapril, trandolapril, and perindopril) may improve insulin sensitivity.[337] Not only do some ACE-Is improve insulin sensitivity, all have been shown to reduce urinary protein excretion, which may contribute to the renal benefit seen in patients with DM. Both moderate- to high-dose thiazides and beta blockers worsen insulin sensitivity and occasionally precipitate glucose intolerance. Beta blockers increase the risk of developing clinical DM by up to 25 percent.[338] In spite of these metabolic changes, in SHEP, treatment with low-dose chlorthalidone (plus atenolol or reserpine in some volunteers) reduced clinical events in the diabetic subgroup even more than it did in nondiabetics.[339] In the HOPE trial and in CAPPP, incident diabetes was prevented.[312,318] These findings, if confirmed by ALLHAT (STOP-2 did not demonstrate that ACE-Is prevented new DM), indicate that patients at high risk of becoming diabetic (the obese and those with glucose intolerance or other components of syndrome X) also might benefit from treatment with ramapril or an ACE-I.

Hypertensives with Diabetes Mellitus

The combination of hypertension and DM confers much more risk for CV events and renal failure than does either one alone. Angiotensin-converting enzyme inhibitors, diuretics, and beta blockers have been shown consistently to reduce CV and renal risk. There are very few data on other classes of antihypertensive agents, although there are some preliminary studies with ARBs and CAs. JNC VI recommended that clinicians should feel "compelled" to give hypertensive patients with type 1 DM an ACE-I only because the only randomized clinical trial that has clearly demonstrated the utility of ACE-Is in reducing clinical events was done in a group of type 1 diabetic patients with hypertension.[316] Although no large, long-term events trials have been completed that have proved the special value of ACE-Is in patients with type 2 DM, many feel that the benefit shown for type I diabetic patients also can be assumed to occur for type 2 diabetic patients, and so ACE-Is were recommended by JNC VI as a specific indication.[11] Others argue that if BP control is achieved, it does not matter what drug or drugs are used. In UKPDS, the group that received the ACE inhibitor captopril did no better than did the group that received atenolol. This lends some support to the argument that BP control, not how it is accomplished, is the key factor in reducing events in type 2 diabetic patients.[325]

Although some experts have raised concern about the safety of DHP CAs in type 2 diabetic patients, the Syst-EUR study, in which these drugs were the initial therapy, demonstrated that the benefit accrued was greater in diabetic patients than it was in other patients.[340] Just as with SHEP, the results of a properly done clinical trial disproved surrogate end-point-based hypotheses from other sources of data such as observational studies, case-control studies, and meta-analyses of smaller trials.

Trials of CV mortality involving nondihydropyridine CAs in high-risk hypertensive patients have not been completed. However, nondihydropyridine CAs have been shown to reduce CV mortality after an MI and slow the progression of diabetic nephropathy.[341,342] Moreover, their use in combination with ACE-Is

lowers urinary protein excretion, and unlike DHP CAs, they have additive effects to reduce proteinuria independent of BP reduction.[343,344] This combination appears to be particularly useful in diabetic patients with nephropathy and proteinuria.

From the available data, it would appear that in people with DM, the most important factor in reducing mortality and preserving renal function is reducing BP to goal (Table 51-23).

Left Ventricular Hypertrophy and Heart Failure

Left ventricular hypertrophy results from chronic elevations in arterial pressure that cause cardiac myocyte hypertrophy and remodeling of the coronary resistance vessels. This leads to perivascular fibrosis of the intramyocardial arteries and arterioles. Over time, these changes in the myocardium contribute to the development of ventricular wall stiffness and diastolic dysfunction.[345]

Left ventricular hypertrophy is a robust independent risk factor for CV and premature mortality.[227] It is especially common in the elderly, particularly in elderly women, and often is associated with diastolic dysfunction. It appears that all antihypertensive agents that are recommended for initial therapy reduce LV mass. Data from meta-analyses have suggested that agents that block the RAA system reduce LV mass better than do other antihypertensive agents.[235] However, TOMHS and the Veterans Administration (VA) study of monotherapy found that there was no difference among antihypertensive agents in their ability to regress LVH.[236,237] Moreover, in TOMHS, nutritional hygienic measures such as weight loss, reduced Na^+ and alcohol intake, and exercise were effective by themselves in regressing LV mass. Perhaps the most important factor responsible for LV mass regression is the prolonged reduction of systolic BP.

Heart Failure

Hypertension has been identified as a major risk factor for the subsequent development of HF, the onset of which typically occurs many years later.[346] For many un- or undertreated hypertensives, LVH is an important intermediate step, resulting in "hypertensive heart disease" with impaired LV filling and increased ventricular stiffness. This type of HF (which has been seen in up to 40 percent of hospitalized patients with an antecedent history of hypertension) is commonly called diastolic dysfunction.[233] The more common type of "systolic dysfunction" associated with a reduced LV ejection fraction most often is due to previous MI (for which hypertension is also an important risk factor). In a meta-analysis of clinical trials in hypertension, there was a 42 percent reduction in HF incidence among hypertensives randomized to either a low-dose diuretic or a beta blocker.[342]

Distinguishing between the two subtypes of HF is most easily done by quantitation of the LV ejection fraction.[347] The results dictate the therapy. Patients with low ejection fractions ("systolic HF") improve both BP and long-term prognosis with ACE-Is and diuretics, to which are sometimes added beta blockers, spironolactone, and/or other drugs.[314,347-349] The role of ARBs is controversial unless cough or other adverse effects preclude an ACE-I. In the first (but small) direct comparison of captopril and losartan [Evaluation of Losartan In The Elderly (ELITE)], there was a survival benefit (a tertiary hypothesis) attributed to the ARBs, which the larger study (ELITE II), with exactly the same protocol, did not confirm.[350] If cough or other adverse effects of an ACE-I preclude its use, an ARB becomes the rational choice. Ongoing research may define the benefit of using both an ACE-I and an ARB simultaneously in patients with systolic HF. The role of DHP CAs and other direct-acting vasodilators (e.g., hydralazine in combination with isosorbide dinitrate) remains controversial.[351] Most authorities recommend these drugs as second- or third-line therapy (after maximum doses of ACE-Is and/or ARBs) if BP is still elevated. Recently, in the Randomized Aldactone Evaluation Study (RALES) trial, spironolactone, an aldosterone antagonist, in doses that do not lower BP reduced morbidity and mortality in patients with HF, most of whom were already taking ACE-Is, aspirin, and diuretics.[349] Many of these patients were also on beta blockers.

Treatment of hypertension with diastolic dysfunction and HF has not been as well studied, but most

authorities recommend using drugs that reduce HR, increase diastolic filling time, and allow the heart muscle to relax more fully: beta blockers or nondihydropyridine CAs.[352,353] Although these options make physiologic sense, no randomized clinical trials have had outcomes that demonstrate their long-term efficacy.[352]

Valvular Disease

The coexistence of hypertension and valvular heart disease is, for most affected patients, simply an occurrence of two common conditions in the same person. There are few syndromes or scenarios in which the two are pathophysiologically connected, but there are some circumstances in which their coexistence has clinical importance, especially in regard to choosing antihypertensive drug therapy.

A murmur of aortic sclerosis is found in approximately 21 to 26 percent of adults over 65 years of age. Recent data from the CV Health Study showed that 29 percent of the 5621 subjects age 65 and over had this valvular abnormality detected on echocardiography; it was found much more commonly among hypertensives and those with LVH.[354] Perhaps most important, its presence was associated with a 50 percent increased risk of CV events over an average of 5 years of follow-up. After adjustment for risk factor differences at baseline (e.g., hypertension), only one of four studied end points retained statistical significance. Calcific aortic stenosis is about 10 times less common but often must be evaluated more extensively, usually with an echocardiogram. Aortic insufficiency in hypertensives is found almost exclusively in patients with isolated systolic hypertension and is most easily recognized by the murmur and several peripheral signs.[355] Unloading the LV with arteriolar vasodilators has long been recommended on a pathophysiologic basis and has been shown in a long-term trial against digoxin to prolong the time until valvular replacement surgery was required.[356] Although nifedipine was used in the study, it is likely that any vasodilator would be more effective than a weakly positive inotropic agent.

Mitral valvular disease is less common than it was in past decades, primarily because of efforts to treat streptococcal pharyngitis. Mitral stenosis is still seen occasionally in citizens of developing countries but is not commonly associated with systemic hypertension. Since digoxin typically is used to control the ventricular rate in atrial fibrillation, antihypertensive drugs that interfere with the excretion of digoxin should be used cautiously. Mitral insufficiency is also less common than it was in the past, but there are few problems specific to this disease that affect hypertension and its therapy.

The right-sided cardiac valves seldom need be considered in the treatment of patients with systemic hypertension. In patients with primary (or secondary) pulmonary hypertension (which can be treated with the usual antihypertensive drugs, although with less success), the status of the right-sided heart valves takes on increased significance.[357] Occasionally, insufficiency of the tricuspid valve is the major diagnostic clue to carcinoid heart disease (associated with weight loss drugs but rarely associated with hypertension).[358]

Microalbuminuria

MA is a predictor of CV and renal death in patients with DM.[359-361] The class of antihypertensive medications known to have the most potent effects on reducing MA is the ACE-Is.[317,359-363] These agents reduce albuminuria by reducing intraglomerular pressure as well as decreasing glomerular size selectivity and partially restoring membrane charge.[362,363] The effects of different classes of antihypertensive agents on MA as well as related metabolic parameters are summarized in Table 51-27.

Table 51-27: Effects of Drugs on Microalbuminuria and Proteinuria

Decrease levels
ACE inhibitors
Angiotensin receptor blockers
Alpha/beta blockers
Nondihydropyridine CAs
Beta blockers
Diuretics
Increase levels
Short-acting dihydropyridine CAs
Minoxidil
No effect
Dihydropyridine CAs (long acting)
Alpha blockers
Central alpha agonists (clonidine, methyldopa)

Both ACE-Is and nondihydropyridine CAs reduce albuminuria and together have additive antialbuminuric effects, in part independently of further reductions in BP.[359,364,365]

The ACE-Is and ARBs are the antihypertensive agents that most consistently reduce proteinuria in response to their BP-lowering effect. Moreover, in the absence of hypertension, these agents prevent the increase of MA to proteinuria and in many cases normalize protein excretion in patients with MA.[366] Nondihydropyridine CAs (diltiazem and verapamil) also have some utility in reducing urinary protein excretion in hypertensive patients with kidney disease.[364] In two studies, these drugs had antiproteinuric effects similar to those of ACE-Is in hypertensive diabetic patients with chronic renal disease and heavy proteinuria.[367,368] Some studies have shown that a high Na^+ intake blunts the antiproteinuric and antihypertensive effects of an ACE-I.[369,370] Increasing dietary salt despite not affecting BP appears to abolish the antiproteinuric effect of the nondihydropyridine CA diltiazem, and so attention should be paid to Na^+ intake in patients with MA/or proteinuria.[368,369] Since there are so many more data, including events data, about ACE-I than about any other agents, including ARBs, ACE-Is should be the first-line treatment of hypertension in DM and should be included in all antihypertensive regimens in such patients if tolerated.

Renal Dysfunction

Any agent or group of agents that adequately lowers BP to levels <130/85 mmHg will slow the progression of nephropathy. Aggressive BP reduction (<125/75 mmHg) is needed to maximally slow the progression of renal disease, especially among patients with elevated serum creatinine. Aggressive BP reduction (<125/75 mmHg) is needed to maximally slow the progression of renal disease, especially among patients with an elevated serum creatinine ≥1.4 mg/dL.[11] ACE-Is will slow the progression of diabetic and nondiabetic nephropathy, assuming BP reduction to levels below 140/90 mmHg.

In spite of the evidence from many long-term clinical trials, there is a general hesitancy among clinicians to use ACE-Is in such patients. This stems from a rise in serum creatinine that predictably occurs when the

drug is given. It is common to see increases in serum creatinine of up to 25 percent above baseline within 2 to 3 months of ACE-inhibitor initiation. An analysis of long-term clinical trials has confirmed that this reduction in renal function plateaus within a month.[371] In a study from Scandinavia, ACE-Is were discontinued after an average follow-up of 6 years of therapy. The glomerular filtration rate (GFR) returned to levels not significantly different from baseline even though within the first 4 months after ACE-I initiation there was a clear initial reduction in GFR by an average of 8 to 10 percent below baseline.[372] This return to baseline GFR has not been reported with any other class of antihypertensive agent studied and suggests that ACE-Is prevented the expected deterioration of renal function over time. If the serum creatinine continues to rise, especially after 1 month of therapy, evaluation for renal artery stenosis may be indicated.

There are also concerns about hyperkalemia. This should be worrisome only if the serum K^+ rises ≥0.5 meq/L.

The role of ARBs in the treatment of nephropathy and reducing CV events has not been settled. All animal studies and one completed clinical trial in patients with HF suggest that these agents are as good as ACE-Is in slowing the progression of renal disease and reducing proteinuria and CV events.[360,365] Whether ARBs are better than ACE-Is or even equivalent remains to be proved. Two ongoing clinical trials in subjects with diabetic nephropathy are scheduled to be completed by 2002 and will answer the question definitively.[319]

Thus, while any class of antihypertensive agent may be used to achieve this new recommended lower level of BP to preserve renal function, certain principles should be kept in mind.

- BP will never be controlled adequately in patients with significant renal insufficiency (serum creatinine >1.8 mg/dL) without the use of a diuretic (usually a loop diuretic).
- Long-acting loop diuretics are preferred, or if furosemide is used, it needs to be given twice a day.
- Various combinations of medications will be needed to achieve BP reduction. One of these drugs should contain an ACE-I. If side effects are noted with the ACE-I, an ARB may be substituted to ensure renal protection and BP reduction.

Since CV is the most common cause of death in people with renal disease, beta blockers clearly also have a role in therapy. These agents do not have synergistic or additive effects on BP in the presence of agents such as clonidine.[373]

Coronary Artery Disease

Since hypertension is a major risk factor for CAD, it is not surprising that a large number of patients have both conditions. It is unlikely on ethical grounds that a placebo-controlled trial will be done with any single antihypertensive drug in such patients. The presence of CAD in a patient with hypertension is likely to influence both the choice of drugs used to treat the patient and the BP goal to be achieved. Because both beta blockers and CAs are effective antihypertensive agents with major antianginal efficacy, they are often the preferred agents for initial treatment, especially in the common setting of unstable angina pectoris.[374] A recent meta-analysis suggested that the former are more effective, although the latter are more commonly used.[375] The recent HOPE trial showed a large survival benefit for high-risk hypertensives (most of whom had known CAD) treated with ramapril.[318] None of the volunteers in HOPE had known HF at enrollment in which this degree of benefit would have been expected. This has been interpreted by some as evidence in favor of this class of medication or even for this specific agent for all hypertensive patients with CAD.

The issue of how low to reduce BP in the setting of CAD is controversial. The concept of the J-shaped curve has been supported by data in patients with coronary disease, mostly using beta blockers.[328] Diastolic pressures less than 82 mmHg were associated with a higher risk of coronary events, and the rationale proposed was that since coronary artery filling occurs during diastole, reducing perfusion pressure during this time might increase coronary ischemia. These and other data led to the HOT study, in which 18,790 hypertensive patients without known coronary disease were randomized to one of three diastolic BP goals: ≤90, ≤85, and ≤80 mmHg.[324] After 3.8 years, there were no significant differences in major CV events

across the groups, suggesting that there is no increase in risk from lowering diastolic BPs below 80 mmHg. It is unlikely that a similar study in patients with CAD will be done, but some still recommend caution in lowering BP below 85 mmHg in patients with angina and/or known CAD. JNC VI indicates that "BP should be lowered to the usual target range (<140/90 mmHg), and even lower BP is desirable if angina persists."[11] The World Health Organization/International Society of Hypertension's Collaborative Trialists' Group is collecting patient-specific outcome data and eventually may have sufficient power from the clinical trials in this registry for a post hoc analysis comparing levels of achieved BP control among 270,000 hypertensives with or without CAD.[319] Even after such data become available, it probably will be advisable to use beta blockers, CAs, and perhaps nitrates for hypertensive patients with CAD to achieve a slightly lower than usual BP target and to recommend aspirin and intensive treatment of dyslipidemias. Appropriate precautions must be taken for hypertensives also using sildenafil citrate (Viagra). To date, no antihypertensives seem to confer any increased risks when used with this agent, but all nitrate-containing preparations are contraindicated.

After Stroke

Although hypertension is perhaps the most powerful risk factor for acute stroke and "clinically evident cerebrovascular disease is an indication for antihypertensive treatment," optimal BP management depends on the nature, cause, and chronology of the neurologic symptoms.[376] In the immediate setting of acute ischemic stroke, there is controversy about the optimal level of acceptable BP. Appropriate concern has been expressed about possible reduction in blood flow to "watershed" areas of the brain that are already poorly perfused if BP is reduced pharmacologically.[377] Many neurologists have observed acute worsening of cerebrovascular function and evolving neurologic deficits when BP has been reduced "too much" or "too quickly." Most physicians therefore are uncomfortable reducing BP to <180/100 mmHg. Many do not institute treatment until mean arterial pressure is >130 mmHg (e.g., BP >200/100 mmHg), except in the setting of concomitant hemorrhagic transformation or another hypertensive emergency (e.g., aortic dissection, MI, renal failure with bleeding).[378] This level of BP is at least supported by the exclusion criterion from the National Institutes of Health (NIH)-sponsored rt-PA for acute stroke trial; patients with BP >185/110 mmHg were prohibited from getting the thrombolytic agent and were instead suggested to receive antihypertensive therapy.[379] The optimal drug therapy for acute stroke-related hypertension is also ill defined, but most authorities prefer intravenously administered, short-acting agents because they can be discontinued quickly if a patient's neurologic condition deteriorates acutely.[378]

SAFETY (ADVERSE REACTIONS AND SIDE EFFECTS)

The two primary types of adverse reactions and side effects that occur with antihypertensive therapy are clinical and biochemical (Table 51-21). Clinical side effects are directly evident to the patient and are perceived by the patient or the clinician to be related to the drug. The appearance of these adverse reactions requires that the drug be stopped, the dose be reduced, or the patient be willing to remain on therapy until he or she becomes able to tolerate the side effect or until it disappears. The drugs recommended for initial therapy generally cause fewer clinical side effects than do other drugs at doses that lower BP.[11,18,19]

Biochemical side effects may lead to clinically evident adverse reactions (e.g., hypokalemia from thiazide diuretics causing muscle weakness, palpitations, nocturia, or polyuria), but usually the biochemical problems that occur with antihypertensive agents are more troublesome to the clinician than they are to the patient.

The importance of biochemical side effects is usually not that they result in clinically evident problems but the danger that these drug-related permutations of lipids, glucose, or insulin may aggravate other risk factors and accelerate the clinical impact of dyslipidemias, glucose intolerance, or insulin resistance. Whether the minor and often short-term effects on triglycerides, HDL-C, or TG that result from therapy with thiazides or beta blockers are responsible for an increase in ischemic heart disease remains to be proved. It is of great interest that in ALLHAT the biochemical profile of the group receiving the alpha blocker seemed favorable (lower triglycerides, TG, and glucose and higher K^+) compared with the group on chlorthalidone, yet the diuretic prevented CV events more successfully.[321] The remaining treatment arms of

ALLHAT (DHP CA and ACE-I versus diuretic) should definitely delineate the role of these metabolic changes.

At the doses that are now recommended, these changes and the electrolyte disturbances noted with thiazides are modest, although it is still possible that at high doses, thiazides could reduce serum K^+ sufficiently to increase the rate of sudden cardiac death. Whether the increases in insulin resistance that are seen with thiazide diuretics and beta blockers and the hypokalemia that is seen with thiazide diuretics have precipitated DM sooner or in patients who would not otherwise have become diabetic also remains to be proved. Although it is not certain that these metabolic adverse reactions are clinically relevant, it may be prudent to select another option for patients with DM or a dyslipidemia so long as BP is reduced to goal. Certain types of dual therapy also may ameliorate biochemical adverse reactions. Angiotensin-converting enzyme inhibitors and ARBs and thiazides, when given together, produce few, if any, of the metabolic abnormalities associated with thiazides alone.[380] Several fixed-dose combinations or these classes of drugs are available and may be appropriate as initial therapy[11] (Table 51-21).

The incidence of clinical side effects tends to rise with increasing doses with all classes of drugs, with the exception of ACE-Is and ARBs. Patients who develop an adverse reaction on a high dose of a drug or on a dose they previously tolerated do not necessarily need to have that drug discontinued. Instead, the dose can be lowered and another antihypertensive can be added to reduce BP to goal. The primary problems with ACE-Is are cough and angioedema, both of which tend to be idiosyncratic and occur with all representatives of that class of agents. Reducing the dose or changing to a different ACE-I is rarely helpful. Angiotensin-converting enzyme inhibitors should be increased to the maximum recommended dose before therapy is abandoned or another agent is added unless a low-dose fixed-dose combination is felt to be more appropriate. Angiotensin II receptor blockers as a class appear to be the best tolerated of all currently available antihypertensive agents.[381] Although some experts feel that they should be reserved for initial therapy only in patients who have developed a cough with ACE-Is, they are also an excellent option for patients who have no complaints when treatment is started and patients in whom a drug that primarily blocks the RAA system appears to be a good option. When VALUE and LIFE are completed, it will be known whether ARBs are as good a choice as the other four classes of antihypertensives available.

DEMOGRAPHIC CONSIDERATIONS

Blacks and Other Ethnic Minorities

Some classes of antihypertensive agents reduce BP more or less effectively in certain ethnic groups. Thiazide diuretics, for example, are more effective in blacks than in whites, whereas ACE-Is, ARBs, and beta blockers are more effective at lower doses in whites. Many blacks respond to agents that block the RAA system, but they often need higher doses than do whites or Asians.[382] Studies in African-Americans have demonstrated that starting with higher doses of an ACE-I makes this class quite efficacious in lowering BP in this population.[383] Therefore, if a black hypertensive patient would benefit from the special properties that these drugs may have in type 1 diabetic patients or in HF, for example, they definitely should be used even if additional agents will be needed to get BP to goal. Peripheral alpha blockers, alpha/beta blockers, and CAs are equally effective in all types of hypertensive patients in all ethnic groups. In general, the response rates to antihypertensive agents in Hispanics is intermediate between that seen in whites and that seen in blacks, while east Asians, though not necessarily south Asians (patients from the Indian subcontinent), often need lower doses than do whites.

The Elderly

All classes of antihypertensive agents lower BP effectively in older persons, although the doses needed to reach goal are often lower than the doses necessary in young and middle-aged hypertensive patients.[384,385] Certain drugs and certain classes of drugs, however, should be avoided or used with caution in older hypertensives. These include agents, such as peripheral alpha blockers, that can exacerbate the postural fall in BP seen more frequently in older individuals with baroreceptor dysfunction; nondihydropyridine CAs and beta blockers that may aggravate subtle or subclinical conduction defects or precipitate systolic

dysfunction and HF; and verapamil, which may not be well tolerated in some older persons already bothered by constipation. Cough from an ACE-I may be more common in older women. Diuretics and dihydropyridine DHP CAs have both been shown to reduce morbidity and mortality in older persons with stage 2 or 3 isolated systolic hypertension, making them excellent choices in such patients.[269-271] What is often forgotten in regard to many classes is that the benefits of effective treatment are more evident in older hypertensives who are at higher risk than are younger hypertensives.[385] Therapy should not be withheld for fear of toxicity or lack of efficacy in the elderly.

Children

The diagnosis and treatment of hypertension in children are different from those in adults, primarily because of the limited experience with antihypertensive drug therapy in children and the low risk of CV events in younger individuals.[386,387] Most pediatricians are very comfortable measuring and monitoring BP in their patients, but few nonnephrologists commit the expected 1 percent of their patients to drug therapy. Because of a higher incidence of secondary hypertension than there is in adults, most hypertensive children have at least an evaluation of the kidneys and urinary tract before beginning treatment.[387]

The diagnosis of hypertension in pediatric patients is truly population-based, since the 5 percent of children with the highest BP are diagnosed with "significant hypertension" and the highest 1 percent are deemed eligible for pharmacologic treatment.[387] The diagnostic cutoffs for hypertension in youth are age- and weight-dependent, and "growth charts" for plotting the progress of a child's BP against age often are completed by pediatricians for height, weight, and, more recently, BP. More frequent measurements and attention to BP are warranted when a child's BP exceeds the 90th percentile. Treatment of hypertension in children begins with lifestyle modifications, since they are likely to be beneficial as a child grows into adolescence and adulthood.[386,387] Because few registration studies of antihypertensive drugs include children (owing to informed consent complexities and risk management issues), there are limited data on the benefits of specific drugs in hypertensive children. Although the recommended treatment algorithm is based on time-tested drug use in adults, there is a growing awareness of the possibility of long-term adverse effects with diuretics and especially beta blockers (which make exercise more difficult and may lead to weight gain) and a growing use of both ACE-Is and CAs. Antihypertensive drugs that are used frequently in children are shown in Table 51-28; the doses typically are based on the body weight of the child.

Table 51-28: Antihypertensive Drugs Frequently Used in Children

Drug	Initial Dose	Usual Maximum Dose
Intravenously administered		
Sodium nitroprusside	0.5 μg/kg/min	8 μg/kg/min
Labetalol	1 mg/kg/h	3 mg/kg/h
Orally administered		
Hydrochlorothiazide	1 mg/kg/day	2-3 mg/kg/day
Furosemide	1 mg/kg/day	12 mg/kg/day
Bumetanide	0.02-0.05 mg/kg/day	0.3 mg/kg/day
Propranolol	1 mg/kg/day	8 mg/kg/day
Atenolol	1 mg/kg/day	8 mg/kg/day
Captopril (for neonates)	0.03 mg/kg/day	2 mg/kg/day
Captopril (for children)	1.5 mg/kg/day	6 mg/kg/day

Enalapril	0.15 mg/kg/day	40 mg/day
Nifedipine (extended release)	0.25 mg/kg/day	3 mg/kg/day
Prazosin	0.05-0.1 mg/kg/day	0.5 mg/kg/day
Minoxidil	0.1-0.2 mg/kg/day	1 mg/kg/day

SOURCE: Adapted from Sinaiko AR. Current concepts: Hypertension in children. *N Engl J Med* 1996; 335:1968-1973.

SPECIAL SITUATIONS

Pregnancy

Hypertension is found in about 10 percent of pregnancies and is the major cause of perinatal morbidity and mortality in most developed countries. Because of the unique patient population, hypertension in pregnancy has a special definition, four specific types, and a treatment algorithm that recognizes the need to assess outcomes in both mother and baby. Since most pregnancies are managed by obstetricians, most of the authoritative pronouncements about this condition have been advanced by expert panels drawn from that discipline.[388,389] In the United States, hypertension in pregnancy is defined as either BP >140/90 mmHg on two measurements at least 4 h apart or a diastolic BP >110 mmHg at any time during pregnancy or up to 6 weeks postpartum.[389]

The classification of hypertension in pregnancy typically requires some knowledge of BP status before conception. If there was preexisting hypertension, the patient is said to have "chronic hypertension," which can be diagnosed before 20 weeks' gestation and persists at least 42 days postpartum. Preeclampsia is hypertension appearing after 20 weeks' gestation, associated with proteinuria (at least 300 mg per 24-h collection or 2+ on a random dipstick), which typically resolves within 42 days after delivery. Hypertension with superimposed preeclampsia is a combination of the two. The term *Hypertension unclassified* typically is used only when none of the above criteria are met and the BP status before conception or during the first trimester is unknown.

There has been a great effort to elaborate both the cause and the effective treatment for preeclampsia, but neither has been identified. A large number of demographic, genetic, laboratory parameters, and other factors have been associated with a higher risk of preeclampsia, but none has been accepted as the underlying "cause" (Table 51-29). Even more interesting are recent clinical trials that attempted to prevent preeclampsia with low-dose aspirin or Ca^{2+} supplementation.[390,391] Despite a great deal of evidence in smaller studies, typically in high-risk women, the large NIH-sponsored megatrials have been unsuccessful in showing benefit from these inexpensive preventive measures. In addition, since aspirin tends to delay parturition and increase the likelihood of bleeding, few obstetricians routinely recommend it.

Table 51-29: Factors Associated with Altered Risk of Preeclampsia

Genetic markers
Angiotensinogen gene polymorphism
Tumor necrosis factor-alpha gene polymorphism
Mitochondrial transfer RNA gene mutation
Congenital thrombophelias
Resistance to activated protein C (factor V Leiden, perhaps the most common form of hereditary prothrombotic disorder)
Mutation in gene for prothrombin factor II
Hyperhomocysteinemia (mutation C677T)
Protein S deficiency
Antiphospholipid antibody syndrome
Protein C and antithrombin deficiencies

SOURCE: Adapted from Shear R, Leduc L, Rey E, Moutquin J-M. Hypertension in pregnancy: New recommendations for management. *Curr Hypertens Reports* 1999; 1:529-539.

Treatment of elevated BP during pregnancy traditionally has begun with bed rest, followed by methyldopa as the primary drug, based on its long history of efficacy and lack of adverse effects on babies. For severe hypertension (BP >160 or 169/109 mmHg) in outpatients that is not controlled with these measures to a diastolic BP between 90 and 100 mmHg, hydralazine, labetalol, and nifedipine routinely are added in succession.[392,393] Angiotensin-converting enzyme inhibitors and ARBs are contraindicated because of renal abnormalities in the fetus, and diuretics typically are avoided because of the risk for oligohydramnios. For intrapartum management, until delivery can be achieved, intravenous Mg^{2+} sulfate has been a mainstay for the prevention of progression of preeclampsia to seizures and other more serious complications.

Hypertension during pregnancy also carries prognostic significance for future health problems as the woman ages. Sixty percent of women with early-onset preeclampsia have abnormalities on renal biopsy and a higher risk of persistent hypertension after delivery. Women who develop hypertension during pregnancy not only are at higher risk for hypertension later in life but also have a roughly twofold increase in the risk of death from CAD.

Hypertensive Emergencies and Urgencies

Although great strides have been made in the treatment of hypertension since the First Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure in 1977, some patients still present to physicians' offices and emergency departments with hypertensive crises.[393] Fortunately, there now are excellent medications available for both acute, in-hospital treatment and outpatient management; these improvements have led to a decrease in the 1-year mortality rate after a hypertensive emergency from 80 percent (1928) to 50 percent (1955) to only 10 percent (Fig. 51-1).

The primary pathophysiologic abnormality in patients who experience hypertensive crises is the alteration of autoregulation in certain vascular beds (especially cerebral and renal), which often is followed by frank arteritis and ischemia in vital organs.[394] Autoregulation is the ability of blood vessels to dilate or constrict to maintain normal organ perfusion. Normal arteries from normotensive individuals can maintain flow over a wide range of mean arterial pressures, usually 60 to 150 mmHg. Chronic elevations of BP cause compensatory functional and structural changes in the arterial circulation and shift the autoregulatory curve

to the right; this allows hypertensive patients to maintain normal perfusion and avoid excessive blood flow at higher BP levels.[395] When BP increases above the autoregulatory range, tissue damage occurs. An understanding of autoregulation is also important for therapy, since the sudden lowering of BP into a range that would otherwise be considered normal may reduce BP below the autoregulatory capacity of the hypertensive circulation and lead to inadequate tissue perfusion (Fig. 51-2). In the later stages of a hypertensive crisis, pathologists can demonstrate cerebral edema and both acute and chronic inflammation of the medium and small arteries and arterioles, often associated with necrosis.

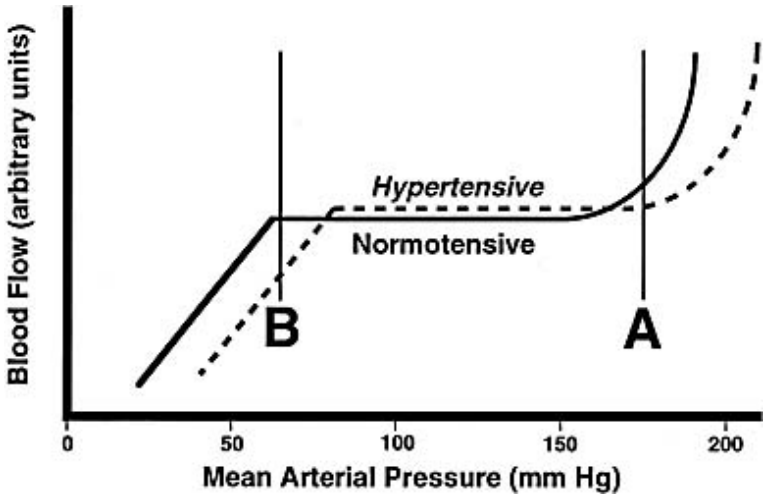

Figure 51-2: Blood pressure versus flow relationships in normotensive (*dark curve*) and hypertensive (*dotted curve*) persons, based on cerebral blood flow data of Strandgaard et al.[395] Chronically hypertensive persons can autoregulate their blood flow within the normal range despite higher blood pressures (e.g., vertical line "B"). Lowering BP in the setting of a hypertensive emergency to what might be considered "normal" (in a normotensive person, e.g., vertical line A) probably will put BP below the autoregulatory threshold and may compromise local circulation.

Hypertensive crises occur in a variety of clinical settings. The most common is a chronic and often untreated patient with stage 3 essential hypertension (i.e., usual BP ≥ 180/110) whose BP rises above the autoregulatory range, triggering the pathophysiologic sequence outlined above. Identical crises can occur, however, any time there is an acute or rapid rise in BP in a normotensive or minimally hypertensive individual, such as a child or a woman during pregnancy. Hypertensive crises can most easily be recognized by the association of an extremely elevated BP with physical examination or laboratory findings that indicate acute TOD. The actual levels of BP are of little import.

The initial evaluation of a severely hypertensive patient includes a thorough inspection of the optic fundi (looking for acute hemorrhages, exudates, or papilledema); a mental status assessment; a careful cardiac, pulmonary, and neurologic examination; a quick search for clues that might indicate secondary hypertension (e.g., abdominal bruit, striae, radial-femoral delay); and laboratory studies to assess renal function (dipstick and microscopic urinalysis, serum creatinine).[394]

There are several different types of common clinical presentations of hypertensive emergencies.

The neurologic crises are the most difficult to distinguish from one another (Table 51-30). Hypertensive encephalopathy is typically a diagnosis of exclusion; hemorrhagic and thrombotic strokes usually are diagnosed after focal neurologic deficits are corroborated by CT. Subarachnoid hemorrhage is diagnosed by the typical findings on lumbar puncture. The management of each of these conditions is somewhat different in that nimodipine may be the drug of choice for most neurologic crises because of its antihypertensive and anti-ischemic effects. Many physicians still prefer nitroprusside or another intravenous vasodilator because it can be discontinued rapidly if BP goes too low.[396] Goal BP also depends on the presenting diagnosis and is usually lower for encephalopathy than it is for acute stroke in evolution (

Table 51-30).

Patients who present with hypertensive crises involving cardiac ischemia/infarction or pulmonary edema can be managed with either nitroglycerin or nitroprusside, although typically a combination of drugs (including an ACE-I when there is HF) is used in these settings.[396] Efforts to preserve myocardium and open the obstructed coronary artery (by thrombolysis, angioplasty, or surgery) also are indicated.

Patients with aortic dissection are managed in a somewhat different fashion.[397] A beta blocker is added to the intravenous vasodilator, and the goal BP is much lower: Typically 120 mmHg systolic is recommended, but 100 mmHg systolic may be even better. Pharmacologic therapy is only a temporary adjunct to definitive surgical therapy, which should be planned with dispatch, although long-term medical therapy may be more appropriate in some patients.[398]

Hypertensive crises involving the kidney commonly are followed by a further deterioration in renal function even when BP is lowered properly. Some physicians prefer fenoldopam to nicardipine or nitroprusside in this setting because of its lack of toxic metabolites and specific renal vasodilating effects.[396,399,400] Blood pressure should be reduced about 10 percent during the first hour and a further 10 to 15 percent during the next 1 to 3 h. The need for acute dialysis often is precipitated by BP reduction, but many patients are able to avoid dialysis in the long term if BP is carefully and well controlled during follow-up.

Hypertensive crises resulting from catecholamine excess states [pheochromocytoma, monoamine oxidase (MAO) inhibitor crisis, cocaine intoxication, etc.] are best managed with an intravenous alpha blocker (phentolamine), with the beta blocker added later, if necessary. Many patients with severe hypertension caused by sudden withdrawal of antihypertensive agents (e.g., clonidine) are easily managed by reinstituting such therapy.

Hypertensive crises during pregnancy must be managed in a more careful and conservative manner because of the presence of the fetus. Magnesium sulfate, methyldopa, and hydralazine are the drugs of choice, with oral labetalol and nifedipine being drugs of second choice in the United States. Delivery of the infant often assists in the management of hypertension in pregnancy and often is hastened by the obstetrician under these conditions.

Hypertensive urgencies are situations in which acute TOD is not present; they require somewhat less aggressive management and nearly always can be handled with oral antihypertensive agents without admission to the hospital. Nifedipine, clonidine, captopril, labetalol, and several other short-acting antihypertensive drugs have been used for this problem. Nifedipine has been reported to cause precipitous hypotension, stroke, MI, and death and, according to the U.S. Food and Drug Administration, "should be used with great caution, if at all."[401,402] Otherwise, none of these drugs seems to have a major advantage over all the others, and all are effective in most patients.[403] *The most important aspect of managing a hypertensive urgency is to assure compliance with antihypertensive therapy during long-term follow-up.*

Patients presenting with a hypertensive emergency should be diagnosed quickly and started promptly on effective parenteral therapy (often nitroprusside 0.5 μg/kg per minute) in an intensive care unit. BP should be reduced about 25 percent gradually over 2 to 3 h. Oral antihypertensive therapy (often with an immediate-release CA) can be instituted after 6 to 12 h of parenteral therapy; evaluation for secondary causes of hypertension may be considered after transfer from the intensive care unit. Because of advances in antihypertensive therapy and management, "malignant hypertension" should be malignant no longer.

The situation in hemorrhagic stroke is slightly more complex because acute hypertension often is seen in such patients even if there has been no antecedent history of elevated BP. It is not clear if acute BP lowering will reduce or increase the complication rates (from worsened cerebral ischemia in other areas or making a zone surrounding the hemorrhage ischemic). As a result, it is recommended not to treat hypertension beyond a mean arterial pressure of >130 mmHg, and even then it is controlled rather more slowly into an intermediate range (e.g., 160/100 mmHg). Some have claimed that previously hypertensive patients with acute intracerebral hemorrhage should be managed even less aggressively.

Appropriate BP reduction in the setting of acute subarachnoid hemorrhage is even more controversial.[379] Even associating higher BP levels with higher rates of rebleeding has been difficult. If BP lowering is desired (e.g., if mean arterial pressure is >130 mmHg), a short-acting intravenous drug (e.g., nitroprusside) typically is recommended, since it can be discontinued quickly and the patient can be given fluids to restore the previous BP level if the neurologic status worsens.

DOSE SCHEDULE (DOSAGE AND CHRONOTHERAPY)

It is clear that BP needs to be controlled for 24 h. Preparations that are active once a day are easier for patients to remember to take, but adherence to treatment may not be substantially worse if twice-a-day preparations are used. In fact, patients may be better protected if they fail to remember to take one dose of a twice-a-day medication and be uncovered for 12 hours than if they skip a once-a-day pill and are unprotected for a considerably longer period.

In addition to "controlling BP" over 24 h, regimens should pay some attention to the circadian rhythm of BP and HR. Many of the sequelae of hypertension have a strong circadian variation, with a peak incidence in the early morning. Recent meta-analyses have quantitated the excess risk of heart attack during the period from 6 A.M. to noon at 40 percent, sudden cardiac death at 29 percent, and stroke at 49 percent compared with what would be expected if these events happened evenly or randomly throughout the day.[404,405] Since most patients administer antihypertensive agents in the morning, most authorities recommend long-acting drugs that should cover the early-morning period, when blood pressure, pulse, and cardiovascular risk are highest. Although many of the currently used medications have short intrinsic elimination half-lives, pharmaceutical technology has made available several methods of making sustained-release compounds from short-acting drugs.[406,407]

Recently, a chronobiological approach to antihypertensive therapy has become available.[407] This is currently available only for two preparations of verapamil.[408] These drug-delivery systems release active drug for 18 to 20 h, beginning between 2 A.M. and 4 A.M., leaving the patient with no active drug in the circulation from about 10 P.M. to 2 A.M. The rationale for this approach is that BP falls normally at night coincident with the usual circadian rhythm and active drug might cause excessive lowering of BP during the middle of the night.[409] These sustained-release preparations provide adequate active drug as the BP rises before awakening and during the peak time of CV events (the period between 6 A.M. and noon). The same matching of drug delivery to BP is not achieved by giving "homeostatically" designed drugs (i.e., all the others) at night. Such agents were designed for morning use, and giving them at night causes the risk of lowering BP too far during sleep.[198]

The putative advantage of such a system is that it would not excessively lower BP during sleep (when BP is typically at its nadir anyway) and would deliver an agent that is both hypotensive and HR-lowering at the time of day when BP, HR, and CV risk are nearly maximal.[198] The long-term consequences of this strategy are being tested in the CONVINCE trial with 16,602 subjects; conclusions may be available in 2002.[322]

DRUG INTERACTIONS

The selection of the initial agent to treat hypertension must be done with the understanding that many hypertensive patients may not reach goal BP on that agent alone and will therefore need additional antihypertensive therapy. Furthermore, many hypertensive patients need to take medications for other conditions, and so the problem of drug-drug interactions is particularly pertinent.

Certain combinations of antihypertensive agents are particularly effective, such as thiazide diuretics with beta blockers, ACE-Is, or ARBs.[380] Combinations of ACE-Is with CAs (both DHP and non-DHP) are also effective. Moreover, combinations of the two subtypes of CAs are synergistic with regard to BP reduction.[409] Dihydropyridine CAs and beta blockers are also very effective combinations. Nondihydropyridine CAs and beta blockers should not be used because of the risk of excessive bradycardia and conduction defects. Thiazide diuretics are also effective with all other antihypertensive drugs, including CAs, and always should be included in a triple-drug regimen. Little is known about the efficacy of

combining alpha blockers with central and peripheral sympatholytics or with ACE-Is or ARBs.

Recently, a series of low-dose fixed-dose combinations have been introduced that have fewer clinical side effects than occur when the components are used as monotherapy (Table 51-21). The best example is the combination of a DHP CA with an ACE-I. These fixed-dose combinations have a significantly lower incidence of edema than that seen when a DHP CA is given alone.[380] The incidence of cough, however, is not lessened when these drugs are combined. The appeal of a low-dose fixed-dose combination is that BP can be reduced further with fewer adverse reactions with two drugs at lower doses than might occur when one or the other component is pushed to the full dose. The added advantage is that the patient needs to take fewer pills to get BP to goal and so adherence to the regimen tends to improve (see below).

Most commonly used antihypertensives do not have any serious drug-drug interactions with anticoagulants, platelet inhibitors, or antibiotics. Nondihydropyridine CAs, beta blockers, and possibly telmisartan (an ARB) must be used with care in patients who are taking digitalis preparations.[381] Nonsteroidal anti-inflammatory agents may raise BP and interfere with the activity of all antihypertensive agents because of their Na^+-retaining properties.[410]

ADHERENCE

Fewer than 50 percent of patients continue taking the initially prescribed antihypertensive drug therapy for a year.[411,412] The proportion who properly adhere to therapy improves only modestly when the drugs and medical care are provided free of charge. Recent estimates indicate that about 10 percent of the overall expenditures on hypertension in the United States are wasted because of nonadherence to medical advice and antihypertensive drug therapy.[413] Patients who do not follow the advice of their physicians and do not take their medications correctly have an *infinite* cost/benefit ratio because they incur all the cost associated with the therapy but derive *none* of the benefits of treatment.

Assessing adherence with antihypertensive medications is generally difficult, but several simple measures often are recommended.[11,38,414] Some medications induce physical signs that are absent in those who have not recently taken them, e.g., bradycardia with beta blockers, orthostatic BP change with alpha blockers, and an increase in serum urate with diuretics. A telephone call to the patient's pharmacy generally will reveal how many times the prescribed medications have been refilled during the last year.[415] Several interventions have been advocated to improve adherence with medications (Table 51-31).

Table 51-31: Strategies to Improve Medication Adherence

Educate patient regarding proper use of medications
Improve patient's social support network (e.g., spouse or caretaker)
Increase patient's autonomy and involvement in decision making (when appropriate)
Remove barriers to compliance with pill taking
Integrate into activities of daily living (e.g., brushing teeth)
Avoid large ('horse') pills
Avoid bad-tasting formulations (e.g., lactulose, quinine)
Simplify the therapeutic regimen
Minimize number of pills
Minimize frequency of pill taking
Minimize inconvenience of pill taking

Provide positive attitude and positive reinforcement about achieving therapeutic goals
Maintain continuity of care with same practitioner
Use well-tolerated antihypertensive drug therapy individualized for each patient

There is concern, however, that administering long-acting drugs will lower blood pressure to a relatively constant degree during the day and night. This may lead to hypoperfusion of vital organs during the night that will not be symptomatic.[408]

MECHANISM OF ACTION OF THE DRUG AND PATHOPHYSIOLOGY OF THE PATIENT'S HYPERTENSION

Some have felt that physicians could be much more successful in treating hypertensive patients if they could base therapy on the reason why the patient is hypertensive (the pathophysiologic abnormality responsible for the patient's hypertension) and match that information to the mechanism of action of antihypertensive drugs. If physicans truly could know precisely why an individual was hypertensive and easily and safely obtain such information, treating hypertension would be not be complicated. If it really were known exactly how drugs work, those decisions would be much simpler. This approach, while intellectually appealing, has problems.

The first difficulty is that attempts to profile patients either biochemically using PRA, for example, or hemodynamically by measuring cardiac output and peripheral vascular resistance are too expensive and potentially invasive to do in everyone. In addition, these methods are not precise enough to provide the kind of necessarily definitive information needed to predict the response to therapy in a particular patient. Furthermore, trying to base therapy on the presumed pathophysiology in an individual or group of individuals would be expected to have is also imprecise. This approach runs the risk of denying certain patients the potential benefits of certain classes of drugs. Although it is true that blacks and older persons tend on the average to have low or suppressed PRA, many do not. Also, many patients with a low PRA will respond to drugs, such as ACE-Is or ARBs, that are less effective on the average in hypertensives with this renin profile. In the VA trial of monotherapy, selecting initial treatment on the basis of PRA was less effective than simply using age and ethnicity (thiazide diuretics and CAs for older patients and blacks and ACE-Is and beta blockers for whites and in those less than 60 years of age).[382] However, neither method correctly predicted a good response in more than 63 percent of the patients.

The second issue that complicates this approach is that many, if not all, drugs have more complex mechanisms of action than they were originally thought to have and work well in patient subgroups in whom they were supposed to be ineffective. For example, thiazide diuretics not only reduce plasma volume but also are vasodilators after 4 weeks of therapy. It should not have been surprising that these agents are effective and very well tolerated in older persons even though many of those patients tend to have a modestly decreased plasma volume compared with younger hypertensives. Although it is true that ACE-Is usually suppress the endocrine RAA system, the antihypertensive effect is still evident even when plasma AII concentration returns to pretreatment levels. This is good evidence that there is a tissue site of action for these drugs or that other mechanisms, perhaps the stimulation of bradykinin or NO, participate in how ACE-Is lower BP and that the initial formulation of their mechanism of action was incomplete. This also explains why some patients with low PRA (a measure of the activity of the *endocrine* RAA system) respond well to these agents or to ARBs, which suppress the RAA system at the angiotensin AT_1 receptor in tissues throughout the body. Calcium antagonists were presumed to work best in older hypertensives and in those with suppressed PRA, but these agents are equally effective in all subgroups of hypertensives.[237]

Perhaps the major flaw in the reasoning that drugs can be used to "probe" the pathophysiologic abnormality causing a patient's hypertension is the concept that there is one overriding abnormality responsible for that patient's elevated BP. In all likelihood, more than one, if not many, of the systems that control BP, many of which are discussed in this chapter, are dysfunctional simultaneously and single or combinations of pharmacologic agents that reduce BP do so by correcting more than one abnormality.[10]

The choice of initial therapy therefore should be based primarily on evidence from clinical trials that document a reduction in CV events and/or renal disease progression. However, despite the fact that one cannot precisely determine the mechanism or mechanisms of action of drugs and that it is impossible to elucidate precisely why a particular patient is hypertensive, the empirical approach to treating hypertension dramatically reduced the rate of stroke and CAD after physicians began to treat hypertension aggressively. This approach, though far from perfect, has paid dividends.

COST

The economics of hypertension and its therapy are complex, but the simple fact is that if a person cannot afford to pay for the drug chosen by the health care provider, the completed prescription will do little good in the long term.[52,53] Many pharmacists and businesspeople associated with health care believe that the agent with the lowest purchase price is the best, but this oversimplification omits the costs of extra visits to health care providers, laboratory testing, and adverse drug experiences that result in emergency room visits or hospitalization.[415] Such global evaluations of the economics of hypertension and its therapy are rare. It is possible for a more expensive but better-tolerated drug (e.g., an ARB) to actually be less expensive in the long term than another agent that produces many side effects, some of which must be evaluated by laboratory testing, physician visits, and even hospitalization. There is also the possibility that some of the newer (and currently more expensive) agents are more effective in lowering BP and reducing cardiovascular events (which currently account for 82 percent of expenditures related to hypertension in the United States) than are some of the older agents; this alone may be sufficient to make them more cost-effective than the time-tested agents.

Generically available drugs are usually less expensive to purchase than their branded counterparts and are strongly favored in most managed care pharmacy plans by both mandates to physicians and lower copayments by patients.[416] Some organized health care plans insist that the first month of antihypertensive therapy always involve a low-dose thiazide diuretic because of its proven efficacy and low cost. Although JNC VI "favored" low-dose diuretics and beta blockers for uncomplicated hypertension, it did, for the first time, suggest that hypertensives with another "compelling condition" would benefit even more from other classes of antihypertensive agents. There are now more data to suggest that in the long term it matters more what BP level is achieved during treatment than which agent is chosen initially to begin the lowering.

Many authorities are concerned that achieving the new, lower target BPs for diabetic and renally impaired hypertensives will cost more, as it will require more visits to health care providers and more antihypertensive medications. These increases in short-term expenditures are likely, however, to be offset by a lower future incidence of expensive outcomes, including heart attack, stroke, ESRD, and HF, at least for diabetic patients over age 60 in the United States.[332]

Many proposals for reducing the high cost of antihypertensive therapy have been advanced. JNC VI has suggested withholding drug therapy for 6 to 12 months from those at low risk (risk groups A and B) with stage 1 hypertension and giving it instead to patients in risk group C with BP ≥130/85 mmHg.[11] In stage 2 to 3 hypertension, wider use of combination drug tablets has been advocated, as these tablets typically cost much less than two separate prescriptions for the same doses of individual agents. Some formularies and pharmacy benefits managers prefer agents that have all doses priced identically, with the theory that a pill splitter can then be used to divide one tablet into two or more days' treatment. Aggressive health care plans have implemented strategies that prohibit the use of more expensive medications (e.g., ARBs) unless two physicians independently ascribe an adverse effect to a less expensive drug (e.g., an ACE-I), and others require three separate ACE-Is to be administered sequentially before an ARB can be dispensed.

Until a universal pharmacy benefits program is instituted, there are likely to be wide variations in the pricing and cost of antihypertensive agents. Although it is difficult for physicians to stay abreast of fluctuations in these costs, it is important that all health care providers attempt to provide tolerable antihypertensive medications at the lowest possible cost for the benefit of the patient, the health plan, and the national budget.

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Chapter 51: HYPERTENSION: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

SUMMARY AND RECOMMENDATIONS

Although there are numerous options and many sources of error, the successful pharmacologic treatment of a hypertensive patient need not be too complicated, although it also should not be oversimplified. Once the diagnosis has been established and the routine evaluation and any more complex tests believed to be necessary have been completed, lifestyle modification should begin. Lifestyle modification should be given time to work unless the patient is in a group for which drug therapy is indicated (together with lifestyle modifications at the initiation of treatment). Drug therapy is indicated in all hypertensive patients if goal BP is not reached with lifestyle modification alone.

The following steps are recommended for choosing a regimen and then altering it until the goal is reached:

- Deal first with cost. If the patient is unable to afford any but the least expensive drugs or cannot pay for the one that is selected, price becomes the primary issue.
- Ascertain whether other risk factors or comorbidity is present. Avoid drugs that may worsen these factors or conditions and choose the ones that may tend to improve them.
- Find out what clinical adverse reactions the patient would find the most troublesome and avoid agents that are more likely to cause or exacerbate these problems. Some patients are not concerned by certain side effects that are very troublesome for others.
- Consider demographic issues and select the class of drug with a higher probability of success if options are available.
- Start with the lowest effective dose and plan to see the patient within 2 to 4 weeks unless the severity of the patient's hypertension or another problem warrants an earlier visit. Carry out appropriate biochemical monitoring when necessary. In some patients, start with a fixed-dose combination when it appears appropriate.
- Increase the dose if goal BP has not been reached or if there has been only a minimal response. Do not increase the first dose or any dose prematurely. Give each dose adequate time to be fully effective. If intolerable side effects occur and are likely to be drug-related or if there has been no response, only then switch to another appropriate agent for monotherapy.
- Continue the process of dose titration and monitoring until the maximum recommended dose has been reached. Stopping before the full dose has been reached leads to a situation in which the patient is treated with multiple agents at subtherapeutic doses when only one or two drugs are necessary.
- If the drug of first choice fails to reduce BP to goal, add a second agent that has a different mechanism of action and is known to have additive antihypertensive effects to the first-choice agent. A fixed-dose combination that combines two drugs in the desired doses also could be used at this time.
- Titrate the second drug to the full dose, as was done for the first drug, and continue appropriate monitoring. If the two-drug combination fails, consider a specific cause for the patient's refractory hypertension, and if none is evident, add a third drug, being sure that a diuretic is part of the regimen. Consider a referral to a hypertension specialist.
- Plan to see a patient who is at goal at least once every 3 months to be sure that BP control is sustained.
- Reinforce the need for adherence to the regimen and always question each patient carefully

about adverse reactions. Although some patients will not reach goal with this approach even with the many effective treatment options that are available, most will come under control or close to it. Patients who do this can anticipate substantial long-term benefit with an extended life expectancy and a much reduced risk of stroke, ischemic heart disease, HF, and probably renal failure and dementia.

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Chapter 51: HYPERTENSION: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

CONCLUSION

Although treating high BP can be costly and at times seem unrewarding, the benefits to individual patients and to society make the effort worthwhile. Physicians must be careful not to become apathetic about hypertension. The problem has not been solved and will not be solved until all hypertensive patients are able to avail themselves of what has been among the most successful examples of preventive medicine.

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Part 8: PULMONARY HYPERTENSION AND PULMONARY DISEASE
Chapter 52:

PULMONARY HYPERTENSION

Author: Lewis J. Rubin

Pulmonary hypertension is a hemodynamic abnormality common to a variety of conditions that is characterized by increased right ventricular (RV) afterload and work. The clinical manifestations, natural history, and reversibility of pulmonary hypertension depend heavily on the nature of the pulmonary vascular lesions and the etiology and severity of the hemodynamic disorder. For example, subacute or chronic hypoxia predominantly causes increased muscularization of the small muscular pulmonary arteries and arterioles while leaving the intima relatively intact. Relief of the hypoxia improves or occasionally reverses the process with little or no pathologic residue.[1,2] In contrast, the lesions of systemic sclerosis (scleroderma), which tend to be confined to the intima of the small pulmonary arteries and arterioles, are usually progressive and irreversible. In contrast to scleroderma and chronic hypoxia, which spare the pulmonary capillary bed, the pulmonary capillaries are the primary site of involvement in pulmonary capillary hemangiomatosis.[3] Because of its large capacity, its great distensibility, its low resistance to blood flow, and the modest amounts of smooth muscle in the small arteries and arterioles, the pulmonary circulation is not predisposed to become hypertensive. When total cross-sectional area is decreased, such as by destruction or obliteration of lung tissue or occlusive lesions in the resistance vessels, pulmonary arterial pressures increase. The degree of pulmonary hypertension that develops is a function of the amount of the pulmonary vascular tree that has been eliminated. Pulmonary hypertension is usually secondary to cardiac or pulmonary disease. Although primary pulmonary hypertension (PPH) is uncommon, it has attracted considerable attention as a distinctive clinical entity in which intrinsic pulmonary vascular disease is free of the complicating features of secondary pulmonary hypertension contributed by diseases of the heart and/or lungs. Mild or even moderate pulmonary hypertension can exist for a lifetime without becoming evident clinically. For example, native residents at high altitude, in whom mild to moderate pulmonary hypertension is a natural result of sustained exposure to hypoxia, can function normally. When pulmonary hypertension does become manifest clinically, the symptoms tend to be nonspecific (Table 52-1).

Table 52-1: Symptoms of Primary Pulmonary Hypertension

Dyspnea	Palpitations
Fatigue	Orthopnea
Dizziness	Cough
Syncope	Hoarseness
Chest Pain	

DEFINITIONS

Pulmonary *arterial* hypertension can be either acute or chronic. The acute form is usually a result

of either pulmonary embolism (see Chap. 53) or the adult respiratory distress syndrome. This chapter deals with *chronic* pulmonary arterial hypertension.

Pulmonary *venous* hypertension usually is encountered clinically as a consequence of left ventricular (LV) failure or mitral valvular disease. Occasionally, it may occur in the course of fibrosing mediastinitis. Only rarely is the entity known as pulmonary veno-occlusive disease (PVOD) encountered. Even though pulmonary hypertension may be confined, at the outset, to the pulmonary veins (e.g., in acute mitral insufficiency), sooner or later pulmonary arterial hypertension supervenes. The hallmarks of pulmonary venous hypertension are pulmonary congestion and edema. For practical purposes, pulmonary venous hypertension is said to exist when pulmonary venous (or left atrial) pressure rises above 15 mmHg.

Cor pulmonale signifies the presence of pulmonary hypertension in the setting of chronic respiratory disease.[4] The degree of pulmonary hypertension that develops in patients with chronic lung disease tends to be less severe than in connective tissue diseases, chronic thromboembolic disease, or primary pulmonary hypertension. Pulmonary hypertension may be severe, however, in some patients with interstitial lung disease.

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Chapter 52: PULMONARY HYPERTENSION

NORMAL PULMONARY CIRCULATION

Structure

Immediately before birth, pulmonary and systemic arterial blood pressures are about equal and on the order of 70/40 mmHg, with a mean of 50 mmHg. Immediately after birth, with closure of the ductus arteriosus and initiation of ventilation, pulmonary arterial pressure falls rapidly to about one-half of systemic levels. Thereafter, pulmonary arterial pressures gradually decrease over several weeks to reach adult levels[5] (see also Chap. 70).

In some neonates, the normal pulmonary hypertension of the fetus fails to recede normally, generally due to either a developmental anomaly or a relentless increase in pulmonary vascular tone. In such infants, the persistent pulmonary hypertension and RV failure may become life-threatening. Surgical intervention or temporizing measures, such as the use of inhaled nitric oxide (NO) or extracorporeal membrane oxygenation (ECMO), may be useful in reversing the pulmonary vascular abnormalities.[6]

In the normal adult at sea level, the small muscular arteries and arterioles in the lungs are thin-walled and contain very little smooth muscle. In contrast, in the fetus or the adult who has lived under hypoxic conditions (e.g., native residents at high altitude), the media of the arterioles are thickened, and the muscle extends distally into precapillary vessels that are ordinarily devoid of muscle; i.e., the precapillary vessels undergo "remodeling."[7]

Endothelium and Endothelium-Smooth Muscle Interactions

In addition to its role as a semipermeable barrier between blood and interstitium, the endothelium serves a wide array of biologically important functions, the net effect of which is the processing of blood flowing through the lungs. Among these functions are the synthesis, uptake, storage, release, and metabolism of vasoactive substances; transduction of blood-borne signals; modulation of coagulation and thrombolysis; regulation of cell proliferation; engagement in the local inflammatory and proliferative reactions to injury; involvement in immune reactions; and angiogenesis (see also Chap. 4). Some of the enzymes involved in these processes, such as the angiotensin-converting enzyme, are found on the surface of endothelial cells; others, such as 5′-nucleotidase, are found within the cell.[8] Hence it is appropriate to regard endothelium as an organ with diverse metabolic and endocrine functions, one that is unique because of its strategic location as a continuous, monolayered lining of blood vessels throughout the body. It is also important to bear in mind that the lungs contain the largest expanse of endothelium in the body.

The cells that comprise the monolayered endothelial lining communicate not only with each other by anatomic junctions and bridges but also with the underlying smooth muscle by way of biologically active substances.[9] This interaction participates in regulating normal vasomotor tone as well as in response to the administration of vasoactive substances. It is not difficult to imagine that damage to the lining cells, proliferation of the intima, or hypertrophy of the smooth muscle will upset the normal interplay.

Hemodynamics

For the adult pulmonary circulation, the definition of *normal* depends on the altitude. The normal pulmonary hemodynamics of adults residing at sea level and above sea level are compared in Table 52-2. At *sea level*, a cardiac output of 5 to 6 L/min is associated with a pulmonary arterial pressure of about 20/12 mmHg, with a mean of about 15 mmHg. At an altitude of 15,000 ft, the same level of blood flow is associated with somewhat higher pressures (see Table 52-2). Pulmonary arterial pressures also tend to increase somewhat with age.

Table 52-2: Values of Normal Pulmonary Circulation at Sea Level and Altitude

	Sea Level	Altitude (~15,000 ft)
Pulmonary arterial pressure (P_{PA}), mmHg	22/12, 15	38/14, 25
Cardiac output (Q), L/min	6.0	6.0
Left atrial pressure (P_{LA}), mmHg	5.0	5.0
Pulmonary vascular resistance (PVR),[a] (mmHg/L)/min (R units)	1.7	3.3

[a]> To convert T units to CGS units (dynes·s/cm^2), multiply R units by 80.

A pressure drop of only 5 to 10 mmHg between the pulmonary artery and left atrium accompanies the cardiac output of 5 to 6 L/min (see Table 52-2). Determination of pulmonary vascular resistance, calculated as the ratio of the difference in mean pressure at the two ends of the pulmonary vascular bed (pulmonary arterial pressure minus left atrial pressure divided by the cardiac output; see Table 52-2), has proved to be a practical clinical tool for assessing the hemodynamic state of the pulmonary circulation and for distinguishing between active and passive changes in the pulmonary resistance vessels (e.g., the effect of administering a vasodilator agent to a patient with pulmonary hypertension). In practice, since the left atrium may not be readily accessible, pulmonary wedge pressure generally is substituted for left atrial pressure.

Another approach to defining certain characteristics and the behavior of the pulmonary arterial tree, i.e., elastic properties and geometry, is the calculation of pulmonary arterial input impedance. This approach has more physiologic than clinical value. It takes into account the pulsatile nature of pulmonary arterial pressures and flow. Like vascular resistance, it is defined as a ratio. But instead of a ratio involving *mean* pressures and blood flow, the ratio is of the amplitudes of pulsatile pressure to oscillatory flow near the beginning of the pulmonary artery at a particular frequency. Values for the ratio are obtained by resolving mathematically the pulsatile pressure and flow curves into their sinusoidal components.

Although calculated pulmonary vascular resistance has proved useful in assessing the state of the normal and abnormal pulmonary circulation, and even though a change in calculated resistance often can be helpful in deciding whether pulmonary vasoconstriction or vasodilatation has occurred, translation of a calculated ratio into vasomotor activity has to be made with caution.[4] For example, changes in calculated pulmonary vascular resistance are not readily interpretable when a vasodilator agent evokes multiple hemodynamic changes simultaneously (e.g., simultaneous changes in pulmonary vascular pressures and blood flow). Also, a clinical shortcut, such as the substitution in the numerator of the pulmonary arterial pressure for the pressure *drop* between the pulmonary artery and left atrium, may be useful empirically but deprives the calculation of any physiologic meaning. Finally, the clinical significance of a value calculated for pulmonary vascular resistance depends heavily on the implications of the hemodynamic changes on the work of the right ventricle. For example, the same decrease in calculated pulmonary vascular resistance brought about by two different pulmonary vasodilators may affect the work of the right ventricle differently: Should one agent elicit a *decrease* in pulmonary arterial pressure along with an *increase* in cardiac output (an ideal response), it is more apt to be of long-term benefit than another agent that, while increasing the cardiac output, fails to decrease the pulmonary arterial pressure.

In the normal lung, a considerable increase in cardiac output, i.e., two to three times that at rest, generally increases pulmonary arterial pressure by only a few millimeters of mercury. On the other hand, in pulmonary hypertensive states, in which the distensibility and extent of the pulmonary vascular bed have been restricted by disease, pulmonary arterial pressure increases along with even small increments in pulmonary blood flow. Changes in pulmonary blood volume are much more subtle than changes in blood pressure or flow in their hemodynamic effects; they are also much more difficult to quantify. Clinical clues

can be helpful in recognizing that the pulmonary blood volume has increased. Often a fullness of the pulmonary vascular pattern on the chest radiograph along with evidences of interstitial edema suggests that pulmonary blood volume has increased acutely. In chronic mitral stenosis or LV failure, the pulmonary blood volume is not only increased but is also redistributed toward the apices of the lungs, i.e., "cephalization."

Autonomic innervation of the pulmonary vascular tree plays much less of a role in modulating vasomotor tone than do local stimuli, particularly hypoxia. Indeed, hypoxia can exert its pulmonary pressor effect in the isolated lung, i.e., one that is devoid of external innervation. The mechanism by which hypoxia exerts its local pressor effect is not fully characterized but appears to involve altered smooth muscle cell membrane ion channel activity.[2] Acidosis potentiates the hypoxic pressor effect. Hypercapnia also exerts a pulmonary pressor effect, presumably by way of the local acidosis that it generates, but it is less powerful than hypoxia as a pulmonary vasoconstrictor agent.

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Chapter 52: PULMONARY HYPERTENSION

PULMONARY HYPERTENSION: GENERAL FEATURES

Clinical Manifestations

Pulmonary hypertension is a final common hemodynamic consequence of multiple etiologies and diverse mechanisms. As noted earlier, most cases of pulmonary hypertension are secondary (Table 52-3). Among the underlying causes of pulmonary hypertension are mechanical compression and distortion of the resistance vessels of the lungs (e.g., by diffuse pulmonary fibrosis), hypoxic vasoconstriction (e.g., in severe obstructive airways or diffuse parenchymal diseases), intravascular obstruction (e.g., thromboemboli or tumor emboli), and combinations of mechanical and vasoconstrictive influences. The significance of pulmonary hypertension, however, is that if it is uncontrolled, it leads to RV failure. Once pulmonary arterial pressures reach systemic levels, RV failure becomes inevitable.

Table 52-3: Nomenclature and Classification of Pulmonary Hypertension

Diagnostic Classification
1. Pulmonary arterial hypertension
1.1 Primary pulmonary hypertension
(a) Sporadic
(b) Familial
1.2 Related to
(a) Collagen-vascular disease
(b) Congenital systemic to pulmonary shunts
(c) Portal hypertension
(d) HIV infection
(e) Drugs/toxins
(1) Anorexigens
(2) Other
(f) Persistent pulmonary hypertension of the newborn
(g) Other
2. Pulmonary venous hypertension
2.1 Left-side atrial or ventricular heart disease

- 2.2 Left-side valvular heart disease
- 2.3 Extrinsic compression of central pulmonary veins
  - (a) Fibrosing mediastinits
  - (b) Adenopathy/tumors
- 2.4 Pulmonary veno-occlusive disease
- 2.5 Other

3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Sleep-disordered breathing
- 3.4 Alveolar hypoventilatory disorders
- 3.5 Chronic exposure to high altitude
- 3.6 Neonatal lung disease
- 3.7 Alveolar-capillary dysplasia
- 3.8 Other

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

- 4.1 Thromboembolic obstruction of proximal pulmonary arteries
- 4.2 Obstruction of distal pulmonary arteries
  - (a) Pulmonary embolism (thrombus, tumor, ova and/or parasites, foreign material)
  - (b) In-situ thrombosis
  - (c) Sickle cell disease

5. Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature

- 5.1 Inflammatory
  - (a) Schistosomiasis
  - (b) Sarcoidosis
  - (c) Other
- 5.2 Pulmonary capillary hemangiomatosis

Special Studies

The "gold standard" for the diagnosis of pulmonary hypertension is right-sided heart catheterization. This technique enables the direct determination of right atrial and ventricular pressures, pulmonary arterial pressure, pulmonary wedge pressure (as an approximation of pulmonary venous pressure), pulmonary blood flow (cardiac output), and the responses of these parameters to interventions (vasodilators, oxygen, exercise). From the measurements and samples obtained during cardiac catheterization, pulmonary vascular resistance can be calculated (see Table 52-2). As a rule, noninvasive methods are less reliable and less informative.

CHEST RADIOGRAPHY

The findings on the chest radiograph depend on the duration of the pulmonary hypertension and the etiology. The characteristic findings of pulmonary hypertension are enlargement of the pulmonary trunk and hilar vessels in association with attenuation (pruning) of the peripheral pulmonary arterial tree (Fig. 52-1). Right-sided heart enlargement can be best detected radiographically on the lateral view as fullness in the retrosternal airspace. In secondary pulmonary hypertension, changes in the lungs (e.g., hyperinflation, fibrosis) and in the position of the heart and diaphragm often mask the radiologic changes of pulmonary hypertension. Contrast angiography has a role in the workup for pulmonary hypertension when chronic thromboembolic disease, which may be treated surgically, is suspected.[8]

THE ELECTROCARDIOGRAM

The electrocardiogram (ECG) can disclose hypertrophy of the right ventricle and is more reliable in respiratory disorders that do not involve the parenchyma of the lungs (e.g., alveolar hypoventilation and sleep apnea) than in obstructive airways disease or parenchymal lung disease.

ECHOCARDIOGRAPHY

The amount of reliable information obtained by Doppler and two-dimensional echocardiography depends greatly on the commitment of individual clinics to standardizing and perfecting these noninvasive techniques. In general, echocardiographic techniques have proved useful in providing a measure of RV thickness as an index of RV hypertension. In some clinics, reliable estimates of the level of pulmonary hypertension have been obtained by determining regurgitant flows across the tricuspid and pulmonic valves using continuous-wave Doppler echocardiography.[9] In patients in whom the pulmonic valve has been visualized, its behavior during the cardiac cycle also has been used to estimate the level of pulmonary arterial pressure. Probably one of the more rewarding applications of echocardiography has been as an alternative to repeated cardiac catheterization in tracing the course of the disease and in assessing the effects of therapeutic interventions (e.g., pulmonary vasodilators) in some patients (see also Chap. 13).

LUNG SCANS

Ventilation-perfusion scans are of most value in the diagnosis and exclusion of pulmonary thromboembolic disease (see below).

RADIONUCLIDE STUDIES

The response of the RV ejection fraction to exercise is assessed in some clinics using radionuclide angiography. Scintigraphy using thallium-201 also has been useful in detecting hypertrophy of the right ventricle due to pulmonary hypertension (see also Chap. 16).

LUNG BIOPSY

The sampling of lung tissue by open thoracotomy or thoracoscopy occasionally is helpful in identifying the etiology of the pulmonary hypertension, e.g., in the setting of suspected pulmonary vasculitis. However, the procedure carries substantial risk in these hemodynamically compromised individuals. Attempts to predict responsiveness to vasodilators on the basis of lung biopsy have met with limited success.[10]

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Chapter 52: PULMONARY HYPERTENSION

SECONDARY PULMONARY HYPERTENSION

Cardiac and/or respiratory diseases are the most common causes of secondary pulmonary hypertension. Pulmonary thromboembolic disease ranks third. Cardiac disease leads to pulmonary hypertension by increasing pulmonary blood flow (e.g., large left-to-right shunts) or by increasing pulmonary venous pressure (e.g., LV failure). Almost invariably, secondary influences such as intimal proliferation in the pulmonary resistance vessels add a component of obstructive pulmonary vascular disease.[11] In respiratory disease, the predominant mechanism for the pulmonary hypertension is an increase in resistance to pulmonary blood flow arising from perivascular parenchymal changes coupled with pulmonary vasoconstriction due to hypoxia. In pulmonary thromboembolic disease, clots in various stages of organization and affecting pulmonary vessels of different size increase resistance to blood flow.[11]

Cardiac Disease

The mechanisms of pulmonary hypertension usually are quite different in acquired disorders of the left side of the heart than in those of congenital heart disease.

ACQUIRED DISORDERS OF THE LEFT SIDE OF THE HEART

LV failure is the most common cause of pulmonary hypertension. Among the various etiologies, myocardial disorders and lesions of the mitral and aortic valves predominate. Both categories of lesions lead to an increase in pulmonary venous pressure that, in turn, evokes an increase in pulmonary arterial pressure. Presumably, the increase in pulmonary arterial pressure is reflex in origin. In time, three types of morphologic changes supervene: (1) occlusive intimal and medial changes not only in pulmonary venules and veins but also in the precapillary vessels, (2) perivascular interstitial edema and fibrosis that, under the influence of gravity, cause vascular and perivascular changes to be most marked in the dependent portions of the lungs, and (3) occlusion of small pulmonary vessels by emboli or thrombi when the right ventricle fails and cardiac output decreases. The medical management of myocardial failure is considered in Chap. 21. The treatment of congenital heart disease and of mitral valvular disease is usually mechanical (e.g., surgical or balloon mitral valvuloplasty). The prospect for relief of the pulmonary venous hypertension, such as by mitral valve commissurotomy or replacement, depends on the reversibility of the pulmonary vascular and perivascular lesions.

Although LV failure is the most common cause of RV failure, rarely is the level of pulmonary hypertension that accompanies LV failure sufficient to account for the RV failure. RV failure, secondary to LV failure, is usually attributed to failure of the muscle in the shared ventricular septum.

CONGENITAL HEART DISEASE

Pulmonary hypertension is part of the natural history of many types of congenital heart disease and is often a major determinant of the clinical course, the feasibility of surgical intervention, and the outcome (see Chaps. 63 and 64). Congenital defects of the heart associated with large left-to-right shunts (e.g., atrial septal defect) or abnormal communications between the great vessels

(e.g., patent ductus arteriosus) are commonly associated with pulmonary arterial hypertension. Pulmonary hypertension occurs in both "pretricuspid" congenital defects (e.g., secundum atrial septal defect) and "posttricuspid" congenital defects (e.g., ventricular septal defect). Important differences exist in the natural history of these two categories. Their differences are considered elsewhere in this book (see Chap. 70). The major cause of pulmonary hypertension in congenital heart disease is an increase in blood flow, an increase in resistance to blood flow, or most often, a combination of the two. In congenital heart disease with right-to-left shunting (systemic hypoxemia), pulmonary vasoconstriction adds to the resistance to blood flow. Erythrocytosis, acting by way of increased viscosity and propensity to thrombosis, also contributes to the increase in resistance. Although the increase in pulmonary vascular tone elicited by hypoxia contributes to the increase in pulmonary vascular resistance, the predominant resistance is offered by anatomic changes in the walls of the small muscular arteries and arterioles. Patients with congenital heart disease and pulmonary hypertension who become pregnant are at increased risk of sudden death both in the course of delivery and in the immediate postpartum period.

Depending on the nature of the congenital cardiac defect, vasodilators sometimes are helpful in diminishing heightened pulmonary vasomotor tone. Caution is required in administering such agents to patients with congenital heart disease because of the potential to increase right-to-left shunting by reducing systemic vascular resistance to a greater degree than its pulmonary counterpart. Phlebotomy, with replacement of fluid (e.g., plasma or albumin), is helpful in congenital cyanotic heart disease in which severe hypoxemia has evoked a large increase in red cell mass. Once again, caution is required to avoid depletion of iron stores and to avoid reduction in the circulating blood volume.

THROMBOEMBOLIC DISEASE

Thromboembolic disease is a form of occlusive pulmonary vascular disease. It may be acute or chronic. In the United States and Europe, clots originating in peripheral veins represent a common cause of chronic occlusive pulmonary vascular disease. Elsewhere in the world, other intravascular particulates may cause pulmonary vascular occlusive disease. For example, in Egypt, where schistosomiasis is endemic, pulmonary vascular disease stemming from ova lodged in pulmonary vessels and hypersensitivity reactions to the organism (usually situated outside the lungs) is not uncommon. In some parts of Asia, filariasis is reputed to be an important cause of pulmonary hypertension. Tumor emboli to the lungs from extrapulmonary sites (e.g., the breast) can cause pulmonary hypertension by invading the adjacent minute vessels of the lungs. Intravenous drug use may be associated with talc or cotton fiber embolism to the lungs, which can result in a granulomatous pulmonary arteritis.

The *syndromes of thromboembolic pulmonary hypertension* can be categorized according to the segments of the pulmonary arterial tree that are primarily affected: (1) small (muscular pulmonary arteries and arterioles), (2) intermediate, and (3) large central arteries. Some overlap among these categories is inevitable because clots lodged in large vessels are fragmented by the churning motion of the heart, and both the parent clot and its derivatives tend to move peripherally for final lodging.

Occlusion of Small Muscular Arteries and Arterioles by Organized Thrombi

At autopsy, small thrombi, predominantly recent in origin, are commonplace in the small pulmonary vessels of patients with pulmonary hypertension who have developed heart failure preterminally. In contrast is the syndrome of widespread pulmonary vascular occlusion by organized thrombi in the small pulmonary arteries and arterioles. Once attributed to multiple pulmonary emboli, these lesions are now regarded as organized, in situ thrombi.[12] The syndrome is rare and indistinguishable during life from primary pulmonary hypertension except by lung biopsy. Histologic identification of these lesions serves little purpose in management. After a

ventilation-perfusion scan has excluded chronic proximal thromboembolism (see below), treatment consists of long-term anticoagulation to prevent further clotting using warfarin or related agents, antiplatelet agents, or both.

Occlusion of Intermediate Pulmonary Arteries by Emboli

This syndrome is by far the most common of the three.[12] It is thought to be caused by multiple emboli released from vessels in the upper legs and thighs that progressively amputate the pulmonary arterial tree. Ventilation-perfusion scans and selective angiography demonstrate the pulmonary vascular occlusion, although both studies tend to underestimate the degree of obstruction compared with direct inspection of the vascular tree at surgery or postmortem (see Chap. 53). The major therapeutic concern in these patients is to exclude chronic proximal pulmonary thromboembolism (see below) and to prevent recurrent thromboemboli. Treatment involves the use of anticoagulants of the warfarin type and antiplatelet agents.

Chronic Proximal Pulmonary Thromboembolism

In some patients who have survived large to massive pulmonary emboli, resolution fails to occur, and the clots become organized and incorporated into the walls of the major pulmonary arteries, leading to pulmonary hypertension (Fig. 52-2). Overwhelming the capacity of the local fibrinolytic mechanisms also allows the clot to propagate, to obstruct large segments of the pulmonary vascular bed, and to decrease the compliance of the central pulmonary vessels. By the time the diagnosis is made, the obstructing lesions in the central pulmonary arteries have become an integral part of the vascular wall through the processes of endothelialization and recanalization.[12]

The importance of recognizing *proximal* pulmonary thromboembolism as a cause of pulmonary hypertension is the possibility of relieving the pulmonary hypertension by surgical intervention, i.e., by pulmonary thromboendarterectomy. Ventilation-perfusion lung scanning is the critical diagnostic test. As a rule, patients with proximal pulmonary thromboembolism show two or more segmental perfusion defects. If the perfusion defects are segmental or larger, selective pulmonary angiography is called for to define the location, extent, and number of pulmonary vascular occlusions.[13] [14] Cardiac catheterization for selective pulmonary angiography also enables hemodynamic assessment. Fiberoptic angioscopy, helical computed tomographic scanning, and magnetic resonance imaging may be helpful in defining the lesions of proximal thromboembolic pulmonary hypertension[15] (see also Chap. 53).

Surgery is advocated for patients with pulmonary hypertension who have persistent clot in lobar or more proximal pulmonary arteries after at least 6 months of anticoagulation. Thromboendarterectomy is done via a median sternotomy using deep hypothermic cardiopulmonary bypass with intermittent periods of circulatory arrest. Postoperatively, hemodynamic improvement is usually quite dramatic.[8,14] Reperfusion pulmonary edema can be a severe complication immediately after the obstruction has been relieved. In experienced hands, mortality is on the order of 5 percent. After the operation, patients are placed on lifelong anticoagulants. A filter is usually placed in the inferior vena cava to further prevent recurrence.

Respiratory Diseases and Disorders

In addition to intrinsic pulmonary diseases, disturbances in respiratory muscle function or in the control of breathing also can lead to pulmonary hypertension. Among the intrinsic lung diseases are those affecting the airways (e.g., chronic bronchitis) as well as those affecting the parenchyma (i.e., emphysema, pulmonary fibrosis). Among the ventilatory disorders are the syndromes of alveolar hypoventilation due to respiratory muscle weakness and sleep-disordered breathing.

INTRINSIC DISEASES OF THE LUNGS AND/OR AIRWAYS

Diseases that affect the parenchyma of the lungs or the tracheobronchial tree can elicit pulmonary hypertension in different ways depending on the underlying disease (Fig. 52-3). In obstructive airways disease, ventilation-perfusion abnormalities cause vasoconstriction due to arterial hypoxemia. In diffuse fibrosis, several mechanisms act in concert: Loss of vascular surface area due to lung destruction, loss of vascular compliance due to hyperinflation-induced vascular compression, and vascular remodeling due to hypoxic vasoconstriction all promote an increased pulmonary vascular resistance.

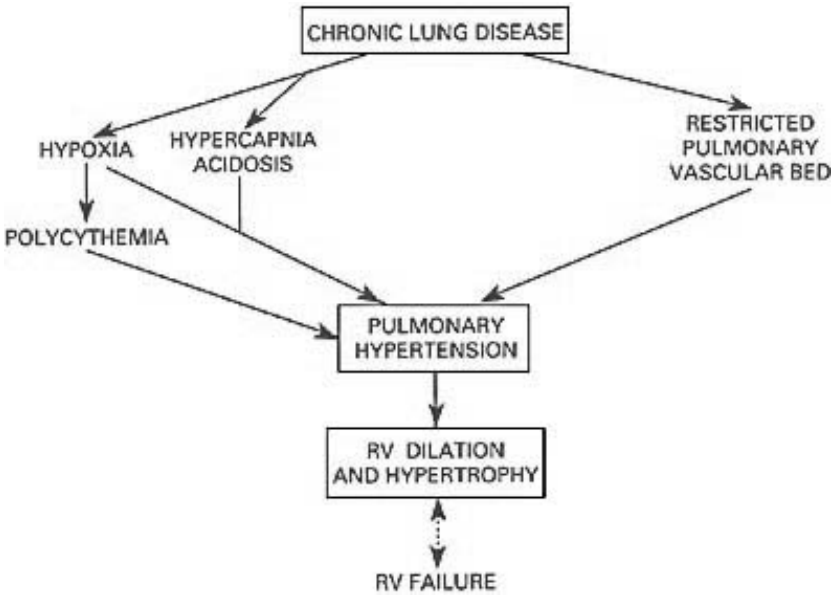

Figure 52-3: The evolution of RV failure in chronic obstructive airways disease (chronic bronchitis and emphysema; COPD). The factors on the left arise primarily from the bronchitis; those on the right from emphysema.

INTERSTITIAL FIBROSIS

Pulmonary sarcoidosis, asbestosis, and idiopathic and radiation-induced fibrosis are common causes of widespread pulmonary fibrosis that culminates in cor pulmonale. Dyspnea and tachypnea generally dominate the clinical picture of interstitial fibrosis; cough is rarely prominent. As a rule, severe pulmonary hypertension occurs toward the end of the illness, when hypoxemia and hypercapnia are present at rest (see Fig. 52-1). RV failure is a common sequel.

Systemically administered vasodilators have no proven place in dealing with the pulmonary hypertension associated with interstitial fibrosis and may worsen intrapulmonary gas exchange. Recent experience with inhaled vasodilators, such as the prostacyclin analogue iloprost, is encouraging and suggests the possibility of producing selective pulmonary vasodilator and/or antiproliferative effects in this population.[16] Oxygen therapy, particularly during daily activity or sleep, can be important in attenuating the hypoxic pulmonary pressor response. Glucocorticoids and other potent immunosuppressive agents are the mainstay of therapy and often effect some symptomatic relief. The advent of lung transplantation has widened greatly the therapeutic horizons for dealing with widespread interstitial fibrosis.

CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

Chronic bronchitis and emphysema [chronic obstructive pulmonary disease (COPD)] are the most common causes of cor pulmonale in patients with intrinsic pulmonary disease.[17,18] Cystic fibrosis is an example of a mixed airways and parenchymal lung disease in which pulmonary hypertension plays a significant role in outcome.

Cor pulmonale is encountered in two different settings: *acutely* in the setting of decompensation, which is often due to an acute respiratory infection, and *chronically* when progressive lung disease and worsening gas exchange lead to unremitting vascular remodeling.

The "gold standard" for diagnosing pulmonary hypertension in patients with COPD is right-sided heart catheterization. Noninvasive studies, such as echocardiography, have proved useful in some centers.[19,20] RV enlargement, the cardinal sign of pulmonary hypertension, can be difficult to discern in obstructive airways disease because of hyperinflation and cardiac rotation.[21] Once suspicion is raised that the clinical picture of RV failure stems from gas exchange abnormalities, an arterial blood sample will confirm that the P_{O_2} is low (P_{O_2} < 40-50 mmHg) and the P_{CO_2} is high (P_{CO_2} > 50 mmHg). Derangement in gas exchange to this degree is rare in LV failure unless overt pulmonary edema is present.

Electrocardiographic evidence of RV hypertrophy is also often equivocal in patients with chronic obstructive airways disease (chronic bronchitis and emphysema, COPD) because of rotation and displacement of the heart, widened distances between electrodes and the cardiac surface, and the predominance of right-sided heart dilatation over hypertrophy. Because of these limitations, it is not surprising that standard electrocardiographic criteria for RV enlargement apply in about only one-third of patients with COPD who prove to have cor pulmonale at autopsy. Consecutive changes in the ECG are often more useful than a single ECG in detecting RV overload. As the arterial P_{O_2} drops to abnormal levels (e.g., <60-70 mmHg while awake), T waves tend to become inverted, biphasic, or flat in the right, precordial leads (V_1 to V_3); the mean electrical axis of the QRS shifts 30° or more to the right of the patient's usual axis; ST segments become depressed in leads II, III, and aV_F; and right bundle-branch block (incomplete or complete) often appears. These changes tend to reverse as arterial oxygenation improves (see also Chap. 11).

In the patient with COPD with acute cor pulmonale precipitated by a bout of bronchitis or pneumonia, the goal of therapy is to maintain tolerable levels of arterial oxygenation while waiting for the upper respiratory infection to subside. Supplemental oxygen, such as 28% oxygen delivered by a Venturi mask, generally suffices to relieve arterial hypoxemia and to restore pulmonary arterial pressures to normal. Considerable improvement also may be accomplished even in the individual who has chronic pulmonary hypertension by sustained (>18 h/day) breathing of oxygen-enriched air.

Once the right ventricle has failed, inotropic agents should be used cautiously because of the threat of arrhythmias posed by arterial hypoxemia and respiratory acidosis. Moreover, after adequate oxygenation has been achieved, the need for digitalis and diuretics often decreases because the hemodynamic burden on the right ventricle decreases. Even though acute cor pulmonale is largely reversible, each bout appears to leave behind a slightly higher level of pulmonary hypertension after recovery.[17]

Arterial blood gas composition is the therapeutic compass to the control of pulmonary hypertension in COPD. The degree of hypoxia may be underestimated by blood sampling while the patient is awake and at rest, since hypoxemia is more marked during sleep and with physical activity. Determinations of the oxygen saturation during sleep or with ambulation using pulse oximetry are helpful in optimally prescribing supplemental oxygen.

Ensuring the return of arterial oxygenation toward normal is much more vital than is the administration of inotropic agents.[22] When respiratory infection has triggered the episode of pulmonary hypertension, a vital strategy for achieving a lasting improvement in arterial oxygenation is the administration of an appropriate antibiotic. While awaiting the salutary effects of antibiotic therapy, attention is paid to hydration, to postural drainage, and to adequate alveolar ventilation.

Phlebotomy, once popular because of the prospect that increased blood viscosity contributes importantly to the pulmonary hypertension, has fallen into disuse. Polycythemia is rarely severe enough to be a serious problem in cor pulmonale associated with bronchitis and emphysema, and when its is present, it is usually indicative of inadequate relief of hypoxemia with optimal use of supplemental oxygen.

Vasodilators recently have been tried in various types of secondary pulmonary hypertension, including that due to COPD.[23] The agents tried are the same as those outlined for *primary* pulmonary hypertension. They run the risk of aggravating arterial hypoxemia by exaggerating ventilation-perfusion abnormalities. Unfortunately, the efficacy of vasodilator agents in secondary pulmonary hypertension has proved to be far less impressive or predictable than in primary pulmonary hypertension. To date, the safest and most effective approach to pulmonary vasodilatation in obstructive lung disease with arterial hypoxemia is the use of supplemental oxygen.[23]

CONNECTIVE TISSUE DISEASES

Pulmonary vascular disease is an important component of certain connective tissue diseases. Among these, the more common are systemic lupus erythematosus (SLE), the scleroderma spectrum of diseases, and dermatomyositis.[24] The lesions may take the form of interstitial inflammation and fibrosis, obliterative disease, or vasculitis, either singly or in combination. Although pulmonary hypertension can complicate many connective tissue diseases, it has been documented most often in SLE and progressive systemic sclerosis (scleroderma) and its variant syndromes. The possibility has been raised that primary pulmonary hypertension is an inflammatory, or autoimmune, disease. This prospect has gained support from the occasional instances in which the lesions are confined to the pulmonary arterial tree without interstitial involvement and similarities in the histologic appearance of the vascular lesions. The high frequency of both collagen-vascular disease and primary pulmonary hypertension in women and the occurrence of Raynaud's phenomenon in up to 20 percent of patients with primary pulmonary hypertension has been used as additional evidence.[25] Finally, there is a high incidence of positive serologic tests for antibodies (ANA, anti-Ku), particularly in women with primary pulmonary hypertension. With respect to the pathogenesis of the two disorders, the idea has been raised that both the Raynaud's phenomenon and an increase in pulmonary vascular tone represent a widespread vasoconstrictive pulmonary-systemic disorder. However, this hypothesis has not gained universal support.

The lungs and pleura are frequently involved in SLE, with a reported frequency of up to 70 percent. Patients with pulmonary hypertension and SLE are predominantly women; most of these patients also exhibit Raynaud's phenomenon.

The histopathologic lesions in these patients resemble those of primary pulmonary hypertension. Pulmonary hypertension in these patients may originate in microthrombi secondary to the hypercoagulable state caused by lupus anticoagulant or anticardiolipin antibodies in the blood. Less likely is the hypothesis of generalized vasoconstriction noted earlier. Unfortunately, treatment of pulmonary hypertension associated with SLE using either anticoagulants or pulmonary vasodilators has had only modest success. This poor outcome contrasts with the results obtained in patients with active pulmonary vasculitis, who may either improve or stabilize their

vascular disease with immunosuppressive agents.

In progressive systemic sclerosis (scleroderma) and its variants, such as the CREST syndrome (*c*alcinosis, *R*aynaud's syndrome, *e*sophageal involvement, sclerodactyly, and *t*elangiectasia) and in overlap syndromes (e.g., mixed connective tissue disease), the incidence of pulmonary vascular disease is high. In these patients, pulmonary hypertension is the cause of considerable morbidity and mortality. In a prospective study involving cardiac catheterization of patients with progressive systemic sclerosis or the CREST syndrome variant, pulmonary hypertension, either as an isolated finding or in association with pulmonary parenchymal or cardiac disease, was found in up to one-third of patients with progressive systemic sclerosis and in up to one-half of patients with the CREST syndrome.[26] The pulmonary vascular disease may be independent of pulmonary or other visceral disease. As in the case of SLE, the pathology of these lesions is often indistinguishable from that of primary pulmonary hypertension. Vasodilator therapy has not proved to be highly effective; however, continuous intravenous epoprostenol recently has been shown to improve hemodynamics and exercise tolerance.[27]

ALVEOLAR HYPOVENTILATION IN PATIENTS WITH NORMAL LUNGS

In patients who hypoventilate despite normal lungs (alveolar hypoventilation), the primary pathogenetic mechanism is alveolar hypoxia potentiated by respiratory acidosis.[28] These abnormal alveolar and arterial blood gases play the same role in eliciting pulmonary hypertension in patients with alveolar hypoventilation as in those in whom the abnormal alveolar and blood gases are the result of ventilation-perfusion abnormalities. In individuals with normal lungs, the alveolar hypoventilation generally originates from an inadequate ventilatory drive (e.g., after encephalitis), covert obstruction of the upper airways (e.g., in the sleep apnea syndromes), an ineffective chest bellows (e.g., after poliomyelitis or polymyositis), or lungs entrapped by neoplasm or fibrosis (e.g., in trapped lung caused by asbestosis).

Regardless of etiology, whether pulmonary hypertension will occur in patients with alveolar hypoventilation and normal lungs depends on the whether there is sufficient alveolar and arterial hypoxia to raise pulmonary arterial pressures considerably. In the sleep apnea syndromes, severe arterial hypoxemia and pulmonary hypertension that develop initially only during sleep may become self-perpetuating and carry over into wakefulness, although this only occurs in those with severe disturbances in respiration during sleep.[29]

For the patient with alveolar hypoventilation with combined respiratory and cardiac (right ventricular) failure, the highest therapeutic priority is to improve oxygenation. Assisted ventilation, particularly during sleep, may be particularly helpful in improving oxygenation and reducing hypercapnia (e.g., continuous positive airway pressure) breathing. Pharmacologic therapy is rarely needed for patients with alveolar hypoventilation because of the efficiency of assisted ventilation coupled with oxygen therapy in promoting pulmonary vasodilatation.

PREVIOUS | NEXT

Chapter 52: PULMONARY HYPERTENSION

PRIMARY (UNEXPLAINED) PULMONARY HYPERTENSION

Definition

PPH is a disorder intrinsic to the pulmonary vascular bed that is characterized by sustained elevations in pulmonary artery pressure and vascular resistance that generally lead to RV failure and death.[25] The diagnosis of PPH requires the exclusion on clinical grounds of other conditions that can result in pulmonary artery hypertension[30] (see Table 52-3). PPH is a rare disease, with an incidence of 1 to 2 per million.[31] Its prevalence is about 0.1 to 0.2 percent of all patients who come to autopsy.

The clinical diagnosis of PPH rests on three different types of evidence: (1) clinical, radiographic, and electrocardiographic manifestations of pulmonary hypertension, (2) hemodynamic features consisting of abnormally high pulmonary arterial pressures and pulmonary vascular resistance in association with normal left-sided filling pressures and a normal or low cardiac output, and (3) exclusion of the causes of secondary pulmonary hypertension.

SPECIAL TYPES

Certain associations of PPH have attracted interest because of their prospects for shedding light on some etiologies. These include so-called anorexigen-induced pulmonary hypertension, familial pulmonary hypertension, human immunodeficiency virus (HIV) infection-associated pulmonary hypertension, and portal-pulmonary hypertension.[30-33] In each of these, the clinical findings and the histologic appearance of the lungs at autopsy are identical to those which characterize the sporadic form of PPH. This diversity in associations underscores the likelihood that so-called PPH is the final common expression of heterogeneous etiologies.

General Features

After puberty, females predominate, those between 10 and 40 years of age being most often affected. Before puberty, no sex difference is discernible. The textbook picture of a patient with PPH is that of a young woman in the prime of life who develops one or more of the symptoms in Table 52-1 without discernible cause. Sex and age are sometimes useful in distinguishing clinically between the likelihood of PPH and pulmonary thromboembolic disease. The latter generally favors men, particularly in their later years.[25]

As a rule, median survival of patients can be predicted on the basis of the New York Heart Association functional classification: 6 months for class IV, 2½ years for class III, and 6 years for classes I and II. Unless interrupted by sudden death, which occurs in approximately 15 percent of patients, the usual downhill course terminates in intractable RV failure.[34]

Etiology

The common denominator in the pathogenesis of PPH appears to be injury to the layers of the vascular wall of the small muscular pulmonary arteries and arterioles.[35] In response to injury, the

intima of these vessels proliferates so that the endothelium changes from a single flat layer to a piled-up projection that narrows the caliber of the vascular lumen. Along with intimal proliferation, the media of the affected vessels hypertrophy.[36]

The primary site of injury in PPH remains uncertain. Recent studies have implicated an intrinsic defect in ion channel function and calcium homeostasis in vascular smooth muscle,[37] whereas others have shown that endothelial function is disturbed, leading to altered production or handling of a variety of endothelial-derived vasoactive substances.[35] These abnormalities, coupled with altered platelet-endothelial interactions that predispose to intravascular thrombosis, lead to an inexorable course of enhanced vascular reactivity, proliferation and remodeling, and progressive obliterative vasculopathy. Diverse etiologies seem to be capable of eliciting PPH[38] (Table 52-4). For example, ingestion of the anorexigens fenfluramine and its isomer dexfenfluramine has been demonstrated to markedly increase the risk of PPH,[31] ingestion of toxic oil elicited an outbreak of pulmonary hypertension in Spain,[39] and HIV infection, even in the absence of the acquired immune deficiency syndrome, also has been implicated.[32]

Table 52-4: Suggested Mechanisms for Primary Pulmonary Hypertension

Proposed Mechanism	Evidence
Early/sustained vasoconstriction kinetics	Altered smooth muscle cell calcium
	Endothelial dysfunction
Genetic predicposition identified	Familial disease with gene locus
	?Susceptibility with exposures, e.g., anorexigens, HIV, portal hypertension
Pulmonary thrombosis/embolism arteries/arterioles	Widespread occlusion of ?Altered endothelial-platelet interaction
Autoimmune disease	Raynaud's phenomenon and antinuclear antibodies common, female gender predilection

For a long while, virtually all reports of PPH dealt with sporadic cases. An epidemic in Europe between 1967 and 1970 that was linked to the use of Aminorex, an anorectic agent, raised the prospect of hereditary predisposition, since only 1 in 1000 who took the drug developed pulmonary hypertension. More recently, the fenfluramines have been associated with both severe pulmonary hypertension and valvular heart disease.[31,40] The recent toxic oil epidemic in Spain has reinforced the concept of individual susceptibility to pulmonary vasotoxic agents.[39]

In recent years, an increasing number of patients have been identified in whom PPH is genetically linked.[41] In these individuals, the hereditary pattern is that of autosomal dominance with incomplete penetrance. The locus of the familial gene recently has been localized to the long arm of chromosome 2.[42] One major insight provided by the families with PPH is the diversity of pulmonary vascular lesions in members of the same family.[41]

Pathology

The evolution of PPH depends on progressive attenuation of the pulmonary arterial tree, which gradually increases pulmonary vascular resistance to the point of eliciting RV strain and failure. The seat of the disease is in the small pulmonary arteries (between 40 and 100 mm in diameter) and arterioles. The obliterative lesions can affect one or more layers of these vessels. In some instances, medial hypertrophy predominates; in others, it is the intima that proliferates. In addition, evidence of inflammation also may be present[36] (Fig. 52-4).

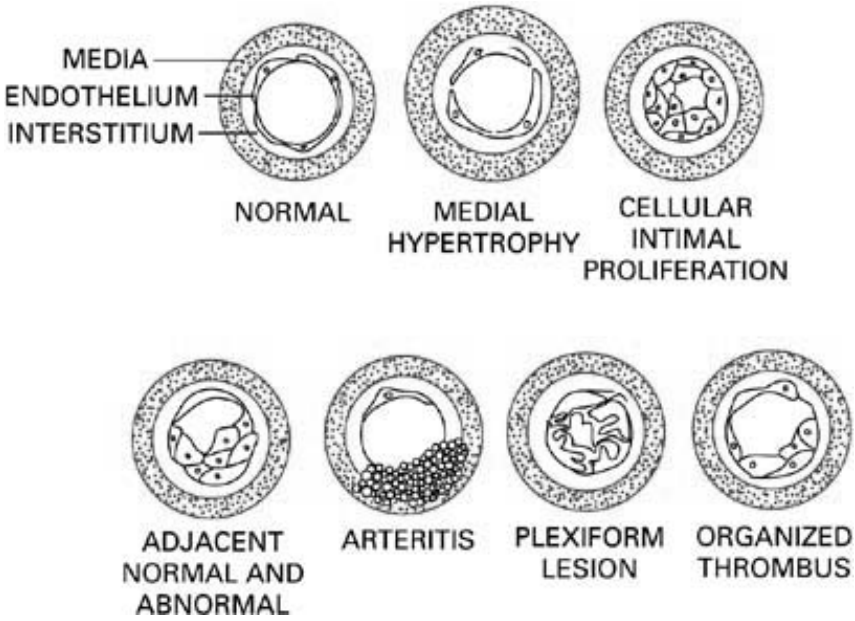

Figure 52-4: Vascular lesions in primary pulmonary hypertension. The plexiform lesion, once believed to be the histologic hallmark of primary pulmonary hypertension, has emerged as only one feature of a constellation of lesions.

Histologic examination of the lung identifies a constellation of pulmonary precapillary lesions that are consistent with the clinical diagnosis of PPH, i.e., plexiform lesions, angiomatoid lesions, concentric intimal fibrosis, and necrotizing arteritis. The pathologist is often hard-pressed to distinguish between organized clots in small vessels that initiate the pulmonary hypertension and those which result from the obliterative pulmonary vascular disease. Recent clots in small pulmonary arteries and arterioles are common at autopsy in patients with PPH, particularly when the right ventricle has failed and cardiac output falls. Although similar clots may not have initiated the pulmonary hypertension process in PPH, it seems reasonable that more often they are complicating features that aggravate and exaggerate pulmonary vascular obstruction.

Pathophysiology

The hemodynamic hallmarks of PPH in the resting patient were indicated earlier: a combination of a high pulmonary arterial pressure, a normal or low cardiac output, and a normal left atrial (pulmonary wedge) pressure. As a result of this hemodynamic pattern, calculated pulmonary vascular resistance is high, generally leading to the logical conclusion that the resistance vessels, i.e., the small muscular arteries and arterioles, are the predominant sites of vascular obstruction. During exercise, as cardiac output increases, pulmonary arterial pressures increase further; the increments in pressure in the pulmonary hypertensive circuit are much more striking than in the normotensive pulmonary circulation owing to the inability to dilate existing vasculature or recruit unused vessels to accommodate the rise in pulmonary blood flow.

Pulmonary vasodilators are currently administered acutely for testing the responsiveness of the pulmonary circulation.[30] Among these, inhaled NO and intravenous prostacyclin have become the "gold standards." Several clinical and hemodynamic changes are sought as desirable end points: (1) improvement in exercise tolerance and in the quality of life; the increase in physical capacity, attributable to an increase in cardiac output, in turn improves oxygen delivery to peripheral organs and tissues; (2) a decrease in the level of pulmonary arterial hypertension, with evidence of regression of RV hypertrophy or dilatation, or both; (3) a decrease in calculated pulmonary vascular resistance; optimally, this decrease should entail an increase in cardiac output (with minimal increase in heart rate) accompanied by a decrease in pulmonary arterial pressure; and (4) since pulmonary vasodilators are also systemic vasodilators, pulmonary vasodilatation has to be effected without evoking undue systemic hypotension and tachycardia.

The combination of right-sided heart catheterization and vasodilator testing is particularly useful not only for defining the hemodynamic state of the patient but also in providing a hemodynamic baseline for future invasive and noninvasive studies, such as serial echocardiograms.

Clinical Picture

In its early stages, the disease is difficult to recognize. In the sporadic case, the first clue is often an abnormal chest radiograph (see Fig. 52-1) or ECG indicative of RV hypertrophy (Fig. 52-5). Both are late manifestations. The existence of RV enlargement is generally confirmed by echocardiography. By the time these changes appear, however, pulmonary hypertension is moderate to severe. Initial complaints, particularly easy fatigability and dyspnea, tend to be discounted, i.e., attributed to being "out of shape," except when the index of suspicion is high, e.g., with a history of ingestion of anorectic agents or of familial pulmonary hypertension (see Table 52-1).

When the disease is advanced, the activities of daily life are progressively circumscribed by increasing nonspecific discomfort. Dyspnea, particularly during physical activity, becomes incapacitating. Some patients develop an angina type of chest pain along with breathlessness. Other common symptoms are weakness, fatigue, and exertional or postexertional syncope (see Table 52-1). Infrequently, an enlarged pulmonary artery causes hoarseness because of compression of the left recurrent laryngeal nerve. In time, right-sided heart failure develops.

Patients with severe pulmonary hypertension seem prone to sudden death. Death has occurred unexpectedly during normal activities, cardiac catheterization, and surgical procedures and after the administration of barbiturates or anesthetic agents. The mechanisms for sudden death are not clear and may include arrhythmias or acute pulmonary thromboembolism. In a few instances, severe bradycardia and atrioventricular (AV) dissociation have preceded cardiac arrest.

It was noted earlier that as far as clinical manifestations and physical examination are concerned, PPH has an advantage over secondary pulmonary hypertension in that its manifestations are not obscured by those of underlying cardiac or respiratory disease. On physical examination, the jugular venous pulse usually shows a prominent *a* wave. RV hypertrophy causes a heave along the left sternal border, and a distinct systolic impulse is palpable over the region of the main pulmonary artery (see Chap. 10). The pulmonic component of the second sound is markedly accentuated, the second heart sound is narrowly split, and an ejection click is heard in the pulmonic area. Often a fourth heart sound emanating from the hypertrophied right ventricle is heard at the lower left sternal border. The murmur of tricuspid regurgitation is best heard along the sternal border with the patient in the supine position and can be accentuated with inspiration. In some patients, a midsystolic murmur is audible at the pulmonic area; as pulmonary arterial pressures approximate systemic arterial levels, the murmur of pulmonary valvular regurgitation often appears (see also Chap. 10).

The onset of RV failure is accompanied by jugular venous distention and a gallop (S_3); inspiration intensifies the gallop. The liver becomes enlarged and tender, and hepatojugular reflux can be elicited. Hydrothorax and ascites are seen as RV failure progresses.

Special Studies

Direct determination of pulmonary circulatory pressures by right-sided heart catheterization is the only way to definitively establish the diagnosis of pulmonary hypertension; however, other studies that are less direct can strongly suggest that it is present. Since the diagnosis of "primary" is one of exclusion, a number of tests are undertaken, usually in the hope of identifying a more treatable disease than PPH.[38]

CHEST RADIOGRAPHY AND ELECTROCARDIOGRAPHY

In the early stages, the chest radiograph is generally normal. Later it shows cardiac enlargement in association with enlargement of the pulmonary trunk, while the peripheral pulmonary arterial branches are attenuated; the lung fields appear oligemic (see Fig. 52-1). Although fullness of the central pulmonary arterial trunks and peripheral "pruning" are distinctive, appearances vary somewhat from patient to patient in accord with the level and pace of the pulmonary hypertension and the age of the patient. Radiographic evidence of RV enlargement usually becomes overt only late in the course of the pulmonary hypertension. The ECG almost always shows right axis deviation, RV hypertrophy, and, usually, right atrial enlargement (see Chap. 11).

THE ECHOCARDIOGRAM

Two-dimensional echocardiography confirms the enlargement and hypertrophy of the right atrium and ventricle, tricuspid regurgitation, and pulmonic valvular regurgitation. At the same time, LV structure and function are normal. The magnitude of the velocity of the tricuspid regurgitant jet using Doppler techniques can provide a noninvasive estimate of RV peak systolic pressure. The determination of RV ejection fraction using radionuclide techniques can be helpful in evaluating the extent to which the excessive RV afterload has compromised the right ventricle. This applies not only to PPH but also to other disorders that lead to severe pulmonary hypertension (e.g., COPD and congenital heart disease) (see also Chap. 14).

Lung Scans

Lung scans are particularly helpful in suggesting the possibility of large, long-standing organized clots in the major pulmonary arteries that may be amenable to surgical removal (thromboendarterectomy). The lung scan in PPH fails to disclose major perfusion defects. Angiography is done to exclude pulmonary emboli in cases where the scan is equivocal. Scanning over the brain or kidneys may disclose the presence of an intracardiac or intrapulmonary right-to-left shunt.

RIGHT-SIDED HEART CATHETERIZATION

Cardiac catheterization is invaluable in quantifying the hemodynamic abnormalities, in excluding cardiac causes of pulmonary arterial hypertension, and in assessing the hemodynamic responses of the heart and pulmonary circulation to vasodilator agents.[4]

Diagnosis

The diagnosis of PPH rests on two pillars: (1) the detection of pulmonary hypertension and (2) the exclusion of known causes of high pulmonary arterial pressure. The history is of utmost importance. Before categorizing pulmonary hypertension as "primary" or "unexplained," due regard must be paid to the exclusion of known etiologies (see Table 52-3), particularly thromboembolic disease and connective tissue disorders. Account also should be taken of the likelihood of familial disease. Pulmonary function tests are useful in excluding diffuse pulmonary disorders, particularly interstitial fibrosis and granuloma. Serologic testing can point the way to covert connective tissue disorders. Abnormal liver function tests can signal the coexistence of portal and pulmonary hypertension. The value of cardiac catheterization in eliminating acquired or congenital heart disease was indicated earlier. Unfortunately, by the time pulmonary hypertension complicating heart disease is recognized, the anatomic lesions often are too far advanced for the obliterative pulmonary vascular disease to be reversible. One notable exception is the dramatic improvement that often follows surgical removal of organized clots from the walls of major pulmonary arteries.

Treatment

For the past few decades, treatment of PPH has repeatedly turned to the use of vasodilators in the hope that an increase in pulmonary vascular tone contributed importantly to the high pulmonary arterial pressures. Although the bulk of the pulmonary vascular obstruction was clearly anatomic, vasodilators offered the prospect not only of decreasing pulmonary arterial pressures somewhat, and therefore the hemodynamic burden on the right ventricle, but also of prompting reversibility of the anatomic lesions, such as muscular hypertrophy, that resulted simply from the high pulmonary arterial pressures. Unfortunately, the use of vasodilators, which could affect the systemic as well as the pulmonary circulation and which often were accompanied by undesirable side effects, led to progressive disenchantment with one agent after another.

The situation has changed considerably during the past decade. The introduction of acute vasodilator testing for responsiveness helped to confirm the idea that in about one-third of patients, heightened pulmonary vasomotor tone helped to sustain the pulmonary hypertension. An optimal "responder" to acute testing manifested an increase in cardiac output along with a decrease in pulmonary arterial pressure and in pulmonary vascular resistance without affecting systemic arterial pressure unduly. Improvement in exercise tolerance accompanied the increase in cardiac output. Another landmark was the introduction of calcium channel blocking agents that could be taken orally, and in general, those who were highly responsive during acute testing could be maintained at lower pulmonary arterial pressures by these agents. A third insight was that even patients who failed to satisfy the criteria for a good hemodynamic response to acute vasodilator testing might respond to continuous infusion of epoprostenol. Indeed, a substantial number of such patients have been treated in this way for years, and even more have used continuous intravenous epoprostenol as a transition to transplantation of the lung or lungs or of heart and lungs. During this evolution, heart-lung and then lung transplantation became increasingly feasible and available, although the donor supply is still a limiting factor.

As a result of these advances, a patient with PPH has several therapeutic options, ranging from oral calcium channel blocking agents to continuous infusion of prostacyclin to lung transplantation. However, none of these modalities is free of complications. The oral calcium channel blocking agents generally have to be administered in large doses that are often accompanied by undesirable side effects.[43] The continuous infusion of a vasodilator, such as prostacyclin, runs the risks not only of a permanently placed intravenous catheter but also of drug-related side effects that can preclude dose increases.[44,45] Transplantation offers the substitution of immunosuppression and its attendant risk of infection as a better option than chronic cor pulmonale and RV failure.[46] Despite the limitations of each of these therapeutic modalities, together they provide a graduated therapeutic approach that has provided, at each stage, a better quality of life for many individuals with PPH. Moreover, they have prompted the search for

agents that can be used in place of prostacyclin, which, until now, has required intravenous infusion; prostacyclin analogues that are delivered subcutaneously and by aerosol are currently under investigation. Other novel approaches include chronic ambulatory NO, which can be administered by inhalation.

VASODILATOR AGENTS

Various agents have been tried over the years as pulmonary vasodilators. These include α-adrenergic antagonists, β-adrenergic agonists, diazoxide, hydralazine, nitrates, and angiotensin-converting enzyme inhibitors. In general, these have not withstood the test of time. Experience has taught that untoward reactions can occur with any pulmonary vasodilator, even when low doses are used. Three categories of agents continue to hold promise, however: calcium channel blocking agents, arachidonic acid metabolites, and NO.

DRUGS THAT BLOCK CALCIUM TRANSPORT

The designation *calcium channel blocker* refers to a heterogeneous group of agents of different structural, pharmacologic, and electrophysiologic properties. The agents in this category currently receiving the most clinical attention as potential pulmonary vasodilators are nifedipine and diltiazem. Of the two, nifedipine is the more popular. Verapamil generally is not used because of its undesirable negative inotropic effect.

Nifedipine

Note that this use is not listed in the manufacturer's directive. Nifedipine is a synthetic agent that is unrelated to other vasoactive or cardiotonic drugs. It is a potent systemic vasodilator that is used for the treatment of coronary vasospasm. Although it has significant direct negative inotropic effects, these are usually not prominent clinically because of the reflex sympathetic stimulation of the heart; it does not possess antiarrhythmic properties. It is now the preferred agent for therapy of patients who manifest acute vasoreactivity when tested with short-acting agents under hemodynamic monitoring.

Sustained-release preparations are used, with the dosage generally titrated to the maximal tolerable level based on avoiding untoward systemic effects, i.e., hypotension, headache, dizziness, and flushing. Considerable caution is necessary in administering the higher dosages, however, because side effects can occur precipitously and be life-threatening. In one study, 64 patients with PPH were treated acutely with high doses of calcium channel blockers. Seventeen patients responded to treatment with nifedipine (13 patients) or diltiazem (4 patients) and were alive after 5 years.[46]

In experienced centers, the trial of nifedipine or diltiazem orally is preceded by use of testing of acute vasoreactivity using one or more of three agents: (1) inhaled NO, in concentrations of 10 to 40 ppm for 5 to 10 min, (2) prostacyclin (PGI_2, Epoprostenol, Flolan), administered intravenously in increasing doses (starting dose of 1-2 ng/kg/min followed by successive increments every 15 min of 2 ng/kg/min until a maximal dose of 12 ng/kg/min is reached or until side effects preclude further increases), and (3) adenosine (50-200 ng/kg/min). Only patients who manifest significant reductions in pulmonary vascular resistance (usually >20-30 percent), resulting from a fall in pulmonary artery pressure without systemic hypotension and accompanied by an unchanged or increased cardiac output, are considered candidates for chronic therapy with oral calcium channel antagonists.

Arachidonic Acid Metabolites

Epoprostenol (Flolan, prostacyclin, PGI_2), a metabolite of arachidonic acid, and its analogues continue to be a major focus of attention as treatments for a variety of forms of pulmonary hypertension. The pulmonary endothelium elaborates prostacyclin into the bloodstream, where it has a short biologic half-life, i.e., 2 to 3 min. In principle, it is attractive for the treatment of pulmonary hypertension on several accounts: (1) it is a pulmonary vasodilator, (2) it inhibits platelet aggregation, and (3) it inhibits proliferation of vascular smooth muscle. Unfortunately, it suffers the disadvantage of requiring continuous intravenous infusion, which is currently being done using portable pumps.[44,45] Analogues that can be given orally, subcutaneously, or by the inhaled route are under investigation. Success in long-term management recently has been reported using aerosolized iloprost, a stable prostacyclin analogue.[16,47] Currently, its most effective use is for long-term management in patients with severe (NYHA classes III or IV) primary pulmonary hypertension who are unresponsive to or are not candidates for therapy with calcium channel blockers.[44,45,48]

Nitric Oxide

NO is synthesized in endothelial cells from one of the guanidine nitrogens of L-arginine by the enzyme NO synthase. It has proved to be the endothelial-derived relaxing factor that contributes to the low initial tone of the pulmonary circulation. It has the advantage of other vasodilators of selectively relaxing pulmonary vessels without affecting systemic arterial pressure. It is currently being used as a test of vasoreactivity in a wide variety of pulmonary hypertensive states including PPH and also has been used to control pulmonary hypertension in the syndrome of persistent pulmonary hypertension in the newborn.[49, 50-51]

Anticoagulants

Since 1984, when Fuster et al.[52] in a nonrandomized clinical trial showed that long-term survival was improved in patients with PPH by anticoagulant therapy (warfarin in low doses), the use of anticoagulants has been incorporated into the therapeutic regimen in patients with PPH. This practice is supported by the high incidence of antemortem clots found at autopsy in the small pulmonary arteries and arterioles of patients with PPH. Moreover, in a recent trial that separated "responders" from "nonresponders" to calcium channel blockers, survival was significantly better in those given warfarin than in those who were not anticoagulated.[43] The advent of RV failure increases the propensity for clotting in the pulmonary circulation. The usual goal of anticoagulation is to achieve and maintain an INR of 2 to 2.5.[53]

ATRIAL SEPTOSTOMY

Blade-balloon atrial septostomy has been performed in patients with severe RV pressure and volume overload refractory to maximal medical therapy.[54] The goal of this approach is to decompress the overloaded right heart and improve systemic output of the underfilled left ventricle. Improvements in exercise function and signs of severe right-sided heart dysfunction such as syncope and ascites have been observed. Since the creation of an interatrial communication will result in an increased venous admixture, worsening hypoxemia is an expected outcome. The size of the septostomy that is created should be monitored carefully to achieve the ideal balance of optimizing systemic oxygen transport and reducing right-sided heart filling pressures without overfilling a noncompliant left ventricle or producing extreme degrees of venous admixture.

LUNG TRANSPLANTATION

Only one-third of patients with PPH are responsive to long-term oral vasodilator therapy. Of the

remainder, approximately 65 to 75 percent maintain sustained clinical improvement with long-term continuous intravenous therapy using prostacyclin. When pulmonary hypertensive disease has progressed, or threatens to progress, to the stage of RV failure, the physician and patient are left with few therapeutic options other than lung transplantation. Lung transplantation is currently being done at specialized centers and is almost invariably handicapped by a shortage of donor lungs, which can lead to long delays. Single- or double-lung transplantation has largely replaced heart-lung transplantation. Often, hemodynamic improvement is dramatic,[55] but transplantation for PPH poses not only a considerable surgical risk but also the prospect of opportunistic infections that accompanies lifelong immunosuppression.[56] Rejection phenomena, notably bronchiolitis obliterans, are the major limiting factor to prolonged survival. The median survival after lung transplantation is approximately 3 years.[46] Recurrence of PPH after transplantation has not been reported.

Prognosis

The diagnosis of PPH carries with it a poor prognosis unless medical or surgical therapy succeeds in decreasing pulmonary vascular resistance. Although death usually occurs within a few years after the onset of symptoms, instances of long-term survival do occur. Although sudden death accounts for 10 to 15 percent of all PPH-related deaths, the prognosis is largely determined by the severity of pulmonary hypertension and right-sided heart dysfunction.[34]

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Chapter 52: PULMONARY HYPERTENSION

PULMONARY VENO-OCCLUSIVE DISEASE AND PULMONARY CAPILLARY HEMANGIOMATOSIS

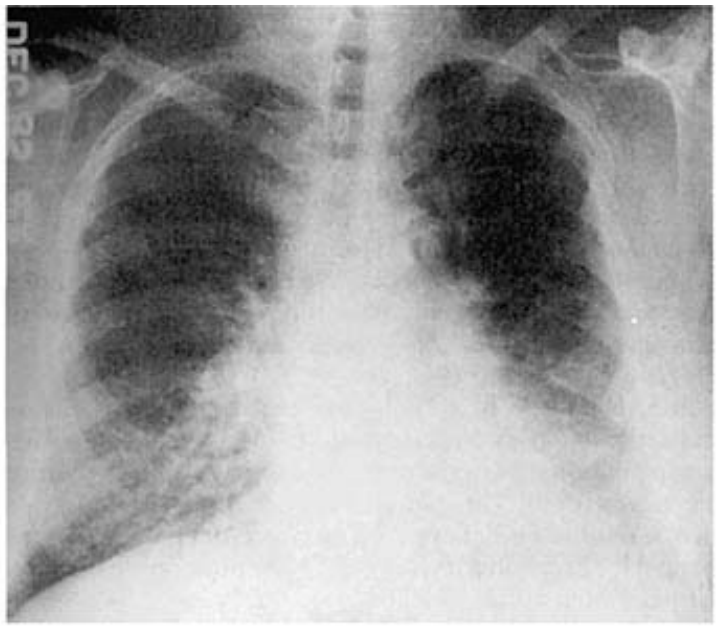
These are the least common of all types of unexplained pulmonary hypertension. Not infrequently, the patient is thought to have primary pulmonary hypertension until manifestations inconsistent with pulmonary precapillary disease, such as pulmonary congestion and edema or severe hypoxemia, redirect attention to the vascular bed distal to the arterioles, i.e., the capillaries, pulmonary small veins, and venules. The pathogenetic mechanism of POVD is unknown but may begin as an inflammatory-thrombotic process in the small pulmonary veins and venules and ends in fibrous obliteration of the venous and venular lumens. Presumably as a secondary phenomenon, the distal pulmonary arterial tree also develops obstructive lesions that are generally proliferative ("reactive") rather than inflammatory in nature; the intervening capillary bed is generally normal. The pulmonary veno-occlusive lesions have been attributed to an inflammatory response to vascular injury, followed by thrombosis and scarring. Among the postulated etiologies (based on exceedingly sparse evidence) are viral illness, chemotherapy, toxins, autoimmune disease, and mediastinal fibrosis.[36]

Both POVD and capillary hemangiomatosis can be familial. When the pulmonary hypertension is suspected of originating distal to the pulmonary capillary bed, mitral valve disease, myocardial dysfunction, or even left atrial myxoma has a greater likelihood of being the cause than does POVD.

Clinical Picture

Predominantly children and young adults are affected, but the age has ranged from infancy to 48 years. Clinical suspicion of this disorder generally arises when a patient with congested and edematous lungs proves to have a normal mitral valve and left ventricle.

The cardinal signs are dyspnea and fatigue on exertion in conjunction with evidence of pulmonary hypertension; the pulmonary venous rather than pulmonary arterial etiology is suggested by radiologic evidence of postcapillary pulmonary hypertension without evidence of involvement of the left side of the heart (Fig. 52-6*A*). Pleural effusions are common. Cyanosis, syncope, hemoptysis, and finger clubbing have been inconsistent findings. Moderate to severe hypoxemia, due to intrapulmonary shunting through the abnormal capillary network, is a hallmark of capillary hemangiomatosis. Rarely, systemic embolization may occur.



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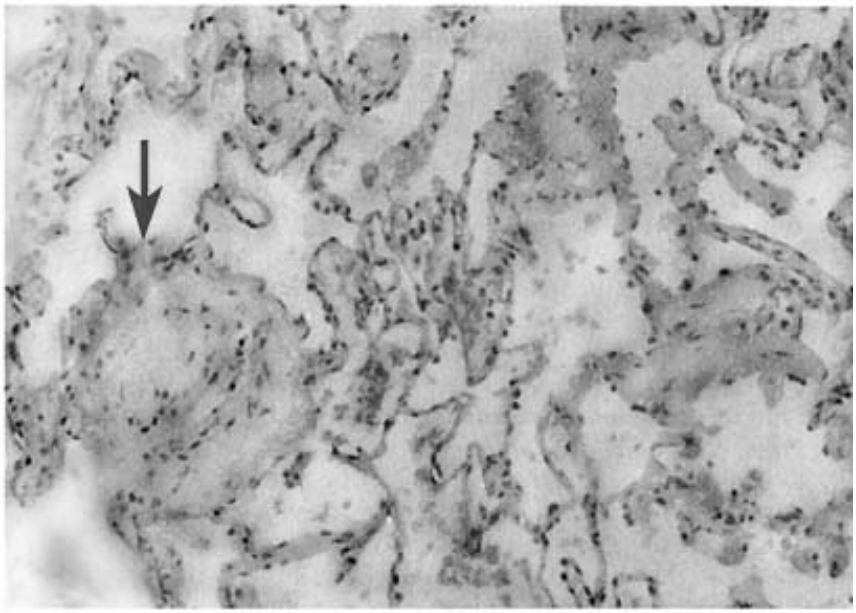

B

Figure 52-6: POVD proven by open lung biopsy. *A*. Chest radiography. Pulmonary interstitial edema is marked at both bases. *B*. Lung biopsy. In addition to obliterative pulmonary venular disease, the pulmonary arterioles (*arrow*) showed intimal proliferation and medical hypertrophy. (Courtesy of Dr. G. G. Pietra.)

Hemodynamics

Cardiac catheterization discloses a high pulmonary arterial pressure with a normal pulmonary wedge (and LV end-diastolic) pressure. The low wedge pressure has been attributed to discontinuities and channels of high resistance between the pulmonary capillaries and the pulmonary and bronchial venous channels so that wedging interrupts all sources of flow distal to the area blocked by the catheter.[30] When epoprostenol is administered to a patient with POVD, an acute pulmonary edema pattern may ensue, resulting from increasing pulmonary blood flow in the face of downstream vascular obstruction.[48,57] Although not universally present, this response is virtually diagnostic of POVD. Patients with capillary hemangiomatosis may experience worsening

hypoxemia with epoprostenol, attributable to increased shunting through the low-resistance capillary meshwork.

Pathology

Few lung biopsies have been done during life. At autopsy, both lungs are involved. The lungs are the seat of congestion, edema, and focal fibrosis, which may become extensive. The venous lesions may be more marked in one region than in another. Although the small pulmonary arteries as well as the small pulmonary veins are affected, the lesions are different (see Fig. 52-6*B*). Most striking are the morphologic changes in the pulmonary veins and venules, which are narrowed or occluded by intimal proliferation and fibrosis; up to 95 percent of the veins and venules may be affected in this way, but complete occlusion is uncommon. Bronchial veins and bronchopulmonary anastomoses share in the occlusive process. Hypertrophy in the walls of the pulmonary arteries may be quite striking. POVD, to varying degrees, also may coexist with capillary hemangiomatosis. Thrombi in the pulmonary arteries are common.[36]

Treatment

Medical management has been disappointing, since the lesions generally are irreversible. An occasional patient has been reported to do well with medical therapy,[58] although most experienced clinicians consider both POVD and capillary hemangiomatosis to be contraindications to the use of oral vasodilators or intravenous epoprostenol. The usual duration after recognition ranges from a few weeks in infants to several years in adults, with 7 years being the maximum. The treatment of choice is probably lung transplantation.

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Part 8: PULMONARY HYPERTENSION AND PULMONARY DISEASE
Chapter 53:

PULMONARY EMBOLISM

Author: Victor F. Tapson

Approximately 100,000 patients in the United States die each year directly due to acute pulmonary embolism (PE), with another 100,000 deaths occurring in patients with concomitant disease in whom PE contributes significantly to the demise of the patient.[1,2] A substantial number of patients die from PE prior to being diagnosed. Many of these deaths appear to be preventable. Autopsy studies have repeatedly documented the high frequency with which PE has gone unsuspected and undetected.[3] Despite advances in diagnostic technology and therapeutic approaches, PE remains underdiagnosed and prophylaxis continues to be dramatically underutilized. Pulmonary embolism nearly always results from deep venous thrombosis (DVT) of the proximal deep veins of the legs, that is, including the popliteal veins, and their vicinity, although axillary and subclavian vein thrombi may also embolize. Venous thromboembolism (VTE) represents the clinical spectrum of DVT and PE and occurs extraordinarily commonly in hospitalized patients, particularly after major surgery.

Because DVT and PE are so commonly clinically unsuspected, considerable diagnostic and therapeutic delays result and substantial morbidity and mortality are the ultimate consequence. The risk factors for DVT are discussed below, followed by the pathophysiology of acute PE. Because of the potential overlap with regard to the diagnostic approach to suspected DVT and PE, these are discussed in the same section. The principles of management of DVT and PE are addressed. Finally, the less common entity of chronic thromboembolic pulmonary hypertension is reviewed.

ACUTE DEEP VENOUS THROMBOSIS: RISK FACTORS AND PATHOGENESIS

Virchow proposed that the pathogenesis of DVT was based upon several potential initiating events, including stasis, venous injury, and hypercoagulability. Risk factors for DVT are based upon these processes (Table 53-1). Thrombosis may develop within the lumen of any vein as well as in the right side of the heart. Extensive investigation has been undertaken of the veins of the lower extremities, since most significant PE originate from this location. Although thrombi may form at any point along the vein wall, most originate in valve pockets. The veins of the calf are the most common site of origin, with subsequent extension of the clot prior to embolization.[4] If the clot does propagate, it usually remains attached at its base and floats in the vein more proximally. Eventually, it may expand to fill the vessel entirely, with both retrograde and further proximal extension. If embolization does not occur, the thrombosis can partially or completely resolve via three mechanisms, which include recanalization, organization, and lysis. Fatal PE is the most feared complication of DVT. Chronic thrombophlebitis with recurrent pain and swelling can be incapacitating. Frequently more than one risk factor for venous thrombosis is present and knowledge of these risk factors provides the rationale for both prophylaxis and clinical suspicion.

Table 53-1: Risk Factors for Venous Thromboembolism

Acquired factors
Age greater than 40
Prior history of venous thromboembolism
Prior major surgical procedure
Trauma
Hip fracture
Immobilization/paralysis
Venous stasis
Varicose veins
Congestive heart failure
Myocardial infarction
Obesity
Pregnancy/postpartum period
Oral contraceptive therapy
Cerebrovascular accident
Malignancy
Severe thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Antiphospholipid antibody syndrome (including lupus anticoagulant)
Inherited factors
Antithrombin III deficiency
Factor V Leiden (activated protein C resistance)
Prothrombin gene (G20210A) defect
Protein C deficiency
Protein S deficiency
Dysfibrinogenemia
Disorders of plasminogen
Hyperhomocysteinemia

Acquired Risk Factors

Most venous thrombi arise in venous valves, where blood flow tends to stagnate. The increased frequency of thrombosis with advanced age and immobilization further emphasizes the importance of stasis in thrombogenesis. Immobility, regardless of the cause, discourages venous return and contributes to stasis. Acute paraplegia significantly increases the risk of DVT (particularly in the paralyzed limb), and the period of highest risk appears to be the first 2 weeks after the onset of the paralysis.[5] Prolonged bed rest or long automobile or airplane trips may be the only obvious risk factors in patients developing thromboemboli. Obesity also appears to increase the risk of VTE. Information extrapolated from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) suggests that the relationship of obesity and VTE are not entirely understood and that further clarification would be useful.[6] Although obesity is commonly believed to be a significant risk, it is likely that immobility and stasis are contributing factors. Age appears to increase mortality due to PE,[7] and it appears that PE is suspected less commonly prior to death in the elderly patient.[8] The risk of VTE is particularly high in those of the elderly with concomitant cardiac disease or cancer.

Antecedent pulmonary thromboembolism forecasts an appreciable risk of recurrence in the hospitalized patient. Surgical patients with a previous history of VTE who do not receive prophylaxis develop postoperative DVT in more than 50 percent of cases.[9] Surgery itself significantly enhances the risk. Even surgery patients without significant additional risk factors develop venography-proven DVT in nearly 20 percent of cases if neither pharmacologic nor mechanical prophylaxis is applied.[10] Prophylactic anticoagulation is initiated either prior to surgery or shortly thereafter to prevent the development of intraoperative and early postoperative thrombosis. Total hip and total knee replacement patients not receiving prophylaxis develop DVT in more than 50 percent of cases.[11] These orthopedic settings have been comprehensively investigated, prompted by the increasing use of low-molecular-weight heparin (LMWH). Spinal or pelvic surgery place patients at particularly high risk for VTE.

Trauma, particularly of the lower extremities and pelvis, heightens the risk of DVT. Pulmonary embolism has been identified at autopsy in as many as 60 percent of patients with lower extremity fractures,[12] and mortality has been attributed to PE in as many as 50 percent of patients dying after hip fracture.[13] The incidence of VTE increases with time after the traumatic event. Autopsy-confirmed PE in patients surviving for less than 24 h after trauma has been demonstrated in 3.3 percent, increasing to 5.5 percent in those surviving up to 7 days. Pulmonary emboli occurred in 18.6 percent of those surviving for a longer period.[14] Venous catheters (particularly in the jugular, subclavian, or femoral veins) traumatize veins as well as serving as potential nidi for thrombosis. Associated cancer or immobility is often present in these individuals. Symptomatic PE can originate from catheter-induced (or non-catheter-induced) upper extremity thrombi, although this appears much less commonly than when the leg or pelvic veins are the source. Upper extremity (axillary-subclavian) thrombosis may also occur due to the effort-induced syndrome described by Paget-Schroetter.[15]

Recent epidemiologic analyses as well as autopsy data suggest that patients with cardiac and malignant disease are particularly predisposed to VTE.[7,16] Although myocardial infarction without anticoagulation has been associated with a significant incidence of DVT, more recent therapeutic strategies have had a beneficial impact.[17] Several of the large, multicenter, placebo-controlled acute myocardial infarction trials have indicated that the use of thrombolytic therapy has reduced the incidence of VTE.[18,19]

Malignancies clearly augment the risk of VTE, although the precise pathogenesis of

thromboembolism in cancer is not well understood.[16] It is clear, however, that numerous mechanisms-including intrinsic tumor procoagulant activity and extrinsic factors such as chemotherapeutic agents and indwelling access catheters-contribute to this process. The thrombophilic tendency associated with cancer is often amplified by weakness and reduced ambulation with venous stasis. A recent analysis, based upon data from the PIOPED trial, revealed that of 399 patients with PE, 73 (18.3 percent) had cancer.[7] Pancreatic, lung, gastric, genitourinary tract, and breast malignancies are associated with a particularly high risk of DVT and PE. It appears that about half of all cancer patients and about 90 percent of those with metastases exhibit abnormalities of one or more coagulation parameter. The most common abnormalities include elevation of clotting factor levels (fibrinogen, factors V, VIII, IX, and XI), fibrinogen and fibrin degradation products, and thrombocytosis.[16]

Most tumor cells produce both tissue factor and cancer procoagulant.[16,20] Tissue factor appears to be the primary coagulant factor implicated in promoting fibrin deposition and is expressed in situ as well as in isolated cells of numerous cancers.[21] Tumor cell expression of tissue factor also promotes metastatic dissemination.[21] Cancer procoagulant is a cysteine protease that activates factor X. Mucin, a glycoprotein produced by certain tumors, possesses a sialic acid moiety that may nonenzymatically cleave factor X to Xa. Plasminogen activator inhibitor type 1 (PAI-1) is secreted by numerous tumor cells and inhibits plasmin generation, augmenting the thrombophilic state as well as possibly also promoting tumor metastasis dissemination.[21] Other procoagulant properties of tumor cells include expression of cytokines such as IL-1β and tumor necrosis factor alpha (TNF-α), which, in turn, regulate expression of procoagulants and mediate interactions between tumor cells, platelets, leukocytes, and endothelial cells. Thrombin, certain cytokines, and growth factors such as vascular endothelial growth factor (VEGF) can stimulate endothelial cells to synthesize tissue factor, further potentiating a procoagulant surface and leading to fibrin deposition on vessel walls. Activated protein C inhibitor may contribute to a prothrombotic state, as it can inhibit both fibrinolysis and the protein C anticoagulant pathway.[21]

Chemotherapy, with resulting neutropenia and sepsis, often necessitates hospitalization and bed rest, which contributes further to the high risk of VTE. Following the administration of various chemotherapeutic agents, changes in the levels of coagulation factors, suppression of anticoagulant and fibrinolytic activity, and direct endothelial damage have been documented clinically and experimentally.[22] Hormonal therapy, particularly tamoxifen in breast cancer adjuvant therapy, is also associated with an increased risk of thromboembolism, particularly when combined with chemotherapy. The thrombophilic state induced by chemotherapeutic agents has recently been reviewed.[22] Further comprehensive research will more clearly elucidate the mechanisms underlying thrombophilia in cancer patients. In spite of the clear association, there is no convincing evidence that an aggressive search for cancer is warranted in patients presenting with apparently idiopathic DVT.[23]

Pregnancy and the postpartum period are the most common settings in which women under age 40 acquire thromboembolic disease. Venous thrombosis develops in these settings five times more often than in age-matched women not on oral contraceptives.[24] Although DVT appears to be more common in the third-trimester and postpartum than prior to delivery, the risk is clearly considerable throughout pregnancy.[24] Cesarean section further augments the risk. Oral contraceptives are associated with the development of VTE, although the precise risk has been controversial.[25] The risk increases with third-generation agents (agents containing desogestrel or gestodene as the progestogen component).[26,27] Results from a clinical trial evaluating hormonal replacement therapy indicated that such therapy increased the incidence of VTE in women 45 to 64 years of age. A yearly total of 16.5 cases of VTE per 100,000 women may be attributed to hormonal replacement therapy.[28] The risk of VTE also appears to be highest during the first year of exposure to hormonal replacement.[29] It has not been clearly established that previous use

increases the risk.[30] Although such therapy is associated with obvious benefits, physicians must consider other potential risk factors for VTE before prescribing hormonal replacement therapy.

Other disease states and clinical settings enhance the risk of VTE. Most intensive care unit patients can be considered at risk for VTE because of their multiple risk factors, including significant underlying disease, immobility, and venous injury due to trauma or central venous catheters. These patients should receive some form of DVT prophylaxis and a high index of suspicion for VTE should be maintained in appropriate clinical circumstances.

Inherited Risk Factors

Inherited thrombophilias result in variable degrees of VTE risk. Individuals with, for example, antithrombin III or factor V Leiden deficiency without significant superimposed risk factors such as surgery or immobilization often do not suffer from VTE until an additional risk factor develops. The factor V Leiden mutation is a common genetic polymorphism associated with activated protein C resistance and appears to be present in approximately 4 to 6 percent of the general population.[31] The relative risk of a first idiopathic venous thrombosis among men heterozygous for the mutation has been shown to be three- to sevenfold higher than that of those not affected.[31] Another thrombophilic mutation has been identified in the 3′ untranslated region of the prothrombin gene (substitution of A for G at position 20210), and this mutant allele is present in 2 percent of the general population.[32] This prothrombin gene defect increases the risk of DVT by a factor of 2.7 to 3.8.[32,33] It appears that carriers of both factor V Leiden and the prothrombin G20210A defect have an increased risk of recurrent DVT after a first episode and are candidates for lifelong anticoagulation.[34] There has been increasing interest in the potential role of homocysteine in VTE. In vitro, homocysteine has potentially thrombogenic effects, including injury to vascular endothelium and antagonism of the synthesis and function of nitric oxide.[35] Coexisting hyperhomocysteinemia has been shown to increase the risk for thrombosis in patients with factor V Leiden.[36] However, the thermolabile methylenetetrahydrofolate reductase gene variant is not independently associated with thrombosis, emphasizing that the precise role of homocysteine in venous thrombosis is unclear. Thus, interactions between the genetic factors (defects in enzymes) that control homocysteine metabolism and nutritional factors (folate, vitamin B_6, and vitamin B_{12} deficiencies) that affect homocysteine metabolism appear to warrant additional investigation with regard to VTE. It would appear certain that additional inherited thrombophilic disorders will be identified that may explain some of the "idiopathic" cases.

NEXT

Chapter 53: PULMONARY EMBOLISM

ACUTE PULMONARY EMBOLISM: PATHOPHYSIOLOGY

Gas-Exchange Abnormalities

The effect of PE on oxygenation and hemodynamics depends upon the extent of obstruction of the pulmonary vascular bed and the severity of underlying cardiopulmonary disease. Hypoxemia develops in the preponderance of patients with PE and has been attributed to various mechanisms. When no previous cardiopulmonary disease is present, lung regions with low ventilation/perfusion ratios and shunting due to perfusion of atelectatic areas appear to be the predominant mechanisms of hypoxemia. Hypoxemia leads to an increase in sympathetic tone with systemic vasoconstriction and may actually increase venous return with augmentation of stroke volume, at least initially, if there is no significant underlying cardiac or pulmonary pathology already present.

Hemodynamic Alterations

Massive emboli can cause profound hemodynamic compromise. In the setting of massive emboli, cardiac output is diminished but may be initially sustained as the mean right atrial pressure increases. The increased pulmonary vascular resistance impedes right ventricular outflow with a reduction in left ventricular preload. When no underlying cardiopulmonary disease is present, occlusion of 25 to 30 percent of the vascular bed by emboli results in a rise in pulmonary artery pressure (PAP). As the extent of vascular obstruction increases, hypoxemia worsens, stimulating vasoconstriction and a further rise in PAP. Greater than 50 percent obstruction of the pulmonary arterial bed is generally present before there is substantial elevation of the mean pulmonary artery pressure. When the extent of embolic occlusion approaches 75 percent, the right ventricle must generate a systolic pressure in excess of 50 mmHg and a mean PAP of greater than 40 mmHg to preserve pulmonary perfusion.[37] Although a hypertrophied right ventricle (in an otherwise normal patient) may theoretically be capable of achieving pressures this high, a normal right ventricle is unable to and will fail.[37] In reality, individuals with significant underlying cardiopulmonary disease and superimposed PE are more inclined to develop a more profound deterioration in cardiac output than normal individuals with PE, whether or not right ventricular hypertrophy is present. Furthermore, a depressed cardiac output in the absence of an elevated right atrial pressure suggests that the PE is superimposed upon preexisting cardiac disease. Right ventricular failure develops more frequently in the setting of PE when the patient has underlying coronary artery disease.[38] Aggressive hemodynamic support may sustain some patients with massive embolism at least temporarily, even when the right ventricle is dilated and hypocontractile, but any further increment in embolic burden may be fatal.

Chapter 53: PULMONARY EMBOLISM

DIAGNOSIS OF DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Venous thromboembolism represents the spectrum of one disease. Most clinically significant PE arise from the prior development of DVT in the lower extremities, with subsequent embolization to the lungs. Patients may present with symptoms of either DVT, PE, or both. At the present time, the diagnostic strategy involves recognition of certain symptoms and signs of DVT and/or PE and usually involves an imaging study directed at either the legs or the lungs, depending upon the presentation. Ventilation/perfusion (/) scanning has been the diagnostic cornerstone for patients with suspected PE for decades. However, the contrast-enhanced computed tomography (CT) scan is being used increasingly as experience and technology improve. The diagnostic approach to acute DVT and PE has recently been exhaustively reviewed and presented as clinical practice guidelines by the American Thoracic Society.[39]

Lower extremity ultrasound is the most common leg study utilized, and the / scan still appears to be the most frequently utilized lung imaging study. It is important to realize that an increasingly common diagnostic strategy in patients presenting with suspected PE but with a nondiagnostic lung imaging study is to perform a lower extremity study in hopes of proving that DVT is present.

History and Physical Examination

The clinical diagnosis of both DVT and PE, based upon the history and physical examination, are insensitive and nonspecific. Patients with lower extremity DVT may be asymptomatic or may have erythema, warmth, pain, swelling, and/or tenderness. These findings are not specific for DVT but suggest the need for further evaluation. The differential diagnosis of DVT includes cellulitis, edema from other causes, musculoskeletal pain, or trauma (some of these may be concomitant and may or may not be related). Pulmonary embolism must always be considered when unexplained dyspnea is present. Dyspnea as well as pleuritic chest pain and hemoptysis are common in PE but are nonspecific. Coughing may be present, and while sometimes caused by PE, it more commonly occurs with bronchitis or pneumonia. It is far less common than shortness of breath. Anxiety, light-headedness, and syncope are all symptoms that may be caused by PE but may also be due to a number of other entities that result in hypoxemia or hypotension. Tachypnea and tachycardia are the most common signs of PE but are also nonspecific. Syncope or sudden hypotension should suggest the possibility of massive PE. The cardiac and pulmonary physical examinations are both nonspecific. A pleural rub or accentuated pulmonic component of the second heart sound may suggest PE but can also be explained by other disorders. In spite of the limitations of the history and physical examination for DVT and PE, the index of clinical suspicion becomes a more useful parameter when considered in conjunction with additional studies and / scanning.[40] Dyspnea, tachypnea, clear lung fields, and hypoxemia may often be attributed to a flare of chronic obstructive disease or asthma when underlying PE is present. Thus, diagnostic efforts aimed at possible VTE should still be considered despite alternative explanations if risk factors and the clinical setting are suggestive.

Laboratory Testing

Routine laboratory testing is not useful in proving or refuting the presence of DVT or PE but may

be helpful in confirming or excluding alternative or concomitant diagnoses. For example, leukocytosis and pulmonary infiltrates may suggest pneumonia, and worsening hypercapnia in a patient with known chronic obstructive lung disease may suggest a flare of the underlying lung disease. It is important to realize, however, that acute PE can develop in the setting of other cardiopulmonary disorders that do not exclude the possibility of concomitant PE.

D-DIMER TESTING

The D-dimer is a specific derivative of cross-linked fibrin. Measurement of circulating plasma D-dimer has been comprehensively evaluated as a diagnostic test for acute VTE, both independently and together with other diagnostic measures. A normal enzyme-linked immunosorbent assay (ELISA) appears to be sensitive in excluding PE. When the D-dimer level is 500 μg/L or greater, the sensitivity and specificity for PE have been shown to be 98 and 39 percent, respectively.[41] The sensitivity of the plasma D-dimer appears to remain high up to 1 week after presentation. In another prospective analysis, 96 percent of 79 patients with high-probability / scans had an elevated D-dimer concentration.[42] Thus, increased levels of cross-linked fibrin degradation products are an indirect but suggestive marker of intravascular thrombosis in addition to indicating fibrinolysis. Although the sensitivity of the D-dimer appears high, the specificity is not high enough to be diagnostic. Patients with both suspected and proven DVT and PE often have underlying disease states that also cause the D-dimer to be elevated.

When clinical studies comparing D-dimer with the results of other diagnostic tests for VTE are reviewed, there appear to be appreciable differences in assay performance, heterogeneity among the patient population, and inconsistent use of definitive diagnostic criteria for venous thromboembolism.[43,44] The number of available D-dimer assays, including rapid bedside assays, is increasing. It appears that results of clinical studies utilizing one manufacturer's D-dimer assay cannot be extrapolated to another study using another manufacturer's assay. No single assay has been established as superior to all the others. The ELISA assays are sensitive but cannot be performed rapidly. The latex tests, while rapid, have not been proven to be sufficiently sensitive. A rapid, quantitative, immunoturbidimetric technique has been evaluated that recognizes the D-dimer epitope by using antibody-coated latex particles.[45] In at least one study, the degree of abnormality of this D-dimer test appeared to correlate with the extent of the DVT, with proximal thrombosis producing higher D-dimer levels.[45] In addition, patients presenting immediately after the onset of symptoms were found to have higher D-dimer levels than patients examined after a few days. Thus, certain quantitative D-dimer tests may prove to offer additional information regarding the acuity and extent of thromboembolic disease. Future studies of D-dimer techniques should be rigorous with regard to the definitive presence or absence of DVT and/or PE as well as addressing issues such as duration of symptoms, presence of comorbid disease, and extent of thrombosis.

Recently, both DVT and PE management studies have been performed, with therapeutic decisions based, to some extent, upon D-dimer results. When a bedside whole-blood agglutination D-dimer assay and impedance plethysmography were both negative in patients with suspected DVT and anticoagulation was withheld, the negative predictive value was 98.5 percent (95 percent confidence interval, 96.3-99.6) based upon 3 months of follow-up.[46] For the D-dimer test alone, the negative predictive value was 97.2 percent. A diagnostic protocol including an assessment of clinical probability, / scan, ELISA plasma D-dimer, and lower extremity ultrasound (US) was utilized in 308 consecutive patients presenting to the emergency room with suspected PE.[47] Of these patients, 106 (34 percent) had diagnostic / scans (high probability in 63 and normal in 43). The noninvasive evaluation was diagnostic in 125 patients (62 percent). In 48 patients, PE was ruled out by a nondiagnostic lung scan together with low clinical probability. In 53 cases, it was ruled out by a quantitative D-dimer of less than 500 μg/L. Only 77 of the 202 patients with

nondiagnostic / scans required pulmonary angiography. At 6 months follow-up, only 2 of the 199 patients in whom the diagnostic protocol had ruled out PE had a VTE event. Using the same cutoff value for the quantitative D-dimer, these investigators subsequently reported that of 198 patients with suspected PE and a D-dimer <500 μg/L, 196 were free of PE, one had PE, and one was lost to follow-up.[48] Thus, the negative predictive value of the D-dimer was approximately 196 of 198 (99 percent). Although these data represent the work of only one group of investigators, they are promising. Rapid bedside assays are becoming more available and additional outcome studies will help to clarify their role. At present, plasma D-dimer measurements should be interpreted with caution and in the context of other diagnostic tests.

ARTERIAL BLOOD GAS ANALYSIS

Hypoxemia, while not universal, is extremely common in acute PE. Some patients, particularly young individuals without underlying cardiopulmonary disease may have a normal Pa_{O_2}. In a retrospective study of hospitalized patients with PE, the Pa_{O_2} was greater than 80 mmHg in 29 percent of patients less than 40 years old, compared with 3 percent in the older group.[49] However, the alveolar-arterial (A-a) difference was elevated in all patients. Thus, as age increases, it becomes even less likely that a patient with PE will have a normal room air Pa_{O_2}. In the PIOPED, a subset of patients suspected of PE without a history or evidence of underlying cardiac or pulmonary disease was evaluated, and the Pa_{O_2} and A-a difference values were compared.[50] Patients with and without PE could not be distinguished based upon either of these values. However, the A-a difference was elevated by more than 20 mmHg in 76 of 88 (86 percent) patients with PE. The diagnosis of acute PE cannot be excluded based upon a normal Pa_{O_2}, and although the A-a difference is usually elevated, it may very rarely be normal in patients without preexisting cardiopulmonary disease. An important tenet should be that unexplained hypoxemia, particularly in the setting of risk factors for DVT, should suggest the possibility of PE.

Electrocardiography

Electrocardiography (ECG) cannot be relied upon to rule in or rule out PE, though ECG proof of a clear alternative diagnosis, such as myocardial infarction, is useful when PE is among the possible diagnoses. The potential coexistence of PE together with another process must, however, be a consideration. ECG findings in acute PE are generally nonspecific and include T-wave changes, ST-segment abnormalities, and left- or right-axis deviation. The changes that do occur are likely caused by right ventricular dilation. The "classic" S1Q3T3 pattern described by McGinn and White[51] in 1935 in seven patients with acute cor pulmonale secondary to PE was subsequently demonstrated to be present in about 10 percent of PE cases.[52] In patients without underlying cardiac or pulmonary disease from the Urokinase Pulmonary Embolism Trial (UPET), electrocardiographic abnormalities were documented in 87 percent of patients with proven PE.[53] These findings were not specific for PE, however. In this clinical trial, 26 percent of patients with massive or submassive PE and 32 percent of those with massive PE had manifestations of acute cor pulmonale, such as the S1 Q3 T3 pattern, right bundle-branch block, P-wave pulmonale, or right axis deviation. Such changes are thus seen in a minority of patients. The low frequency of specific ECG changes associated with PE was confirmed in the PIOPED study.[50] It has been recently suggested that the anterior subepicardial ischemic pattern is the most frequent ECG sign of massive PE.[54]

Chest Radiography

The chest radiograph is abnormal in the majority of patients with PE, but the findings are

nonspecific. Atelectasis, pulmonary infiltrates, pleural effusion, and mild elevation of a hemidiaphragm may be present.[50] Classic radiographic evidence of pulmonary infarction (Hampton's hump) or decreased vascularity (Westermark's sign) are suggestive but uncommon. A normal chest radiograph in the presence of significant dyspnea and hypoxemia without evidence of bronchospasm or anatomic cardiac shunt is strongly suggestive of PE. In most situations, however, the chest radiograph cannot be used to definitively diagnose or exclude PE. Although exclusion of other processes such as pneumonia, congestive heart failure, pneumothorax, or rib fracture (which may cause symptoms similar to acute PE) is important, PE often coexists with other underlying lung diseases.

Imaging Studies for Pulmonary Embolism

VENTILATION/PERFUSION SCANNING

Ventilation/perfusion scanning has been the pivotal diagnostic test for approaching suspected PE for many years. However, even in patients in whom PE is ultimately proven, the / scan is most commonly nondiagnostic. Certain / scan readings are of substantial utility, however. Normal and high-probability scans are considered diagnostic. A normal perfusion scan excludes the diagnosis of PE with enough certainty that further diagnostic testing is unnecessary. Matching areas of decreased ventilation and perfusion in the presence of a normal chest radiograph suggests a process other than PE. However, low- or intermediate-probability (nondiagnostic) scans are commonly found with PE, and particularly when clinical suspicion is high, additional testing is necessary. In the PIOPED study, the utility of / scanning combined with clinical assessment of patients with suspected PE was prospectively evaluated.[40] Patients with PE had scans that were of high, intermediate, or low probability, but so did most individuals without PE. Although the specificity of high-probability scans was 97 percent, the sensitivity was only 41 percent. Of interest, 33 percent of patients with intermediate-probability scans and 12 percent of patients with low-probability scans were diagnosed definitively with PE by pulmonary arteriography. When the clinical suspicion of PE was considered very high, the positive predictive value of high-probability scans for PE was 96 percent. More interestingly, in those with high clinical suspicion and intermediate- and low-probability scans, it was 66 and 40 percent, respectively. Thus, further diagnostic testing for PE should be performed even when the lung scan is of low or intermediate probability if the clinical setting suggests PE. Although the / scan may sometimes be diagnostic of PE or exclude the possibility with sufficient certainty, it is often nondiagnostic. The latter fact emphasizes the need to further improve our diagnostic resources.

PULMONARY ARTERIOGRAPHY

Pulmonary arteriography is the established "gold standard" diagnostic technique for the diagnosis of PE. It is a very sensitive and specific test. However, for smaller (subsegmental) emboli, it appears less accurate. Two referee readers from the PIOPED agreed on the presence or absence of subsegmental emboli in only 66 percent of cases.[55] In another study, using selective pulmonary arteriography, there was excellent agreement on main, lobar, and segmental emboli but only 13 percent agreement on subsegmental emboli.[56] The significance of such emboli is unclear, however, and may depend upon the presence of underlying cardiopulmonary disease, the extent of concurrent DVT, and the continued presence or absence of risk factors for DVT. Arteriography is safe in most instances. Complications related to this technique among 1111 patients suspected of PE in the PIOPED study included death in 0.5 percent and major nonfatal complications in 1 percent.[55] An increasingly utilized alternative to pulmonary arteriography is to perform lower extremity studies when the / scan is nondiagnostic; if DVT is discovered, the therapeutic approach is generally the same as if an arteriogram were positive for PE. If serial lower extremity testing is

negative, the chances of significant PE or morbidity from a subsequent event appears unlikely.[57] However, the ease with which serial testing can be performed is variable, and arteriography is often the best alternative when the leg test is negative, since the sensitivity of ultrasound for DVT is substantially lower in patients with asymptomatic DVT. Lower extremity testing is being increasingly utilized in patients with nondiagnostic lung scans and in stable patients; this appears to be appropriate.[39] Pulmonary arteriography has also been performed at the bedside utilizing a Swan-Ganz catheter.[58] However, accurate interpretation of arteriography, particularly in the case of submassive emboli, is crucial.

ECHOCARDIOGRAPHY

Echocardiography is not usually used for approaching the patient with suspected PE, although it may suggest its presence in some clinical settings, and it has been suggested as a potential means by which to determine the need for thrombolytic therapy.[59] Echocardiography can often be performed more rapidly than either / scanning or pulmonary arteriography and may suggest hemodynamically significant PE.[60] Studies of patients with documented PE have revealed that more than 80 percent of patients have imaging or Doppler abnormalities of right-ventricular size or function that may suggest acute PE.[60,61] However, patients who are acutely ill with suspected PE often have underlying cardiac or pulmonary disorders such as chronic obstructive lung disease, and neither right-ventricular dilation nor hypokinesis can be reliably used even as indirect evidence of PE in these settings. Intravascular ultrasound imaging has been utilized in both the experimental and clinical setting to image large emboli.[62-64] This technique can be performed at the bedside. Although the technique may be less sensitive and specific and more time-consuming in the setting of smaller emboli, further investigation may be warranted.

COMPUTED TOMOGRAPHY

Contrast-enhanced spiral (helical) CT scanning has been increasingly investigated and utilized in patients with clinically suspected acute and chronic PE. This technique involves continuous movement of the patient through the scanner with concurrent scanning by a constantly rotating gantry and detector system.[65] A helix of projecting data is obtained. Continuous volume acquisitions can be obtained during a single breath, and with newer scanners, breath-holding may be less important. Rapid scans can be obtained, facilitating imaging in critically ill patients. Limitations of helical CT scanning in early clinical studies included poor visualization of horizontally oriented vessels in the right middle lobe and lingula because of volume averaging.[66] The peripheral areas of the upper and lower lobes may be inadequately scanned and the presence of inter-segmental lymph nodes may result in false-positive studies. Multiplanar reconstructions in coronal, sagittal, or oblique planes aid in distinguishing lymph nodes from emboli (see also Chap. 17).

Computed tomography scanning may reveal emboli in the main, lobar or segmental pulmonary arteries with >90 percent sensitivity and specificity.[66-69] Accurate results have been reported for large PE.[70,71] However, for subsegmental emboli, the sensitivity and specificity appear to be lower. The incidence of isolated subsegmental emboli appears to be approximately 6 to 30 percent, with the former figure likely being more representative.[55,72] Of note, even with the gold standard diagnostic test (arteriography), two referee readers from the PIOPED agreed on the presence or absence of subsegmental emboli in only 66 percent of cases.[55] Another study, using selective pulmonary arteriography, indicated excellent agreement on main, lobar, and segmental emboli but only 13 percent agreement on subsegmental emboli.[56] Thus, this apparent limitation with spiral CT scanning is also a concern with angiography. The incorporation of CT scanning into diagnostic algorithms for PE is being endorsed increasingly.[73] However, no prospective

multicenter randomized clinical trials large enough to unequivocally prove the sensitivity and specificity of contrast-enhanced CT scanning in patients with suspected PE have been performed. Most have been single-center trials of moderate size. The value of CT for large emboli appears clear, however.

Sensitivity and specificity data from several large studies evaluating helical CT scanning for acute PE are shown in Table 53-2. Contrast-enhanced electron-beam CT also appears useful in diagnosing acute PE.[69,74] In one comparison with pulmonary angiography, only 8 of 720 vascular zones (1.1 percent) were considered inadequately visualized with electron-beam CT. As with spiral CT, three-dimensional reconstruction techniques can be applied to the pulmonary vessels to better define vessels located within the plane that has been sectioned. Another important advantage of these CT techniques over the / scan is the concomitant ability to define nonvascular structures such as airway, parenchymal, and pleural abnormalities, lymphadenopathy, and cardiac and pericardial disease. Prospective randomized clinical trials comparing these techniques with the standard diagnostic approach to PE will help to determine their precise role. It appears that CT scanning is being increasingly utilized.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is also being utilized to evaluate clinically suspected PE at some centers.[75,76] One clinical trial compared MRI with spiral CT: the average sensitivity of CT for five observers was 75 percent and of MRI 46 percent.[77] The average specificity of CT was 89 percent, compared with 90 percent for MRI. Sensitivity and specificity values for expert readers were higher, however. Spiral CT may be somewhat more useful than MRI for detecting PE at the present time, but MRI has several attractive advantages, including excellent sensitivity and specificity for the diagnosis of DVT. As in the case of CT scanning, the diagnosis of entities other than PE using MRI is a major advantage over the / scan.

Diagnostic algorithms for patients presenting with suspected DVT and PE have been recommended in the American Thoracic Society Consensus Statement and allow for a certain degree of flexibility with regard to specific diagnostic modalities utilized.[39]

Imaging Studies for Deep Venous Thrombosis

A number of diagnostic techniques can be utilized to evaluate the patient with suspected DVT. Compression US is the most common technique used in the United States and in many other areas of the world. Impedance plethysmography is used at some centers, and a number of important clinical trials have been performed utilizing this technique. MRI appears to have some important advantages, but it has not generally been used as a first-line test. Venography remains the gold standard, but has been necessary less often at many centers in view of the accuracy of US. Each diagnostic technique has advantages and limitations. Although diagnostic algorithms may be suggested for suspected DVT, these are institution-specific, depending upon resources and available expertise with certain techniques. Newer diagnostic testing modalities, such as scanning with technetium 99m-labeled glycopeptide IIb/IIIa receptor antagonists, appear promising but will not be discussed.[78]

CONTRAST VENOGRAPHY

Although contrast venography remains the gold standard for the diagnosis of DVT, it has been less commonly used since the advent of US. Venography should be performed whenever noninvasive testing is nondiagnostic or impossible to perform. It is an invasive procedure that may

result in superficial phlebitis or hypersensitivity reactions, but it is generally safe and accurate.

IMPEDANCE PLETHYSMOGRAPHY

Impedance plethysmography has been carefully studied in patients presenting with suspected acute DVT. It has proven reliable for the detection of proximal DVT (including that occurring in and above the popliteal vein). Preliminary studies suggested greater than 90 percent sensitivity and 97 percent specificity for DVT involving the proximal lower extremity, although less than 30 percent of isolated calf vein thromboses were detected.[79,80] Although this modality is sometimes portable, it does require access to the calf and thigh for electrode and cuff placement. The specificity of IPG is affected by disorders that obstruct venous outflow, such as tumor or hematoma. Plaster casts or external fixation of extremities limits the utility of this technique. Some investigators have emphasized the potential limitations of IPG.[81] Among the limitations of the technique are its inability to detect asymptomatic/nonobstructive proximal DVT, or calf DVT and its lack of utility for diagnoses other than DVT.[39] It is used much less commonly than compression US.

ULTRASONOGRAPHY

Compression US with venous imaging is a portable, accurate, and widely available diagnostic technique for proximal lower extremity DVT. Combined with a Doppler reading, this technique is referred to as *duplex ultrasonography*. Ultrasound technology has been further sophisticated by the development of color duplex instrumentation that display Doppler frequency shifts as color superimposed on the gray-scale image. The color duplex images display both mean blood flow *velocity*, expressed as a change in hue or saturation, and *direction* of blood flow, displayed as red or blue. US imaging techniques can also identify or suggest the presence of pathology other than DVT-for example, Baker's cysts, hematomas, lymphadenopathy, arterial aneurysms, superficial thrombophlebitis, and abscesses may be suggested or diagnosed.[82] The sensitivity and specificity of US for symptomatic proximal DVT has been well above 90 percent in most recent clinical trials.[83,84] There are limitations, including insensitivity for asymptomatic DVT (less than 50 percent), operator dependence, the inability to accurately distinguish acute from chronic DVT in symptomatic patients, and insensitivity for calf vein thrombosis.[85-87] Compared with other technology, it is relatively inexpensive and is the preferred diagnostic modality for the straightforward case of symptomatic suspected proximal DVT.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) has clear advantages as a diagnostic test for suspected DVT and appears to be an accurate noninvasive alternative to venography.[88] A major feature of this technique is excellent resolution of the inferior vena cava and pelvic veins.[89,90] Preliminary experience with MRI suggests that it is at least as accurate as contrast venography or US imaging and more sensitive than US for pelvic vein thrombosis.[88-90] Simultaneous bilateral lower extremity imaging can be accomplished, and MRI appears to accurately distinguish acute from chronic DVT. This technique appears to be useful in distinguishing other entities such as cellulitis or a Baker's cyst from acute DVT. As with many other diagnostic techniques, its utility depends to a certain degree on the experience on the part of the reader. There is the additional advantage of evaluating a patient for the entire spectrum of VTE in one imaging session by scanning the legs and pelvis as well as the lungs. MRI is used by some medical centers when the initial diagnostic test (usually US) is nondiagnostic (see also Chap. 18).

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Chapter 53: PULMONARY EMBOLISM

PREVENTION OF DEEP VENOUS THROMBOSIS

Background

Prophylaxis for DVT is effective.[91] A substantial reduction in the incidence of DVT can be accomplished when individuals at risk receive appropriate preventive care, as such measures appear to be grossly underutilized. A review of the use of prophylaxis for DVT in 16 Massachusetts hospitals revealed that such therapy was administered to only 44 precent of high-risk patients in teaching hospitals and only 19 percent in nonteaching hospitals.[92] The frequency of prophylaxis ranged from 9 to 56 percent among hospitals. Another retrospective analysis revealed that only 97 of 250 patients (39 percent) at *very high risk* for DVT received any form of prophylaxis and that of these 97, only 64 (66 percent) received appropriate care.[93] Prophylaxis can be pharmacologic (anticoagulation) or nonpharmacologic. Low-molecular-weight heparin (LMWH) products have been increasingly utilized in clinical practice for both prevention and treatment of established VTE. Extensive literature is now available supporting the use of these preparations for DVT prevention. The LMWH preparations are advantageous in that they produce a more predictable dose response and are administered subcutaneously only once or twice daily (without monitoring) depending on the preparation (see "Management of Established Venous Thromboembolism," below).[94] Early ambulation whenever possible is always recommended in postoperative patients.

General Medical Patients

Patients are stratified according to DVT risk, and certain prophylactic measures are more appropriate for some patients than for others. Generally, low-dose anticoagulation with standard, unfractionated heparin or LMWH is indicated in medical or surgical patients deemed at risk for DVT. When standard heparin is used for prophylaxis in general medical patients, 5000 U delivered subcutaneously every 8 to 12 h is generally adequate. LMWHs have also been studied in general medical patients. In a large double-blind, randomized clinical study comparing two different doses of subcutaneous LMWH (enoxaparin) delivered once daily to acutely ill medical patients, the higher dose (40 mg) proved more effective than the lower dose (20 mg).[95] The incidence of DVT was 5.5 percent in the former group and 14.9 percent in the latter.

When prophylactic anticoagulation is contraindicated, mechanical devices (intermittent pneumatic compression) are utilized. Anticoagulation together with pneumatic compression is appropriate in patients deemed at exceptionally high risk or with multiple risk factors for DVT.

General Surgical Patients

In general surgery patients, a number of prophylactic strategies have been employed. An overview of the results of randomized trials in surgical patients demonstrated the substantial benefit of DVT prophylaxis.[91] In this review of more than 70 randomized trials involving 16,000 patients, it was demonstrated that perioperative use of subcutaneous heparin could prevent about half of all PE and about two-thirds of all DVT. In a large meta-analysis, the value of prophylaxis to reduce the incidence of DVT was confirmed; it was also suggested that intermittent pneumatic compression

plus the use of gradient compression stockings may result in the lowest incidence of postoperative DVT.[96] Other combined treatments were associated with lower rates than heparin alone and appear appropriate in patients at exceptionally high risk. For those patients undergoing minor operations who are less than 40 years old and have no additional risk factors for DVT, no prophylaxis other than early ambulation is recommended. Older patients undergoing major operations without additional risk factors should receive either standard, unfractionated heparin, LMWH, or intermittent pneumatic compression. When additional risk factors are present in the latter group, standard heparin every 8 h or LMWH should be administered. Enoxaparin has been FDA-approved for prophylaxis in patients undergoing elective abdominal surgery (40 mg subcutaneously once daily). A second preparation, dalteparin, has also been approved in the United States for once-daily use as prophylaxis for elective abdominal surgery.

Other High-Risk Patients

Certain orthopedic populations at particularly high risk for acute DVT have been carefully studied with well-designed randomized clinical trials, which led to the approval of enoxaparin by the FDA for prophylaxis against DVT in patients undergoing elective total hip or knee replacement. The approved dosing regimens are 30 mg subcutaneously twice daily initiated within 12 to 24 h after surgery, and 40 mg once daily initiated preoperatively. The duration of prophylaxis depends upon whether the patient is ambulatory and upon additional risk factors. At least one large randomized, placebo-controlled clinical trial suggested a lower incidence of DVT with more prolonged (1 month) outpatient prophylaxis in this patient population.[97] LMWHs have also been evaluated in trauma patients at risk for DVT and have proven efficacious in this patient population.[98] Intermittent pneumatic compression should be utilized if anticoagulation prophylaxis is contraindicated.

A number of LMWH preparations are currently being investigated. It is important to realize that these preparations are not identical and the results of clinical trials with one agent cannot be extrapolated to another. Detailed recommendations for DVT prophylaxis are published and updated every 2 to 3 years (American College of Chest Physicians Consensus).[99]

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Chapter 53: PULMONARY EMBOLISM

MANAGEMENT OF ESTABLISHED VENOUS THROMBOEMBOLISM

Assuring adequate oxygenation and hemodynamic support for PE is of paramount importance. Such supportive measures for massive PE are discussed further on in this chapter (see "Hemodynamic Management of Massive Pulmonary Embolism," below). Pain control and elevation of the leg are recommended for DVT, particularly severe, symptomatic acute iliofemoral DVT. Certain recommendations, such as bed rest in patients with established DVT, have not been well substantiated, but this measure should be instituted when significant symptoms are present. The major focus for effective therapy of VTE involves anticoagulation.

Anticoagulation

When DVT or PE is diagnosed or strongly suspected, anticoagulation therapy should be initiated immediately unless contraindications exist. The diagnosis must be confirmed if anticoagulation is to be continued.

STANDARD, UNFRACTIONATED HEPARIN

Standard heparin has been the time-honored parenteral anticoagulant based upon its prompt antithrombotic effect in preventing thrombus growth. The major anticoagulant effect of heparin is accounted for by a unique pentasaccharide with a high-affinity binding sequence to antithrombin III, which is present on only one-third of heparin molecules.[100] The interaction of heparin with antithrombin III markedly accelerates its ability to inactivate thrombin, factor Xa, and factor IXa. Heparin also catalyzes the inactivation of thrombin by a second plasma cofactor, heparin cofactor II. Heparin does not directly dissolve thrombus, but it allows the fibrinolytic system to act unopposed and more readily reduces the size of the thromboembolic burden.[100] Although thrombus growth can be prevented, early recurrence can develop even during therapeutic anticoagulation.

When intravenous standard, unfractionated heparin is instituted, the activated partial thromboplastin time (APTT) should be aggressively followed at 6-h intervals until it is consistently in the therapeutic range of 1.5 to 2.0 times control values.[101] This range corresponds to a heparin level of 0.2 to 0.4 U/mL as measured by protamine sulfate titration. Heparin can be administered by several protocols, but a weight-based approach has been shown to substantially enhance the chances of attaining the therapeutic range quickly. Heparin can be administered as an intravenous bolus of 5000 U followed by a maintenance dose of at least 30,000 to 40,000 U every 24 h by continuous infusion.[102] The lower dose is administered if the patient is considered at high risk for bleeding. This aggressive approach decreases the risk of subtherapeutic anticoagulation and, although supratherapeutic levels are sometimes achieved initially, bleeding complications do not appear to be increased.[102] More recent data continue to support aggressive heparin dosing. An alternative regimen consisting of a bolus of 80 U/kg followed by 18 U/kg/h has been recommended.[103] [104] Subsequent adjusting of the heparin dose should also be weight-based (Table 53-3). This approach was recommended by the recent American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy.[104] Warfarin therapy may be initiated as soon as the APTT is therapeutic and heparin should be maintained until a therapeutic International Normalized Ratio (INR) of 2.0 to 3.0 has been overlapped with a

therapeutic APTT for 2 consecutive days. This initial anticoagulation approach applies to both acute DVT and PE. Although proximal lower extremity thrombus is more likely to result in PE, calf thrombi should still be treated aggressively with anticoagulation or followed with noninvasive testing over 10 to 14 days for extension into the popliteal vein.[105,106] The spectrum of upper extremity venous thrombosis is variable and includes patients with peripherally and centrally placed intravenous catheters as well as those with underlying malignancy. Symptomatic patients with documented upper extremity DVT should be anticoagulated.[107] Prophylacticanticoagulation in patients with long-term indwelling catheters should also be instituted.[104,108]

LOW-MOLECULAR-WEIGHT HEPARIN

Mechanisms of Action and Pharmacology

Low-molecular-weight heparin is being utilized increasingly for acute venous thromboembolism. These agents differ in a number of respects from standard, unfractionated heparin. Standard heparin consists of lengthy glycosaminoglycan polymers that are heterogenous in size, with a mean molecular weight of approximately 15,000 Da. LMWHs, also glycosaminoglycans, are prepared by chemical or enzymatic depolymerization and are approximately one-third of the size of unfractionated heparin. These LMWH fractions are also diverse, with a mean molecular weight of 4000 to 5000 Da. The difference in size between unfractionated heparin and LMWH results in an altered anticoagulant profile.[109] Only one-third of the LMWH molecules contain the pentasaccharide required for antithrombin III binding. Maximal inhibition of thrombin requires the binding of heparin to both antithrombin III and the activated enzyme. In contrast, the accelerated inactivation of factor Xa by the heparin/antithrombin III combination requires only the binding of unfractionated heparin to antithrombin III and does not require the formation of the ternary complex. Heparin molecules smaller than 18 saccharide units are unable to bind thrombin and antithrombin III simultaneously, precluding maximal acceleration of the inactivation of thrombin by antithrombin III. These smaller LMWH molecules do, however, retain their ability to catalyze the inhibition of factor Xa by antithrombin III. For this reason, LMWH fractions appear to have relatively more anti-Xa than antithrombin activity and significantly less effect upon the APTT. While the ratio of anti-Xa to antithrombin of heparin is 1:1, the LMWH preparations have significantly higher ratios. In addition, other anticoagulant properties such as stimulation of tissue factor pathway-inhibitor release appear to be responsible for the effect of these agents, suggesting more reason for variability among them.[109] While the different preparation methods result in products with similar molecular profiles, structural variations remain, which impart significant differences in their biologic actions. Chemical modifications of various portions of the molecules, charge density, and the degree of desulfation all affect the characteristics of the final product. Because of these differences, antithrombin III activity, the effects on tissue-factor-pathway inhibitor, platelet factor 4, and heparin cofactor II would be expected to be different for the different preparations. Other potential dissimilarities between heparin and LMWH and between the individual LMWH preparations include differences in stimulation of the release of tissue plasminogen activator and prostacyclin. A major advantage of these preparations over unfractionated heparin is substantially enhanced bioavailability. This has been shown to differ for different LMWH preparations as well. Each of the LMWH compounds should be considered a distinct agent and they should not, at the present time, be considered interchangeable. Important characteristics and advantages of the LMWH preparations are shown in Tables 53-4 and 53-5.

Clinical Trials and Indications

Numerous clinical trials have strongly suggested the efficacy and safety of LMWH for treatment of established acute proximal DVT, using recurrent symptomatic VTE as the primary outcome

measure.[110-116] Treatment with LMWH is more convenient for the patient and for the nursing staff for several reasons. A continuous intravenous line is not required, as these agents can be administered once or twice per day subcutaneously at therapeutic doses. In most cases monitoring of the APTT is not required. Patients can be monitored by measuring levels of factor X, and certain patient populations, such as significantly obese individuals or those with renal insufficiency, are probably best managed with such monitoring. There has not been complete agreement on the approach to these individuals. Outpatient therapy for stable patients with DVT is increasing significantly. In two large, randomized (Canadian and European) trials, therapy with LMWH (enoxaparin and fraxiparine, respectively) was compared with that using standard weight-based unfractionated heparin.[110,111] The LMWH patients were treated entirely as outpatients or continued at home after a brief hospitalization. The outpatient LMWH regimens proved safe and effective. Three meta-analyses examined the use of LMWH compared with unfractionated heparin in the initial treatment of acute proximal DVT.[117-119] Although there was overlap among the clinical trials included in the analyses, they have helped to confirm the efficacy and safety of LMWH for the treatment of established DVT. At the present time, only one LMWH (enoxaparin) is FDA-approved for use in the United States for treatment of established DVT in the outpatient setting or for DVT (with or without PE) in the inpatient setting. Unlike the regimen for prophylaxis, in which a fixed dose of enoxaparin is utilized, a weight-based dosing regimen is employed for treatment of established VTE. For outpatient therapy, the recommended dose of enoxaparin is 30 mg subcutaneously every 12 h, while for inpatient treatment both 30 mg every 12 h and 40 mg once daily have been studied and FDA-approved. In addition to being more convenient, the LMWH preparations appear to be cost-effective, particularly when outpatient therapy is utilized.[120] Some of the different LMWH products and their prophylaxis and treatment regimens are listed in Table 53-6. The appropriate steps in instituting anticoagulation with enoxaparin for established VTE, including outpatient therapy, are shown in Table 53-7.

LONG-TERM THERAPY FOR DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Documented proximal DVT or PE should be treated for 3 months with oral warfarin, keeping the INR at 2.0 to 3.0. Individuals unable to take warfarin can be treated with long-term subcutaneous heparin or LMWH. More prolonged therapy is indicated when significant risk factors persist. Furthermore, patients in whom no clear risk factors exist (idiopathic VTE) appear to benefit from more prolonged anticoagulation.[121] In a double-blind study, patients completing 3 months of anticoagulation for a first episode of idiopathic VTE were randomized to receive either warfarin (INR 2.0 to 3.0) or placebo for an additional 24 months, and there was a substantial reduction in recurrences in the warfarin group without a statistically significant increase in bleeding.[121] Both short- and long-term anticoagulation guidelines are outlined in the ACCP Consensus Conference guidelines.[104]

OTHER ANTICOAGULANTS

Newer anticoagulants are being explored. Heparin works indirectly, requiring antithrombin III as a cofactor, and its effects vary considerably between patients. Hirudin is a direct thrombin inhibitor that has several advantages over heparin, including efficacy against fibrin clot-bound thrombin. It does not require any cofactors and is not inactivated by platelet factor 4 or plasma proteins. This drug, derived from the saliva of the medicinal leach (*Hirudo medicinalis*), appears promising. Data from several clinical myocardial infarction trials suggested that hirudin is at least as safe as heparin.[122,123] Recombinant hirudin has been examined for prophylaxis of DVT in patients receiving total hip replacement and resulted in a low rate of proximal DVT.[124] As with heparin, these direct thrombin inhibitors have very narrow therapeutic indices. Other direct thrombin

inhibitors and substances such as selective factor Xa inhibitors and tissue factor pathway inhibitor (TFPI) merit further investigation in the treatment of acute VTE.[125-130]

COMPLICATIONS OF ANTICOAGULATION

Complications of heparin include bleeding and heparin-induced thrombocytopenia (HIT). The rates of major bleeding in recent trials using standard heparin by continuous infusion or high-dose subcutaneous injection have been less than 5 percent.[104] Heparin-induced thrombocytopenia typically develops 5 or more days after the initiation of heparin therapy, and occurs in 5 to 10 percent of patients.[131-133] If a patient is placed on heparin for VTE and the platelet count progressively decreases to 100,000/mm^3 or less, heparin therapy should be discontinued. Although the risk of HIT appears to be lower with LMWH, it is important for clinicians to realize that HIT can occur with the use of either form of heparin.[134] Over the past decade, there have been many important advances in the pathogenesis, diagnosis, and treatment of HIT, which represents one of the most common immune-mediated adverse drug reactions.[135] This entity is caused by heparin-dependent IgG antibodies that recognize complexes of heparin and platelet factor 4, leading to activation of platelets via platelet Fc gamma IIa receptors. Formation of procoagulant, platelet-derived microparticles, and, possibly, activation of endothelium generate thrombin in vivo. The generation of thrombin helps to account for the strong association between HIT and thrombosis, including the recently recognized syndrome of warfarin-induced venous limb gangrene. This syndrome develops during warfarin treatment of HIT and deep venous thrombosis when acquired protein-C deficiency leads to the inability to regulate thrombin generation in the microvasculature. The diagnosis of HIT can be made confidently when one or more typical clinical events (most frequently, thrombocytopenia with or without thrombosis) occur in a patient with detectable HIT antibodies. The pivotal role of thrombin generation in this syndrome provides a rationale for the use of anticoagulants that reduce thrombin generation (danaparoid) or inhibit thrombin (lepirudin).

Vena Cava Interruption

In patients with established VTE in whom heparin therapy cannot be continued, inferior vena cava (IVC) filter placement can be undertaken to prevent lower extremity thrombi from embolizing to the lungs. These devices have been widely used for nearly two decades. The essential indications for filter placement include contraindications to anticoagulation, recurrent embolism while on adequate therapy, and significant bleeding complications during anticoagulation.[136] Filters are sometimes placed in the setting of massive PE when it is believed that any further emboli might be lethal.[136] A number of filter devices exist, but the Greenfield filter design has been most widely used. These devices can be inserted via the jugular or femoral vein and are effective. Complications are unusual.[137] Possible mechanisms of IVC filter failure include filter migration; improper filter positioning, allowing thrombi to bypass the filter; and formation of thrombosis proximal to the filter or on the proximal tip of the filter with subsequent embolization. Rare complications include clinically significant perforation of the IVC, migration to the heart, and displacement of the filter during insertion. Rarely, these devices may erode into the wall of the IVC. Occasionally, IVC obstruction due to thrombosis at the filter site may occur. Deaths due to filter placement are extraordinarily uncommon. Anticoagulation is generally continued when a filter is placed unless it is contraindicated. Temporary filters have been placed in individuals deemed at extremely high risk for DVT yet unable to receive anticoagulant prophylaxis, such as certain trauma patients.[138]

Thrombolytic Therapy

Acceleration of clot lysis in PE using thrombolytic therapy was first documented several decades

ago.[139-141] The prospective, multicenter, randomized UPET evaluated 160 patients with arteriographically proven PE.[53] Thrombolysis was accelerated in patients receiving urokinase compared with those on heparin when pulmonary arteriograms and lung perfusion scans were examined 24 h after treatment. Subsequently, the difference between the two groups diminished and by day 5 the improvement in each group was similar. There were no differences in the frequency of recurrent PE or mortality rate within 2 weeks of treatment. The lack of reduction in mortality may have been explained by the fact that only 7 percent of the patients in the clinical trial were classified as having massive PE with shock. The second phase of this clinical trial also documented the efficacy of streptokinase administered over 24 h.

Both urokinase and streptokinase were approved for use in pulmonary embolism. In 1980, the National Institutes of Health issued consensus guidelines for PE thrombolysis and recommended thrombolytic therapy for patients with obstruction of blood flow to a lobe or multiple pulmonary segments and for patients with hemodynamic compromise regardless of the size of the PE.[142] Recombinant tissue plasminogen activator (t-PA) was subsequently approved for use for the treatment of PE and is administered as a 100-mg intravenous infusion delivered over 2 h.[143] Even shorter infusion durations have been evaluated, and future clinical trials may lead to wider acceptance of these regimens. At present, the above t-PA regimen is the most rapidly administered protocol that is currently approved for use.

At the present time, the clearest indication for the use of thrombolytic therapy is in patients with hemodynamic instability (hypotension) when there are no concomitant contraindications.[144,145] Patients with severely compromised oxygenation should also be considered.[144] Stable patients with a significant embolic load are individualized, often receiving treatment in the absence of absolute or relative contraindications. For example, a strong case for thrombolytic therapy can be made when the embolic load visualized on the imaging study is extensive (defect involving the equivalent of half of the pulmonary vascular bed) or with echocardiographic evidence of right ventricular dysfunction without clear hemodynamic instability.[146,147] Another setting in which thrombolytic therapy may be considered is when extensive DVT accompanies a submassive PE. No clinical studies have been undertaken to support this indication. Perhaps future trials will clarify more controversial guidelines.

The recommendations for use of thrombolytic therapy in PE have been carefully reviewed.[146] Potential indications are presented in Table 53-8. Approved regimens for the treatment of PE are presented in Table 53-9. Coagulation assays are not necessary during thrombolysis, since the approved regimens are administered as fixed doses. Heparin should be withheld until the thrombolytic infusion is completed. The APTT is then determined and heparin is initiated without a loading dose if this value is less than twice the upper limit of normal. If the APTT exceeds this value, the test is repeated every 4 h until it is safe to proceed with heparin. The method of delivery of thrombolytic agents has also been investigated. Although a number of investigators have employed standard or low-dose intrapulmonary arterial thrombolytic infusions in order to deliver a high concentration of drug in close proximity to the clot,[148,149] intravenous therapy appears adequate in most settings.[150] More direct techniques, such as catheter-directed administration of intraembolic thrombolytic therapy are discussed below.

The use of thrombolytic therapy for DVT without PE is more controversial. A comprehensive review of the literature suggests that use of streptokinase may be associated with a reduction in postphlebitic syndrome when used for acute DVT, although bleeding is increased with thrombolytic therapy.[151] Future studies may clarify the role of thrombolytic therapy for DVT. It is reasonable to consider systemic thrombolytic therapy in patients with proximal occlusive DVT associated with significant swelling and symptoms when there are no absolute or relative contraindications.

The major complication resulting from thrombolytic therapy is bleeding. These agents are not fibrin-specific and any clot, whether pathologic or protective, is subject to lysis. Although hemorrhagic complications in the UPET were relatively high, further experience with thrombolytic therapy has suggested that adverse effects are reduced when venous cut-downs and unnecessary arterial phlebotomy are avoided.[152] Thus, when thrombolytic therapy is administered, invasive procedures should be minimized. The most devastating complication associated with this treatment is the development of intracranial hemorrhage.[153] Clinical trials have suggested that this occurs in significantly less than 1 percent of patients. Contraindications to systemic thrombolytic therapy in VTE are listed in Table 53-10. Bleeding related to thrombolytic therapy requires immediate management. Bleeding from vascular puncture sites should be addressed with manual compression followed by a pressure dressing. Intracranial bleeding requires immediate discontinuation of thrombolytics or anticoagulants, and emergent neurologic and neurosurgical consultation should be obtained. A noncontrasted brain CT scan should be performed. Retroperitoneal hemorrhage may develop from a vascular puncture above the inguinal ligament and may be life-threatening. Severe or refractory bleeding should be addressed with transfusion of 10 U of cryoprecipitate and 2 U of fresh frozen plasma, and heparin can be reversed with protamine. A comprehensive review of thrombolytic therapy for acute VTE has been published.[154]

Table 53-10: Thrombolytic Therapy for Acute Pulmonary Embolism: Contraindications

Absolute
Intracranial tumor or hemorrhagic stroke
Previous head trauma or cranial surgery
Active or recent gastrointestinal/internal bleeding
Relative
Thrombocytopenia or coagulopathy
Uncontrolled severe hypertension
Cardiopulmonary resuscitation
Surgery or biopsy within the previous 10 days

Catheter-Directed Techniques

The intravenous route has been the primary method of delivery, but local thrombolytic therapy has been utilized in massive PE. Intrapulmonary arterial delivery of thrombolytic agents by bolus or prolonged infusion with or without concomitant heparin has been utilized for massive PE (see "Thrombolytic Therapy," above).[148,149] These studies have generally been small and uncontrolled. Although intrapulmonary arterial delivery of thrombolytic agents appears to offer no advantage over the intravenous route,[150] *intraembolic* thrombolytic infusions may offer advantages over merely infusing the agents into the pulmonary artery. Such techniques have been applied in both animal models of PE and in patients, with enhanced thrombolysis.[155,156] Lower than conventional doses of t-PA or urokinase are delivered via a catheter imbedded directly within massive emboli over 10 to 20 min.[155,156] Combining thrombolytic therapy via direct delivery (at

low doses) with the possible mechanical benefits of direct intraembolic infusion could prove advantageous over the intravenous route, particularly in the setting of contraindications to thrombolytic therapy. Larger randomized studies would be needed to demonstrate the efficacy, potential advantages, and safety of such techniques. The implementation of these techniques, as well as the catheter-directed administration of intraembolic thrombolytic therapy described above, depend upon the experience of the medical team involved. Transvenous embolectomy without thrombolysis, via a suction-catheter device, has been proven quite effective by some[157,158] but is not widely performed. In an experience spanning 7 years, one group successfully extracted emboli in 11 of 18 patients with massive PE utilizing this technique; 13 survived their hospital stay while 5 died.[158]

Catheter-directed techniques have been successfully employed in the setting of acute iliofemoral DVT utilizing urokinase doses ranging from 1.4 to 16 million U delivered over an average of 30 h.[159,160] Results from a national registry of patients with iliofemoral thrombosis treated with local, catheter-directed therapy indicates that this approach is frequently successful.[160] Randomized trials may be appropriate.

Surgical Embolectomy

Pulmonary embolectomy may be performed in the setting of acute massive PE. The advent of thrombolytic therapy has reduced the number of potential candidates, but contraindications to these agents are relatively common. Although many patients die from PE before surgical embolectomy can be performed, some deteriorate hours after the initial episode, suggesting that surgery may occasionally be appropriate. In one case series of 71 embolectomies performed for acute PE using cardiopulmonary bypass, hospital mortality was 29 percent.[161] However, the mortality in those patients who had not sustained a cardiac arrest preoperatively was only 11 percent.

Hemodynamic Management of Massive Pulmonary Embolism

Massive PE should always be a consideration in the setting of the sudden onset of hypotension or extreme hypoxemia. Electromechanical dissociation or sudden cardiac arrest should always make massive PE suspect. If the patient is stable enough, lung imaging (generally / scan or spiral CT scan) should be performed when possible. Echocardiography may support the diagnosis of massive PE and may also suggest that aggressive intervention including thrombolytic therapy be considered.[146,147] When massive PE associated with hypotension and/or severe hypoxemia is suspected, supportive treatment is immediately initiated. Intravenous saline can be rapidly infused, but caution is recommended because right ventricular function is often markedly compromised. Dopamine or norepinephrine appear to be the favored choices of vasoactive therapy in massive PE and should be administered if the blood pressure is not rapidly restored.[162] Death from massive PE results from right ventricular failure, and dobutamine has been recommended by some as a means by which to augment right ventricular output.[163,164] A vasopressor such as norepinephrine combined with dobutamine might offer optimal results, and further exploration of such combined therapy would prove enlightening. Oxygen therapy is administered and thrombolytic therapy should be administered if hypotension is present and there are no contraindications. Intubation and mechanical ventilation are instituted as needed to support respiratory failure. Surgical embolectomy may be indicated, particularly if thrombolytic therapy cannot be administered.

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CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

In the majority of cases of acute PE, the patient either dies or completely recovers; however, a substantial residual thromboembolic burden occasionally remains and/or continues to form.[165,166] In these patients, the clot becomes organized and adherent and is not amenable to thrombolysis. If the obstruction becomes extensive, pulmonary hypertension develops. At least 50 percent of patients who develop chronic thromboembolic pulmonary hypertension have no documented history of DVT or PE, and this feature greatly impedes the diagnosis. Most patients have no identifiable coagulopathy. Dyspnea with exertion and fatigue are the most common complaints. The nonspecific nature of these findings may substantially delay the correct diagnosis. The physical examination generally reveals a right ventricular heave, a loud P_2, a right ventricular S_3, and tricuspid regurgitation consistent with pulmonary hypertension. In 20 percent of patients, one or more murmurs may be auscultated over the lung fields.

The chest radiograph usually reveals right ventricular enlargement and enlarged main pulmonary arteries. ECG changes are consistent with pulmonary hypertension. Arterial blood gases generally reveal hypoxemia with a widened A-a difference, although some patients may only demonstrate exercise-induced hypoxemia. Echocardiography documents pulmonary hypertension and enlargement of the right ventricle. Chest CT scanning is prudent and may reveal other rare causes of pulmonary hypertension, such as mediastinal fibrosis, and may, in fact, demonstrate evidence of chronic thrombi. With chronic thromboembolic pulmonary hypertension, the / scan nearly always indicates a high probability of PE, but occasionally it is less impressive. Right heart catheterization and pulmonary arteriography are performed, both to establish the diagnosis with certainty and to determine operability. Pulmonary angioscopy has frequently proven complementary to arteriography in assessing these patients.

Although anticoagulation should be instituted and IVC filters are recommended in patients with chronic thromboembolic pulmonary hypertension, the only means by which to alleviate symptoms and affect survival is with surgery. The University of California at San Diego has been a leading center for the evaluation and surgical therapy of these patients. Pulmonary thromboendarterectomy is performed via median sternotomy on cardiopulmonary bypass, and the overall mortality, which has continued to improve, is now less than 5 percent. Lung transplantation can sometimes be performed in patients in whom thrombi are too distal to extract.

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SUMMARY

Venous thromboembolism represents a spectrum consisting of DVT and PE. It is a common cause of death, particularly in hospitalized patients with significant risk factors, and is frequently not diagnosed until autopsy. The history and physical examination for both DVT and PE consist of suggestive but generally very nonspecific findings. These findings, particularly in the setting of risk factors for VTE, are important in raising the level of suspicion for VTE, leading to diagnostic testing. Preventive measures in patients at risk are crucial. Anticoagulation represents appropriate therapy for most patients with VTE. Low-molecular-weight heparins are being used increasingly in established VTE as well as for prophylaxis. Thrombolytic therapy should be considered in massive PE in the absence of contraindications, and guidelines for the use of these agents is evolving. Placement of a filter in the inferior vena cava is indicated when anticoagulation is contraindicated. Newer agents such as direct thrombin inhibitors are being explored. Future clinical trials will help to clarify the roles of both the newer diagnostic modalities and therapeutic strategies.

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Part 8: PULMONARY HYPERTENSION AND PULMONARY DISEASE
Chapter 54:

CHRONIC COR PULMONALE

Author: John H. Newman

DEFINITION

Cor pulmonale is a term that describes the pathologic effects of lung dysfunction on the right side of the heart. Pulmonary hypertension is the link between lung dysfunction and the heart in cor pulmonale. Cor pulmonale occurs as a late manifestation of many diseases of the lung, but the common thread in each case is increased right ventricular afterload. Cor pulmonale can be an elusive clinical diagnosis because pulmonary hypertension can exist without clinical manifestations and because clinical signs, such as dyspnea, may be shared with the underlying disease. Acute pulmonary hypertension leads to acute dilatation of the right ventricle; chronic pulmonary hypertension leads to ventricular hypertrophy followed by dilatation. The presence of overt right-sided heart failure is not essential to make the diagnosis of cor pulmonale, but right-sided heart failure is a common consequence. The clinical manifestations of cor pulmonale relate to alterations in cardiac output, salt and water homeostasis, and in most cases, gas exchange in the lung. Right-sided heart dysfunction secondary to left-sided heart failure, valvular dysfunction, or congenital heart disease is excluded in the definition of cor pulmonale.[1] Pulmonary venous obstruction is a cause of cor pulmonale; pulmonary venoocclusive disease is usually considered in the spectrum of primary pulmonary hypertension.

As a concept, cor pulmonale was introduced over 200 years ago, but the exact origin of the term is uncertain.[2] Osler[3] commented in the first edition of his textbook that "hypertrophy of the right ventricle . . . results from increased resistance in the pulmonary circulation, as in cirrhosis of the lung and emphysema." McGinn and White[4] apparently were the first to use the term *acute cor pulmonale* in the discussion of a case of acute, massive thromboembolism in 1935. William Harvey's discussion of the relationship of the lung and right side of the heart in *De Motu Cordis*[5] showed remarkable insight into the limitations of the right ventricle.

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Chapter 54: CHRONIC COR PULMONALE

INCIDENCE, ETIOLOGIES, AND PATHOLOGY

Emphysema and chronic bronchitis cause over 50 percent of cases of cor pulmonale in the United States. The prevalence of cor pulmonale is difficult to determine because cor pulmonale does not occur in all cases of chronic lung disease and because routine physical examination and laboratory tests are relatively insensitive to the presence of pulmonary hypertension. The prevalence of chronic obstructive lung disease in the United States is about 15 million, directly resulting in approximately 70,000 deaths per year and contributing to about 160,000 other deaths.[6] It has been estimated that cor pulmonale accounts for 5 to 10 percent of organic heart disease. Cor pulmonale was present in 20 to 30 percent of admissions for heart failure in one study.[7] It is likely that cor pulmonale is a complication in a high percentage of cases. Gazes[8] found that 9.2 percent of cases of heart disease that came to autopsy had right heart abnormalities.

Chronic cor pulmonale occurs most frequently in adult male smokers, although the incidence in women is increasing as heavy smoking in females becomes more prevalent. A list of all diseases that may lead to cor pulmonale would be extensive and is not included in this chapter, but the major types of disease processes are listed in Table 54-1. Two important causes of cor pulmonale, thromboembolism and primary pulmonary hypertension, are discussed in Chaps. 52 and 53.

Table 54-1: Etiologies of Chronic Cor Pulmonale by Mechanism of Pulmonary Hypertension

I. Hypoxic vasoconstriction
   A. Chronic bronchitis and emphysema, cystic fibrosis
   B. Chronic hypoventilation
      1. Obesity
      2. Sleep apnea
      3. Neuromuscular disease
      4. Chest wall dysfunction
   C. High-altitude dwelling and chronic mountain sickness (Monge's disease)

II. Occlusion of the pulmonary vascular bed
   A. Pulmonary thromboembolism, parasitic ova, tumor emboli
   B. Primary pulmonary hypertension
   C. Pulmonary venocclusive disease/pulmonary capillary hemangioma
   D. Sickle cell disease/sickle crisis/marrow embolism
   E. Fibrosing mediastinitis, mediastinal tumor
   F. Pulmonary angiitis from systemic disease
      1. Collagen vascular diseases
      2. Drug-induced lung disease
      3. Necrotizing and granulomatous arteritis

III. Parenchymal disease with loss of vascular surface area
   A. Bullous emphysema, alpha$_1$ antiproteinase deficiency, hyperinflation
   B. Diffuse bronchiectasis, cystic fibrosis
   C. Diffuse interstitial disease
      1. Pneumoconiosis

2. Sarcoid, idiopathic pulmonary fibrosis, histiocytosis X
3. Tuberculosis, chronic fungal infection
4. Adult respiratory distress syndrome
5. Collagen vascular disease (autoimmune lung disease)
6. Hypersensitivity pneumonitis

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) causes cor pulmonale through several interrelated mechanisms, including hypoventilation, hypoxemia from ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch, and reduction of perfused surface area.[9,10] Patients with more prominent hypoxemia and alveolar hypoventilation develop erythrocytosis, edema, and early onset of cor pulmonale ("blue bloaters").[10] Patients in whom dyspnea on exertion is the most prominent symptom have less hypoventilation and less hypoxemia at rest and therefore develop cor pulmonale later ("pink puffers"). Some of the differences between blue bloaters and pink puffers may relate to ventilatory drives; patients with low drives may be more likely to fit the blue-bloater category, whereas pink puffers strive to maintain normal arterial pH and gas tensions.[12] Another hypothesis is that blue bloaters have more inflammatory bronchitis and that pink puffers suffer more from pure emphysema.[10] *Physical examination* in advanced COPD shows an increase in the thoracic diameter, flattened diaphragms, hyperresonance to percussion, decreased breath sounds with expiratory wheezes, distant heart sounds, distended neck veins during expiration, and a palpable liver. Liver enlargement and leg edema are manifestations of fluid retention, and right-sided heart failure and may or may not be present. The *chest roentgenogram* may show characteristic changes of emphysema such as hyperlucent lungs, bullae, increased anteroposterior (AP) diameter, and flattened diaphragms. In some cases, increased bronchovascular markings and air bronchograms suggest the presence of thickened or inflamed airways. On the other hand, the chest roentgenogram may not show characteristic findings or be indicative of the severity of the physiologic impairment. Pulmonary function tests show an increased residual volume and total lung capacity, decreased forced vital capacity (FVC), and markedly decreased expiratory flow rates (FEV_1, FEF_{25-75}). Arterial blood studies at rest can be normal when disease is mild but in severe disease show decreased P_{O_2}, increased P_{CO_2}, and decreased pH. With cor pulmonale, P_{O_2} is likely to be below 55 mmHg. Desaturation increases with exercise and frequently during sleep. The $\dot{V}/\dot{Q}$ inequality and alveolar hypoventilation both contribute to the hypoxemia. A P_{CO_2} above 45 mmHg at rest defines net alveolar hypoventilation. Asthma is a form of COPD that rarely, if ever, leads to chronic cor pulmonale, probably because asthma is usually a disease of intermittent airways obstruction.

Cor pulmonale in COPD is related to the severity of lung dysfunction, and pulmonary hypertension is a manifestation of advanced disease. Exercise limitation in COPD is usually due to limitation of ventilatory capacity, not cardiac reserve, although sedentary patients develop deconditioning, which reduces exercise performance. No single test of lung function-such as spirometry, lung volumes, carbon monoxide diffusing capacity (DL_{CO}), blood gas tension, or radiography-is highly predictive of cor pulmonale because abnormalities such as reduced surface area and hypoxic vasoconstriction add independently to pulmonary artery pressure.[10]

Diffuse Interstitial Lung Disease

These patients have dyspnea, tachypnea, exercise intolerance, and occasionally clubbing of the digits. Basilar crackles are heard frequently on auscultation of the chest and may persist throughout inspiration. The *chest roentgenogram* shows diffuse reticular, reticulonodular, or

fibrotic lesions, but the appearance does not always correlate well with physiologic impairment. In some disease presentations, such as desquamative interstitial pneumonitis, there may be an alveolar filling pattern with air bronchograms. A lung biopsy frequently is required to identify the basic pathologic process, and even then the exact etiology may not always be determined. Transbronchial biopsy can be diagnostic in some interstitial diseases such as sarcoidosis, and bronchoalveolar lavage may point to a diagnosis in many cases.[13] *Pulmonary function tests* show a restrictive process with reduced lung volumes, decreased compliance, and decreased diffusing capacity without airway obstruction. The vital capacity is reduced, and the forced expiratory volume in 1 s (FEV_1) as a percentage of FVC is usually at least 80 percent. At first, P_{O_2} decreases during exercise but is kept at normal levels at rest by hyperventilation. As the disease becomes more severe, P_{O_2} is low at rest. The course and prognosis of interstitial lung disease depend on the specific etiology, and there is wide variation among and within diseases.[13]

The presence of cor pulmonale in interstitial lung disease implies extensive lung dysfunction, perhaps with vascular involvement (as in systemic lupus erythematosus), and cor pulmonale may not occur even in end-stage disease. Treatment of idiopathic pulmonary fibrosis frequently is unsatisfactory despite the use of high-dose corticosteroids and either cyclophosphamide or azathiopirine. Recent trials using interferon-alpha with corticosteroids show promise of improved efficacy.[14]

Hypoventilation Syndromes

Some disorders (i.e., kyphoscoliosis) may impair or restrict mechanisms of ventilation, causing general alveolar hypoventilation and alveolar hypoxia.[15] Extreme obesity may be associated with hypoventilation, cyanosis, polycythemia, and somnolence (without intrinsic lung disease), often called the *pickwickian syndrome*.[16] Patients with daytime somnolence, morning headaches, and personality disturbances have been found to have periodic apnea during sleep associated with sleep deprivation, loud snoring, hypoxemia, and hypercapnia caused by upper airway obstruction (i.e., by the tongue, enlarged tonsils, or collapse of pharyngeal walls). Brainstem abnormalities such as Arnold-Chiari malformation also may cause respiratory center depression and primary hypoventilation. Neuromuscular diseases such as postpolio syndrome and chronic Guillain-Barré syndrome may present with cor pulmonale and right-sided heart failure.[17] Diagnosis of hypoventilation is confirmed by blood gas analysis, a depressed ventilatory response to inhaled CO_2, tests of pulmonary hypoventilation, or sleep studies. It has become apparent that disordered ventilation during sleep is a major component of many hypoventilation syndromes.[18] In all cases of hypoventilation, the main stimulus for pulmonary hypertension is hypoxic vasoconstriction, a response of the pulmonary arterioles to alveolar hypoxia. The respiratory acidosis that may accompany hypoventilation augments the vasoconstrictor response to hypoxia. Noninvasive assisted nocturnal ventilation with continuous positive airway pressure (CPAP), with or without added O_2 is the most efficacious therapy in most patients with nocturnal hypoventilation.[17]

Pulmonary Vascular Disease

Chronic cor pulmonale is a consequence of several diseases that involve the pulmonary vessels. Primary pulmonary hypertension and recurrent (or unresolved) pulmonary emboli are described in detail in Chaps. 59 and 60. Sickle cell disease, from SS or SC hemoglobinopathy, can cause cor pulmonale after multiple episodes of pulmonary infarction from focal pulmonary sickling, fat embolism, or thromboembolism.[18,19] Pulmonary venoocclusive disease is a rare disease of the pulmonary veins that presents with pulmonary hypertension and variable pulmonary infiltrates. It occasionally occurs in human immune deficiency virus (HIV) infection and after bone marrow transplantation.[20]

Cirrhosis of the liver is usually associated with pulmonary vasodilatation, but occasionally a

disorder clinically and pathologically identical to primary pulmonary hypertension emerges.[21] HIV infection is a new cause of pulmonary vascular disease resembling primary pulmonary hypertension.[22] Collagen-vascular disease can cause cor pulmonale by primary vasculitis as well as by diffuse interstitial fibrosis. Systemic sclerosis, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) are the collagen-vascular diseases that most commonly cause pulmonary arteritis. Patients with SLE and RA frequently present with primary interstitial lung disease. Occasionally, the presentation is that of cor pulmonale without interstitial disease but with primary pulmonary arteritis.[23] Cor pulmonale is not reported as a feature of Goodpasture's syndrome or idiopathic pulmonary hemosiderosis. Historically, dietary pulmonary hypertension has occurred as a result of the use of Aminorex in Europe, contaminated canola oil in Spain, and in eosinophilia myalgia syndrome in the United States related to contaminated tryptophan.[24] The new anorectic drug dexfenfluramine has caused pulmonary hypertension in France and recently has been banned in the United States by the Food and Drug Administration (FDA) because of its association with primary pulmonary hypertension and perhaps valvular dysfunction.[25]

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Chapter 54: CHRONIC COR PULMONALE

PATHOPHYSIOLOGY

Increased pulmonary vascular resistance (PVR) and pulmonary hypertension are central mechanisms in all cases of cor pulmonale.[10] Physiologic mechanisms of pulmonary arterial pressure are shown in Table 54-2. These variables can be described in part by Poiseuille's law. Fortunately, most pulmonary diseases and disorders do not produce enough pulmonary hypertension to cause cor pulmonale.

Table 54-2: Genesis of Pulmonary Vascular Pressure: Poiseuille's Law

Flow = cardiac output (usually ↑ elevated in COPD; if PRV is fixed. ↑ CO will ↑ PAP).
= numerical constant related to tubular structure of vessels.
n = blood viscosity (increased in polycythemia vera, secondary erythrocytosis, and cryoglobulinemia).
N = number of perfused vessels of a particular radius. *N* is decreased in any occlusive or destructive disease (see Table 61-1). *N* for pulmonary capillaries is >200 million.
= radius of a vessel is a critical determinant of flow (*r* is decreased by vasoconstriction, luminal obstruction, or hyperinflation. A change in *r* from 1to 2 units changes resistance 16-fold).
Pla = left atrial pressure. Passive pulmonary hyperten- sion can result from left atrial pressure elevation due to either LV or valvular disease.

Normal Pulmonary Circulation

The primary function of this unique high-flow, low-pressure, low-resistance system is to provide blood for gas exchange, and it is ideally structured for this function. It receives and transmits the entire cardiac output at low hydrostatic pressures primarily because of three characteristics: (1) the pulmonary arteries are thin-walled with little resting muscular tone, (2) there is negligible vasomotor control by the autonomic nervous system at rest in the adult, and (3) many small arterioles and alveolar capillaries produce a high surface area that can be recruited when needed to expand the pulmonary vascular bed, resulting in a decreased PVR. Normal mean pulmonary artery pressure (PAP) is about 12 to 17 mmHg; PAP above 20 mmHg at rest suggests pulmonary hypertension. Flow of blood from the main pulmonary artery (PA) through the pulmonary capillaries to the left atrium is accomplished by a pressure drop of only 5 to 9 mmHg, compared with an arterial-to-venous gradient of 90 mmHg in the systemic circuit. Thus normal PVR is 10- to 20-fold less than systemic vascular resistance.

Pulmonary Hypertension

The effective cross-sectional area of the pulmonary vascular bed must be reduced by 25 to 50 percent before any change in PAP can be detected at rest. Exercise causes increased PAP because of increased pulmonary blood flow in the normal bed, and exercise will dramatically raise PAP if the vascular bed is reduced. Obliterative vascular diseases increase PVR by vascular luminal occlusion, whereas diffuse interstitial diseases act primarily by compression and obliteration of small vessels. Hyperinflation in COPD increases PVR partly by compressing intraalveolar vessels, reducing the cross-sectional area of the bed. It is now well established, however, that arteriolar constriction resulting from alveolar hypoxia is the predominant cause of pulmonary hypertension in chronic airways diseases.[1,10,26,27]

PULMONARY ARTERIOLAR CONSTRICTION

The most important cause of pulmonary vasoconstriction is alveolar hypoxia. The mechanism of hypoxic pulmonary vasoconstriction is unknown. It is thought to be due either to mediator release from some unknown effector cell or a direct action of hypoxia on pulmonary vascular smooth muscle K channels.[28,29] The degree of hypoxic vasoconstriction depends primarily on the alveolar P_{O_2}, and when alveolar P_{O_2} is less than 55 mmHg, PAP rises sharply (Fig. 54-1). When PAP is greater than 40 mmHg due to hypoxia, arterial oxygen saturation is very likely less than 75 percent.[26] There is large individual variability in the hypoxic pressor response, and hypoxic vasoconstriction is enhanced by acidosis and blunted by alkalosis. Acidosis also has a mild direct pressor effect on the pulmonary circulation.[28] Extensive investigations into the mechanism of hypoxic vasoconstriction have shown that many local and circulating mediators of pulmonary vascular tone are capable of modulating the hypoxic pressor response but that no single mediator yet discovered is solely or predominantly responsible[28] (Table 54-3).

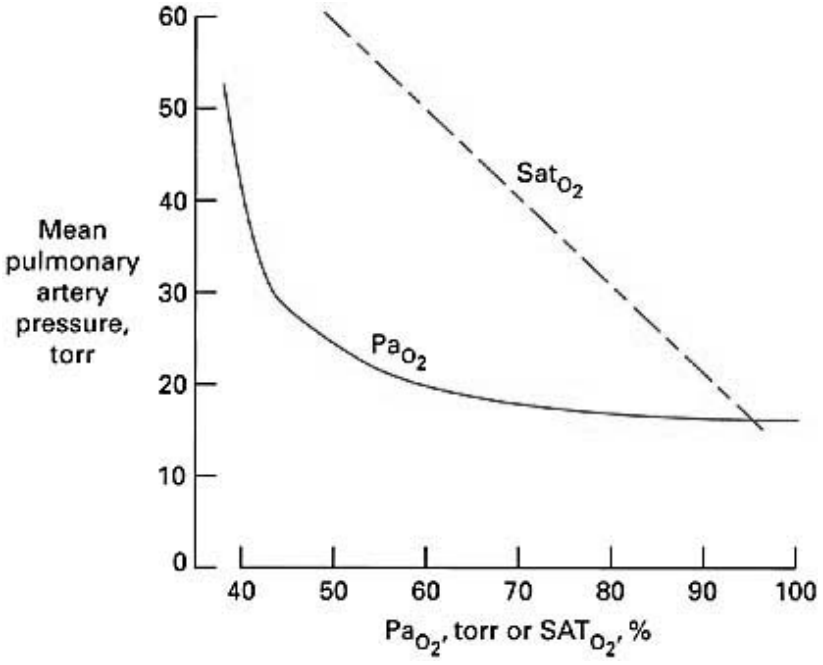


Figure 54-1: Pulmonary arterial pressure as a function of Pa_{O_2} or oxyhemoglobin saturation in humans. Pulmonary arterial pressure rises sharply as Pa_{O_2} decreases below 55 mmHg. (Redrawn from Reeves JT, Grover RF. High altitude pulmonary hypertension and pulmonary edema. *Prog Cardiol* 1975; 4:105, and from Burrows B. Anaerobic infections of the lung and pleural space. *Am Rev Respir Dis* 1974; 110:64, with permission.)

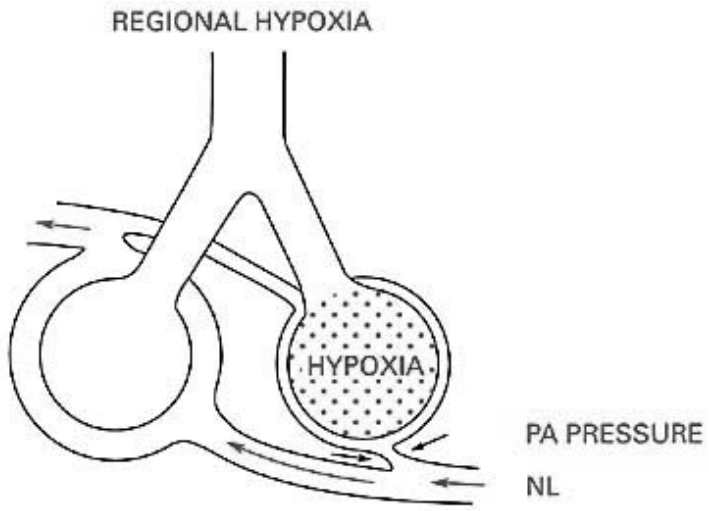
Table 54-3: Endogenous Pulmonary Vasomotor Tone

Dilator	Constrictor
Beta-adrenergic	Alpha-adrenergic agonists
Histamine H_2	Histamine H_1
Prostacyclin (PGI_2), PGE_1	PGE_2, PGF_{1a}, Thromboxane A_2 PGD_2
Acetylcholine*	Serotonin
Oxygen	Hypoxia

Bradykinin	Angiotensin II
Vasoactive intestinal polypeptide	Platelet activating factor>Endothelin
Nitric oxide	Leukotriene C_4/D_4
Atrial natriuretic peptide	Vasopressin
Adenosine	

*The response of the pulmonary vascular bed is tone-dependent. When the pulmonary circulation is preconstricted, acetylcholine is a vasodilator through the release of endothelium-derived NO.

Hypoxic vasoconstriction in a region of lung where ventilation is diminished probably serves to maximize net arterial oxygenation by diverting blood from the hypoxic region to better-ventilated areas. Because the pulmonary vascular bed is capable of significant recruitment, localized hypoxic vasoconstriction does not cause pulmonary hypertension. Generalized hypoxia causes generalized hypoxic vasoconstriction and the development of pulmonary hypertension (Fig. 54-2). In COPD, the first episodes of alveolar hypoxia may occur during sleep, and it gradually becomes more prevalent thereafter.[30] Any cause of alveolar hypoventilation (see Table 54-1) can result in chronic cor pulmonale through the mechanism of hypoxic pulmonary vasoconstriction, including entities as different as diffuse emphysema and kyphoscoliosis[9,15] (see also Chap. 59).



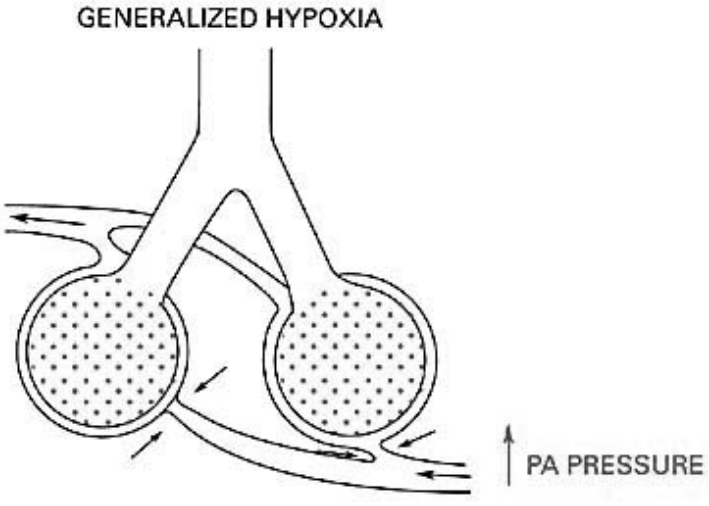


Figure 54-2: Hypoxic pulmonary vasoconstriction maximizes arterial oxygenation by diverting blood away from areas of regional hypoxia toward better-ventilated zones. Generalized hypoxia causes generalized hypoxic vasoconstriction and results in pulmonary hypertension. (From Newman JH. Pulmonary vascular reactivity in primary pulmonary edema. *Semin Respir Med* 1983; 4:299; reproduced with permission of the publisher. Courtesy of J. V. Weil.)

OTHER CONTRIBUTIONS TO PULMONARY HYPERTENSION

Increases in cardiac output and blood volume or direct effects of acidosis and/or hypoxia on the myocardium may contribute to pulmonary hypertension. Increased blood flow such as occurs with exercise engenders an increased PAP, and in such a situation, the effects of hypoxia and acidosis also will be exaggerated.[26] Sustained or repetitive severe hypoxemia causes secondary erythrocytosis. Blood viscosity increases rapidly after the hematocrit exceeds about 55 percent, raising PVR and also decreasing cerebral function. If left ventricular failure (LVF) is superimposed on an already reduced pulmonary vascular bed, pulmonary hypertension will be augmented by elevated downstream left atrial pressure. Once established, pulmonary hypertension may be self-perpetuating. A sustained increase in PAP in patients with diffuse lung disease causes muscular hypertrophy in the walls of small arteries, with extension of muscle toward alveolar vessels, further increasing PVR and PAP. Chronic hypoxia alone results in muscularization of pulmonary arterioles and exaggerated increases in PAP with stimuli.[26,31]

Right Ventricular Response to Pulmonary Hypertension

The right ventricle is thin-walled and eccentric and better able to handle an increase in volume load than to meet an increased pressure load.[10] The primary cause of right ventricular strain and failure (RVF), therefore, is a chronic pressure load (afterload). Small increases in PAP may result in large increases in right ventricular work. Pulmonary hypertension at rest indicates a high baseline resistance, and small changes in blood flow will cause large increases in PAP.

Response of the right ventricle to pulmonary hypertension depends on the acuteness and severity of the pressure load. Acute cor pulmonale (see Chaps. 59 and 60) occurs after a sudden and severe stimulus (i.e., massive pulmonary emboli) with ventricular dilatation and failure but without hypertrophy. Acute cor pulmonale may develop within minutes to hours. Chronic cor pulmonale, however, is associated with a more slowly evolving and slowly progressive hypertension,[33] and the response involves increased protein synthesis and right ventricular hypertrophy (RVH).[34] The severity of the hypertension, the rapidity with which it becomes severe, and the possible eventual onset of RVF are influenced by factors that intercede intermittently, such as (1) *alterations in ventilatory function,* causing alveolar pressure changes with effects on chamber function, (2) *alterations in gas exchange,* with more or less severe hypoxemia, hypercapnia, and acidosis, and (3) *alterations in volume load,* as influenced by exercise, heart rate, polycythemia, or renal retention of salt and water associated with cor pulmonale. At some stage, the myocardium is unable to function at the high-pressure load, dilates, and fails. RVF may occur relatively early in some patients with chronic bronchitis and emphysema because of sustained hypoxemia and hypercarbia, but it occurs later in patients with diffuse interstitial lung disease because the degree of RVH helps to maintain blood flow even when PAP is high.[33] Extreme pulmonary hypertension and RVH can occur in normal persons living at high altitude (>10,000 ft, or 3033 m) with no evidence for heart failure.[34] Thus the right ventricle can develop into an efficient high-pressure pump over time and sustain normal function for months to years.

Left Ventricular Function in Cor Pulmonale

Dysfunction of the left ventricle occurs in some patients with cor pulmonale, but the evidence available indicates that cor pulmonale per se does not cause disease of the left side of the heart. The likelihood in most cases is that left-sided heart dysfunction coexisting with cor pulmonale results from other known causes, such as coronary ischemia or systemic hypertension. Left ventricular failure is a serious complication in cor pulmonale because the increase in left atrial pressure and in lung water further impairs lung function, increases the work of breathing, increases PAP, impairs gas exchange, and may induce

respiratory failure. When underlying disease of the left ventricle is present, the direct effects of hypoxia, hypercapnia, and acidosis arising from primary lung disease may precipitate left ventricular failure.[10,35,36]

Several lines of evidence point to mechanical effects of lung dysfunction and right ventricular dilatation on performance of the left ventricle.[36,37] Wide swings in transpulmonary pressure in obstructive lung disease can reduce left ventricular filling and increase left ventricular afterload.[38] Hypertrophy and elevated end-diastolic pressure of the right ventricle in cor pulmonale can reduce left ventricular compliance and impair left ventricular filling through effects on the shared ventricular septum.[39] Despite these effects, most patients with chronic cor pulmonale demonstrate normal resting cardiac output, normal pulmonary artery wedge pressure, and normal resting left ventricular ejection fraction.[40] The majority of patients with abnormal left ventricular ejection fraction in either compensated or decompensated chronic lung disease probably have demonstrable coronary artery disease.

Edema Formation and Cor Pulmonale

Peripheral edema occurs in some cases of chronic cor pulmonale. The mechanism of edema formation is poorly understood but is probably related to increased systemic venous pressure, hypercarbia, and hypoxemia.[10,41] The presence of pulmonary hypertension per se does not appear to be sufficient to cause fluid retention until right atrial pressure becomes elevated. Decreased clearance of aldosterone from the passively congested liver contributes to salt retention but is likely not an initiating event. Plasma volume is increased, however, in chronic cor pulmonale.[10]

Hypercarbia stimulates plasma renin activity, and hypercarbic, edematous patients with COPD have increased plasma levels of aldosterone and antidiuretic hormone.[42,43] This pattern occurs despite oxygen therapy in these patients. Thus not only increased salt retention but also impaired water excretion contributes to edema in chronic hypercapnia. Atrial natriuretic peptide is elevated in cor pulmonale in response to elevated right atrial pressure and perhaps acidosis.[10] Severe hypoxemia is associated with reduced renal blood flow and glomerular filtration rate and a decrease in urine sodium excretion.[10] Other mechanisms of edema formation are increased systemic capillary hydrostatic pressure, related to increased venous pressure and blood volume; and perhaps inappropriate release of arginine vasopressin.[10] Many mechanisms appear to be operating to produce edema in chronic cor pulmonale, several of which are related to the primary pulmonary dysfunction, especially in COPD. The exact mechanisms and sequence of events leading to edema are difficult to determine in any specific case. Pulmonary edema and pleural effusion are not seen as a consequence of chronic cor pulmonale.

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CLINICAL MANIFESTATIONS OF COR PULMONALE

Symptoms

Clinical manifestations of cor pulmonale are often obscured by the signs and symptoms of underlying disease and therefore are closely related to the pulmonary disease or disorder. It is necessary first to recognize the type and severity of lung disease and then to look for cor pulmonale.

There is no history that is specific for cor pulmonale. Episodes of leg edema, atypical chest pain, dyspnea on exertion, exercise-induced peripheral cyanosis, prior respiratory failure, and excessive daytime somnolence are all historical clues suggesting the presence of cor pulmonale. Chest pain may be due to strain or distortion of the chest wall (musculoskeletal) or may be related to right ventricular ischemia. Cough and complaints of easy fatigability are common. Some patients with nocturnal hypoventilation and sleep apnea may present with personality changes, mild systemic hypertension, and headache. Shortness of breath is nearly a universal symptom in cor pulmonale. The degree of activity that leads to dyspnea should be quantified because patients reduce activities to avoid dyspnea. Thus the naive question of whether a patient is short of breath may lead to a negative reply because the patient is less and less active. Abdominal pain may result from liver and bowel congestion if RVF is present.

Physical Examination

The earliest signs are those associated with long-standing pulmonary hypertension. The most sensitive sign for pulmonary hypertension is an accentuated pulmonary component of S_2, which also may be palpable in the pulmonic area, and right ventricular lift of the sternum may be seen. With very high PAP, characteristic diastolic and systolic murmurs of pulmonary valvular and tricuspid valvular regurgitation may be heard together with a systolic ejection sound and right ventricular S_3 gallop. In overt RVF, cardiac enlargement, distended neck veins, hepatomegaly, and peripheral edema are present. Symptoms or signs suggestive of heart failure-such as dyspnea, orthopnea, peripheral edema, palpable liver, and distended neck veins-however, can be observed in patients with COPD without RVF. But when neck veins are distended during inspiration as well as expiration, RVF is more likely present. Hyperinflated lungs alter the position of the heart and frequently make the examination difficult. The apical impulse and the right ventricular lift are often not palpable, and the right ventricular S_3 gallop may be heard in the epigastrium. In emphysema, the heart sounds may be best heard in the subxiphoid area. Extremities may be warm due to peripheral vasodilatation caused by hypercapnia, or there may be cyanosis due to low flow or hypoxemia.

ELECTROCARDIOGRAM

Electrocardiographic patterns are influenced by many factors such as PAP, rotation, and displacement of the heart by hyperinflated lungs, arterial blood gases, myocardial ischemia, and metabolic disturbances. The value of the electrocardiogram (ECG) in diagnosis of cor pulmonale, therefore, depends on the underlying disease and complicating conditions. Absence of changes indicating right ventricular disease does not rule out cor pulmonale because the ECG may be

normal in advanced cor pulmonale. An example of RVH is shown in Fig. 54-3. The standard criteria for right ventricular enlargement were absent in two-thirds of patients with COPD who had RVH on postmortem examination.[1] It has been suggested that when classic RVH changes are absent, diagnosis should be based on the combination of rS in V_5 to V_6, RAD, qR in aV_R, and P pulmonale.[44] Tall peaked P waves in leads II and aV_F may reflect positional changes rather than right atrial enlargement. Right bundle-branch block occurs in about 15 percent of patients. A pattern of S_1, Q_3, and T_3 carries reasonable sensitivity and specificity for cor pulmonale in COPD.[45] Arrhythmias are infrequent in uncomplicated cor pulmonale, but when present, they are mostly supraventricular and may reflect blood gas abnormalities, hypokalemia, or excess of drugs such as digitalis, theophylline, and beta agonists. Multifocal atrial tachycardia is associated with decompensated COPD and is best treated by attention to the underlying disease rather than by antiarrhythmic drugs. Ventricular arrhythmias, when they occur, are associated with a high mortality.

CHEST ROENTGENOGRAM

The radiographic findings of pulmonary hypertension in patients with normal lung parenchyma (such as in primary pulmonary hypertension) are well described[46,47] (Fig. 54-4). Most diseases that cause cor pulmonale have grossly abnormal chest roentgenograms, and the radiologic diagnosis of pulmonary hypertension in these diseases is more difficult. Right ventricular enlargement may be difficult to detect in the vertical heart of emphysema, and comparison with previous films may be helpful. In the most obvious cases of cor pulmonale, there is right ventricular and PA enlargement, but pulmonary hypertension precedes right ventricular dilatation. One indicator of pulmonary hypertension is measurement of the dimensions of the right and left PAs. Enlargement is considered to exist if the diameter of the right descending PA is greater than 16 mm and the left descending PA is greater than 18 mm.[48] These findings occurred in 43 of 46 patients with known pulmonary hypertension, but the true sensitivity and specificity of these measurements are not known.

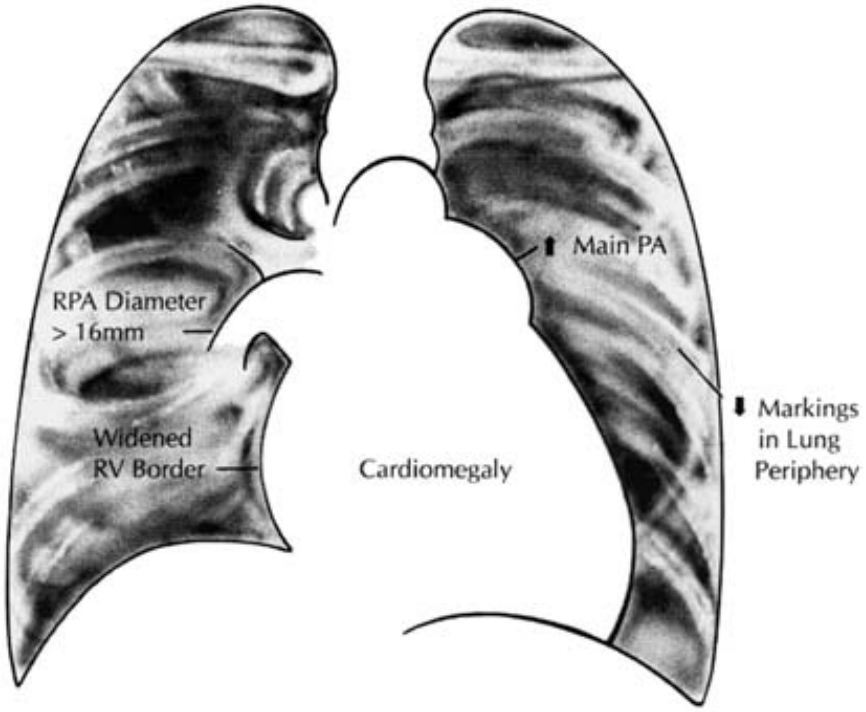

Figure 54-4: Classic features of the chest radiograph in severe pulmonary hypertension. The

enlarged pulmonary arteries can be mistaken for hilar adenopathy, and the large main pulmonary artery obscures the aortic arch. Right descending PA diameter greater than 16 mm suggests severe pulmonary hypertension.

ECHOCARDIOGRAM

Advances in echocardiography make this a useful test where cor pulmonale is suspected.[49] The standard M mode reliably detects right ventricular dilatation and is best able to display the anteriormost right ventricular wall near the interventricular septum. Two-dimensional echocardiography allows improved visualization of right ventricular chamber size and wall thickness, as well as changes in the interventricular septum resulting from RVH.[49,50] Because the right ventricle is asymmetric, measurement of right ventricular volume is difficult even with twodimensional views. Right ventricular pressure overload usually is detected by hypertrophy of the anterior right ventricular wall and by dilatation of the chamber. Hypertrophy of the septum can be found, and paradoxical septal encroachment into the left ventricular chamber can be seen in severe cor pulmonale.[53] Right ventricular volume overload, as in atrial septal defect, causes dilatation as the predominant finding, often in association with abnormal ventricular septal motion.[51]

Echo-Doppler techniques have become the noninvasive standard to detect pulmonary hypertension and to measure cardiac output. These techniques are relatively accurate when PAP is above 30 mmHg, but they may not detect milder but pathologic pulmonary hypertension.[52, 53] Echo Doppler is useful for longitudinal follow-up of pharmacologic treatment of pulmonary hypertension and cor pulmonale.

RIGHT-SIDED HEART CATHETERIZATION

Right-sided catheterization is the only technique available for the direct measurement of PAP, PA wedge pressure, and cardiac output. It is occasionally important in differentiating cor pulmonale from left ventricular dysfunction when the clinical presentation is confusing. This is especially true in patients with primary pulmonary hypertension (PPH) or unresolved pulmonary emboli, where airway function may appear normal, or with restrictive cardiomyopathy (see Chap. 75). In cor pulmonale, PA diastolic pressure is usually significantly higher than wedge pressure, unlike LVF or mitral stenosis, where the diastolic-wedge pressure gradient is smaller in most patients. Mean PAP can be very high in obliterative vascular diseases but only moderately high in interstitial lung diseases.[36] In COPD, PAP is related to the level of hypoxemia; it is not usually as severely increased as in PPH and generally will be decreased by chronic oxygen administration.[26,54,55] About 50 percent of patients with severe COPD have pulmonary hypertension at rest; in those patients with normal resting values, PAP may rise with exercise.[10,54] Serial catheterization in patients with COPD and pulmonary hypertension has revealed remarkable stability of pulmonary hemodynamics.[56]

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USUAL STRATEGY OF WORKUP

Because of the diversity of diseases that cause cor pulmonale, no single strategy of workup exists. When lung parenchymal or airways disease is present, pulmonary function tests frequently will reveal the nature and degree of impairment.[57] Spirometry, lung volumes (functional residual capacity), DL_{CO}, and an arterial blood sample for pH, P_{O_2}, and P_{CO_2} should be obtained.

Transbronchial biopsy via a fiberoptic bronchoscope, bronchoalveolar lavage, and open lung biopsy are diagnostic options in patients with interstitial lung disease. If the hematocrit is above 50 percent, it gives a clue to the presence of chronic hypoxemia, nocturnal hypoventilation, or polycythemia vera. Patients with cryptogenic pulmonary hypertension should receive a perfusion radionuclide lung scan to detect pulmonary emboli or other causes of obstruction of the pulmonary arteries such as fibrosing mediastinitis. If pulmonary vasculitis is suspected, serum can be screened for the presence of antinuclear antibody, hepatitis B surface antigen, rheumatoid factor, and cryoglobulins. Factor V_{Leiden} is likely to be a frequent abnormality in thrombotic pulmonary hypertension,[58] and the antiphospholipid antibody syndrome may cause cor pulmonale.[59]

Polysomnography should be performed in patients with cor pulmonale and any sign or symptoms of sleep apnea. Exercise tests occasionally will reveal desaturation or ventilatory limitations that denote significant lung dysfunction not appreciated on examination at rest. Echo Doppler is an important addition to the noninvasive workup of a patient suspected to have pulmonary hypertension.

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NATURAL HISTORY AND PROGNOSIS

Prognosis depends more on control of the underlying lung disease than on control of pulmonary hypertension in most cases. Patients with COPD have hypoxic pulmonary hypertension that is partially reversible, and RVF can be improved with appropriate therapy. Even with repeated episodes of RVF, some patients have long survivals.[1,10] The pink puffers tend to live longer than the blue bloaters.[10] Once RVF occurs, prognosis is poor; patients with COPD receiving nasal oxygen have about a 50 percent 2-year survival, but some patients survive for 5 to 8 years.[27] In patients with alveolar hypoventilation but no alteration in lung structure, the natural history is one of progressive worsening of pulmonary hypertension due to sustained hypoxemia and hypercapnia. If alveolar ventilation is improved prior to the development of nonreversible changes in vessel walls, the prognosis is good.

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MEDICAL TREATMENT

The underlying lung disease is the focus of therapy and is the best way to reduce the right ventricular pressure work associated with the disease. If RVF has not appeared, a major goal is to prevent its onset. When it appears, it should be treated, but the response will be poor unless cardiac work is reduced by control of pulmonary hypertension.

Treatment to Decrease Pulmonary Hypertension

Relief of hypoxia is of prime importance in reducing pulmonary hypertension, both to prevent and to treat cor pulmonale. This may be done in two ways: (1) treatment of the underlying disease and (2) O_2 administration.[55] Neither will lower PAP in all patients because hypertension is often intractable in those with an anatomic restriction of the pulmonary vascular bed. Most patients with chronic cor pulmonale have a component of hypoxic pulmonary vasoconstriction, and all patients should be treated with oxygen in amounts adequate to restore arterial O_2 tension to greater than 60 mmHg. Corticosteroids may be helpful in some patients with interstitial lung disease and in patients with a bronchospastic component of COPD. Measures should be instituted to treat the systemic disease with which obliterative vascular disease is associated or to prevent further pulmonary emboli if this is the problem.

In COPD, the primary focus is relief of hypoxemia by restoration of effective ventilation or by O_2 administration. Net alveolar ventilation may be improved by therapy, including bronchodilators for bronchospasm, antibiotics to prevent or treat acute exacerbations of bronchitis, bronchial toilet for removal of secretions, and avoidance of airway irritants such as tobacco smoke. Nocturnal aspiration of gastric fluid is now known to be a common cause of exacerbation of chronic lung disease. Tranquilizers, sedatives, and narcotics should be avoided in unstable patients and patients with hypoventilation. Correction of hypoxia and acidosis may produce a striking reduction in PAP. In diseases that alter lung function but not structure, effective alveolar ventilation must be restored by treatment of the underlying disease or by use of mechanical ventilation. Short-term ventilatory stimulants may be useful in some cases of decreased ventilatory drives, although nasal CPAP has become the first choice in most cases of sleep apnea.[10]

Adequate oxygenation may prevent the onset of heart failure, both acutely and over a long period of time. Any patient with cor pulmonale and RVF should be given sufficient O_2 to restore P_{O_2} to levels above 60 mmHg, but it should be given cautiously when P_{CO_2} is high and the threat of respiratory acidosis is present. Oxygen therapy is usually well tolerated in patients with stable lung disease but not in patients with acute acidosis or respiratory muscle fatigue. When low-flow nasal O_2 causes significant increases in P_{CO_2}, mechanical ventilation may be required to relieve hypoxia. Studies have shown conclusively that home oxygen therapy, nocturnal or continuous, is beneficial in keeping patients with severe COPD functioning better for longer periods of time; it may be effective both in treating cor pulmonale and in postponing its onset.[27,55] Continuous 24 h/day oxygen therapy is the desired goal in most patients, because desaturation occurs during both sleep and physical activity.

Treatment of Heart Failure

Cor pulmonale is heart disease, and while treatment of the lung disease and relief of hypoxia are necessary to reduce cardiac work, general principles of management of heart failure apply. Diuretics and phlebotomy can be appropriate measures for treatment of RVF. Pulmonary vasodilators are efficacious in some patients with primary pulmonary hypertension but are of unproven value in cor pulmonale from COPD.[61]

Beneficial effects of digitalis are not as obvious as in LVF, and arrhythmias caused by digitalis may occur at relatively low serum levels in patients with hypoxia and acidosis. Susceptibility to digitalis intoxication is enhanced in pulmonary disease.[62] Its use in cor pulmonale therefore has been controversial. Nevertheless, studies have shown that *digitalis improves right ventricular function in cor pulmonale, and it is an appropriate drug for treatment of RVF when given cautiously and at carefully controlled dosage levels*.[63] It should not be used during the acute phases of respiratory insufficiency when there are large fluctuations in levels of hypoxemia and acidosis but is reserved for the time when the patient is stabilized. Heart rate in this setting cannot be used as a guide for the level of digitalization. It is also reasonable to question whether or not patients with cor pulmonale who continue to have overt RVF after relief of hypoxemia in intensive therapy for the underlying lung disease will benefit from the use of digitalis. Digitalis is appropriate if there is known or suspected concurrent left ventricular systolic dysfunction.

Vasodilator therapy to reduce right ventricular afterload has been recognized as a potential treatment strategy for several years. Vasodilator therapy has the disadvantage of being secondary therapy that is not aimed at the primary lung dysfunction. Vasodilator use has not become widespread because of small observed reductions in pulmonary hypertension and occasional worsening of gas exchange.[61]

Diuretics are effective in the treatment of RVF, and indications for their use are the same as in other forms of heart disease. Pulmonary function is improved by diuretics in patients with COPD who have hypervolemia.[64] The effects of diuretics should be monitored carefully by measurement of arterial P_{O_2}, P_{CO_2}, and pH because acid-base abnormalities are often present in cor pulmonale. Contraction alkalosis can be a problem in hypercarbic patients with a large buffer base who have had vigorous diuresis.

When the hematocrit is above 55 to 60 percent, phlebotomy may reduce PAP and PVR and possibly improve right ventricular function.[65] The phlebotomy should be in small volumes (200-300 mL) and done cautiously.

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SURGICAL TREATMENT

There is no surgical treatment for most diseases that cause chronic cor pulmonale. Pulmonary embolectomy is extremely efficacious for unresolved pulmonary emboli causing chronic thrombotic pulmonary hypertension (see Chap. 60). Adenoidectomy in children with chronic airways obstruction and uvulopalatopharyngeoplasty in selected patients with sleep apnea can relieve cor pulmonale related to hypoventilation. Single-lung, double-lung, and heart-lung transplantations are all used for salvage in the terminal phase of several diseases complicated by cor pulmonale.[66] *The diseases most commonly treated by lung transplantation are primary pulmonary hypertension, emphysema, idiopathic pulmonary fibrosis, and cystic fibrosis*. Two-year survival for single- and double-lung transplant has risen to 60 percent, still lower than the approximately 80 percent for heart transplant alone. One interesting finding is that the right ventricle can recover function after lung transplant even after the chronic stress of severe pulmonary hypertension. Volume-reduction surgery for selected patients with emphysema improves ventilatory function and gas exchange, and the long-term benefit of this approach is under study.[67]

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Part 9: VALVULAR HEART DISEASE
Chapter 55:

ACUTE RHEUMATIC FEVER

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DEFINITION

Rheumatic fever is an inflammatory disease that occurs as a delayed nonsuppurative sequel to group A streptococcal infection of the pharynx. It involves the heart, joints, central nervous system, skin, and subcutaneous tissues with varying frequency. Its clinical manifestations include migratory polyarthritis, fever, carditis, and, less frequently, Sydenham's chorea, subcutaneous nodules, and erythema marginatum. Rheumatic fever is a clinical syndrome for which no specific diagnostic test exists. No symptom, sign, or laboratory test result is pathognomonic, although several combinations of them are diagnostic. Its importance relates to involvement of the heart, which, though rarely fatal during the acute stage, may lead to rheumatic valvular disease, a chronic and progressive condition that causes cardiac disability or death many years after the initial event.

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ETIOLOGY

Antecedent infection of the upper respiratory tract with the group A streptococcus is necessary for the development of rheumatic fever. Cutaneous streptococcal infection may lead to acute glomerulonephritis but has never been demonstrated to cause rheumatic fever. The evidence establishing the group A streptococcus as the etiologic agent of rheumatic fever is only indirect, because the organism cannot be recovered from the lesions and there is no experimental animal model. Nevertheless, the evidence from clinical, immunologic and epidemiologic studies is overwhelming.

At least one-third of patients deny previous sore throat, and cultures of the pharynx are often negative for group A streptococci at the onset of rheumatic fever. However, an antibody response to streptococcal extracellular products can be demonstrated in almost all cases,[1] and the attack rate of acute rheumatic fever is strongly correlated with the magnitude of the antibody response.[2]

A clear sequential relationship between outbreaks of streptococcal pharyngitis or scarlet fever and rheumatic fever has been demonstrated in epidemiologic studies of military recruit camps, and such outbreaks can be eradicated when streptococcal infection is controlled by chemotherapy.[3] Prompt and effective penicillin therapy of streptococcal pharyngitis prevents the initial attack of rheumatic fever (so-called primary prevention),[4] and continuous chemoprophylaxis against streptococcal infection (secondary prophylaxis) prevents its recurrences.[5]

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Chapter 55: ACUTE RHEUMATIC FEVER

EPIDEMIOLOGY

Rheumatic fever is a major health problem in the developing countries of Asia, Africa, the Middle East, and Latin America. It is difficult for physicians trained in North America to comprehend the magnitude of the problem. A World Health Organization survey conducted between 1986 and 1990 estimated the prevalence of rheumatic fever and chronic rheumatic heart disease per 1000 schoolchildren to be 12.6 in Zambia, 10.2 in Sudan, and 7.9 in Bolivia.[6] Hospital statistics from many developing countries reveal that 10 to 35 percent of all cardiac admissions are for rheumatic fever and rheumatic heart disease.[6,7] It has been estimated that there are at least 50,000 cases of rheumatic fever annually in India and more than 1 million people with rheumatic heart disease.[7] Exceedingly high attack rates have been reported among aboriginal populations in New Zealand and Australia.[8]

Acute rheumatic fever is most common among children in the 5- to 15-year age group. There is no clear-cut sex predilection, although there is a female preponderance in rheumatic mitral stenosis and in Sydenham's chorea. The attack rate of acute rheumatic fever following untreated exudative tonsillitis varies, depending upon the epidemiologic circumstances and the rheumatogenic potential of prevalent streptococcal strains. This rate has been reported to approximate 3 percent during epidemics in military recruit camps[9] but only 0.4 percent after endemically occurring infections in untreated children in civilian populations.[10] Acute rheumatic fever is more likely to occur after those streptococcal infections judged to be more severe by clinical and immunologic criteria (i.e., exudative tonsillopharyngitis, vigorous rises in serum titers of antistreptolysin O, and prolonged convalescent streptococcal throat carriage). Nevertheless, approximately one-third of the cases occur after asymptomatic streptococcal infections. A striking feature of the epidemiology of acute rheumatic fever is the propensity of patients who have suffered an initial attack to experience recurrences of the disease following group A streptococcal infections.

Strains of group A streptococci vary in their propensity to elicit acute rheumatic fever. Although the precise factor or factors that confer this property are unknown, highly rheumatogenic strains share certain biological characteristics. Only a limited number of the more than 90 streptococcal M-protein types have been strongly and repetitively associated with rheumatic fever.[11] These strains are often heavily encapsulated, a feature manifest by the formation of mucoid colonies on blood-agar plates. Their M-protein molecules share a particular surface-exposed antigenic domain against which rheumatic fever patients mount a strong immunoglobulin G response.[12] These characteristics were established, however, by study of rheumatic fever cases and outbreaks in the United States and Great Britain; they remain to be validated for cases occurring in third-world countries or among aboriginal populations.

The twentieth century witnessed a dramatic decline in the incidence of rheumatic fever and rheumatic heart disease in the industrialized nations.[13] The incidence of rheumatic fever and the prevalence of rheumatic heart disease are now very low in North America and western Europe. Rates fewer than 2 per 100,000 schoolchildren have been reported from several areas in the United States. The disease is very rare in affluent suburban populations[14] but persists among disadvantaged families dwelling in the crowded inner cities.[14,15] The higher incidence rates reported among blacks than among whites appear to be due to socioeconomic rather than genetic factors.

The reasons for the recent decline in the incidence of rheumatic fever in developed countries are multifactorial. One of the factors was likely an improvement in living standards, including a decrease in household crowding. Crowding favors interpersonal spread of group A streptococci and probably enhances streptococcal virulence by human passage. Although the diminution was well under way prior to the introduction of penicillin, this highly effective antimicrobial may have contributed to the decline in initial attacks of rheumatic fever and clearly contributed to a decrease in mortality by preventing repetitive attacks in patients compliant with programs of secondary prophylaxis.

There is no evidence of a decline in the frequency of streptococcal pharyngitis concomitant with the dramatic decline in rheumatic fever incidence. This strongly suggests that there have been changes in the rheumatogenicity of streptococcal strains currently prevalent in civilian populations of North America and western Europe. This concept was further validated by the isolation of strains manifesting the abovementioned rheumatogenic phenotypic characteristics during a resurgence of rheumatic fever that occurred in certain American communities toward the end of the century (see below).

In the mid-1980s, after decades of decline, outbreaks of rheumatic fever occurred in numerous cities and in two military recruit camps in the United States.[13,16] Strains of group A streptococci recovered from patients with acute rheumatic fever and their families and those found in community and training camp surveys were generally high-mucoid and often belonged to well-established rheumatogenic serotypes (serotypes 3 and 18). A survey of hospitals conducted by the American Heart Association indicated that the reported outbreaks were focal and not nationwide.[17] The largest epidemic occurred in Salt Lake City, Utah, and the surrounding intermountain area,[18] where over 500 cases were diagnosed between 1985 and 1999.

Surprisingly, the epidemiologic features of several of the civilian outbreaks-including the largest one in Salt Lake City-differed from the traditional patterns described above in that the victims were predominantly white middle-class children living in the suburbs. Only one-third of the children with rheumatic fever in Salt Lake City had a sore throat of sufficient severity that the parents considered taking them to a physician.[19] Most such outbreaks appear to have subsided during the 1990s, but that in Salt Lake City is continuing as of this writing.

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PATHOGENESIS

The exact mechanism by which the group A streptococcus causes rheumatic fever remains unexplained. Possibilities include (1) toxic effects of streptococcal products, particularly streptolysins S or O, which are capable of inducing tissue injury; (2) a serum sickness-like reaction; and (3) autoimmune phenomena induced by the similarity or identity of certain streptococcal antigens to wide variety of human tissue antigens.[20] Although no mechanism has been unequivocally proven, autoimmunity or, more precisely, molecular mimicry appears to be most likely.[21] There are shared epitopes between cardiac myosin and streptococcal M protein that lead to cross-reactive humoral and T-cell immunity against group A streptococci and the heart.[22] Epitopes of streptococcal M protein also share antigenic determinants with heart valves, sarcolemmal membrane proteins, synovium, and articular cartilage.[23] Circulating antibodies that react with neurons of the caudate and subthalamic nuclei and with group A streptococcal cell membranes have been found in many children with Sydenham's chorea.[24] Injection of streptococcal mucopeptide-polysaccharide cell wall complex can induce chronic nodular lesions in the dermal connective tissue in experimental animals.[25] These cross-reactive and toxic phenomena could explain many of the clinical manifestations of rheumatic fever, but, in the absence of a credible animal model of the disease, there is no direct proof that they do so.

During active rheumatic carditis both the number of helper (CD4) lymphocytes and the ratio of CD4 to CD8 cells are increased in the heart valves, and the production of interleukin-1 and interleukin-2 is reportedly increased.[26,27] Scarring and collagen deposition in the valves and destruction of myocytes may result.

The fact that, even in severe epidemics of exudative pharyngitis, rheumatic fever affects only a small proportion of infected persons, coupled with the known familial aggregation of rheumatic fever cases, has long suggested the possibility of a genetic predisposition to rheumatic attacks. Studies of the distribution of class 1 HLA antigens in rheumatics versus controls have been inconclusive. A statistically significant association has been reported between certain of the class II HLA antigens (HLA-DR2 in blacks[28] and HLA-DR4 in whites[29]) and rheumatic fever. An intriguing potential link between the genetic constitution of the human host and susceptibility to rheumatic fever is the identification of certain alloantigens that are expressed in a higher proportion of circulating B lymphocytes of rheumatic subjects and their family members than in those of patients with poststreptococcal glomerulonephritis or normal controls.[30]

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PATHOLOGY

Acute rheumatic fever is characterized by exudative and proliferative inflammatory lesions of the connective tissue, most notably of the heart, joints, and subcutaneous tissue. When carditis ensues, all layers of the heart are involved. Pericarditis is common and fibrinous pericarditis is occasionally present. The pericardial inflammation usually resolves over time with no clinically significant sequelae, and tamponade is rare. In fatal cases, myocardial involvement leads to globular enlargement involving all four chambers of the heart. In the myocardium, initially there is fragmentation of collagen fibers, lymphocytic infiltration, and fibrinoid degeneration. This is followed by the appearance of myocardial Aschoff nodules, which are considered pathognomonic of acute rheumatic fever. The Aschoff nodule consists of an area of central necrosis surrounded by lymphocytes, plasma cells, and large mononuclear and giant multinucleate cells. Many of these cells have an elongated nucleus with a clear area just within the nuclear membrane ("owl-eyed nucleus"). These cells are called *Anitschkow myocytes*, although histochemical studies suggest that they are of macrophage-histiocyte origin.[31] Aschoff nodules may also be found in endomyocardial biopsy specimens obtained from patients with acute rheumatic carditis.[32]

Endocardial involvement is responsible for chronic rheumatic valvulitis.[33] Small fibrinous, verrucous vegetations, 1 to 2 mm in diameter, are seen on the atrial surface at sites of valve coaptation and on the chordae tendineae. Even when no vegetations are present, there is edema and inflammation of the valve leaflets. A thickened and fibrotic patch (MacCallum's patch) may be found in the posterior left atrial wall. It is believed to be the effect of the mitral regurgitant jet impinging on the left atrial wall.[33] Healing of the valvulitis leads to granulation and fibrosis of the leaflets and fusion of the chordae. Valvular stenosis or incompetence may result. The mitral valve is involved most frequently, followed by the aortic valve. Tricuspid and pulmonic valves are usually spared.

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CLINICAL MANIFESTATIONS

Rheumatic fever may involve different organ systems such as heart, joints, skin, and central nervous system. The clinical picture depends upon the systems involved, and the manifestations may appear singly or in various combinations (Table 55-1). Five clinical features (carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum) are so characteristic of the disease that they are classified as major manifestations according to the Jones criteria (Table 55-2).[34] Additional findings such as fever, arthralgia, heart block, and acute-phase reactants in the blood (i.e., elevation of erythrocyte sedimentation rate and serum concentration of C-reactive protein) are commonly present in acute rheumatic fever but are nonspecific in nature and are therefore classified as minor manifestations.

Table 55-1: Clinical Manifestations of Acute Rheumatic Fever

General
High fever, lassitude, prostration, tachycardia
Cardiac
Cardiomegaly, congestive heart failure
Acute pericarditis, pericardial effusion
Apical pansystolic murmur (mitral regurgitation)
Apical middiastolic murmur (Carey Coombs)
Basal diastolic (aortic regurgitation)
Dermatologic
Subcutaneous nodules
Erythema marginatum
Rheumatologic
Arthralgia
Migratory polyarthritis
Neurologic
Sydenham's chorea

Table 55-2: Guidelines for the Diagnosis of the Initial Attack of Rheumatic Fever (Jones criteria, updated in 1992)[a]

Major Manifestations	Minor Manifestations	Supporting Evidence for Antecedent Group A Streptococcal Infection
Carditis	Clinical findings	Positive throat culture or rapid streptococcal antigen test
Polyarthritis	Arthralgia	
Chorea	Fever	
Erythema marginatum	Laboratory findings	Elevated or rising streptococcal antibody titer
Subcutaneous nodules	Elevated acute phase reactants	
	Erthrocyte sedimentation rate	
	C-reactive protein	
	Prolonged P-R interval	

[a]If supported by evidence of preceding group A streptococcal infection, the presence of two major manifestations or one major and two minor manifestations indicates a high probability of acute rheumatic fever.

SOURCE: From Dajani et al.[34] Reproduced by permission of *JAMA* 1992; 268:2069-2073, copyrighted 1992, American Medical Association.

The latent period from the onset of streptococcal sore throat to the onset of initial and recurrent attacks of rheumatic fever varies between 1 and 5 weeks with a median of 19 days. The mode of onset is quite variable. An abrupt onset with fever and toxicity is common in patients in whom acute polyarthritis is the presenting complaint. The onset may be insidious or even subclinical when mild carditis is the initial manifestation. Most attacks begin with polyarthritis, and occasionally this may be preceded by abdominal pain and fleeting signs of peritoneal inflammation, which may be misdiagnosed as acute appendicitis. Overall, arthritis occurs in approximately 75 percent of first attacks, carditis in 40 to 50 percent, chorea in 15 percent, and subcutaneous nodules and erythema marginatum in less than 10 percent.[35] These figures may vary widely, however.

Carditis

Carditis is the only manifestation of acute rheumatic fever that has the potential to cause long-term disability and death. Severe mitral regurgitation (or, possibly, severe myocarditis) may precipitate intractable heart failure and may be fatal during the acute phase of the disease. Fortunately, this complication is quite rare. Carditis, if present, usually appears within the first 3 weeks of the illness. The cardiac involvement is frequently mild or even asymptomatic, but occasionally the course can be fulminant. The diagnosis of carditis requires the presence of one of the following four manifestations: (1) organic cardiac murmurs not previously present, (2) cardiomegaly, (3) pericarditis, (4) congestive heart failure.

Valvulitis is associated with characteristic murmurs that are almost always present unless they are obscured by a loud pericardial friction rub, a large pericardial effusion, or low cardiac output. Mitral regurgitation leads to a blowing holosystolic murmur best heard at the apex and radiating to the axilla and occasionally to the base of the heart or the back. Hemodynamic and surgical pathologic studies conducted in South African patients suggest that mitral annular dilatation is usually the initial abnormality and predisposes to lengthening or rupture of the chordae tendineae and prolapse of the anterior leaflet.[36,37] Increased flow across the mitral valve in the presence of valvulitis may produce a middiastolic murmur (Carey Coombs murmur) that follows an S_3 gallop. This murmur is always accompanied by a systolic murmur of mitral regurgitation. It is not diagnostic of rheumatic fever because other conditions that lead to increased flow

across the mitral valve can cause a similar murmur, and in children an S_3 gallop can be physiologic. The Carey Coombs murmur can be differentiated from the diastolic rumble of mitral stenosis by the absence of an opening snap, presystolic accentuation, and loud first sound. A high-pitched decrescendo basal diastolic murmur of aortic regurgitation may also be heard. It is best heard along the left sternal border, over the aortic area, in expiration with the patient leaning forward (see also Chap. 57).

Myocarditis in the absence of valvulitis is not likely to be rheumatic in origin. Tachycardia is common. S_3, S_4, or summation gallops may be audible. Cardiomegaly may be noted on the chest roentgenogram or echocardiogram. In acute congestive heart failure, rapid distention of the hepatic capsule may lead to right-upper-quadrant discomfort and tenderness. Congestive heart failure is usually caused by left ventricular volume overload associated with severe mitral or aortic regurgitation.

In the presence of pericarditis, a pericardial friction rub or muffled heart sounds due to a large effusion may be noted. The presence of effusion should be confirmed by echocardiography. Large effusions leading to tamponade are rare. Pericarditis in the absence of valvular involvement is rarely due to acute rheumatic fever, and other causes should be sought.[34]

Polyarthritis

Arthritis is the most frequent major manifestation of rheumatic fever.[38] Any joint may be affected, but involvement of larger joints such as knees, ankles, elbows, and wrists is more common. The spine is only rarely affected. Several joints are involved in quick succession, and each for a brief period of time, resulting in the typical picture of migratory polyarthritis accompanied by signs and symptoms of an acute febrile illness. A striking feature of rheumatic arthritis is its dramatic response to salicylate therapy. Thus, the typical migratory polyarthritis pattern may not be present if effective anti-inflammatory therapy is administered early in the course of the disease.

The synovial fluid contains numerous white blood cells with a marked preponderance of polymorphonuclear leukocytes. Bacterial cultures are sterile. Inflammation of any one joint subsides spontaneously within a week and the entire bout of polyathritis rarely lasts more than 4 weeks. Resolution is complete with no residual joint damage. A possible exception is the so-called Jaccoud deformity of the metacarpophalangeal joints. This is a periarticular fibrosis and not a true synovitis, and its relation to rheumatic fever is unclear.[39]

Subcutaneous Nodules

These nodules are seen in only 1 to 21 percent of patients with rheumatic fever.[38] They are most often associated with carditis and rarely appear as an isolated manifestation of rheumatic fever. They are round, firm, painless, freely movable subcutaneous lesions varying in size from 0.5 to 2.0 cm. They occur in crops and are usually found over bony surfaces and over tendons such as elbows, knees, and wrists, the occiput and vertebrae (Fig. 55-1). They last for a week or two and disappear spontaneously. Similar nodules also occur in rheumatoid arthritis and systemic lupus erythematosus.

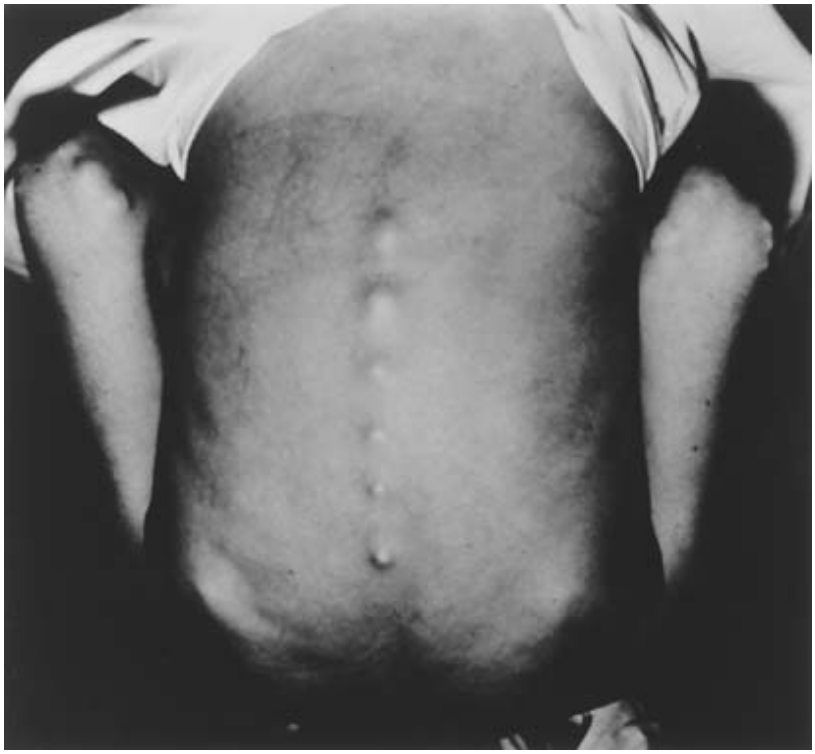

Figure 55-1: Subcutaneous nodules on the spine and elbows. (Courtesy of Dr. Benedict F. Massell.)

Erythema Marginatum

This rash is usually found on the trunk and proximal parts of the extremities, with the face being spared. It begins as an erythematous macule or papule that extends outward while skin in the center returns to normal. Lesions may merge and form serpiginous patterns. They are never pruritic or indurated, blanch on pressure, and are not influenced by anti-inflammatory therapy. The rash is evanescent, migrating from place to place and leaving no residual scarring. Individual lesions may appear and disappear in minutes to hours. Erythema marginatum has also been reported in sepsis, drug reactions, and glomerulonephritis.

Sydenham's Chorea (St. Vitus Dance)

This neurologic disorder often occurs in isolation, either unaccompanied by other major manifestations of rheumatic fever or after a latent period of several months, at a time when all other manifestations of rheumatic fever have subsided. It is characterized by rapid, purposeless, involuntary movements, most noticable in the extremities and face. The arms and legs flail about in erratic, jerky, uncoordinated movements. The speech is usually slurred and jerky. The involuntary movements disappear during sleep and may be suppressed by sedation. The patient is unable to sustain a tetanic muscular contraction. Emotional lability is characteristic of Sydenham's chorea and may often precede other neurologic manifestations. The duration of the chorea is variable, and its severity may wax and wane. Most patients recover in 6 months. Long-term sequelae such as convulsions, learning disabilities, and behavior problems are rare but have been reported in a small number of patients. Experience with brain imaging is limited but isolated case reports suggest that magnetic resonance imaging or computed tomographic scans may reveal abnormalities in the caudate nuclei, putamen, and substantia nigra.[40]

Rarely, chorea may be due to other conditions that affect the basal ganglia, including collagen vascular, endocrine, neoplastic, genetic, metabolic, and infectious disorders.[41] Perhaps the most frequent differential diagnostic consideration is systemic lupus erythematosus. The relationship of chorea occurring during pregnancy (chorea gravidarum) to acute rheumatic fever remains unclear.

Minor Manifestations

Minor manifestations of rheumatic fever include fever, arthralgia, and laboratory evidences of inflammation

(Table 55-2). Fever usually ranges from 38.4 to 40°C and rarely lasts for more than 3 to 4 weeks. Arthralgia is pain in one or more joints without objective evidence of inflammation. In diagnosing rheumatic fever using the Jones criteria, arthralgia should not be considered a minor manifestation when arthritis is present.

Other Clinical Features

Abdominal pain in rheumatic fever is the result of peritoneal inflammation and may be confused with acute appendicitis or sickle cell crisis. Because it occurs at the onset of the illness, other manifestations of rheumatic fever may not yet be present. Epistaxis has been reported as a manifestation of rheumatic fever, but it is not clear to what extent it may be attributable to the large doses of aspirin administered for treatment of the disease. Tachycardia may be out of proportion to fever and persists during sleep.

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LABORATORY FINDINGS

A mild to moderate normochromic normocytic anemia and leukocytosis with an increased proportion of polymorphonuclear leukocytes are common. Elevated serum levels of C-reactive protein and an increased erythrocyte sedimentation rate are almost always present, indicating acute inflammation. An exception is "pure" chorea, which may appear after these markers of inflammation have returned to normal.

Throat cultures are usually negative for group A streptococci by the time rheumatic fever appears. Streptococcal antibody tests provide evidence for antecedent streptococcal infection and include antistreptolysin O (ASO), anti-DNAse B, and antihyaluronidase. These antibodies reach peak titer at about the time of onset of acute rheumatic fever. The ASO is elevated in 80 percent or more of patients with rheumatic fever. A battery of these three tests will establish the presence of immunologically significant infection with group A streptococcus in 95 percent of patients.[42] The normal ranges for these titers vary depending upon the test used, patient's age, and geographic locale. ASO titers greater than 200 Todd units per milliliter in adults and 320 Todd units in children are generally considered elevated. In patients seen early during the course of rheumatic fever, rising antibody titers may be seen. An elevated streptococcal antibody titer is not diagnostic of rheumatic fever, but the diagnosis is very unlikely if all three tests (ASO, anti-DNAse B, and antihyaluronidase) are negative (see section on "Diagnosis" below (or exceptions).

Electrocardiogram

Persistent sinus tachycardia that does not resolve during sleep is common in the presence of carditis.[43] Sinus bradycardia and sinus arrhythmia may be present in some patients and can be abolished by the administration of atropine. Prolongation of the PR interval is a common abnormality. In various studies, the incidence varied from 10 to 84 percent.[43] A recent study of the resurgence of rheumatic fever[18] described the electrocardiographic findings in 232 patients. Alterations in atrioventricular conduction were noted in 74 patients (32 percent). Of these, 66 had a prolonged PR interval, 4 had transient episodes of AV block, and 4 had transient episodes of AV dissociation.

Some investigators have suggested that the AV conduction delay is a manifestation of carditis.[43] However, the response to atropine and the lack of correlation with clinical carditis suggests that this is a nonspecific finding.[34] Transient complete heart block that causes Stokes-Adams attacks has been described. Bundle-branch blocks are rare. Atrial flutter and fibrillation have been described in the presence of carditis. Low QRS voltage may be noted if a large pericardial effusion is present.

Echocardiogram

Few studies have used echocardiography to evaluate and follow up patients with rheumatic carditis.[44] During the resurgence of rheumatic fever in Salt Lake City, two-dimensional and Doppler echocardiograms were performed in children with rheumatic fever.[18] During the acute phase of rheumatic carditis, echocardiographic evidence of mitral regurgitation ws often found even when a murmur was not audible ("silent mitral regurgitation").

Valvular thickening and the presence of nodular lesions on the body and tips of the mitral leaflet have been described.[45] These are most likely echocardiographic equivalents of rheumatic verrucae. The key features of rheumatic mitral valvulitis were annular dilation and elongation of the chordae to the anterior leaflet, resulting in mitral regurgitation with a posterolaterally directed jet.[18] In an echocardiographic study of 73 patients with active rheumatic carditis and mitral regurgitation, it was noted that 90 percent of patients had elongated mitral valve chordae, 94 percent had prolapse of the anterior leaflet of the mitral valve, and 96 percent had annular dilation.[46] The resulting mitral regurgitant jet was directed toward the posterolateral wall of the left atrium. The site where this jet strikes the posterior left atrial wall corresponds with the site of endocardial thickening described at autopsy as MacCallum's patch. Rheumatic carditis can be differentiated from the common mitral valve prolapse syndrome because only the coapting portion of the anterior mitral leaflet prolapses and there is no billowing of the medial portion of the leaflet.

In the past congestive heart failure seen in acute rheumatic fever was attributed to myocarditis. Recent echocardiographic studies have shown that patients with rheumatic fever and congestive heart failure have preserved left ventricular systolic function and severe mitral regurgitation.[45,47] Thus the etiology of heart failure appears to be acute mitral regurgitation and not myocarditis.[19,44] Although these findings are interesting, experience is limited, and it is not yet clear the extent to which echocardiography has incremental diagnostic value when added to the clinical findings in the diagnosis of carditis or in ascertaining the likelihood of development of chronic rheumatic heart disease.

Endomyocardial Biopsy

Rheumatic fever is basically a clinical syndrome for which no specific diagnostic test exists. However, the presence of Aschoff nodules on histologic specimens obtained at surgery and autopsy can be considered diagnostic of rheumatic fever. Percutaneous transvenous myocardial biopsy is now feasible and may be useful in the diagnosis.[48] Aschoff nodules and interstitial mononuclear infiltrates with or without myocyte necrosis have been described in the myocardial biopsy specimens of four patients with acute rheumatic fever.[49-52] To determine the role of myocardial biopsy in the diagnosis of rheumatic carditis, a prospective study was performed in 54 patients.[32] Among 11 patients with definite clinical rheumatic carditis, 3 (27 percent) had Aschoff nodules in the biopsy specimen; the remainder had evidence of myocarditis, but the abnormalities were not diagnostic of rheumatic carditis. Among patients with suspected rheumatic carditis, myocardial specimens were diagnostic only in a minority of cases. The investigators concluded that the role of myocardial biopsy in the diagnosis of rheumatic fever was limited.

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DIAGNOSIS

The diagnostic criteria for acute rheumatic fever were originally proposed by T. Duckett Jones 1944 and have been later modified and updated by the American Heart Association (Table 55-2).[34] Based on their diagnostic importance, clinical and laboratory findings are divided into major and minor manifestations. If supported by evidence of a preceding group A streptococcal infection, the presence of two major manifestations, or of one major and two minor manifestations indicates a high probability of acute rheumatic fever. Supporting evidence of a previous group A streptococcal infection is a prerequisite for fulfilling the criteria.

There are some circumstances in which the diagnosis of rheumatic fever can be made without strictly adhering to the Jones criteria. Chorea may not occur until several months after the antecedent streptococcal pharyngeal infection. Isolated carditis that does not provoke congestive failure may not be recognized during the acute phase of illness yet may persist for months. In these situations, markers of inflammation may no longer be present and antistreptococcal antibody titers may have returned to normal by the time the illness comes to light. Moreover, in patients with previous rheumatic fever or established rheumatic heart disease, recurrences are common and a presumptive diagnosis of a recurrence may be made in the presence of a single major or several minor manifestations.[34]

Overdiagnosis must be avoided. Following well-documented group A streptococcal pharyngitis, vague signs and symptoms and nonspecific laboratory abnormalities may appear. Discomfort in the extremities, borderline temperature elevation, increased intensity of functional murmurs, tachycardia, elevated erythrocyte sedimentation rate, and prolonged PR interval may occur in the absence of major manifestations. These patients do not develop rheumatic heart disease on follow-up.[34] Thus the diagnosis of rheumatic fever should not be made in the absence of major manifestations. There is no evidence that temporarily withholding salicylates or corticosteriods has any adverse effect on the long-term prognosis. Thus premature administration of these drugs before the symptoms become distinct should be avoided.

Because acute rheumatic fever can have such diverse manifestations (acute polyarthritis, congestive heart failure, chorea, or combinations of these) and because there is no specific diagnostic test for the disease, the differential diagnostic possibilities in an individual case may be quite broad. Among the diseases that need most frequently to be differentiated are rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, serum sickness, sickle cell crisis or cardiopathy, rubella arthritis, septic arthritis (especially gonococcal arthritis in adolescent patients), Lyme disease, infective endocarditis, viral myocarditis, and early stages of Henoch-Schönlein purpura. Less frequent differential diagnostic considerations include gout, sarcoidosis, Hodgkin's disease, and leukemia. Choreiform movements have been described in patients with systemic lupus erythematosus, neoplasms involving the basal ganglia, Legionnaire's disease, hypoparathyroidism, antiphospholipid syndrome, Wilson's disease, and Huntington's disease. Chorea is also seen occasionally in women taking oral contraceptives, and during pregnancy ("chorea gravidarum").

In areas of low rheumatic fever incidence, the Jones criteria are perhaps most useful in excluding the diagnosis. The specificity of the criteria is most problematic when the diagnosis is based upon acute polyarthritis as a single major manifestation plus laboratory findings indicative of acute

inflammation. In such cases, there must be clear-cut supporting laboratory evidence of recent streptococcal infection and alternative diagnoses must be carefully ruled out.

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TREATMENT

Antibiotics neither modify the course of the disease nor prevent the development of rheumatic carditis. Nevertheless, a course of antibiotics to eradicate group A streptococci remaining in the pharynx and tonsils is usually given. Penicillin G benzathine (1.2 million units intramuscularly as a single injection) is the treatment of choice for patients who are not allergic to penicillin. Erythromycin is prescribed for the penicillin-allergic patient. An oral cephalosporin is an acceptable alternative if the penicillin allergy is not of the immediate type. Following this, continuous prophylactic therapy is given to prevent streptococcal pharyngitis (see below).

Anti-inflammatory drugs provide dramatic clinical improvement but are not curative and do not prevent development of rheumatic heart disease.[53] Aspirin is very effective in reducing fever, toxicity, and inflammation of the joints. It is given as tolerated in a dosage of 90 to 100 mg/kg/day in children and 6 to 8 g/day in adults in divided doses every 4 h. A serum salicylate level of 20 to 25 mg/dL is adequate. Adverse effects include salicylism and gastrointestinal bleeding. The precise dose of aspirin is determined by the severity of symptoms, clinical response, salicylate levels, and tolerance to the drug. After 2 weeks of therapy, a reduced dose of aspirin may be used for another 6 weeks.

Corticosteroids are used in patients with carditis manifest by heart failure and in patients who do not tolerate aspirin or whose symptoms do not respond well to this drug. Prednisone 40 to 60 mg a day in divided doses is given for 2 to 3 weeks and the dosage is gradually reduced over the following 3 weeks. In some patients symptoms of rheumatic fever may reappear when the anti-inflammatory therapy, especially steroids, is stopped. Continuing aspirin therapy for 1 month after steroids are discontinued can prevent this. Although the use of nonster oidal anti-inflammatory drugs seems reasonable in patients who cannot tolerate salicylates and who do not require corticosteroids, there is a paucity of data on the use of these agents in acute rheumatic fever. Thus, their role in management remains to be defined.

Congestive heart failure is managed in the conventional manner. Digoxin should be used cautiously in the presence of myocarditis. After the acute attack subsides, the level of physical activity is determined by the cardiac status. Patients without residual cardiac disease do not require restriction of physical activity. In the rare instances in which patients with acute rheumatic fever develop intractable heart failure, mitral valve repair or replacement may be life-saving (see also Chap. 57).

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PROGNOSIS

Manifestations of chronic rheumatic heart disease include mitral and aortic insufficiency or stenosis, congestive heart failure, and atrial fibrillation. The ultimate cardiac prognosis of an individual rheumatic fever attack is rather directly related to the severity of cardiac involvement during the acute phase provided that the patient is protected from recurrent attacks (see below). In the United Kingdom-United States Collaborative Study,[54] only 6 percent of the patients with no carditis or only questionable carditis during their attack of acute rheumatic fever were found to have heart murmurs when reexamined 10 years later. Heart disease was present at follow-up in 30 percent of the patients initially found to have only apical systolic murmurs, in 40 percent of those with basal diastolic murmurs during the acute phase, and in 68 percent of those who initially suffered from congestive heart failure, pericarditis, or both. Some patients with "pure" chorea may later develop rheumatic heart disease, even though carditis was not recognized during the initial attack. In such cases, however, it may be that the initial findings of carditis were no longer prominent by the time that chorea (which often occurs after a long latent period) manifested itself.

Prevention

The risk of developing rheumatic fever following a symptomatic or asymptomatic streptococcal infection is much higher in patients who have experienced a previous attack than in nonrheumatic individuals. In some studies the recurrence rate following immunologically confirmed streptococcal upper respiratory infection has been as high as 16 percent.[2] In patients with rheumatic heart disease, recurrent attacks lead to progressive damage. Although patients who did not suffer carditis initially are less prone to develop it in the event of a recurrence, exceptions do occur. It is therefore crucial that rheumatic fever patients be protected optimally from streptococcal infections. This is accomplished by continuous antimicrobial prophylaxis.[55]

The recommended prophylactic regimens are shown in Table 55-3. The optimal duration of antibiotic prophylaxis remains controversial. The risk of acute rheumatic fever declines with age and the number of years since previous attack. The recommendations of the American Heart Association for the duration of secondary prophylaxis are given in Table 55-4. The decision to discontinue rheumatic fever prophylaxis must be individualized on the basis of risk of recurrence and the probable consequence of a recurrence. It should be noted that health care workers, individuals who have contact with schoolchildren, military recruits, and residents of areas with a high incidence of rheumatic fever are at increased risk for streptococcal infection. This fact should be taken into account when considering discontinuation of prophylaxis.

Table 55-3: Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)

Agent	Dose	Mode
Benzathine penicillin G	1 200 000 U every 4 weeks[a]	Intramuscular
	or	
Penicillin V	250 mg twice daily	Oral
	or	
Sulfadiazine	0.5 g once daily for patients	Oral
	≤27 kg (60 lb)	

	1.0 g once daily for patients	
	>27 kg (60 lb)	
For individuals allergic to penicillin and sulfadiazine		
Erythromycin	250 mg twice daily	Oral

[a]In high-risk situations, administration every 3 weeks is justified and recommended.

SOURCE: From Dajani et al.[55] Reproduced by permission of *Pediatrics* 1995; 96:758-764.

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Part 9: VALVULAR HEART DISEASE
Chapter 56:

AORTIC VALVE DISEASE

Author: Shahbudin H. Rahimtoola

The assessment and management of patients with valvular heart disease has undergone many changes in the past four decades. The incidence of acute rheumatic fever has declined, and as a result rheumatic heart disease is not the most important cause of valve disease in the developed countries. Prolapse of the mitral valve and congenital aortic valve disease are now the most common valvular lesions. Valve surgery has been the major therapeutic advance in treating patients with severe valve disease; in fact, most patients with severe valve disease are now considered candidates for surgery. Echocardiography/Doppler ultrasound has a very important role in the diagnosis and follow-up of these patients. Cardiac catheterization/angiography remains an extremely important diagnostic procedure that is needed in almost all patients being considered for interventional therapy. Catheter balloon valvuloplasty is a useful technique for the treatment of some stenotic cardiac valves.

AORTIC VALVE STENOSIS

Aortic stenosis (AS) is obstruction to outflow of blood flow from the left ventricle to the aorta. The obstruction may be at the valve, above the valve (supravalvular), or below the valve (subvalvular).[1] Supravalvular AS is a congenital lesion. Subvalvular AS results either from a discrete fibromuscular obstruction, which is a congenital lesion, or from a muscular obstruction (hypertrophic cardiomyopathy).

Etiology

The most common causes of AS are congenital,[2,3] rheumatic, and calcific (degenerative) (Table 56-1). Calcific AS is seen in patients 35 years of age or older and is the result of calcification of a congenital or rheumatic valve or of a normal valve that has undergone "degenerative" changes.[4] Recent data suggest that degenerative/calcific AS may represent an immune reaction to antigens present in the valve[5] and is related to atherosclerosis.[6]

Table 56-1: Etiology of Aortic Valve Stenosis

I. Congenital
II. Acquired
    A. Rheumatic
    B. Calcific (degenerative/autoimmune)
    C. Rare causes
        1. Obstructive infective vegetations
        2. Homozygous type II hyperlipoproteinemia
        3. Paget's disease of bone
        4. Systemic lupus erythematosus
        5. Rheumatoid involvement
        6. Ochronosis (alkaptonuria)
        7. Irradiation

Rare causes of AS include obstructive, infective vegetations that are usually large, e.g., those seen in fungal

endocarditis. Atherosclerotic AS is seen most frequently in patients with severe hypercholesterolemia and is observed in children and young adults with homozygous type II hyperlipoproteinemia.[7,8] Paget's disease of the bone,[9] end-stage renal disease,[10,11] systemic lupus erythematosus, rheumatoid involvement, ochronosis,[12] and irradiation are other rare causes of AS.

At the present time, calcific AS in the older patient is the most common valve lesion requiring valve replacement.[4,13] Among patients under the age of 70, congenital bicuspid valve accounted for one-half of the surgical cases; degenerative changes were the cause in 18 percent.[4] In contrast, in those aged 70 or older, degenerative changes accounted for almost one-half of the surgical cases and a congenital bicuspid valve for approximately one-quarter of the cases (Fig. 56-1).

Pathology

In congenital AS, the valve may be unicuspid, bicuspid, or tricuspid, depending on the patient's age.[14] In patients under the age of 15 years, over 80 percent of stenotic valves are either unicuspid or bicuspid and 15 to 20 percent are tricuspid. In patients aged 15 to 65 years, 60 percent are bicuspid, 10 percent are unicuspid, and 25 to 30 percent are tricuspid. In patients 65 years of age or over, 90 percent of the valves are tricuspid and 10 percent are bicuspid. Unicuspid valves produce severe obstruction in infancy and are the most frequent malformation found in fatal valvular AS in children under the age of 1 year.[2] Congenital bicuspid valves can produce severe obstruction to left ventricular (LV) outflow after the first few years of life.[3] The valvular abnormality produces turbulent flow, which traumatizes the leaflets and eventually leads to fibrosis, rigidity, and calcification of the valve. In a congenitally abnormal tricuspid aortic valve, the cusps are of unequal size and have some degree of commissural fusion; the third cusp may be diminutive. Eventually, the abnormal structure leads to changes similar to those seen in a bicuspid valve, and significant LV outflow obstruction often results. In calcific AS (so called "degenerative") early changes show chronic inflammatory cell infiltrate (macrophages and T lymphocytes), lipid in lesion and in adjacent fibrosa and thickening of fibrosa with collagen and elastin.[6] These patients also have a higher incidence of risk factors for coronary atherosclerosis.[15]

Rheumatic AS results from adhesions and fusion of the commissures and cusps. The leaflets and the valve ring become vascularized, which leads to retraction and stiffening of the cusps. Calcification occurs, and the aortic valve orifice is reduced to a small triangular or round opening, which is frequently regurgitant as well as stenotic. Importantly, the heart exhibits other evidence of rheumatic heart disease-namely, involvement of the mitral valve and presence of Aschoff's nodules in the myocardium.

Rheumatoid AS is extremely rare and results from nodular thickening of the valve leaflets and the involvement of the proximal part of the aorta. In severe forms of hypercholesterolemia, lipid deposits occur not only in the aortic wall but also in the aortic valve and occasionally produce AS.

The LV is concentrically hypertrophied.[16] The hypertrophied cardiac muscle cells are increased in size, with their transverse diameters ranging from 15 to 70 μm (normal, 10 to 15 μm). There is an increase of connective tissue,[17-19] and a variable amount of fibrous tissue (collagen fibrils) in the interstitial tissue. Usually, the cardiac muscle cells do not degenerate in patients with AS. Myocardial ultrastructural changes[20] may account for the LV systolic dysfunction that occurs late in the disease; such changes include unusually large nuclei, loss of myofibrils, accumulation of mitochondria, large cytoplasmic areas devoid of contractile material, and proliferation of fibroblasts and collagen fibers in the interstitial space.

Subclinical calcific emboli are commonly found in calcific AS if diligently sought at autopsy.

Pathophysiology

With reduction in the *aortic valve area* (AVA), energy is dissipated during the transport of blood from the LV to the aorta. The AVA has to be reduced by about 50 percent of normal before a measurable gradient can be demonstrated in humans.[21] When a pressure gradient develops between the left ventricle and the ascending aorta, LV pressure rises; aortic pressure remains within the normal range until end-stage heart

failure occurs. The relationship of the AVA to cardiac output and pressure gradient is discussed in Chap. 57. As LV pressure rises, ventricular wall stress increases, which leads to impaired LV function. The heart normalizes wall stress by becoming hypertrophic. Since AS develops slowly, hypertrophy develops in proportion to increased intraventricular pressure, and myocardial stress remains normal.[22] *Thus, the major compensatory mechanism by which the heart copes with LV outflow obstruction is ventricular hypertrophy*. LV mass in patients with severe AS undergoing valve replacement averages 229 g/m^2 (normal, 105 g/m^2);[22] at autopsy, left ventricles weighing as much as 1000 g have been reported. LV volume, however, is within the normal range,[22] and so there is a considerable thickening of the LV wall.

The diastolic properties of the LV are affected in AS.[23-27] This diastolic abnormality results from a combination of impaired myocardial relaxation with altered chamber compliance because the hypertrophied LV per se offers increased resistance to filling, and from increased myocardial stiffness because of structural alterations.[27] As a result, LV end-diastolic pressure is elevated, but this is not necessarily a measure of LV failure. Powerful atrial contraction produces the required LV filling and results in an elevated LV end-diastolic pressure (atrial booster pump function).[28,29] The necessary LV filling and fiber length to achieve an adequate stroke volume are achieved by atrial systole, which occupies only a small part of the cardiac cycle. Therefore there is a transient increase in left atrial pressure due to the large *a* wave, but mean left atrial pressure remains in the normal range or is only minimally increased (Fig. 56-2).

Left atrial contraction is therefore of considerable benefit to these patients. Loss of effective atrial contraction, either because of atrial fibrillation or because of an inappropriately timed atrial contraction [e.g., that associated with first-degree heart block or with atrioventricular (AV) dissociation], results in elevations of mean left atrial pressure, reduction of cardiac output, or both and may precipitate clinical heart failure with pulmonary congestion.

Patients with severe LV hypertrophy may exhibit LV diastolic dysfunction, which may produce the syndrome of clinical heart failure (paroxysmal nocturnal dyspnea, orthopnea, and even pulmonary edema) even if LV systolic pump function is normal. In patients 60 years of age or older, a higher percentage of women (41 percent) than men (14 percent) have "excessive" hypertrophy, that is, greater amounts of hypertrophy in spite of similar degrees of severity of AS.[30] They have "supernormal" LV systolic pump function (high LV ejection fraction) and a small, thick-walled chamber with lower end-systolic wall stress (Table 56-2).

LV systolic pump function is determined by myocardial (muscle) function and by a combination of LV afterload and preload. Thus, impaired LV systolic pump function (as measured by ejection fraction) may be the result of afterload-preload mismatch,[31] impaired myocardial function, or both. LV systolic pump function is normal in most patients with severe AS. When the LV hypertrophy alone is not adequate to overcome the outflow obstruction, the left ventricle uses the Frank-Starling mechanism (preload reserve) to maintain systolic pump function. When the preload reserve is no longer adequate, a reduction of LV systolic pump function occurs (Fig. 56-2). In AS, major use of the preload reserve is not a good compensatory mechanism. Even small increases in LV volume may result in major increases in LV end-diastolic pressure because the LV is on the very steep portion of its diastolic pressure-volume curve, and the corresponding increase in mean left atrial pressure produces pulmonary edema. Thus, clinical heart failure may be a result of either LV diastolic dysfunction in the presence of normal LV systolic function or impaired myocardial function producing LV systolic dysfunction, with or without associated LV diastolic dysfunction. Eventually, pulmonary artery, right ventricular, and right atrial pressures are elevated. Peripheral edema results from increases in systemic venous pressure and salt and water retention.

In most patients with AS, cardiac output is in the normal range and initially increases normally with exercise. Later, as the severity of AS increases progressively, the cardiac output remains within the normal range at rest, but, on exercise, it no longer increases in proportion to the amount of exercise undertaken or does not increase at all (fixed cardiac output). With the development of heart failure, there is a reduction in the resting cardiac output and a tachycardia. As a result, stroke volume may be so lowered that it results in a small gradient across the LV outflow tract in spite of severe AS. As the patient's age increases, there is a

progressive decrease of cardiac output with exercise and a progressive increase of LV end-diastolic pressure at equal levels of AVA. This may be related only to LV diastolic dysfunction and is most marked in the older patient.[32]

In severe AS, myocardial oxygen needs are increased because of an increased muscle mass (hypertrophy), elevations in LV pressures, and prolongation of the systolic ejection time (Fig. 56-3). Total coronary blood flow is increased because of the severe LV hypertrophy; however, coronary blood flow per 100 g of LV mass is reduced.[33] As a result, blood flow to the subendocardium[34] is inadequate at rest; and because coronary vasodilator reserve is reduced,[35] myocardial blood flow is also reduced further, relative to need, on exercise. Coronary blood flow is reduced because of a reduced coronary perfusion pressure (the elevated LV end-diastolic pressure lowers the diastolic aortic-LV pressure gradient) and also because the hypertrophied myocardium compresses the coronary arteries as they traverse the myocardium to supply blood to the subendocardium (systolic "milking" of intramural arteries). As a result, patients may have classic angina pectoris even in the absence of *coronary artery disease* (CAD). Associated obstructive CAD from atherosclerosis further increases the imbalance between myocardial oxygen needs and supply (Fig. 56-2).

Clinical Findings

HISTORY

Patients with congenital valve stenosis may give a history of a murmur since childhood or infancy; those with rheumatic ste nosis may have a history of rheumatic fever. Most patients with valvular AS, including some with severe valve stenosis, are asymptomatic. The symptoms of AS are angina pectoris, syncope, exertional presyncope, dyspnea (on exertion, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema), and the symptoms of heart failure. Once symptoms occur in a patient with severe AS, the life span of the patient is very short without surgical treatment. Sudden cardiac death is stated to occur in 5 percent of patients with AS. It occurs only in those with severe valve stenosis, most of whom have had some cardiac symptoms before the fatal episode. Typical angina pectoris occurs with or without associated CAD and results from an imbalance between myocardial oxygen needs and supply (Fig. 56-3).

Syncope is the result of reduced cerebral perfusion. Syncope occurring on effort is caused by either systemic vasodilatation in the presence of a fixed or inadequate cardiac output, an arrhythmia, or both.[36-38] Syncope at rest is usually due to a transient ventricular tachyarrhythmia, from which the patient recovers spontaneously. Other possible causes of syncope include transient atrial fibrillation or transient AV block, during which the ventricle is deprived of the powerful atrial booster pump function and/or the ventricular rate is slow.

Dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema result from varying degrees of pulmonary venous hypertension. Systemic venous congestion with enlargement of the liver and peripheral edema result from increased systemic venous pressure and salt and water retention. There is an increased incidence of gastrointestinal arteriovenous malformations.[39,40] As a result, these patients are susceptible to gastrointestinal hemorrhage and anemia. Calcific systemic embolism may occur.[41,42]

PHYSICAL FINDINGS

There is a spectrum of physical findings in patients with AS, depending on the severity of the stenosis, stroke volume, LV function, and the rigidity and calcification of the valve (Table 56-3). The arterial pulse rises slowly, taking a longer time than normal to reach peak pressure, and the peak is reduced (*parvus et tardus*);[43] the pulse pressure may be narrowed. The anacrotic notch on the upstroke is best appreciated in the carotid arteries. The more severe the valve stenosis, the lower the anacrotic notch on the arterial pulse. A systolic thrill may be felt in the carotid arteries. The jugular venous pulse is normal unless the patient is in heart failure. In the absence of heart failure, the heart size is normal. The cardiac impulse is heaving and sustained in character, and there may be a palpable fourth heart sound (S_4). An aortic systolic thrill is often present at the base of the heart. In 80 to 90 percent of adult patients with severe AS, there is an S_4 gallop

sound, a midsystolic ejection murmur that peaks late in systole, and a single second heart sound (S_2) because A_2 and P_2 are superimposed or A_2 is absent or soft. There is often a faint early diastolic murmur of minimal aortic regurgitation. In the young patient with valvular AS, a systolic ejection sound (systolic ejection click) initiates the systolic murmur but later tends to disappear as AS becomes severe. The S_2 may be paradoxically split due to late A_2, and there may be no early diastolic murmur. In many patients, particularly the elderly, the systolic ejection murmur is atypical, may be soft, is described as a seagull sound (or musical, or cooing), and may be heard only at the apex of the heart (Gallavardin phenomenon). In the presence of heart failure, the jugular venous pressure is often increased, the left ventricle is dilated, a third heart sound is present, and the systolic murmur may be very soft or absent. Thus, the clinical features on physical examination may resemble those of heart failure from a variety of causes, such as dilated cardiomyopathy, rather than AS (see also Chap. 10).

Table 56-3: Physical Examination of Patients with Varying Severity of Aortic Valve Stenosis

	Mild	Moderate	Severe + Normal LV Function	Severe + LV Dysfunction	Severe + Heart Failure[a]
Arterial pulse	Normal	Slowly rising	*Parvus et tardus*	*Parvus et tardus*	Small volume
Jugular venous pulse	Normal	Normal	Normal	Normal	±
Carotid thrill	±	±	±	±	±
Cardiac impulse	Normal	Heaving	Heaving, sustained palpable *a* wave	Heaving	Heaving or reduced
Precordial thrill	±	±	Usually ++	±	-
Auscultation					
S_4	-	±	++	+	-
S_3	-	-	-	±	+
ESS	+	±	-	-	-
Peak of ESM	Early systole	Mid-systole	Late systole	Late to mid-systole, soft	Mid-systole, soft or absent
S_2	Normal	Normal or single	Single or paradoxical	Single	Single

[a]There may be signs of mitral and tricuspid regurgitation and of pulmonary hypertension.
ABBREVIATIONS: S_4 = fourth heart sounds (presystolic gallop); S_3 = third heart sound (diastolic gallop); ESS = ejection systolic sound; ESM = ejection systolic murmur; S_2 = second heart sound.

Severe valvular AS is common in patients 60 years of age or older.[13,44] The clinical features in many of these patients tend to be somewhat different from those typical of younger patients.[44] Systemic hypertension is common, being present in about 20 percent of the patients, half of whom have moderate or severe systolic and diastolic hypertension. A fifth of the patients first present in congestive heart failure. The male:female ratio is 2:1. Because of thickening of the arterial wall and its associated lack of

dispensability, the arterial pulse rises normally or even rapidly, and the pulse pressure is wide. The S_2 is either absent or single. As noted above, the murmur may be high-pitched and musical and may radiate from the base to the apex or may be heard best at the apex, mimicking mitral regurgitation.

CHEST X-RAY

The characteristic finding is a normal-sized heart with a dilated proximal ascending aorta (poststenotic dilation). Calcium in the aortic valve can be seen on the lateral film but is better appreciated by fluoroscopy with image intensification. In the current era, calcification is most easily recognized on twodimensional echocardiography. Calcium in the aortic valve is the hallmark of AS in adults 40 to 45 years of age.[45,46] In patients aged 45 years or above, the diagnosis of severe AS is doubtful if there is no calcium in the aortic valve. The presence of calcium, however, does not necessarily mean that the valve is stenotic or that the AS is severe. In patients with heart failure, the cardiac size is increased because of dilatation of the left ventricle and left atrium; the lung fields show pulmonary edema and pulmonary venous congestion with redistribution of blood flow. In the presence of heart failure, the right ventricle and the right atrium may be dilated.

ELECTROCARDIOGRAM

The *electrocardiogram* (ECG) in severe AS shows LV hypertrophy with or without secondary ST-T-wave changes. It is important to recognize, however, that in about 10 to 15 percent of patients with severe AS, LV hypertrophy cannot be appreciated on the ECG. In fact, the ECG may be entirely normal in some of these patients. The P-wave abnormality (P = 0.12 s) of left atrial enlargement and/or hypertrophy and/or conduction delay is present in over 80 percent.[47] The ECG may show left bundle branch block, right bundle branch block with left or right axis deviation, or, occasionally, isolated right bundle branch block.[48-50] In some patients, the conduction abnormality results from aortic valve calcification extending into the specialized conducting tissue, which may even produce heart block. The patients are usually in sinus rhythm. The presence of atrial fibrillation indicates the presence of either associated mitral valve disease, CAD, or heart failure secondary to aortic valve disease. Atrial fibrillation is relatively common in the elderly with calcific AS, probably because of the increased presence of associated diseases.

Laboratory Investigations

ECHOCARDIOGRAPHY/DOPPLER ULTRASOUND

Echocardiography/Doppler (echo/Doppler) ultrasound (Chap. 13) is an extremely important and useful noninvasive test. On the echocardiogram, the aortic valve leaflets normally are barely visible in systole, and the normal range of aortic valve opening is 1.6 to 2.6 cm. In the presence of a bicuspid aortic valve, eccentric valve leaflets may be seen. The aortic valve leaflets may appear to be thickened as a result of calcification and/or fibrosis; however, the older patient without valve stenosis may also have thickened cusps. The aortic valve may have a reduced opening, but this also occurs in other conditions in which the cardiac output is reduced. The LV hypertrophy often results in thickening of both the interventricular septum and the posterior LV wall. The LV cavity size is normal. All these abnormalities are better appreciated on two-dimensional echocardiography. When LV systolic function is impaired, the left ventricle and left atrium are dilated and the percentage of dimensional shortening is reduced.

In many patients, the severity of AS is incorrectly estimated by M-mode or two-dimensional echocardiography. Neither is a completely reliable technique for assessing the severity of AS. The presence of normal movement of thin aortic leaflets on the echocardiogram, however, is strong evidence against severe AS in adults.

Echo/Doppler, when properly applied, is extremely useful for estimating the valve gradient and AVA noninvasively.[50-56] When compared with results obtained at cardiac catheterization, the standard error of the estimate of mean gradient in the best laboratories is 10 mmHg.[57] Thus, the mean gradient by Doppler can be expected to be within ±20 mmHg (95 percent confidence level) of that obtained at catheterization.[57]

Similarly, the AVA will be within ±0.3 cm^2 of that obtained at cardiac catheterization.[57] A recent study of 156 patients compared AVA obtained by cardiac catheterization with that obtained by Doppler ultrasound.[58] Of 125 patients with AVA 0.8 cm^2 at cardiac catheterization, in 36 (29 percent) Doppler-estimated AVA was ≥0.9 cm^2. In all 7 patients with AVA >1.0 cm^2 by cardiac catheterization, Doppler-estimated AVA was 1.0 cm^2; the findings in these 7 patients must be interpreted cautiously because they were likely to be a highly selected subgroup. Guidelines for assessing severity of AS based on Doppler-obtained gradients are shown in Table 56-4. In a study of 636 patients studied by cardiac catheterization, no single aortic valve gradient was found to be both sensitive and specific for severe AS. A mean gradient of ≥50 mmHg or a peak gradient ≥60 mmHg were "specific" with a 90 percent or more positive predictive value. It was not possible to find a lower limit with 90 percent negative predictive value.[59] Thus, a mean gradient of <50 mmHg is compatible with mild, moderate, or severe AS.

Table 56-4: Suggested Conservative Guidelines for Relating Severity of Aortic Stenosis to Doppler Gradients in Adults with Normal Cardiac Output and Normal Average Heart Rate

Peak Gradient, mmHg	Mean Gradient, mmHg	Severe AS
≥80	≥70	Highly likely
60-79	50-69	Probable
<60	<50	Uncertain

SOURCE: From Rahimtoola,[57] with permission.

Transesophageal echo/Doppler ultrasound is very useful in defining the aortic valve abnormality and in assessing its severity when an adequate examination cannot be obtained with the transthoracic technique.

CARDIAC CATHETERIZATION/ANGIOGRAPHY

Cardiac catheterization remains the standard technique to assess the severity of AS "accurately." This is done by measuring simultaneous LV and ascending aortic pressures and measuring cardiac output by either the Fick principle or the indicator dilution technique. The AVA can be calculated (see Chap. 15). It is important to calculate AVA.[59] AS can be considered to be severe when the valve area is 1.0 cm^2 or less or the AVA index is 0.6 cm^2 per square meter or less (Table 56-5).[57] The state of LV systolic pump function can be quantitated by measuring LV end-diastolic and end-systolic volumes and ejection fraction. *It must be recognized that ejection fraction may underestimate myocardial function in the presence of the increased afterload of severe AS.*

Table 56-5: A Suggested Grading of the Degree of Aortic Stenosis

Aortic Stenosis	AVA, cm^2	AVA Index, cm^2/m^2
Mild	>1.5	>0.9
Moderate	>1.0-1.5	>0.6-0.9
Severe[a]	≤0.8-1.0	≤0.4-0.6

[a]Patients with AVAs that are at borderline values between the moderate and severe grades (0.9-1.1 cm^2; 0.55-0.65 cm^2/m^2) should be considered individually.
ABBREVIATIONS: AVA = aortic valve area.
SOURCE: From Rahimtoola,[57] with permission.

The presence of CAD and its site and severity can be estimated only by selective coronary angiography, which should be performed in all patients 35 years of age or older being considered for valve surgery and in those <35 years if they have LV systolic dysfunction, symptoms or signs suggesting CAD, or two or more risk factors for premature CAD (excluding gender) (Table 56-6). The incidence of associated CAD will vary considerably depending on the prevalence of CAD in the population.[57,60] It was reported to be 50 percent in patients with AS and 20 percent in patients with aortic regurgitation.[57] In general, in persons 50 years of age or older, it is about 50 percent (Table 56-7).[44,61-63]

Table 56-6: Aortic Valve Disease: Indications for Coronary Arteriography

Patients ≥35 years
Patients <35 years:
Left ventricular dysfunction
Symptoms or signs suggesting CAD
Two or more risk factors for premature CAD (excluding gender)

ABBREVIATIONS: CAD = coronary artery disease.
SOURCE: From Rahimtoola,[57] with permission.

Table 56-7: Isolated Aortic Valve Replacement: Incidence of Associated Coronary Artery Disease

	VA Co-op Study[a]	Mayo Clinic[b]	MGH[c] (80-89 years)
Total number of patients	643	618	64
Patients with coronary artery disease	312	321	37
%	49%	52%	58%
1 VD	17%	22%	27%
2 VD	17%	14%	19%
3 VD	15%	17%	13%
Additional LMCAD	-	5%	3%

[a]Sethi GK et al.[61] [b]Mullany CJ et al.[62] [c]Levinson JR et al.[63]
ABBREVIATIONS: LMCAD = left main coronary artery disease; MGH = Massachusetts General Hospital; VA = Veterans Administration; VD = vessel disease.

GATED BLOOD POOL RADIONUCLIDE SCANS

Gated blood pool radionuclide scans provide information on ventricular function similar to that provided by two-dimensional echocardiography and LV cineangiography. These studies are of particular value in the occasional patient in whom LV cineangiography is unsuccessful and echocardiographic studies are suboptimal.

EXERCISE TESTS

It is usually recommended that exercise tests of any kind not be undertaken in patients with severe AS unless there is a specific reason for such studies. Exercise tests in these patients may precipitate ventricular tachyarrhythmias and ventricular fibrillation. If there is doubt about the severity of AS and concern that the patient's symptoms may not be caused by AS, it is usually wise to document the absence of severe AS before performing an exercise test. Occasionally, in a patient with severe AS who denies all symptoms, a closely monitored exercise test by experienced and skilled physician(s) may be needed to assess exercise capacity but should usually *only* be undertaken after exclusion of associated significantly obstructive CAD.

AMBULATORY ECG RECORDING

Ambulatory ECG recordings may be needed in an occasional patient suspected of having an arrhythmia[64,65] or painless ischemia. Occasionally, patients with mild or moderate AS who are symptomatic may be suspected of having an arrhythmia or painless ischemia as a cause of the symptoms. At times, in asymptomatic patients with severe AS, one may need to determine if the patient has painless ischemia (see also Chap. 25).

PROVOCATIVE DIAGNOSTIC TEST

In an occasional patient, the severity of the AS may be in doubt because of a small stroke volume and small mean aortic valve gradient. The AS may be severe or mild to moderate, and the calculated AVA may be very small because of severe stenosis or because the small stroke volume only opens the valve to a limited extent; thus, the AVA will be determined to be small even on echo/Doppler ultrasound. Infusion of an inotropic agent such as dobutamine, which results in increases of stroke volume and heart rate, usually helps one to make a correct diagnosis. In these circumstances, it is important to measure cardiac output and LV and aortic pressures simultaneously and meticulously, both before and during dobutamine infusion. Whether the AS is mild or severe the gradient increases with dobutamine infusion; however, in mild AS the AVA increases significantly; but in severe AS the AVA does not increase or increases minimally (approximately 10 percent).

Clinical Decision Making

There are a number of steps involved in clinical decision making in patients with valvular heart disease (Table 56-8).[57] The first is a complete clinical evaluation, which includes history, physical examination, ECG, and chest x-ray. Next, disease of all cardiac valves, ventricular function, and hemodynamic effects as well as CAD, other cardiovascular disease, and disease of other organs should be diagnosed and the severity assessed. Before proceeding to additional testing, it is important to list the question(s) to be answered and to be reasonably certain that these questions need to be answered. The test(s) that are most likely to provide these answers *in the clinician's own institution* should then be performed, with the following criteria being kept in mind: reliability, accuracy, lowest risk to patient, and reasonable (lowest) cost. The results of the test(s) should be reviewed as they become available, and an overall evaluation/assessment of the patient and, finally, recommendations regarding management should be made.

In a prospective, blinded study of consecutive patients with valvular heart disease, the sensitivity and specificity of diagnosis of AS and the accuracy of assessment of severity of AS were determined (Table 56-9).[66] This study revealed the following important points: (1) Clinical evaluation was sensitive, highly specific, and reasonably accurate in diagnosing AS and was very accurate in assessing its severity when AS

was moderate or severe. This emphasizes the importance of a thorough clinical evaluation of the patient. (2) Echo/Doppler ultrasound improved the accuracy of this assessment to a certain extent. (3) The reason clinical evaluation and echo/Doppler do not have a 100 percent specificity is the inability in an occasional patient to distinguish mild AS from turbulence across a normal or slightly diseased aortic valve. (4) Both clinical evaluation and echo/Doppler ultrasound are excellent in diagnosing the AS as being at least moderate or severe. (5) An important difficulty in diagnosis by clinical evaluation and by echo/Doppler is in not being able to separate accurately all patients with moderate AS from those with severe AS.

Table 56-9: Clinical Decision Making Utilizing Clinical Evaluation and Echo/Doppler in Patients with Aortic Stenosis

	After Clinical Evaluation, %	After Echo/Doppler, %
Diagnosis of AS		
Sensitivity	78	100
Specificity	92	92
Accuracy of diagnosis		
All levels of severity	48	65
Moderate or severe AS	100	100

SOURCE: From Kotlewski et al.,[66] with permission.

Natural History and Prognosis

Valvular AS is frequently a progressive disease, the severity increasing over time.[67-71] The factors that control this progression and the time it takes for severe outflow obstruction to develop are unknown; however, it appears that in the older patient, AS may progress at about twice the rate that it does in the younger patient.[72] In a study of 142 patients with "mild" stenosis (catheterization-proven AVA >1.5 cm^2),[73] the rate of progression to severe stenosis was 8 percent in 10 years, 22 percent in 20 years, and 38 percent in 25 years. At 25 years, 38 percent still had mild AS (Table 56-10). The duration of the asymptomatic period after the development of severe AS is also unknown; some recent data suggest that it may be less than 2 years. The outcome of the asymptomatic patient with severe AS is not known. In the study of 123 asymptomatic patients aged 63 ± 16 years, the actuarial probability of death or aortic valve surgery was 7 ± 5 percent at 1 year, 38 ± 8 percent at 3 years, and 74 ± 10 percent at 5 years.[74] The event rate at 2 years for peak aortic jet velocity by Doppler ultrasound of >4 m/s was 79 ± 18 percent, for 3 to 4 m/s was 66 ± 13 percent, and for <3 m/s was 16 ± 16 percent. However, the limitations of gradients and of aortic peak velocity obtained by Doppler ultrasound should be kept in mind.[75] The overwhelming majority of adults with severe AS who are seen by cardiologists have symptoms.

Table 56-10: Natural History of Mild[a] Aortic Stenosis (*n* = 142)

	10 Years	20 Years	25 Years
Mild	88%	63%	38%
Moderate	4%	15%	25%
Severe	8%	22%	38%

[a]Mild stenosis is defined here as an aortic valve area >1.5 cm^2.
SOURCE: From Horstkotte and Loogen,[73] with permission.

Severe disease in adults is lethal, particularly if the patient is symptomatic, with a prognosis that is worse than for many forms of neoplastic disease.[57] The 3-year mortality is approximately 36 to 52 percent, the 5-year mortality is about 52 to 80 percent, and the 10-year mortality is 80 to 90 percent.[57] A recent study of elderly patients (average age 77 years) showed 1-year and 3-year mortalities were 44 and 75 percent, respectively.[76] With the onset of severe symptoms (angina, syncope, or heart failure), the average life expectancy is 2 to 3 years (Table 56-11).[73,77] Almost all patients with heart failure are dead in 1 to 2 years.[73,77] A combination of symptoms is much more ominous, a sign of a greatly reduced survival. Sudden death, like syncope, occurs in the presence of severe AS. Its exact incidence is difficult to determine but may be about 5 percent.[77] Most but not all of these patients have had some cardiac symptoms before the fatal episode; at times, the only symptom has been exertional presyncope. Patients with aortic valve "sclerosis" have an approximately 50 percent increase in cardiovascular mortality and myocardial infarction.[78] This incidence is lower than in patients with AS, and aortic sclerosis appears to be a marker for vascular atherosclerosis.

Table 56-11: Average Survival of Symptomatic Patients with Severe AS

	Autopsy Data,[a] Years	Post Cardiac Catheterization,[b] Months
Overall	3	23
Angina	5	45
Syncope	3	27
Heart failure	<2	11

[a]From Ross and Braunwald.[77] [b]From Horstkotte and Loogen.[73]

Management

All patients with AS need antibiotic prophylaxis against infective endocarditis (see Chap. 73). Those in whom the valve lesion is of rheumatic origin need additional prophylaxis against recurrence of rheumatic fever. Patients with mild or moderate stenosis rarely have symptoms or complications and do not need any specific medical therapy (Table 56-12). In mild stenosis, the patient should be encouraged to lead a normal life. Those with moderate AS should avoid moderate to severe physical exertion and competitive sports. In patients with mild or moderate AS, if atrial fibrillation should occur, it should be reverted rapidly to sinus rhythm. In severe AS, reversion to sinus rhythm often becomes a matter of some urgency.

Table 56-12: Medical Treatment of Patients with Aortic Valve Stenosis

I. Antibiotic prophylaxis
   A. Infective endocarditis (Chap. 82)
   B. Recurrent rheumatic carditis (Chap. 62)

II. Restriction of activities
   A. Severe exercise
   B. Competitive sports

III. Arrhythmias
   A. Prevent and/or control
   B. Restore sinus rhythm, if possible

IV. Cardiac medications (only if essential)
   A. Avoid negative inotropic and proarrhythmic agents if possible
   B. Diuretics-use cautiously
   C. Arteriolar and venodilators-use cautiously

V. Follow-up of asymptomatic patients
   A. Mild AS: Every 2-5 years
   B. Moderate AS: Every 6-12 months
   C. Develop symptoms: Immediate

SOURCE: Copyright S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C. See Ref. 93.

Operation should be advised for the symptomatic patient who has severe AS. In young patients, if the valve is pliable and mobile, simple commissurotomy or valve repair may be feasible; the operative mortality is <1 percent.[79] It will relieve outflow obstruction to a major degree. In such patients, catheter balloon valvuloplasty is the procedure of choice in experienced and skilled centers. Both of these are palliative procedures that postpone valve replacement for many years. Older patients and even young patients with calcified, rigid valves need valve replacement. The natural history of symptomatic patients with severe AS is dismal, i.e., a 10-year mortality of 80 to 90 percent, but there is good outcome after surgery, particularly in patients without any comorbid cardiac and noncardiac conditions. Given the unknown natural history of the asymptomatic patient with severe AS, which may not be benign,[57] it is reasonable to recommend surgery even to the asymptomatic patient. There is, however, no consensus about valve replacement in the truly asymptomatic patient. Clearly, if the patient has LV dysfunction, then valve replacement should be performed. Some recommend valve replacement in all asymptomatic patients with severe AS, while others would recommend it in those with AVA $\leq$0.7 cm^2 and in selected patients with AVA of 0.76 to 1.0 cm^2 (Table 56-13).

The operative mortality of valve replacement is about 5 percent or less (see Chap. 61).[57,61,62] In patients without associated CAD, heart failure, or other comorbid factors, it may be 1 to 2 percent in centers with experienced and skilled staff.[62] Patients with associated CAD should have coronary bypass surgery at the same time as valve surgery because it results in a lower operative and late mortality (Table 56-14). The operative mortality in octogenarians or older is much higher: up to 6 percent for isolated aortic valve replacement and up to 10 percent for those undergoing aortic valve replacement and associated coronary bypass surgery.

In severe AS, valve replacement results in an improvement of survival (Fig. 56-4),[73,80] even in those with normal preoperative LV function. LV function remains normal postoperatively if perioperative myocardial damage has not occurred.[22,57,81,82] LV hypertrophy regresses toward normal;[22,57,81,82] after 2 years, the regression continues at a slower rate for up to 8 to 10 years after valve replacement.[82] In those with excessive LV hypertrophy preoperatively,[30] the hypertrophy may regress slowly or not at all. These patients may have persistent severe LV diastolic dysfunction, which may be a difficult clinical problem

both in the early postoperative period and after hospital discharge. Their clinical picture subsequently resembles that of patients with hypertrophic cardiomyopathy without outflow obstruction, and they may have to be treated as such. Surviving patients are functionally improved. After aortic valve replacement, the 10-year survival is 60 percent or better and the 15-year survival is 45 percent or better.[83] Approximately one-half of the late deaths are not related to the prosthesis but to associated cardiac abnormalities and other comorbid conditions.[83] Thus, the late survival will vary in different subgroups of patients. The older patients (≥65 years) have a relative 10-year survival (actual survival compared to an age- and gender-matched person in the population) after valve replacement that is significantly better than that of those who are younger (<65 years)-94 percent versus 81 percent (Fig. 56-5).[84]

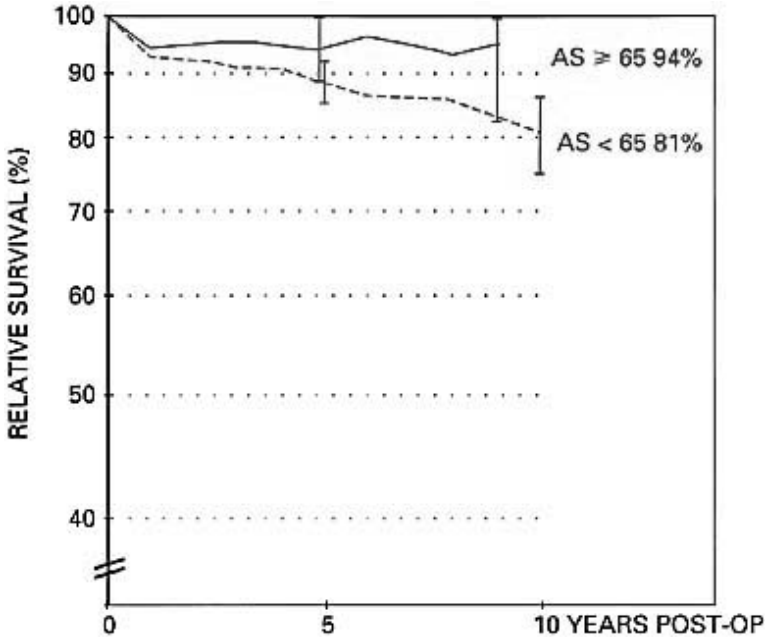

Figure 56-5: Data from the Karolinska Institute in Sweden provided an interesting perspective on the long-term survival after valve replacement in patients aged ≥65 years. They examined the relative survival, i.e., compared the survival of the patient who had undergone aortic valve replacement with another age- and sex-matched person in the same population. Patients under the age of 65 had a relative survival of 81 percent, significantly lower than 100 percent. On the other hand, patients aged ≥65 years who underwent valve replacement had a relative survival of 94 percent at the end of 10 years-not significantly different from 100 percent. These data indicate that (1) survival following valve replacement for AS in patients aged ≥65 years is identical to an age- and sex-matched individual in the population who does not have AS and (2) the late relative survival of patients aged 65 years or greater is much better than that of patients under the age of 65. (From Lindblom et al.,[84] with permission.)

Patients who present with heart failure should be hospitalized and treated with digitalis, diuretics, and *angiotensin-converting enzyme* (ACE) inhibitors and should undergo surgery as soon as possible. ACE inhibitors should be used extremely cautiously if at all. The patient must be monitored and hypotension avoided; a "significant" fall in blood pressure is an indication to discontinue or reduce the dose of ACE inhibitor. If heart failure does not respond satisfactorily and rapidly to medical therapy, surgery becomes a matter of considerable urgency.[85] Catheter balloon valvuloplasty can be an important bridge procedure in selected critically ill patients.[85] It usually improves the patients' hemodynamics and makes them better candidates for valve replacement. Valve replacement in patients with AS and heart failure can be performed at an operative mortality of 10 percent or less.[86] Although this is higher than in patients not in heart failure, the risk is justified because late survival in those who survive the operation is excellent and is far superior to that which can be expected with medical therapy; the 7-year survival of patients who survive operation is 84 percent.[87] The survival is lower in those with associated CAD.[86] The impaired LV function improves in all such patients provided that there has been no perioperative myocardial damage; it becomes normal in two-thirds of the patients (Fig. 56-6).[88] In some patients the improvement is less marked.[86] This is more

likely in those with longer duration of preoperative LV dysfunction and in those with associated CAD. In addition, the operative survivors are functionally much improved. LV hypertrophy and dilatation (if present preoperatively) regress toward normal. Despite the excellent results of valve replacements in patients with severe AS who are in heart failure, it is important to recognize that surgery should *not* be delayed until heart failure develops.

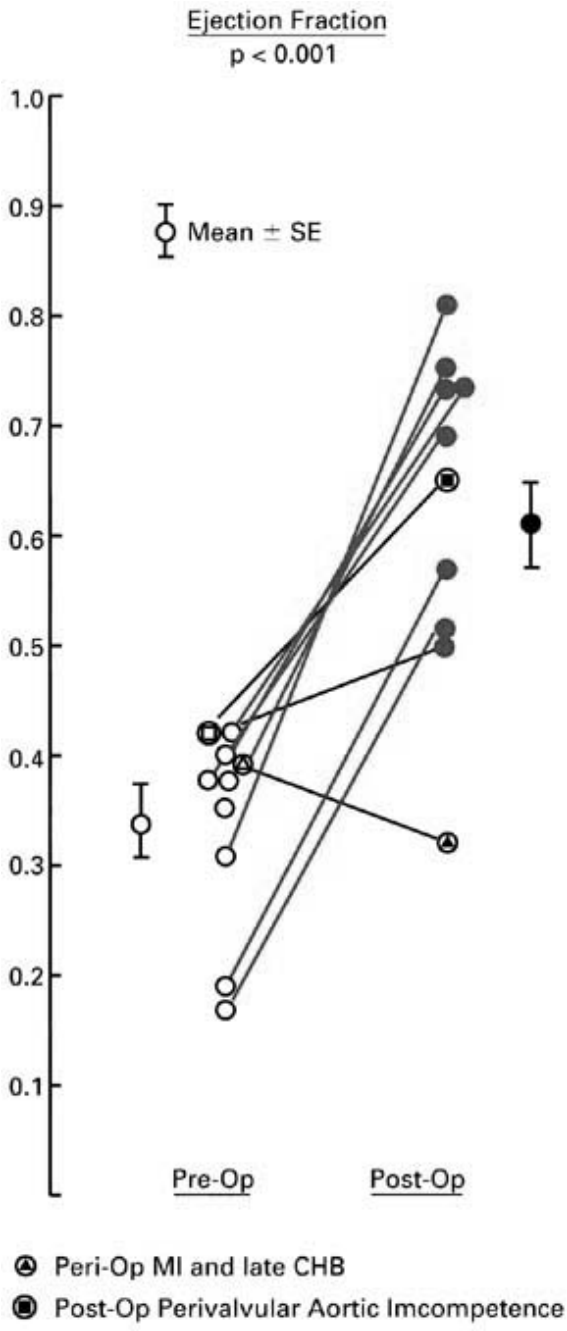

Figure 56-6: These data indicate that there is probably no lower limit of ejection fraction at which time these patients become inoperable. This also indicates that the lower the ejection fraction, the more urgent the need for valve replacement. (From Smith et al.,[88] with permission.)

In the data bases of older patients who underwent catheter balloon valvuloplasty, 6 percent of the patients were in cardiogenic shock.[89,90] The hospital mortality in such patients was very high, almost 50 percent. After hospital discharge, the subsequent mortality is also very high if the patients have not had their stenosis relieved.[90] Thus, these patients need to be treated aggressively with medical therapy with hemodynamic monitoring and need emergent surgery with or without catheter balloon valvuloplasty as a

"bridge" procedure[85] (Table 56-15).

Table 56-15: Suggested Indications for Catheter Balloon Valvuloplasty in Patients with Severe Calcific Aortic Valve Stenosis[a]

I. 'Bridge' procedure to eventual AVR
   A. Cardiogenic shock
   B. Moderate to severe heart failure
   C. Emergent/urgent need for noncardiac therapeutic procedures (e.g., operation)
II. Patient with limited life span
   A. Noncardiac reasons (e.g., carcinoma)
   B. Cardiac reason(s) other than aortic stenosis
III. Others
   A. Patient at extremely high risk for AVR
   B. AVR not desirable for noncardiac reasons or cardiac causes other than aortic stenosis
   C. Patient refuses surgery
IV. Rare
   A. 'Therapeutic test': patients with small stroke volume and small valve gradient, with valve stenosis suspected to be severe but severity in doubt even after provocative diagnostic tests

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[a]Caution should be exercised in recommending this procedure in asymptomatic patients.

ABBREVIATIONS: AVR = aortic valve replacement.
SOURCE: Adapted from Rahimtoola,[85] with permission.

The role of catheter balloon valvuloplasty in the older patient has now been clarified.[57,85] In calcific AS after catheter balloon valvuloplasty, the average increase in AVA is 0.3 cm^2 and the final AVA usually averages 0.8 cm^2; thus, many patients continue to have severe AS.[57,85,89] The 30-day, 1-year, and 3-year mortalities average 14, 35, and 71 percent, respectively, in the older patient (average age 78 ± 9 years) with calcific AS,[89] a mortality rate that may be similar to the natural history of this lesion. This technique is indicated[85] as a bridge procedure in those who need emergent noncardiac surgery and in those who are in heart failure (or in cardiogenic shock), who have an expected limited short life span when operative risks are considered to be prohibitively high, and who refuse surgery. When performed as a bridge procedure, valve surgery should not be unduly delayed. On rare occasions, it may be considered as a therapeutic test in patients in whom AS is suspected to be severe but the severity of the AS is in doubt after all standard tests have been performed (Table 56-15), including provocative diagnostic tests to assess mean aortic gradient, stroke volume, and AVA before and after infusion of dobutamine. Catheter balloon valvuloplasty is the procedure of choice in young patients who have pliable, noncalcified valves with commissural fusion (see Chap. 63).

The recommendations of the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines are shown in Tables 56-16 and 56-17.[91] Guidelines *are not* and *should not* be the law. Application of these guidelines to clinical practice should be based on the following principles: (1) classes I and III applies to all patients in these classes unless there is a specific clinical circumstance not to do so; (2) class II applies to patients in this class depending on the clinical conditions of the patients and the skill and experience at the individual medical center.

Table 56-16: Recommendations for Aortic Valve Replacement in Aortic Stenosis

Indication	Class
1. Symptomatic patients with severe AS	I
2. Patients with severe AS undergoing coronary artery bypass surgery	I
3. Patients with severe AS undergoing surgery on the aorta or other heart valves	I
4. Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves (see sections III.F.6., III.F.7., and VIII.D. of the ACC/AHA Guidelines)	IIa
5. Asymptomatic patients with severe AS and	
▪ LV systolic dysfunction	IIa
▪ Abnormal response to exercise (e.g., hypotension)	IIa
▪ Ventricular tachycardia	IIb
▪ Marked or excessive LV hypertrophy (≥15 mm)	IIb
▪ Valve area <0.6 cm^2	IIb
6. Prevention of sudden death in asymptomatic patients with none of the findings listed under indication 5	III

SOURCE: ACC/AHA Guidelines,[91] with permission.

Table 56-17: Recommendations for Aortic Balloon Valvotomy in Adults with Aortic Stenosis[a]

Indication	Class
1. A 'bridge' to surgery in hemodynamically unstable patients who are at high risk for AVR	IIa
2. Palliation in patients with serious comorbid conditions	IIb
3. Patients who require urgent noncardiac surgery	IIb
4. An alternative to AVR	III

[a]Recommendations for aortic balloon valvotomy in adolescents and young adults with AS are provided in section VI.A. of the ACC/AHA Guidelines.

SOURCE: ACC/AHA Guidelines,[91] with permission.

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Chapter 56: AORTIC VALVE DISEASE

ACUTE AORTIC REGURGITATION

Etiology

The two most common causes of acute *aortic regurgitation* (AR) are infective endocarditis and prosthetic valve dysfunction.[92] Other causes include dissection of the aorta, systemic hypertension, and trauma.[93,94] AR associated with dissection of the aorta indicates that the dissection involves the ascending aorta down to the aortic valve annulus/root. AR associated with systemic hypertension is usually mild and transient; it is associated with severe elevation of aortic pressure, and, when the systemic hypertension is controlled, the AR usually disappears unless permanent changes have occurred in the aortic valve annulus/root or valve leaflets.

Pathophysiology

The LV diastolic pressure-volume relationship plays a very important role in the pathophysiology of acute valve regurgitation (Fig. 56-7).[95,96] Two features should be considered:[92] (1) The ability of the left ventricle to dilate acutely is limited; as a result, the volume overload of acute AR produces a rapid increase of LV diastolic pressure (curve B in Fig. 56-7). (2) The LV diastolic pressure-volume relationship before the onset of acute AR. If the left ventricle is already stiff or less compliant than normal from an associated lesion (e.g., AS or systemic hypertension), the LV diastolic pressure will rise more precipitously as a result of the volume overload of acute AR (curve A) than if the LV were normal (curve B). On the other hand, if the left ventricle is somewhat dilated from a previous lesion, for example, mild AR (curve C), initially the LV pressure will rise more gradually with acute AR but may subsequently rise to the same high levels as that seen with a normal or stiff LV.

Acute AR that is mild produces little or no hemodynamic abnormality, for example, when associated with systemic hypertension. Increasing severity of regurgitation produces greater degrees of hemodynamic abnormalities, and severe AR often produces the clinical picture of "heart failure."

Acute AR that is severe results in a large volume of regurgitant blood; therefore, the volume of blood in the LV in diastole is increased. In an acute situation, the LV end-diastolic volume can only increase mildly (no more than 20 to 30 percent) and the LV diastolic pressure-volume relationships are particularly important. The LV systolic pump function is initially normal (Fig. 56-8). The increased LV diastolic pressure results in increases in mean left atrial and pulmonary venous pressures and produces varying degrees of pulmonary edema.[97] The normal LV systolic pump function in the presence of LV dilatation results in an increase of LV stroke volume. A large percentage of the LV stroke volume is returned to the LV in diastole, however; as a result, the forward stroke volume is reduced. The LV uses two mechanisms: an increase of myocardial contractility and, importantly, a compensatory tachycardia to maintain an adequate forward cardiac output. As a result, the forward cardiac output may be appropriate initially. If the compensatory mechanisms are inadequate, however, forward cardiac output is reduced. Pulmonary edema, with or without an adequate cardiac output, produces the picture of clinical heart failure.[97] Subsequently, LV systolic pump function may become abnormal; when that occurs, the pulmonary edema is further increased and the forward cardiac output is further reduced, leading to more severe manifestations of clinical heart failure.

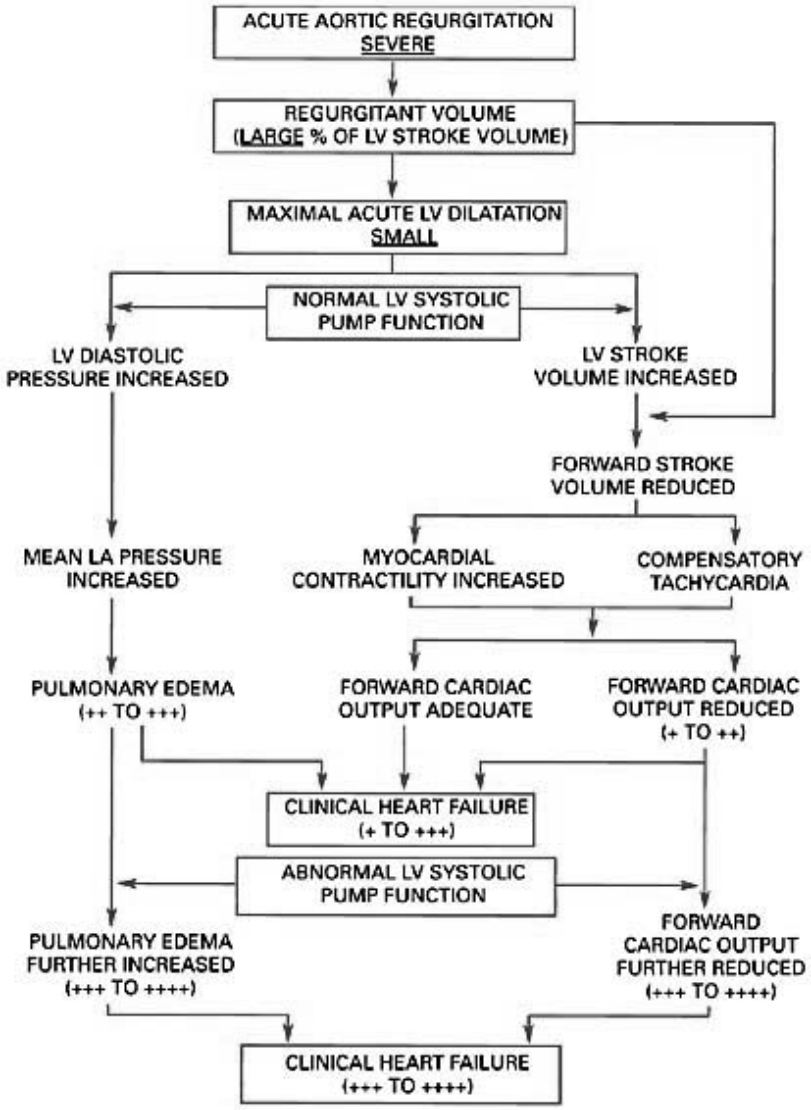

Figure 56-8: Pathophysiology of acute severe aortic regurgitation. Acute AR that is severe results in a large volume of regurgitant blood; therefore, the volume of blood in the left ventricle in diastole is increased. In an acute situation, the LV end-diastolic volume can only increase mildly (no more than 20 to 30 percent) and the LV diastolic pressure-volume relationships are particularly important (see Fig. 56-1). The subsequent findings are dependent on LV systolic pump function, LV diastolic pressure-volume relationship, myocardial contractile state, and compensatory tachycardia (see text for details). (Copyright © by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C. See Ref. 93.)

Clinical Findings

HISTORY, PHYSICAL FINDINGS

The clinical presentations of patients with acute AR are those relating to preexisting disorders that have caused the acute AR. For example, patients may have peripheral signs of infective endocarditis, a history of trauma, or severe chest pain of aortic dissection. The other clinical presentations are those related to the AR itself. If the AR is mild, the patient is usually asymptomatic. In the symptomatic patient, the symptoms are those of heart failure.

On physical examination, the symptomatic patient with acute severe AR usually has a tachycardia. The arterial pulse shows an increased rate of rise of pressure. Systolic pressure is usually normal unless there is very severe heart failure; however, the diastolic pressure is in the normal range or may be decreased. The pulse pressure is usually normal. Thus, although the classic peripheral signs of chronic, severe AR are often absent, an important diagnostic clue is the rapid rate of rise of arterial pressure. The usual clinical signs of

heart failure may be present. On examination of the precordium, the LV impulse is normal or slightly displaced to the left; it is usually hyperkinetic unless LV systolic dysfunction is present. The first heart sound is soft, and the second heart sound is often single and is soft. If pulmonary hypertension is present, P_2 is loud and there is a loud S_3 gallop sound, but an S_4 gallop sound is absent. The clinical sine qua non of AR is the AR murmur, an early or immediate, blowing, decrescendo diastolic murmur beginning after A_2 that is best heard with the diaphragm of the stethoscope. Having the patient sit up and lean forward with the breath held in expiration facilitates the audibility of the murmur in difficult cases. The murmur may be short and soft if the ascending aortic pressure equalizes with LV pressure in early or middiastole. An Austin Flint murmur, if present, occurs in middiastole (see also Chap. 10).

An important clinical picture in intravenous drug abusers[92] includes: (1) a peripheral arterial pulse that has a rapid rate of rise and fall, even though the pulse pressure is small; (2) the telltale signs of intravenous drug abuse; (3) sinus tachycardia; and (4) "normal" heart size with pulmonary edema on chest x-ray.

CHEST X-RAY

The chest x-ray shows a "normal" heart size with pulmonary edema; however, some enlargement of all cardiac chambers and the main pulmonary artery may be present. The aorta is not dilated unless aortic annular/root disease or dissection of the aorta is the cause of the acute AR. The aorta may also be dilated in the older patient and/or in those with an associated disease such as systemic hypertension. The lungs may show the signs of infected pulmonary emboli if there is associated tricuspid valve endocarditis.

ELECTROCARDIOGRAM

The ECG often shows nonspecific ST-T-wave changes and a sinus tachycardia; however, it may be normal. The ECG may show signs that are usually found in the associated causative disorder, e.g., LV hypertrophy with ST-T-wave changes in patients with severe hypertension. The ECG may show a variety of conduction abnormalities (atrioventricular and bundle branch block) including heart block, which, in the presence of infective endocarditis, is a sign of paravalvular/myocardial abscess.

Natural History and Prognosis

The natural history of this condition is variable. If the AR is mild to moderate in severity, these patients are likely to do well with medical therapy. Eventually, the changes of chronic AR will be seen. In patients with severe AR, the natural history depends on whether or not they have heart failure.[98] If heart failure is present, which is common, the prognosis is very poor without valve surgery unless the heart failure can be very easily controlled with medical therapy.

Management

DIAGNOSIS OF AORTIC REGURGITATION

In most instances, the diagnosis can be made by clinical evaluation, which includes the history, physical examination, electrocardiography, and chest x-ray. The diagnosis by physical examination in an acutely ill patient who is in extremis may be difficult.

Transthoracic echo/Doppler ultrasound is an important and valuable noninvasive procedure that should be used in every instance. It will demonstrate the AR and its severity and will provide useful information about the size and function of the left ventricle and other valvular and cardiac abnormalities. If the transthoracic method is not adequate, for example, in the very ill patient, then the transesophageal method should be used (see Chap. 13).

Echocardiography shows the diastolic flutter of the anterior leaflet of the mitral valve. In addition, the echocardiogram may show vegetations on the aortic valve, prolapse of an aortic valve leaflet into the left ventricle in diastole, and premature mitral valve closure. The mitral valve may be seen to open for only a short time because the stroke volume is limited. Occasionally, the aortic valve leaflets have been totally

destroyed, and none are seen on the echocardiogram. Doppler ultrasound can easily demonstrate the AR and provides an estimate of its severity.

Cardiac catheterization and angiography, including coronary arteriography, show the abnormal physiology described, and aortography shows gross AR. These modalities may be needed to make the diagnosis and are usually indicated before surgical intervention. Coronary arteriography is indicated in the appropriate patient (see above). In the extremely ill patient, there is often a need for clinical judgment with regard to the tests that are essential.

Other tests (cine-computed tomography, including fast cine-computed tomography, radionuclide gated blood scan, or ambulatory ECG) may be needed in very special conditions.

DIAGNOSIS OF THE ETIOLOGY OF ACUTE AORTIC REGURGITATION

The diagnosis of the etiology is usually made during the clinical evaluation by finding the usual clinical characteristics of the underlying lesion. Additional laboratory tests will be needed to confirm the diagnosis-for example, blood cultures in those with suspected infective endocarditis.

Echo/Doppler ultrasound (transthoracic and transesophageal) examination is also extremely valuable in diagnosing the underlying lesion. Its widespread availability and comparative ease of use, especially in the very acutely ill patient, make it the noninvasive procedure of choice. The availability of biplane and omniplane transesophageal probes further enhances its value as a diagnostic tool.

Magnetic resonance imaging (MRI) has a very high specificity for the diagnosis of dissection of the aorta[99,100] and, if available, should be used in all hemodynamically stable patients if the diagnosis has not already been made. The availability of biplane or omniplane transesophageal echocardiography markedly improves the specificity and diagnostic accuracy of transesophageal echocardiography. Angiography is also an effective and time-honored method of diagnosing dissection of the aorta.

In summary, clinical evaluation is available in all institutions; echo/Doppler ultrasound is available in almost all institutions. The use of the other tests depends on the availability of equipment and the skill and experience of personnel using the equipment for this purpose at each institution.

BEDSIDE HEMODYNAMIC MONITORING

In acute disorders affecting the left ventricle, there may be a phase lag between the rise in pulmonary venous pressure and the appearance of pulmonary edema on the chest x-ray film. As a result, the reliability of the chest x-ray in demonstrating the presence and severity of elevated left atrial pressure initially is less than satisfactory in the acutely ill patient.[101] If the assessment of left atrial pressure is made by physical examination and chest x-ray, a significant number of errors may be made in these patients with an acute cardiac problem. Therapeutic decisions based on incorrect assessments may result in significant problems; for example, inappropriate diuresis may result in a fall of cardiac output, or inappropriate volume loading may result in a further increase in left atrial pressure. Furthermore, the optimization of filling pressures and cardiac output may not be made accurately in acute heart failure without measuring their actual values. Thus, use of a balloon flotation catheter for bedside hemodynamic monitoring is required in most if not almost all acutely ill patients with acute AR.

TREATMENT

Treatment of the heart failure is directed toward reducing pulmonary venous pressure and increasing cardiac output. In all patients, treatment is also directed toward correcting or controlling the etiologic disease/disorder and/or the altered pathophysiologic state (Table 56-18).[92,98]

Table 56-18: Treatment of Heart Failure in Acute Valve Regurgitation

I. Correct or control altered pathophysiologic state
   A. Reduce pulmonary venous pressure
      1. Diuresis
      2. Vasodilation
      3. Control heart rate and maintain sinus rhythm (digitalis, cardioversion, antiarrhythmics)
   B. Increase cardiac output
      1. Reduction of valve regurgitation (vasodilators)
      2. Inotropic stimulation (digitalis, dobutamine)
   C. Improve left ventricular systolic dysfunction
      1. Reduce pulmonary venous pressure
      2. Increase cardiac output
      3. ACE inhibitors

II. Correct or control underlying disease or disorder
   A. Antibiotics for infective endocarditis
   B. Pharmacologic therapy for systemic hypertension
   C. Surgery for valve regurgitation in infective endocarditis, prosthetic valve dysfunction, dissection of the aorta, trauma

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SOURCE: From Rahimtoola,[92] with permission.

Vasodilators (intravenous nitroprusside for an acute, severe condition) are useful and important in the management of these patients.[102] Vasodilators will produce a reduction of left atrial *v* wave and mean left atrial pressure. They produce a reduction in LV end-diastolic and end-systolic volumes and an increase in LV ejection fraction. The regurgitant fraction and regurgitant volume are reduced; as a result, the forward stroke volume and cardiac output are increased.[102] Digitalis therapy is of significant benefit in the management of heart failure. The combination of various agents (vasodilators, diuretics, and digitalis) tends to produce the maximum benefit in an individual patient; intravenous nitroprusside is often necessary in the acutely ill patient.

Surgical therapy (valve replacement/valve repair or appropriate surgery for dissection of the aorta) is the cornerstone of the most definitive therapy currently available for heart failure in these patients. The management of the patient with heart failure or suspected heart failure is outlined in Fig. 56-9.[98] If the valve regurgitation is due to *dissection of the aorta*, the need for cardiac surgery is an emergency, even if the regurgitation is mild or moderate, because AR indicates involvement of the ascending aorta down to the region of the aortic valve annulus/root (see also Chap. 88). The outcome of the patient with heart failure due to infective endocarditis is very poor with medical therapy but is improved with valve replacement.[103] The indications for surgery in *infective endocarditis* are listed in Table 56-19.[81] Infective endocarditis due to special organisms (e.g., fungi) can only rarely be controlled by pharmacologic therapy alone, and surgery is almost always needed. In these and some other conditions, valve surgery may be needed even if the AR is only mild or moderate. It must be recognized, however, that in 90 to 95 percent of patients needing surgery for endocarditis, the indication for valve surgery is heart failure. When the heart failure is a result of *prosthetic valve dysfunction* or *trauma*, the need for surgery can be an emergency, an urgent situation, or an elective procedure. Prosthetic valves are inherently stenotic. When regurgitation is superimposed, it produces a pressure plus volume overload on the left ventricle that the ventricle may not handle very well acutely. Furthermore, valve regurgitation may be a sign of bioprosthetic valve degeneration or prosthetic endocarditis; in both conditions, prosthetic valve replacement is usually needed even if the valve regurgitation is mild to moderate. Trauma may result in AR from damage to valve leaflets or aortic annulus/root or from dissection of the aorta. If trauma produces dissection of the aorta and AR, the need for surgery may be an emergent one.

Table 56-19: Indications for Surgery in Infective Endocarditis

Congestive heart failure
Infection
Uncontrolled by antibiotic therapy
Fungal
Usually with staphylococcal infection of aortic or mitral valves
Serratia
Usually with gram-negative bacillary infection
Recurrent septic systemic emboli despite adequate antibiotic therapy
Perivalvular and myocardial abscesses
Structural damage to valve in association with other catastrophes (e.g., ruptured sinus of Valsalva)
Very large mobile vegetation

SOURCE: From Rahimtoola,[81] with permission.

In some instances, the heart failure can be controlled completely with pharmacologic therapy, and the left ventricle and left atrium are able to dilate and adapt to the volume overload; in such instances, surgical therapy may be delayed, perhaps for a considerable period of time.

PREVIOUS | NEXT

Chapter 56: AORTIC VALVE DISEASE

CHRONIC AORTIC REGURGITATION

Etiology

In North America, the most common cause of chronic, isolated severe AR is aortic root/annular dilatation that is presumably the result of medial disease. Other common causes include a congenital (bicuspid) valve, previous infective endocarditis, and rheumatic disease.[93,94] Chronic AR also occurs in association with a variety of other diseases (Table 56-20). Between 40 and 60 percent of the surgically removed valves from patients with isolated severe regurgitation are classified as idiopathic. Half of these (or 20 to 30 percent of all the valves removed) show histologic criteria of myxomatous degeneration.[104]

Table 56-20: Etiology of Chronic Aortic Valve Regurgitation

Aortic root dilatation
Congenital bicuspid valve
Previous infective endocarditis
Rheumatic
In association with other diseases
Congenital lesions, e.g., supravalvular or discrete subvalvular AS, ventricular septal defect, and aneurysm of the sinus of Valsalva
Connective tissue disease, e.g., Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome
Autoimmune diseases, e.g., ankylosing spondylitis, rheumatoid arthritis, and systemic lupus erythematosus
Various forms of aortitis and arteritis, e.g., giant-cell arteritis and Takayasu's disease
Syphilis

Pathology

During systole the aortic root/annulus expands by an increase of 14 to 16 percent of the diameter (twice the radius).[105] This causes the commissural attachments to spread apart, initiating the opening of the valves. These movements are continued during LV systole, which produces the forward motion of the blood. The length of the free edge of the cusps equals the diameter of the aortic root/annulus, or roughly one-third of the perimeter. Therefore, dilatation of the aortic root/annulus, if it is not accompanied by an enlargement of the cusps, results in AR.[104]

Depending on the cause, the valve cusps may show thickening, shortening, commissural lesions, or calcification (Fig. 56-10).[106] Regardless of the cause, the LV is dilated and hypertrophied; some of the largest ventricles have been described in association with chronic severe AR. Little pockets may be seen in the LV outflow tract. These are pouches out of the endocardial lining formed by the regurgitant jet(s) striking the left ventricle.

The myocardium is hypertrophied, with replication of sarcomeres in series, elongation of fibers, and wall thickening. The wall is not as thickened as in patients with AS. Ultrastructural changes in the myocardial cells are similar to those seen in AS; an important difference, however, is the frequent presence of degenerated cardiac muscle cells in patients with severe AR. Cardiac muscle cells with mild degeneration show focal myofibrillar lysis, with preferential loss of thick myofilament and focal proliferation of tubules of the sarcoplasmic reticulum. Moderately degenerated muscle cells show a marked decrease in the number of myofibrils and T tubules and proliferation of sarcoplasmic reticulum, mitochondria, or both. Severely degenerated muscle cells usually are present in areas of marked fibrosis; they are often atrophic, have thickened basement membranes, and have lost their intercellular connections. These degenerated cardiac muscle cells may represent the ultrastructural basis for impaired LV function, which is seen more commonly in severe AR than in severe AS.

In patients with rheumatoid arthritis and ankylosing spondylitis, nodules on the outer surface of the anterior leaflet of the mitral valve have been described.

Pathophysiology

In chronic as opposed to acute AR, the AR becomes severe over a period of time; therefore, the LV diastolic pressure-volume relationships are different from those seen in acute AR (Fig. 56-7). If the AR is mild to moderate, the LV end-diastolic volume is increased moderately, the LV diastolic pressure-volume curve is moved to the right (curve B) of normal (curve A), and the LV diastolic pressure is usually normal (Fig. 56-11). In severe AR, the LV diastolic pressure-volume curves are moved further to the right (curves C and D). If the LV systolic pump function is normal, the LV end-diastolic volume can be quite large without significant elevation of LV end-diastolic pressure (curve C). If the LV diastolic volume increases further, however, the LV diastolic pressures will be increased. If LV systolic pump dysfunction supervenes, the LV diastolic pressure-volume curve (curve D) relationships are moved even further to the right, with quite marked LV dilatation and increases in LV diastolic pressure.

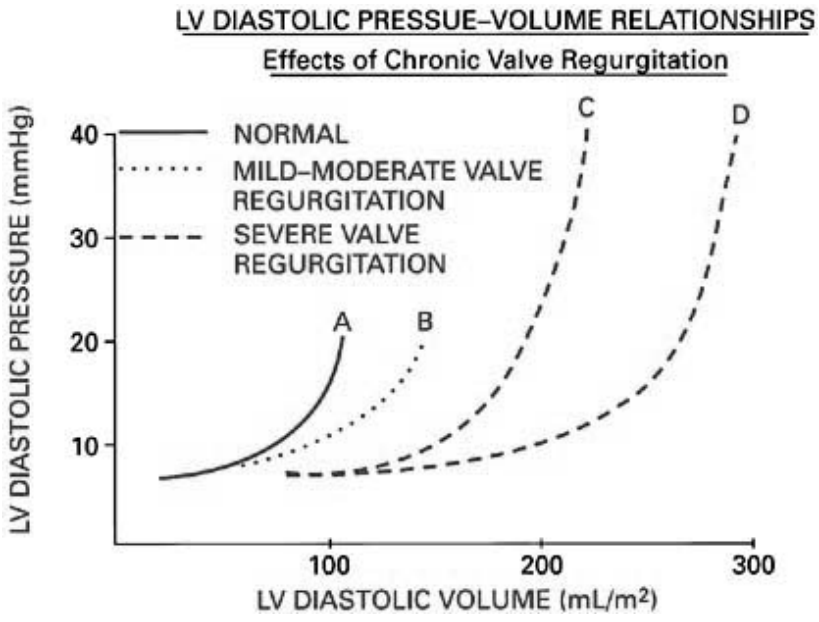

Figure 56-11: In chronic aortic regurgitation as opposed to acute AR, the AR becomes severe over a period of time; therefore, the LV diastolic pressure-volume (P-V) relationships are different from those seen in acute AR (see Fig. 56-7). If the AR is mild to moderate, the LV diastolic P-V curve is moved to the right (*curve B*). In severe AR, the LV diastolic P-V curves are moved further to the right, depending on whether the LV systolic pump function is normal (*curve C*) or abnormal (*curve D*). (From Rahimtoola,[98] with permission.)

The increase of LV end-diastolic volume[107] is a result of the regurgitant volume (and is proportional to the amount of regurgitation) and LV systolic dysfunction. As LV systolic dysfunction supervenes and increases in severity, for any severity of regurgitant volume the LV end-diastolic volume increases further in an attempt to maintain LV stroke volume.

Severe chronic AR results in a large regurgitant volume (a large percentage of LV stroke volume). The left ventricle responds by dilating (average LV end-diastolic volume in patients undergoing surgery was 205 mL/m^2);[22] the dilatation is proportional to the amount of the regurgitant volume. The subsequent large LV stroke volume produces LV systolic hypertension. Both of these increase LV wall stress (afterload), which can result in an impairment of LV function. The heart responds by becoming hypertrophied (average LV mass in patients undergoing valve surgery was 222 g/m^2),[22] and LV systolic pump function remains normal. There is also an alteration of the LV diastolic pressure-volume relationship (Fig. 63-11). As a result, some patients with normal LV systolic pump function become symptomatic[108] because of the abnormal LV diastolic function (Fig. 56-12).

In AR, the left ventricle is ejecting against systemic resistance, and the myocardial tension that is developed to open the aortic valve and eject the huge stroke volume is great. This contrasts with another volume-overload lesion, mitral regurgitation, in which there is a low-resistance chamber into which the LV is also emptying (the left atrium). Thus, for the same degree of regurgitant volume, afterload is higher in AR.

As LV afterload (a combination of LV dilatation, hypertrophy, and systolic hypertension) continues to increase, the LV utilizes two additional compensatory mechanisms, namely, increase of preload and an increase of myocardial contractility. Both of these help maintain normal LV systolic pump function.

When the limit of preload reserve has been reached (afterload mismatch)[31] and/or myocardial contractility is reduced, LV systolic pump function becomes abnormal. At this stage, correction of AR will result in normalization or marked improvement of LV systolic function. The additional LV dilatation also results in further alteration of the LV diastolic pressure-volume relationship (see Fig. 56-6). Clinical heart failure is usually a result of the abnormal LV systolic pump function. In patients with normal LV systolic pump function, clinical heart failure is a result of LV diastolic dysfunction.

Because of the leak of blood from the ascending aorta to the LV in diastole, the aortic diastolic pressure is reduced. The large LV stroke volume (a combination of forward stroke volume and regurgitant volume) results in elevation of the aortic systolic pressure, and thus the pulse pressure is considerably increased. Reduction or normalization of aortic systolic pressure is suggestive of LV systolic dysfunction in these patients.

LV stroke volume in AR consists of the forward stroke volume (blood delivered to the body tissues and the heart), which, multiplied by heart rate, makes up the forward cardiac output, and the regurgitant volume (the volume of blood that regurgitates back to the left ventricle). In the early stages, even in severe AR, the forward cardiac output and LV ejection fraction are normal at rest. During exercise, as in normal individuals, the systemic vascular resistance is decreased[109] and the heart rate is increased, which reduces the length of diastole. Both these factors reduce the regurgitant volume, and forward stroke volume and cardiac output are increased during exercise.[109] Thus, the ejection fraction on exercise is related to both the myocardial contractile state[110] and the fall in systemic vascular resistance.[109] Accordingly, a decline in ejection fraction on exercise cannot be used as a specific marker of LV function in these patients unless the change in systemic vascular resistance has also been measured. A fall of normal resting ejection fraction to less than 0.50 on exercise, however, has been shown to correlate with reduced total body oxygen consumption[103] and increased left atrial pressure during exercise.[109,111] Further impairment of LV function produces demonstrable abnormalities at rest; there is a further increase in LV end-diastolic volume, which helps to maintain forward stroke volume. The resting LV ejection fraction is reduced, and mean left atrial pressure begins to increase. Even at this stage, the forward cardiac output may be maintained in the normal range. The increases in left atrial pressure may produce various grades of pulmonary edema. Finally, in the

state of severe heart failure, the ejection fraction may be low, LV end-diastolic volume is large, and LV end-diastolic pressure is greatly increased and is associated with increases in left atrial, pulmonary, right ventricular, and right atrial pressures. Forward cardiac output is no longer normal. An increase in systemic venous pressure in association with salt and water retention produces engorgement of systemic organs (e.g., the liver) as well as peripheral edema.

In severe AR, myocardial oxygen needs are increased because of increases in LV diastolic and systolic volumes, LV muscle mass (hypertrophy), and LV pressures as well as by prolongation of systolic ejection time. Total coronary blood flow is increased. Coronary reserve, the ability of the coronary blood flow to increase with vasodilatation, however, is significantly reduced,[112-114] probably because of a reduced diastolic aortic-LV pressure gradient and compression of intramyocardial coronary arteries (systolic "milking" of intramural arteries). Therefore, myocardial ischemia is often present on stress in these patients.[112-114] Some patients with severe AR may complain of angina pectoris on effort even in the absence of epicardial CAD. Associated obstructive CAD can be expected to exacerbate further the myocardial ischemia (see Fig. 56-13).

Clinical Features

HISTORY

Patients with mild to moderate AR usually do not have symptoms that can be attributed to the heart. Even patients with severe AR may be asymptomatic. They may complain of pounding of the head or palpitations, which result from their awareness of the beating of a dilated left ventricle that undergoes a large volume change in systole, during either sinus beats or postectopic beats. The main symptoms of severe AR result from elevated pulmonary venous pressures and include dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. When congestive heart failure occurs, patients complain of fatigue and weakness. Angina pectoris occurs in 20 percent of such patients and may be present even if the coronary arteries are normal. Angina associated with syphilitic AR may be due to associated ostial stenosis of the coronary arteries. In such patients, angina often occurs at rest and is difficult to control.

PHYSICAL EXAMINATION

A variety of interesting but not very useful clinical signs may be present in patients with chronic severe AR. These include *de Musset's sign* (bobbing of the head with each heartbeat), *Traube's sign* (pistol-shot sound heard over the femoral artery), *Duroziez's sign* (systolic murmur over the femoral artery when it is compressed proximally and diastolic murmur when it is compressed distally), and *Quincke's pulse* (capillary pulsations that can be detected by pressing a glass slide on the patient's lip or transmitting a light through the patient's fingertips).

The arterial pulse is very characteristic and consists of an abrupt distention with a rapid rise and a quick collapse *(Corrigan's pulse)*. The arterial pulse may be bisferiens, a double impulse during systole. The systolic arterial pressure is increased (in severe AR it averages 145 to 160 mmHg), the diastolic pressure is reduced (in severe AR it averages 45 to 60 mmHg), and the Korotkoff's sounds persist down to 0 mmHg. Even in such instances, however, the recorded intraarterial pressure rarely falls below 30 mmHg. The vasoconstriction that occurs in the presence of heart failure may result in some elevation of the arterial diastolic pressure and should not be interpreted as an improvement in severity of AR. Similarly, LV systolic dysfunction can produce a fall of systolic blood pressure that should not be considered to be an improvement of the AR. The fall of systolic pressure along with elevation of diastolic pressures tends to normalize the pulse pressure. The jugular venous pressure is normal except in heart failure and in those rare instances in which the greatly dilated ascending aorta obstructs the superior vena cava.

On inspection, the chest may rock and the cardiac impulse may be visible. The cardiac impulse is hyperdynamic (Table 56-21). There may be a systolic thrill at the base of the heart, over the carotids, and in the suprasternal notch. This results from a large LV stroke volume across a diseased aortic valve. A diastolic thrill signifies severe AR. The first heart sound is usually soft because the mitral valve leaflets are close to each other at the onset of systole, or there may be premature valve closure. This is exaggerated if

the PR interval is prolonged. The S_2 is usually single because the aortic valve does not close properly[115] or because the LV ejection time is prolonged and the P_2 may not be heard. Often, a systolic ejection murmur, which is sometimes very loud, is present. The clinical sine qua non of AR is an early or immediate, blowing, decrescendo diastolic murmur beginning after A_2. It is best heard with the diaphragm of the stethoscope at the left sternal border or, in difficult instances, by having the patient sit up and lean forward and by auscultating in held respiration at the end of a deep expiration. In severe AR, the murmur may be holodiastolic. When it is soft, its intensity can be increased by having the patient perform isometric exercise, for example, a handgrip, which increases aortic diastolic pressure. At times, this murmur is better heard along the right sternal border, which should draw attention to the possibility that the cause of the AR is aortic root/annular disease (see also Chap. 10). Classically, rupture of the sinus of Valsalva into the right heart chambers produces a continuous murmur.

Table 56-21: Physical Examination of Patients with Varying Severity of Chronic Aortic Valve Regurgitation

	Mild	Moderate	Severe	Severe + LV Systolic Dysfunction	Severe + Heart Failure + LV Systolic Dysfunction
Arterial pulse	Normal	Corrigan's + to + +	Corrigan's + + +	Corrigan's + +	Corrigan's +
Arterial pressure					
Systolic	Normal	Increased + to + +	Increased + + +	Increased + +	Normal/+
Diastolic	Normal	Decreased + to + +	Decreased + + + to + + + +	Decreased + + to + + +	Decreased +
Pulse pressure	Often normal	Increased + to + +	Increased + + + to + + + +	Increased + + to + + +	Increased +
Cardiac impulse	Often normal	Hyperdynamic	Very hyperdynamic visible ± chest may rock	Hyperdynamic	May be hypodynamic
Precordial thrill:					
Systolic	-	±	±	±	-
Diastolic	-	-	±	±	-
Auscultation:					
S_4	-	-	-	-	-
S_1	Normal	Often soft	Soft	Soft	Soft
S_2	Normal	Normal or single	Often single	Often single	Often single
S_3	-	+	+ + to + + +	+ + +	+ + +
ESM	±	+	+ to + +	+ to + +	+
AoDM	+	+ +	+ + + to + + + +	+ + to + + +	+ to + +

Austin Flint murmur	-	-	±	-	-

ABBREVIATIONS: S_1 and S_2 = first and second heart sounds; S_3 = third heart sound (diastolic gallop); S_4 = fourth heart sound (presystolic gallop); ESM = ejection systolic murmur; AoDM = aortic diastolic murmur; - absent; + + + + most prominent; ± present or absent.

In many patients with severe AR, an Austin Flint murmur[116] (see Chap. 10) is present in presystole and/or mid-diastole. Two inferences can be drawn from the presence of an Austin Flint murmur: (1) it signifies that the AR is severe and (2) it requires that associated mitral stenosis be excluded. The most helpful sign at the bedside is the response of the murmur to the inhalation of amyl nitrite. The vasodilatation produced by amyl nitrite increases forward flow, reduces the regurgitant volume, and results in the Austin Flint murmur becoming much softer or disappearing. On the other hand, the increased cardiac output and the tachycardia accentuate or increase the murmur of mitral stenosis. Alternatively, echocardiography can easily demonstrate the presence of organic mitral stenosis.

With severe LV dilatation and/or LV systolic dysfunction, secondary mitral regurgitation may be present with the characteristic holosystolic murmur. Heart failure may be associated with pulmonary congestion/edema, pulmonary hypertension, right ventricular enlargement, tricuspid regurgitation, elevated jugular venous pressure, hepatomegaly, and peripheral edema (see Chap. 20).

CHEST X-RAY

The LV is increased in size, and this can be appreciated on the chest x-ray by an increase in the cardiothoracic ratio. Since the upper limit of normal of the cardiothoracic ratio is 0.49, many patients with increased LV size have an enlarged ventricular volume and may still have a cardiothoracic ratio within the normal range. A better noninvasive quantification of LV size can be obtained by echocardiography. The ascending aorta is dilated throughout, and there may be calcium in the aortic valve. With increased filling pressures in the later stages, there might be evidence of an enlarged left atrium and an increased left atrial and pulmonary venous pressure, which are manifested in the pulmonary vascular shadows by a redistribution of blood flow, pulmonary congestion, and pulmonary edema. In the presence of heart failure, enlargement of the right atrium and superior vena cava may be appreciated. Calcification that is limited to the ascending aorta is strongly suggestive of luetic aortitis.

ELECTROCARDIOGRAM

The ECG shows LV hypertrophy with or without associated secondary ST-T-wave changes. In a small percentage of patients, ECG evidence of LV hypertrophy is absent in spite of severe AR. Conduction abnormalities, such as atrioventricular block or left or right bundle branch block with or without axis deviation, may be present. The PR interval may be prolonged,[117] particularly in patients with ankylosing spondylitis. The rhythm is usually sinus. The presence of atrial fibrillation should make one suspect the presence of associated mitral valve disease or heart failure.

ECHOCARDIOGRAPHY

The sign of AR on echocardiography is diastolic fluttering of the anterior leaflet of the mitral valve. Echocardiography is of particular value for excluding the presence of associated mitral stenosis in patients with an Austin Flint diastolic murmur. LV dimensions are increased, and if ventricular function is normal, the percentage of dimensional shortening is normal. Because of the increase in LV dimensions caused by volume overload, there is separation between the open anterior leaflet of the mitral valve and the endocardial surface of the interventricular septum (septal-E point separation), but this does not necessarily indicate impaired LV function when AR is present. In AR, as in other volume-overload lesions, the response in mild volume overload is an elongation of the heart. Since M-mode echocardiography takes a pencil look at the short axis of the heart, LV dimensions by M-mode echocardiography may appear to be

normal. In such patients, two-dimensional echocardiography is much superior to the M-mode technique for assessing LV volumes and systolic function. A dilated ascending aorta can be detected on echocardiography, as can an enlarged left atrium. Aortic valve vegetations suggest infective endocarditis. Some other conditions can easily be detected by echocardiography, for example, prolapse of the aortic leaflet into the left ventricle in diastole. Doppler ultrasound is useful for diagnosing and assessing the severity of AR. There is a significant incidence of false-positive mild regurgitation. There is also an overlap between the various grades of severity of assessment of AR by Doppler when compared to angiography. Transesophageal echocardiography is a useful technique when transthoracic echocardiogram is unsatisfactory and in certain instances for identifying the anatomy of the valve leaflets and aortic root/annulus; it is essential to evaluate if the valve is suitable for repair. Echo/Doppler ultrasound is also very useful for assessing disease of other valves.

CARDIAC CATHETERIZATION/ANGIOGRAPHY

Cardiac catheterization allows the measurement of intracardiac and intravascular pressures and cardiac output, both at rest and during exercise, and can demonstrate the changes described under "Pathophysiology," above. In addition, other valvular disease-for example, mitral stenosis, aortic stenosis, and mitral regurgitation-can be excluded. LV angiography demonstrates enlarged LV volumes and allows the calculation of LV volumes and LV ejection fraction. Angiography performed with injection of contrast medium in the ascending aorta demonstrates AR and allows a semiquantitative assessment of the degree of AR. In addition, the angiogram demonstrates the dimensions of the aortic root and the state of the ascending aorta. The indications for selective coronary angiography are the same as for aortic stenosis (see Table 56-6).

GATED BLOOD POOL RADIONUCLIDE SCANS

Gated blood pool radionuclide scans also allow the measurement of LV volumes and ejection fraction. In addition, with this technique, it is possible to quantify the amount of AR. These scans, however, assess regurgitation present at both the aortic and mitral valves. Thus, if both valves are incompetent, the total amount of regurgitation present at both valves will be measured. This technique also allows measurement of LV ejection fraction on exercise and on serial studies.

TREADMILL EXERCISE TEST

A treadmill exercise test provides an objective assessment of the degree of functional impairment and documentation of arrhythmias related to exertion. In some patients, however, the exercise test may remain normal despite deterioration of LV function.

AMBULATORY ECG RECORDING

Ambulatory ECG recording may be needed in an occasional patient suspected of having an arrhythmia.

MAGNETIC RESONANCE IMAGING

MRI can demonstrate AR but is rarely needed clinically.

Clinical Decision Making

Please see the equivalent section under "Aortic Valve Stenosis," above. The sensitivity, specificity, and accuracy of diagnosis of chronic AR are shown in (Table 56-22).[66] The following should be noted: (1) The sensitivity, specificity, and accuracy of diagnosing AR after clinical evaluation are good but not quite as good as in AS; (2) echo/Doppler ultrasound improves these criteria to a greater extent than in AS; (3) the difficulties lie in accurately distinguishing patients with mild AR from normal individuals and those with moderate AR and in distinguishing between moderate AR and severe AR; and (4) both clinical evaluation and echo/Doppler ultrasound are excellent in diagnosing the AR as being moderate or severe.

Table 56-22: Clinical Decision Making Utilizing Clinical Evaluation versus Echo/Doppler in Patients with Aortic Regurgitation

	After Clinical Evaluation, %	After Echo/Doppler, %
Diagnosis of AR		
Sensitivity	66	79
Specificity	76	74
Accuracy of diagnosis		
All levels of severity	43	57
Moderate or severe AR	91	100

SOURCE: From Kotlewski et al.,[66] with permission.

Natural History and Prognosis

Patients with mild AR that does not progress should have a normal life expectancy. Their major risk is the development of infective endocarditis and further valve destruction. Patients with moderate AR, if their disease does not progress, would be expected to have a life expectancy that is reasonably close to the normal range. The disease does progress, however, and mortality at the end of 10 years appears to be about 15 percent.

Patients with severe AR are known to have a long asymptomatic period before the condition is discovered. In asymptomatic patients with normal LV function at rest, symptoms and/or LV dysfunction (and/or sudden death) develop at the rate of about 3 to 6 percent per year. The predictor of development of symptoms is LV systolic dysfunction at rest.[118-122] In patients with normal LV systolic function at rest (Table 56-23), the predictors of development of LV systolic dysfunction and/or symptoms are an increased LV size (LV dimension at end-diastole of ≥70 mm and at end-systole of ≥50 mm,[119-121] and LV end-diastolic volume index of ≥150 mL/m^2),[123] and abnormal LV ejection fraction on exercise of <0.50.[111] In smaller people, for example, in women,[122] these values are too large and have to be corrected for body size. The corrected dimensions for end diastole and end systole are 35 mm/m^2 and 25 mm/m^2, respectively. Sudden death in asymptomatic patients appears to occur only in those with a massively dilated left ventricle (LV end-diastolic dimension of ≥80 mm).[119] It is likely that LV dysfunction first appears on exercise and later also at rest; eventually, heart failure ensues. Severe symptoms, however, may occur even when LV systolic pump function is normal at rest (see "Pathophysiology," above). The 5-year mortality of symptomatic patients with severe AR is about 25 percent, and the 10-year mortality averages 50 percent.[118] Once symptoms occur in patients with AR, it is likely that the rate of deterioration will be rapid. Most patients with angina are dead within 4 years.[124] The 2- to 3-year mortality of those with heart failure is 50 to 70 percent. In a recent study, the mortality was 4.7 percent per year, in the symptomatic patient it was 9.4 percent per year[125] and in the asymptomatic patient 2.8 percent, which was not significantly different from age- and gender-matched individuals in the population. In the symptomatic patient, those in the New York Heart Association (NYHA) classes III and IV had an annual mortality of 24.6 percent per year, while in the class II patient it was 6.3 percent per year. In asymptomatic patients, those with LV ejection fraction <0.55, the annual mortality was 5.8 percent per year, and in those with LV end-systolic dimension ≥25 mm/m^2, it was 7.8 percent per year.[125]

Table 56-23: Chronic Severe Aortic Regurgitation: Asymptomatic + Normal LV Function at Rest

		Likelihood of Symptoms or LV Dysfunction or Death, % per Year
LV end-diastolic	≥70 mm	10
dimension	<70 mm	2
LV end-systolic	≥50 mm	19
dimension	40-49 mm	6
	<40 mm	0

SOURCE: From Bonow et al.,[119] with permission.

Management

All patients with AR need antibiotic prophylaxis to prevent infective endocarditis. Patients with AR of a rheumatic origin need antibiotic prophylaxis to prevent recurrences of rheumatic carditis. Patients with syphilitic AR need a course of antibiotics to treat syphilis.

Patients with mild AR need no specific therapy (Table 56-24). They do not need to restrict their activities and can lead a normal life. Patients with moderate AR also usually need no specific therapy. These patients, however, should avoid heavy physical exertion, competitive sports, and isometric exercise.

The value of long-term vasodilators to produce an improvement in LV size and function has been evaluated in two placebo-controlled randomized trials. In the hydralazine trial,[126] 36 percent of the patients were in NYHA functional class II, and patients had moderate to severe AR. Hydralazine produced modest reduction of LV end-diastolic volume and a small increase in ejection fraction at the end of 2 years; however, because of side effects, long-term compliance was poor,[126] which probably accounted for the extremely modest beneficial effects.[127] In asymptomatic patients with severe AR,[128] a calcium channel blocking agent, long-acting nifedipine, produced significant reductions in blood pressure and LV end-diastolic volume and mass and major increases in LV ejection fraction at the end of 1 year. Almost all patients completed the trial. Recently, a prospective randomized trial in *asymptomatic* patients with *normal LV systolic* function[120] showed that at the end of 6 years, 34 ± 6 percent of patients treated with digoxin developed LV systolic dysfunction and/or symptoms and thus needed valve replacement, compared to 15 ± 3 percent of patients treated with long-acting nifedipine ($p < .001$) (Fig. 56-14); 90 percent (23 of 26) of those who needed valve replacement had developed LV systolic dysfunction with or without symptoms; only 3 had become symptomatic without developing LV systolic dysfunction. Accordingly, all asymptomatic patients with severe AR and normal LV systolic function should be treated with a vasodilator (calcium antagonists long-acting nifedipine) unless there is a contraindication to its use.

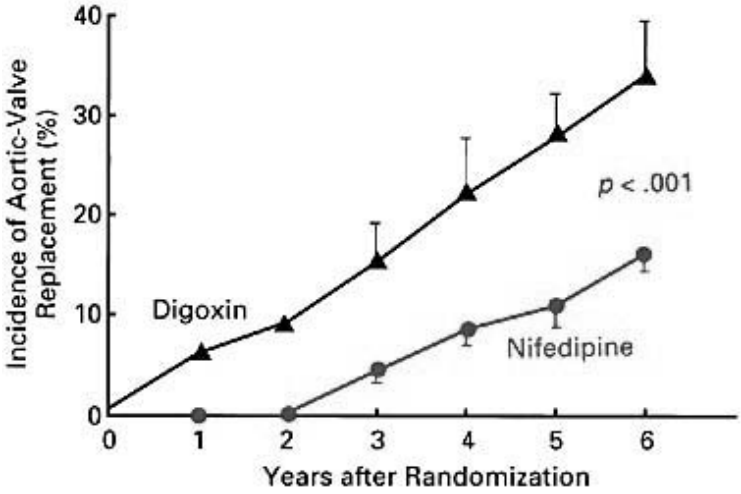

Figure 56-14: This randomized trial demonstrates that long-term vasodilator therapy with nifedipine reduces and/or delays the need for aortic valve replacement in asymptomatic patients with severe AR and normal LV systolic pump function. (From Scognamiglio et al.,[120] with permission.)

The role of nifedipine in patients with moderate AR has not been studied. In view of its beneficial effects in severe AR, long-acting nifedipine could be used in selected patients with moderate AR if there are no contraindications to its use. An acute study showed that nifedipine was superior to an ACE inhibitor,[129] and a 6-month trial showed that the results with captopril were similar to placebo.[130] One study with quinapril involved 10 patients, many of whom had moderate AR.[131] In another study with enalapril, most patients had mild to moderate AR and many had severe systemic hypertension.[132] Moreover, there are no published data to show that ACE inhibitor therapy reduces the need for valve surgery. In brief, ACE inhibitors are not of proven benefit in asymptomatic patients with AR and with normal LV systolic function.

Symptomatic patients with severe AR need medical and surgical treatment. Medical treatment (Table 56-24) consists of the administration of digitalis, diuretics, and vasodilators. Digitalis acts by increasing myocardial contractility, often reducing LV end-diastolic volume while increasing the LV ejection fraction and also the cardiac output if it is reduced in the resting state. Digitalis is clearly indicated in patients with symptoms. The need for and benefits of this therapy in asymptomatic patients have not been well documented. Diuretics are of value when the left atrial pressure is elevated and in the presence of heart failure.

Vasodilators are either arterial, venous, or both. Vasodilators act by reducing the peripheral arterial resistance, which favors forward cardiac output and reduces regurgitant volume; initially, the total LV stroke volume remains unchanged. If the left atrial pressure is elevated and LV ejection fraction reduced, vasodilators frequently result in an improvement in both.

Long-term hydralazine therapy in symptomatic patients results in significant benefit in only 20 to 35 percent of patients.[57] Those who are likely to benefit cannot be predicted. Vasodilators are indicated in patients who refuse surgery or are not operative candidates for any reason.

Vasodilators are also indicated for short-term therapy in patients awaiting valve replacement to optimize their hemodynamics (reduce filling pressures and increase cardiac output) and thus reduce their operative risks. If LV systolic function is normal, they can be given long-acting nifedipine. If they have abnormal LV systolic function, they should be treated with digitalis and ACE inhibitors; diuretics and hydralazine, with or without nitrates, can be used if needed. Small doses of hydralazine (50 mg) are without therapeutic effect in AR, and larger doses (≥100 mg) need to be given only twice daily;[133] the twice-daily regimen reduces the incidence of side effects. Hydralazine should be started in small doses and gradually increased, depending on patient tolerance of the drug.

Vasodilators are of considerable short-term benefit in patients in functional classes III and IV or heart

failure. All such patients need digitalis, diuretics, and ACE inhibitors. In patients in functional class IV with heart failure, vasodilators should ideally be started after the institution of bedside hemodynamic monitoring-that is, measurement of pulmonary artery wedge pressure and cardiac output with the use of balloon flotation catheters. Hemodynamic monitoring accurately identifies patients who need the therapy, since clinical judgments can be wrong. It establishes whether arterial dilators alone will suffice or whether additional venodilators are needed. Finally, it provides information on the optimum dosage of vasodilator therapy. After the initial hemodynamic measurements are made, arterial dilators are given in progressively increasing dosage until an optimum effect on cardiac output has been obtained. If cardiac output does not show any further increase but left atrial pressure is still very high, additional venodilator therapy should be given. If the patient is very ill or the hemodynamic abnormalities are marked, intravenous therapy (e.g., sodium nitroprusside) is the vasodilator of first choice. In this situation, intravenous vasodilator therapy should be used only with bedside hemodynamic monitoring. Inotropic agents, such as dobutamine, may be needed to improve LV function and increase cardiac output. Low-dose dopamine may be of value to increase urinary output.

Patients with severe chronic AR need valve surgery. The correct timing of surgical therapy is now better defined but is not fully clarified. Valve replacement should be performed before irreversible LV dysfunction occurs. The major problem, however, is identifying the precise point at which LV dysfunction will occur. Here, two major difficulties are encountered: (1) patients may already have impaired LV systolic pump function at rest when they first present or at the time of the first symptom and (2) patients with severe symptoms may have normal LV systolic pump function. Patients may be in NYHA functional class III (symptoms with less than ordinary activity), with a normal LV ejection fraction,[108] or they may be in functional class I (asymptomatic), with a reduced LV ejection fraction.[108] A reduced LV ejection fraction demonstrated by two-dimensional echocardiography and/or radionuclide ventriculography is the best noninvasive indicator of depressed LV systolic function.

Decisions about surgery in AR should be based on the clinical functional class and on the LV ejection fraction at rest (Table 56-25).[134] Patients with chronic severe AR who are symptomatic (NYHA functional classes II to IV) need valve replacement. Although there may be some disagreement about recommending valve replacement to patients with normal ejection fraction who are in functional class II, we currently would do so. The benefit from valve replacement has been demonstrated even when the LV ejection fraction is 0.25 or less.[135] As opposed to AS, in which there is no lower level of ejection fraction that indicates inoperability, it is likely that some patients with AR and a very low ejection fraction become inoperable. This level has not been precisely defined but may be about 0.15 or less. There is a need to individualize the need for valve replacement in those with very severe LV systolic dysfunction at rest, in those with very severe LV dilatation (LV end-diastolic volume index ≥300 mL/m^2),[136] and in those with a small regurgitant volume, with a ratio of regurgitant volume to end-diastolic volume of 0.14[137] (Table 56-25). Recent data indicate that patients with severe AR, LV end-diastolic dimension on echocardiography of ≥80 mm, and mild to moderate reduction of LV ejection fraction (mean 0.43) can obtain benefit from valve replacement.[138] Postoperatively, they are symptomatically improved, LV ejection fraction increases, and LV size is reduced; the 5- and 10-year survivals are 87 and 71 percent, respectively.

Although the issue is controversial in some countries, we believe that patients who are in NYHA functional class I (asymptomatic) and have a reduced ejection fraction at rest should be offered aortic valve replacement. If the ejection fraction is normal at rest, one should consider valve replacement in NYHA functional class I patients if they have severe obstructive CAD and/or need surgery for other valve disease (Table 56-25). It is suggested that patients undergo an exercise test during right heart catheterization if the left ventricle is large (LV end-diastolic volume ≥150 mL/m^2, LV internal dimension on M-mode echocardiography of ≥70 mm at end diastole and ≥50 mm at end systole) and/or the LV ejection fraction shows a new, persistent reduction to 0.54 to 0.60; if the patients have reduced exercise capacity on treadmill testing; or if ambulatory ECG monitoring demonstrates ventricular tachyarrhythmias. Valve replacement is recommended if the pulmonary artery wedge pressure during exercise ≥20 to 24 mmHg. Patients with associated significant CAD should have coronary bypass surgery performed at the time of valvular surgery (see "Aortic Valve Stenosis," above, and Table 56-14).

Aortic valve replacement, with or without associated coronary bypass surgery for obstructive CAD, can be performed at many surgical centers with an operative mortality of 5 percent or less (see Chap. 66). In those without associated CAD or reduced LV systolic function, the operative mortality may be in the range of 1 to 2 percent. If aortic valve replacement is successful and uncomplicated, LV volume and hypertrophy regress but do not return to normal; the beneficial effects on LV size, volume, and mass continue to be seen up to 5 years after surgery.[82,139,140] Impaired LV systolic pump function improves postoperatively in 50 percent or more of patients;[135] this improvement is more likely to occur if LV dysfunction has been present preoperatively for 12 months or less, and in this subgroup LV ejection fraction usually normalizes.[140] Even if LV systolic pump function does not improve, there is a reduction in end-diastolic volume and hypertrophy;[125] from a cardiac point of view, this is advantageous to the patient. The 5-year survival of patients undergoing aortic valve replacement in severe AR is 85 percent (this figure includes operative and late cardiac deaths).[134] The 5-year survival of patients with LV ejection fraction ≥0.45 is 87 percent, versus 54 percent in patients with an ejection fraction <0.45.[134] Late survival after valve replacement for chronic severe AR is best predicted by variables indicative of LV systolic pump function. Both the operative mortality and late survival are dependent on cardiac and LV function and associated noncardiac comorbid factors (see "Aortic Valve Stenosis," above, and Chap. 66).

Indeed, in general, the major factors influencing outcome in patients with valvular heart disease are: LV dysfunction and its magnitude, duration of LV dysfunction, degree of LV dilatation, greater NYHA functional class, older age, associated CAD, and comorbid conditions.

New techniques of aortic valve repair are being developed and evaluated, and early results are encouraging in selected subgroups.[105,141,142] It is possible that selected patients may eventually need to have valve repair rather than valve replacement for AR.

The recommendations of the ACC/AHA Practice Guidelines are shown in Table 56-26.[91] Guidelines are *not* and should *not* be the Law. Application of such guidelines to clinical practice should be based on the following principles: (1) classes I and III applies to all patients in these classes unless there is a specific clinical circumstance not to do so; (2) class II applies to patients in this class depending on the clinical conditions of the patients and the skill and experience at the individual medical center.

Table 56-26: Recommendations for Aortic Valve Replacement in Chronic Severe Aortic Regurgitation

Indication	Class
1. Patients with NYHA functional Class III or IV symptoms and preserved LV systolic function, defined as normal ejection fraction at rest (ejection fraction ≥0.50)	I
2. Patients with NYHA functional class II symptoms and preserved LV systolic function (ejection fraction ≥0.50 at rest) but with progressive LV dilatation or declining ejection fraction at rest on serial studies or declining effort tolerance on exercise testing	I
3. Patients with Canadian Heart Association functional Class II or greater angina with or without CAD	I
4. Asymptomatic or symptomatic patients with mild to moderate LV dysfunction at rest (ejection fraction 0.25 to 0.49)	I
5. Patients undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves	I
6. Patients with NYHA functional Class II symptoms and preserved LV systolic function (ejection fraction ≥0.50 at rest) with stable LV size and systolic function on serial studies and stable exercise tolerance	IIa

7. Asymptomatic patients with normal LV systolic function (ejection fraction >0.50) but with severe LV dilatation (end-diastolic dimension >75 mm or end-systolic dimension >55 mm)[a]	IIa
8. Patients with severe LV dysfunction (ejection fraction <0.25)	IIb
9. Asymptomatic patients with normal systolic function at rest (ejection fraction >0.50) and progressive LV dilatation when the degree of dilatation is moderately severe (end-diastolic dimension 70 to 75 mm, end-systolic dimension 50 to 55 mm)	IIb
10. Asymptomatic patients with normal systolic function at rest (ejection fraction >0.50) but with decline in ejection fraction during	
▪ Exercise radionuclide angiography	IIb
▪Stress echocardiography	III
11. Asymptomatic patients with normal systolic function at rest (ejection fraction >0.50) and LV dilatation when degree of dilatation is not severe (end-diastolic dimension <70 mm, end-systolic dimension <50 mm)	III

[a]Consider lower threshold values for patients of small stature of either gender. Clinical judgment is required.

SOURCE: ACC/AHA Guidelines,[91] with permission.

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Figure 56-7: The left ventricular (LV) diastolic pressure-volume (P-V) relationship in acute valve regurgitation. The volume overload of acute AR produces a rapid increase of LV diastolic pressure in a patient with normal LV diastolic P-V prior to the acute AR (*curve B*). The LV diastolic pressure will rise more or less precipitously as a result of the volume overload of acute AR, depending on whether the LV is already stiff (*curve A*) or is somewhat dilated from a previous volume overload (*curve C*). (From Rahimtoola,[98] with permission.)

Figure 56-8: Pathophysiology of acute severe aortic regurgitation. Acute AR that is severe results in a large volume of regurgitant blood; therefore, the volume of blood in the left ventricle in diastole is increased. In an acute situation, the LV end-diastolic volume can only increase mildly (no more than 20 to 30 percent) and the LV diastolic pressure-volume relationships are particularly important (see Fig. 56-1). The subsequent findings are dependent on LV systolic pump function, LV diastolic pressure-volume relationship, myocardial contractile state, and compensatory tachycardia (see text for details). (Copyright © by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C. See Ref. [93].)

Figure 56-9: Role of bedside hemodynamic monitoring in acute aortic regurgitation. All patients with acute AR probably should have this procedure. If the AR is mild and there are no significant hemodynamic abnormalities, then the balloon flotation catheter can be withdrawn. On the other hand, if the AR is moderate to severe and there are significant hemodynamic abnormalities, then the balloon flotation catheter is left in place to guide therapy in the management of these acutely ill patients. If the hemodynamic abnormalities are mild, the patient is treated medically. If these abnormalities are easily controlled, medical therapy is continued and periodic reassessments are made to assess the need for elective surgery. If the hemodynamic abnormalities are not easily corrected or the hemodynamic abnormalities initially are moderate/severe, then surgery is undertaken either emergently or urgently. (From Rahimtoola,[98] with permission.)

Figure 56-10: Pathologic findings in aortic regurgitation depending on the etiology of the AR. (From Waller,[106] with permission.)

Figure 56-11: In chronic aortic regurgitation as opposed to acute AR, the AR becomes severe over a period of time; therefore, the LV diastolic pressure-volume (P-V) relationships are different from those seen in acute AR (see Fig. 56-7). If the AR is mild to moderate, the LV diastolic P-V curve is moved to the right (*curve B*). In severe AR, the LV diastolic P-V curves are moved further to the right, depending on whether the LV systolic pump function is normal (*curve C*) or abnormal (*curve D*). (From Rahimtoola,[98] with permission.)

Figure 56-12: Clinical heart failure is usually a result of the abnormal LV systolic pump function; diastolic dysfunction may also be present in some patients. Clinical heart failure in those with normal LV systolic pump function is a result of LV diastolic dysfunction. (Copyright © by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C. See Ref. [93].)

Figure 56-13: In severe aortic regurgitation, myocardial oxygen needs are increased. Total coronary blood flow is increased, but coronary reserve, i.e., the ability of the coronary blood flow to increase with vasodilatation, is significantly reduced, probably because of a reduced diastolic aortic-LV pressure gradient and compression (systolic milking) of intramyocardial coronary arteries. Therefore, myocardial ischemia is often present on stress in these patients. Associated obstructive coronary artery disease can be expected to further exacerbate the myocardial ischemia. (Copyright © by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C. See Ref. [93].)

Figure 56-14: This randomized trial demonstrates that long-term vasodilator therapy with nifedipine reduces and/or delays the need for aortic valve replacement in asymptomatic patients with severe AR and normal LV systolic pump function. (From Scognamiglio et al.,[120] with permission.)

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Part 9: VALVULAR HEART DISEASE
Chapter 57:

MITRAL VALVE DISEASE

Authors: Shahbudin H. Rahimtoola, Maurice Enriquez-Sarano, Hartzell V. Schaff, Robert L. Frye

MITRAL STENOSIS

Etiology

Mitral stenosis (MS), an obstruction to blood flow between the left atrium (LA) and the left ventricle (LV), is caused by abnormal mitral valve function. In virtually all adult patients, the cause of MS is previous rheumatic carditis.[1] About 60 percent of patients with rheumatic mitral valve disease do not give a history of rheumatic fever or chorea, and about 50 percent of patients with acute rheumatic carditis do not eventually have clinical valvular heart disease.[2] Other causes of MS are all uncommon or rare and are listed in Table 57-1.[2-10] Congenital MS is uncommon. It is usually caused by a "parachute" deformity of the valve, in which shortened chordae tendineae insert in a large, single papillary muscle. MS, usually rheumatic, in association with atrial septal defect is called *Lutembacher's syndrome*. A rare cause of MS is massive mitral valve annular calcification. This process occurs most frequently in elderly patients and produces MS by limiting leaflet motion. When stenosis is present, it is usually mild in degree. Other causes of obstruction to LA outflow include a LA myxoma, massive LA ball thrombus, and cor triatriatum, in which a congenital membrane is present in the LA.

Table 57-1: Causes of Mitral Stenosis

	Involved Structure(s)			
Cause	Leaflet	Chordae	Commissures	Other
Rheumatic fever	+	+	+	
Congenital	+	+		Single papillary muscle
Active infective endocarditis	+			Vegetation
Neoplasm				Mass, pulmonary vein obstruction
Massive annular calcification	+	0	0	Rigid annulus
Systemic lupus erythematosus	+	+	+	Verrucous vegetations may extend into papillary muscles
Carcinoid				Atrial septal defect or lung tumor in order to affect left heart
Methysergide therapy	+	+		Serotonin agonist/antagonist
Hunter-Hurler syndromes				Mucopolysaccharide deposits
Fabry's disease				Aramide trihexoxide deposits
Whipple's disease				PAS-positive macrophage deposits

Rheumatoid arthritis	+	+	+	PAS-positive plasma cell infiltrate

SOURCE: From Kawanishi DT, Rahimtoola SH. Mitral stenosis. In: Rahimtoola SH, ed. *Valvular Heart Disease. II*. St. Louis: Mosby; 1996:8.1-8.24.

Pathology

Acute rheumatic carditis is a pancarditis involving the pericardium, myocardium, and endocardium. In temperate climates and developed countries, there is usually a long interval (averaging 10 to 20 years) between an episode of rheumatic carditis and the clinical presentation of symptomatic MS. In tropical and subtropical climates and in less developed countries, the latent period is often shorter, and MS may occur during childhood or adolescence (see Chap. 55).

The pathologic hallmark of rheumatic carditis is an Aschoff's nodule. The most common lesion of acute rheumatic endocarditis is mitral valvulitis. In this condition the mitral valve has vegetations along the line of closure and the chordae tendineae. Mitral regurgitation (MR) may be present during the acute episode of rheumatic carditis.

MS is usually the result of repeated episodes of carditis alternating with healing and is characterized by the deposition of fibrous tissue. MS may result from fusion of the commissures, cusps, or chordae, or a combination of these.[9,10] Ultimately, the deformed valve is subject to nonspecific fibrosis and calcification. Lesions along the line of closure result in fusion of the commissures and contracture and thickening of the valve leaflets. The chordal lesions are manifest as shortening and fusion of these structures. The combination of commissural fusion, valve leaflet contracture, and fusion of the chordae tendineae results in a narrow, funnel-shaped orifice, which restricts the flow of blood from the LA to the LV. The rapidity with which patients become symptomatic may depend on the number and severity of repeated bouts of rheumatic valvulitis. Frequently, the rheumatic episodes are not clinically apparent.

In pure MS, the LV is usually normal, but there may be evidence of previous carditis with deposition of fibrous tissue. The LA is enlarged and hypertrophied as a consequence of LA hypertension. Mural thrombi are often found in the LA, particularly if atrial fibrillation has been present. Calcification of the mitral valve frequently also involves the mitral annulus.

Pathophysiology

The pathophysiologic features of MS all result from obstruction of the flow of blood between the LA and the LV. With reduction in valve area, energy is lost to friction during the transport of blood from the LA to the LV. Accordingly, a pressure gradient is present across the stenotic valve. The relationship between valve area, cardiac output, flow period, and average diastolic gradient between the LA and the LV is defined by the formula of Gorlin and Gorlin (Chap. 15).

It is readily apparent that maintaining cardiac output when the valve area is small requires a large gradient and thus an elevated LA pressure. Similarly, an increased demand for cardiac output (CO), such as occurs during exercise or pregnancy, results in an increase in gradient and high LA pressures. More subtle is the effect of the length of the diastolic flow period on the relationship between CO and gradient. The time available for diastole is that part of the cardiac cycle occupied by isovolumic contraction and relaxation or by ejection. As the heart rate increases, the total amount of time spent during systole increases despite a reduction in the systolic time per beat.[11,12] *Thus, time available for diastole decreases as the heart rate increases*. Because blood can flow through the mitral valve only during diastole, the flow rate is inversely proportional to the duration of the flow period at a constant stroke volume. Of course, a higher flow rate results in a greater loss of energy to friction and requires a larger gradient and higher LA pressures. It is important to remember that the gradient from LA to LV is a function per beat, not per minute. Thus, the gradient is dependent on the stroke volume and the diastolic filling time as well as the LV diastolic

pressure.

The pressure gradient between the LA and the LV, which increases markedly with increased heart rate or CO, is responsible for LA hypertension. The LA gradually enlarges and hypertrophies. Pulmonary venous pressure rises with LA pressure increase and is passively associated with an increase in pulmonary arterial (PA) pressure (Fig. 57-1). In up to 20 percent of patients, the pulmonary vascular resistance is also elevated,[13] which further increases PA pressure. PA hypertension results in *right ventricular* (RV) hypertrophy and RV enlargement. The changes in RV function eventually result in *right atrial* (RA) hypertension and enlargement and systemic venous congestion; frequently, tricuspid regurgitation also occurs. In a small percentage of patients, there may be regional or global LV systolic dysfunction, the cause or causes of which are not fully understood.[14-18]

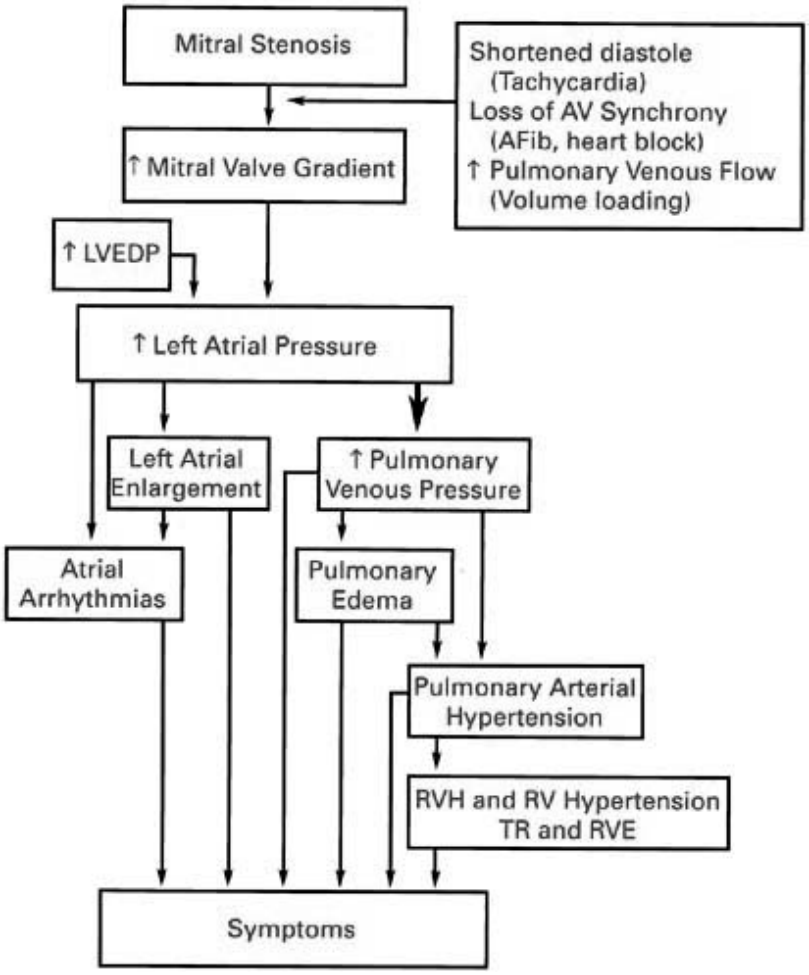

Figure 57-1: Pathophysiology of mitral stenosis. Mitral stenosis results in a diastolic pressure gradient from the LA to the LV. The actual gradient is dependent on the mitral valve area and the mitral valve *flow per diastolic second*. As a result, there is an elevation of LA pressure and therefore also of pulmonary venous pressure. Physiologic and pathologic changes-such as tachycardia and atrial fibrillation (which shorten diastole and may also result in loss of effective atrial contraction) or pregnancy, volume loading, and left-to-right shunts (at ventricular and aortopulmonary levels), which increase pulmonary venous flow-will increase the mitral valve gradient as well as LA and pulmonary venous pressures. An increased LV diastolic pressure will also result in further increase of LA pressure. An elevated LA pressure has several important effects; these include enlargement of the left atrium, atrial arrhythmias, and an increase of pulmonary venous pressure. Pulmonary venous hypertension may result in pulmonary edema and pulmonary arterial hypertension. PA hypertension and RV ventricular hypertension results in RV hypertrophy and may result in tricuspid regurgitation and RV enlargement. All of these changes contribute to producing symptoms. In addition, a fixed or even reduced cardiac output will also contribute to the

symptomatic state of the patient. [Copyright by S. H. Rahimtoola. M.B., F.R.C.P., M.A.C.P., M.A.C.C. (Ref. [10]).]

Pulmonary venous hypertension alters lung function in several ways. Distribution of blood flow in the lung is altered, with a relative increase in flow to the upper lobes and therefore in physiologic dead space. Pulmonary compliance generally decreases with increasing pulmonary capillary pressure, increasing the work of breathing, particularly during exercise. Chronic changes in the pulmonary capillaries and pulmonary arteries include fibrosis and thickening. These changes protect the lungs from the transudation of fluid into the alveoli (alveolar pulmonary edema). Indeed, it is not uncommon to find patients with severe MS whose resting PA wedge pressure (indirect LA pressure) exceeds 25 to 30 mmHg. Capillary and alveolar thickening, which help protect against pulmonary edema, further add to the abnormalities of ventilation and perfusion. Pulmonary vascular changes cause an elevated pulmonary vascular resistance.

In some patients with high pulmonary vascular resistance and RV dysfunction, CO may be low. The body maintains oxygen consumption by extracting more oxygen from the arterial blood, and the mixed venous oxygen content falls. The hemoglobin-O_2 dissociation curve is shifted to the right, facilitating the unloading of oxygen from hemoglobin to the tissues. The reduced CO may result in a *surprisingly small gradient* across the mitral valve despite severe stenosis. Although pulmonary congestion may be less striking in these patients, the CO does not increase normally with exercise, and, typically, the patients are severely limited by fatigue.

Long-standing MS with severe PA hypertension and resultant RV dysfunction may be accompanied by chronic systemic venous hypertension. Tricuspid regurgitation is frequently present, even in the absence of intrinsic disease of this valve. Functional pulmonic regurgitation may also be present. Dependent edema formation and visceral congestion directly reflect elevated systemic venous pressure and salt and water retention. Chronic passive congestion in the liver leads to central lobular necrosis and eventually to cardiac cirrhosis.

Clinical Findings

HISTORY

An asymptomatic interval is usually present between the initiating event of acute rheumatic fever and the presentation of symptomatic MS (averaging 10 to 20 years).[13,19] During this interval, the patient feels well (Table 57-2). Initially, there is little or no gradient at rest, but with increased cardiac output, LA pressure rises and exertional dyspnea develops. As mitral valve obstruction increases, dyspnea occurs at lower work levels. The progression of disability is so subtle and so protracted that patients may adapt by circumscribing their lifestyles. It becomes imperative, then, to document what activities the patient can perform without symptoms and at what activity level symptoms begin; failure to do this often results in an underestimation of disability.

Table 57-2: Symptoms Associated with Mitral Stenosis

On exertion
Dyspnea, wheezing, cough
Fatigue
Diminished activity/or pace of activity
Palpitations
Feeling faint, presyncope, syncope
At rest

Cough, wheezing
Paroxysmal nocturnal dyspnea
Orthopnea
Hemoptysis
Hoarseness (Ortner's syndrome)
From complications of MS

SOURCE: Copyright S. H. Rahimtoola, M.B., F.R.C.P, M.A.C.P., M.A.C.C. (Ref. [10]).

As obstruction progresses, the patients note orthopnea and paroxysmal nocturnal dyspnea that apparently results from redistribution of blood to the thorax on assuming the supine position. With severe MS and elevated pulmonary vascular resistance, fatigue rather than dyspnea may be the predominant symptom. Dependent edema, nausea, anorexia, and right-upper-quadrant pain reflect systemic venous congestion resulting from elevated systemic venous pressure and salt and water retention.

Palpitations are a frequent complaint in patients with MS and may represent frequent premature atrial contractions or paroxysmal atrial fibrillation/flutter. Of patients with severe symptomatic MS, 50 percent or more have chronic atrial fibrillation. Paroxysmal atrial fibrillation may produce pulmonary edema in some patients with MS. The acute increase in LA pressure that produces pulmonary edema results both from a decrease in the diastolic flow period caused by increased heart rate and from a loss of atrial transport function.

Systemic embolism, a frequent complication of MS, may result in stroke, occlusion of extremity arterial supply, occlusion of the aortic bifurcation, and visceral or myocardial infarction. Atrial fibrillation, increasing age of the patient, increasing LA size, and a previous history of embolism are associated with an increased incidence of systemic embolism[13] (Table 57-3).

Table 57-3: Complications of Mitral Stenosis

Arrhythmias
Atrial flutter/fibrillation
Embolism
Systemic-cerebral, coronary, abnormal, peripheral, pulmonary
Acute pulmonary edema
Pulmonary arterial hypertension
Right ventricular hypertrophy/dilatation
Tricuspid regurgitation
Clinical heart failure
Left ventricular dysfunction
Chest pain/angina
Infective endocarditis

SOURCE: Copyright by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C. (Ref. [10]).

Hemoptysis may result from a variety of causes. It is usually due to increased pulmonary venous pressure. Sputum may be blood-stained with paroxysmal nocturnal dyspnea, pink frothy sputum may result from rupture of alveolar capillaries associated with acute pulmonary edema or from pulmonary infarction due to pulmonary embolism, or hemoptysis may be severe and profuse (pulmonary apoplexy). The latter results from rupture of thin-walled, dilated bronchial veins, and although usually not fatal, it may be life-threatening because of aspiration pneumonia or massive hemorrhage. The edematous bronchial mucosa is more likely to be associated with chronic bronchitis, especially in cold and wet climates; it can also result in blood-stained sputum.

Exertional chest pain, typical of angina pectoris, may be present in some patients with severe MS but normal coronary arteries. Severe PA hypertension has been postulated as a cause. Infective endocarditis is an uncommon complication of pure MS.

Progression of symptoms in MS is generally slow but relentless. Thus, a sudden change in symptoms rarely reflects a change in valve obstruction. Rather, there is usually a noncardiac precipitating event or paroxysmal atrial fibrillation. Fever, pregnancy, hyperthyroidism, and noncardiac surgery, all of which increase CO, can precipitate decompensation in patients with moderate to severe MS.

PHYSICAL FINDINGS

During the latent, presymptomatic interval, incidental physical findings may be normal or may provide evidence of mild MS. Frequently, the only characteristic finding noted at rest will be a loud S_1 and a presystolic murmur. A short diastolic decrescendo rumble may be heard only with exercise. In patients with symptomatic stenosis, the findings are more obvious, and careful physical examination usually leads to the correct diagnosis (Chap. 10).

The general appearance of the patient in MS is usually normal. The MS facies, characterized by malar flush (pinkish-purple patches on the cheeks),[13] is uncommon and is caused by peripheral cyanosis, which is usually associated with a low CO, systemic vasoconstriction, and severe PA hypertension. Tachypnea may be present if LA pressure is high. The arterial pulse is normal except for irregularity in atrial fibrillation and is of low volume when CO is reduced. All peripheral pulses should be carefully examined because of the frequency of systemic embolism. The jugular venous pressure may be normal or may show evidence of elevated RA pressure. A prominent *a* wave is a result of RV hypertension/hypertrophy or of associated tricuspid stenosis. A prominent *v* wave is caused by tricuspid regurgitation. Atrial fibrillation produces an irregular venous pulse with absent *a* waves. The chest findings may be normal or may reveal signs of pulmonary congestion with rales or pleural fluid (dullness and absent breath sounds). Marked LA enlargement may produce egophony at the tip of the left scapula.

The precordium is usually unremarkable on inspection. On palpation, the apical impulse should feel normal or is tapping (palpable mitral valve closure or RV forming the cardiac apex). An abnormal LV impulse suggests disease other than isolated MS. A diastolic thrill is usually appreciated only when the patient is examined in the left lateral position. When PA hypertension is present, a sustained RV lift along the left sternal border and pulmonic valve closure may be palpable.

On auscultation in the supine position, the only abnormality appreciated may be the accentuated S_1, which is caused by flexible valve leaflets and the wide closing excursion of the valve leaflets[20] (see also Chap. 10). Failure to examine the patient in the left lateral position accounts for most of the missed diagnoses of symptomatic MS. The diastolic rumble is heard best with the bell of the stethoscope applied at the apical impulse. Nevertheless, the murmur may be localized, and the region around the apical impulse also should be auscultated. The *opening snap* (OS) occurs when the movement of the domed mitral valve into the LV is suddenly stopped.[20] It is heard best with the diaphragm and is often most easily appreciated midway

between the apex and the left sternal border. In this intermediate region, the S_1, the pulmonary component of the second heart sound (P_2), and the OS can be identified. The auscultatory signs of MS in sinus rhythm and in atrial fibrillation are illustrated in Figs. 57-2 and 57-3.

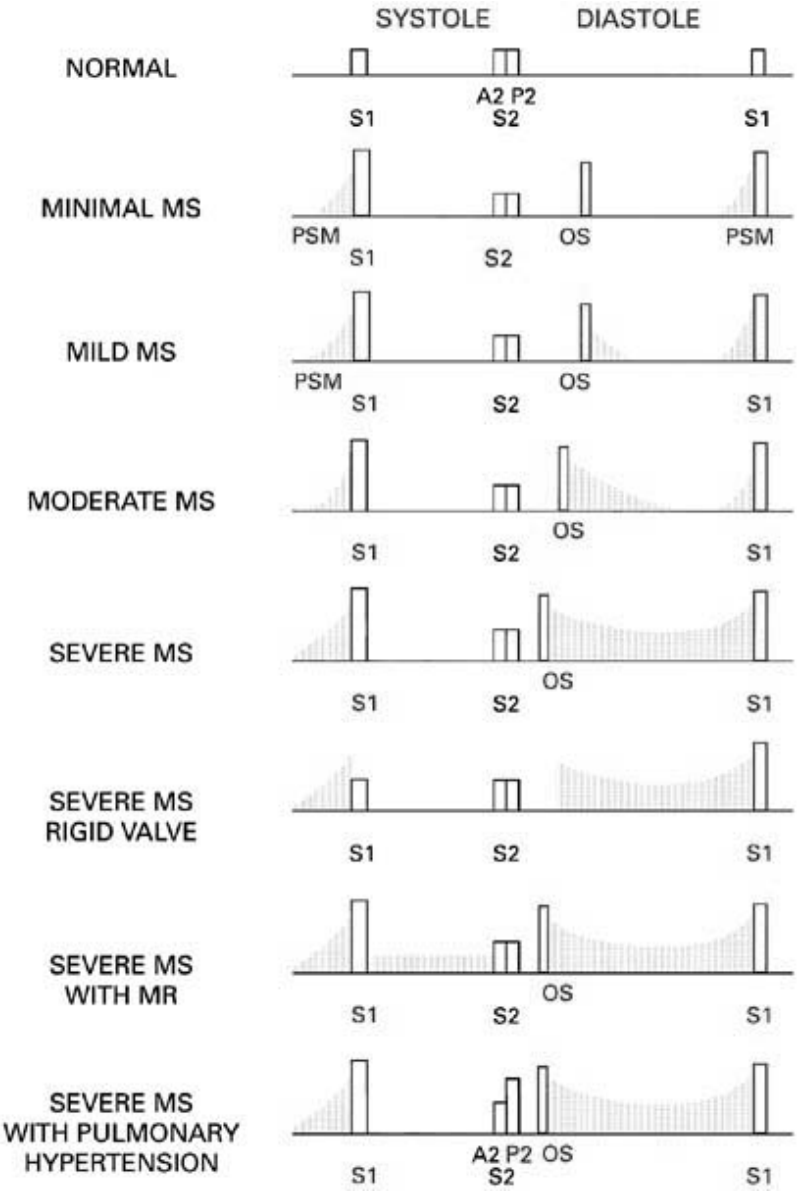

Figure 57-2: Auscultatory signs of MS in patients in sinus rhythm are illustrated. These include a presystolic murmur, loud first heart sound (S_1), an opening snap (OS), and a middiastolic murmur (low-pitched, decrescendo diastolic rumble, rumbling murmur). These signs may be accentuated or at times may be heard only by placing the patient in the left lateral decubitus position. Importantly, these signs are helpful in assessing the severity of the MS; as the MS becomes more severe, the S_2-OS interval is shortened and the length of the middiastolic rumble is increased. In mild OS, the S_2-OS interval is long and the diastolic murmur is short. In moderate MS, the S_2-OS interval is shorter, and although the diastolic murmur is longer at rest, there is usually a gap between the end of the murmur and the onset of the presystolic murmur. In severe MS, the S_2-OS interval is short (usually 0.04 to 0.06 s) and the diastolic murmur is a full-length murmur. With PA hypertension, P_2 is increased in intensity. In the presence of a rigid mitral valve (with or without calcification), S_2 is soft and the OS is usually not heard. A holosystolic murmur of mitral regurgitation may be present. (Adapted and modified from Kawanishi DT, Rahimtoola SH. Mitral stenosis. In: Rahimtoola SH, ed. *Valvular Heart Disease II*. St. Louis: Mosby; 1996:8.1-8.24. Copyright by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C.)

The OS occurs after the LV pressure falls below LA pressure in early diastole. When LA pressure is high, as in severe MS, the snap occurs earlier in diastole (Fig. 57-2). The converse is true with mild MS. The interval between A_2 and the OS varies from 40 to 120 ms. Although the OS is present in most cases of MS, it is absent in patients with stiff, fibrotic, or calcified leaflets. Thus, absence of the OS in severe MS suggests that mitral valve replacement rather than commissurotomy may be necessary.

The low-pitched diastolic rumble follows the OS and is best heard with the bell of the stethoscope. In some patients with low cardiac output or mild MS, brief exercise, such as situps or walking, is adequate to increase flow and bring out the murmur. The murmur is low-pitched, rumbling, and decrescendo. In general, the more severe the MS, the longer the murmur (Fig. 57-2). Presystolic accentuation of the murmur occurs in sinus rhythm and has been reported even in atrial fibrillation. In the latter situation, a brief "presystolic" accentuation is due to narrowing of the mitral orifice produced by ventricular systole before the final, completeclosure of the mitral valve and the mitral component of S_1. A diastolic rumble is not diagnostic of MS and may be heard with increased flow across a normal mitral valve-for example, in ventricular septal defect with a large left-to-right shunt.

The two most important auscultatory signs of severe MS are a short A_2-OS interval (usually 40 to 60 ms) and a full-length diastolic rumble. The A_2-OS interval may be longer if there is associated moderate/severe aortic regurgitation, and the OS may be absent when the mitral valve is rigid. The diastolic murmur may not be full-length in severe MS if the stroke volume is low and there is no tachycardia.

Systolic murmurs also may be heard in association with the murmur of MS. A blowing, holosystolic murmur at the apex suggests associated MR; whereas a systolic blowing murmur heard best at the lower left sternal border that increases with inspiration usually signifies tricuspid regurgitation. The Graham Steell murmur is a high-pitched diastolic decrescendo murmur of pulmonic regurgitation caused by severe PA hypertension. In most patients with MS, such a murmur usually indicates AR instead. In general, a left-sided S_3 is not compatible with severe MS with the possible exception of concomitant severe AR and/or significant LV systolic dysfunction. If an S_3 and a rumble are present, MR is usually the predominant lesion (see also Chap. 10).

ROENTGENOGRAM

The posteroanterior and lateral chest films are often so typical that experienced clinicians can make the tentative diagnosis from them. The thoracic cage is normal. The lung fields show evidence of elevated pulmonary venous pressure. Blood flow is more evenly redistributed to the upper lobes, resulting in apparent prominence of upper-lobe vascularity. Increased pulmonary venous pressure results in transudation of fluid into the interstitium. Accumulation of fluid in the interlobular septa produces linear streaks in the bases, which extend to the pleura (Kerley B lines).[21] Interstitial fluid may also be seen as perivascular or peribronchial cuffing (Kerley A lines). With transudation of fluid into the alveolar spaces, alveolar pulmonary edema is seen. These changes are not specific for MS but represent long-standing elevated LA pressure. Chronic hemosiderin deposition can result in an interstitial radiodensity that does not resolve after the relief of stenosis. PA hypertension results in enlargement of the main PA and right and left main pulmonary arteries.

The cardiac silhouette usually does not show generalized cardiomegaly, but the LA is invariably enlarged. This is manifest in the posteroanterior chest film by a density behind the RA border (double atrial shadow), prominence of the LA appendage on the left heart border between the main PA and LV apex, and elevation of the left main bronchus. The lateral film shows the LA bulging posteriorly. The LV silhouette is normal. The RV may be enlarged if PA hypertension has been present. RV enlargement is usually noted by filling of the retrosternal space, but this is an unreliable sign in adults. The combination of a normal-sized LV, enlarged LA, and pulmonary venous congestion should immediately raise the possibility of MS. Mitral valve calcification is occasionally seen on the plain chest film (see also Chap. 12).

ELECTROCARDIOGRAM

The *electrocardiogram* (ECG) is not usually as helpful as the chest x-ray. Patients in sinus rhythm may have a widened P wave caused by interatrial conduction delay and/or prolonged LA depolarization. Classically, the P wave is broad and notched in lead II and biphasic in lead V_1; it measures 0.12 s or more. Atrial fibrillation is common. LV hypertrophy is almost never present unless there are associated lesions. RV hypertrophy may be present if PA hypertension is marked (see also Chap. 11).

CLINICAL INDICATIONS OF SEVERE MITRAL STENOSIS

Some clinical features make it virtually certain that MS is severe. These include (1) moderate to severe PA hypertension as indicated by clinical and ECG evidence of RV hypertrophy or PA hypertension or both and/or (2) moderate to severe elevation of LA pressure as indicated by orthopnea, a short P_2-OS interval, a diastolic rumble that occupies the whole length of a long diastolic interval in patients with atrial fibrillation, and pulmonary edema on the chest x-ray. In both these clinical circumstances, one must be certain that there is no other cause for elevated LA pressure and that LA hypertension is not caused mainly by a correctable transient elevation of LV diastolic pressure.

Laboratory Tests

ECHOCARDIOGRAPHY/DOPPLER ULTRASOUND

Echocardiography/Doppler ultrasound has proved to be both sensitive and specific for MS when adequate studies are done (Chap. 13).[22-25] False-positive and false-negative results are uncommon. M-mode and two-dimensional echocardiography do not reliably predict the severity of MS. Doppler studies provide an estimate of mitral valve area that is within ±0.4 cm^2 (prior to interventional therapy) of that obtained by cardiac catheterization.[26] The echographic findings of MS reflect the loss of normal valve function. The fusion of commissures results in movement of the anterior and posterior leaflets anteriorly in parallel during diastole. In patients in sinus rhythm, there is an absence of the further opening of the valve that is normally seen with atrial contraction. Other findings include decreased E-to-F slope, decreased mitral valve leaflet excursion, and multiple echoes, indicating thickening or calcification of the valve. LA enlargement is seen. Abnormal pulmonary valve motion and RV enlargement may signify PA hypertension (see also Chap. 13).

Echocardiography is of great value in patients with equivocal signs, in patients with gross PA hypertension, to differentiate MS from an Austin Flint murmur of AR, and in the rare patient with "silent" MS. It is used to assess LV, RV, and atrial size and function; to evaluate the aortic and tricuspid valves; and to estimate PA pressure. When transthoracic echocardiography (TTE) is unsatisfactory, transesophageal echocardiography (TEE) is a useful technique to assess LA thrombus, the anatomy of the mitral valve and subvalvular apparatus, and to assess the suitability of the patient for catheter balloon commissurotomy or surgical valve repair.

Echocardiography/Doppler ultrasound is a most useful test in MS and should be performed in all patients. It is essential to determine suitability of the valve for commissurotomy and/or repair and to determine the likely result.

CARDIAC CATHETERIZATION/ANGIOGRAPHY

In most patients with disabling symptoms from presumed MS, right and left heart catheterization should be performed as part of a preoperative assessment. Simultaneous measurement of cardiac output and the gradient between the LA and the LV and calculation of valve area remain the "gold standard" for assessing the severity of MS (Chap. 15). LV angiography assesses the competence of the mitral valve, an important determinant of operability for mitral commissurotomy. Quantification of LV function provides a useful prognostic indicator of operative and late survival and of the expected functional result. Aortic valve function should be evaluated in all patients. Selective supraventricular aortography should be performed in all patients unless there is a contraindication. Tricuspid valve function can be assessed when there is a question of coexisting lesions. In certain circumstances-for example, in a patient with suspected severe MS

who has a small gradient and mildly elevated LA pressure-dynamic exercise in the catheterization laboratory with measurement of mitral valve gradient, CO and LA and PA pressures can be extremely useful. Another example is a patient with significant symptoms in whom the findings at rest suggest moderate (or even mild) MS. Selective coronary arteriography establishes the site, severity, and extent of coronary artery disease and should be performed in patients with angina, in those with LV dysfunction, in those with risk factors for coronary artery disease, and in those 35 years of age or older who are being considered for interventional therapy.

OTHER INVESTIGATIONS

In most clinical situations, other investigations are not needed. Occasionally, a treadmill exercise test to evaluate functional capacity may be very useful clinically-for example, when a patient denies symptoms in spite of severe hemodynamic abnormalities.

Clinical Decision Making

The reader is referred to the section on aortic stenosis in Chap. 57. In a prospective blinded study of consecutive patients with valvular heart disease, the sensitivity and specificity of diagnosis of MS by clinical evaluation was 86 and 87 percent, respectively. The accuracy of diagnosis of MS for moderate to severe stenosis was 92 percent by clinical evaluation and 97 percent by echocardiography/Doppler ultrasound.[27] This emphasizes the importance of a thorough clinical evaluation. The principal difficulty with both clinical evaluation and echocardiography/Doppler ultrasound is being able to accurately separate in all instances mild from moderate MS and moderate from severe MS.

Natural History and Prognosis

The population presenting with MS is changing because of the sharp decline in the incidence of acute rheumatic fever in the past 40 years (see also Chap. 55). Native-born American citizens with symptomatic MS are presenting at an older age. Young adults in the third and fourth decades with symptomatic MS are more likely to come from low socioeconomic backgrounds and from the inner city or to be immigrants, particularly from Latin America, the Middle East, Africa, or Asia. Therefore, the latent period between acute rheumatic fever and symptomatic MS is variable and appears to be related to the presence of repeated streptococcal infection. Women with MS outnumber men by almost two to one. The most important feature of the asymptomatic interval is the susceptibility to repeated bouts of both rheumatic valvulitis and streptococcal infection. The mechanism for the progression from no symptoms to mild to severe symptoms is progressive stenosis of the mitral valve.

With the onset of exertional dyspnea and fatigue, the valve area is usually reduced to one-half to one-third its normal size. Further small reductions in valve area markedly obstruct flow and result in symptoms with minimal exertion. The interval from initial mild symptoms to disabling symptoms may be 10 years. During this time, the patient is at some risk of death (see below). Permanent injury may result from atrial fibrillation with rapid ventricular rate, resulting in pulmonary edema, and from systemic embolus. Unfortunately, it is not possible to predict who is at risk of embolism. When late functional class II or functional class III symptoms are present, the valve area is usually 1.0 cm^2 or less (in an occasional patient the valve area is 1.2 or 1.3 cm^2), and both rest and exercise hemodynamics are deranged.[2] Further small reductions in valve area result in symptoms at rest.

The 10-year survival of patients with MS who are asymptomatic is approximately 84 percent and that of those who are mildly symptomatic is 34 to 42 percent (Fig. 57-4).[28-30] The 10-year survival of patients who are moderately or severely symptomatic and who do not have therapy is 40 percent or less, and the survival at 20 years is less than 10 percent.[28-30] Patients in the New York Heart Association functional class IV have a very poor survival without treatment[28]: 42 percent at 1 year and 10 percent or less at 5 years. All are dead by 10 years (Fig. 57-5).

Management

MS can be prevented through two approaches (Table 57-4). First, all streptococcal infections should be diagnosed rapidly and correctly treated (Chap. 55). This prevents most initial episodes of acute rheumatic fever. Second, all patients with known previous acute rheumatic fever/rheumatic carditis with or without obvious valve disease should receive appropriate antibiotic prophylaxis against recurrent streptococcal infection (Chap. 55).

Table 57-4: Medical Treatment of Mitral Stenosis

Prevention	
Primary	
Treatment of streptococcal group A infection	
Secondary (antibiotic prophylaxis)	
Recurrent rheumatic fever	
Infective endocarditis	
Restrict activities (moderate/severe MS)	
Severe exercise	
Competitive sports	
Arrhythmias	
Prevent and/or control	
Restore sinus rhythm if possible	
Cardiac medications	
Use only if essential	
Diuretics-use cautiously	
Anticoagulants for systemic/pulmonary emboli	
Elevated pulmonary venous pressure-diuretics	
Heart failure-digitalis, diuretics, ACE inhibitors	
Follow-up of asymptomatic patients	
Mild MS	Every 2-5 years
Moderate MS	Every 1-2 years
Severe MS	Every 6-12 months if interventional therapy not performed
Development of symptoms	Early or 'immediate'

SOURCE: Copyright by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C. (Ref. [10]).

Although the incidence of infective endocarditis is low in isolated MS, all patients exposed to bacteremia should receive appropriate prophylaxis against infective endocarditis (Chap. 73). Family and vocational planning should be considered. Women with this disease should consider bearing children before symptoms

occur, since pregnancy is usually well tolerated with mild MS. Occupations that require strenuous exertion in middle age and later should probably be avoided if possible. In patients with moderate or severe MS, activities such as strenuous exercise and competitive sports should be restricted.[9]

When patients reach the symptomatic threshold, medical treatment may be of some benefit. Digitalis offers no improvement for the patient with normal sinus rhythm and normal LV function. When atrial fibrillation is present, however, digitalis plays a critical role in controlling ventricular rate. In selected patients, beta-adrenergic blocking agents, diltiazem, or amiodarone may be added if digoxin alone is not satisfactory in controlling ventricular rate at rest or on exercise. Beta-adrenergic blocking agents should be used with great caution or not at all in patients with impaired LV function, associated significant aortic stenosis, or other associated severe valvular disease. Digoxin and diltiazem or digoxin and low-dose amiodarone are probably the two best combined regimens. Diuretics reduce pulmonary congestion and peripheral edema and allow most patients freedom from severe salt restriction. For the patient with mild symptoms, maintenance of sinus rhythm is desirable. Cardioversion of atrial fibrillation and maintenance of sinus rhythm using antiarrhythmic therapy with either digitalis and quinidine or digitalis and amiodarone should be offered to these patients. In patients who need interventional therapy, cardioversion is usually performed after completion of the procedure. Anticoagulation with warfarin is usually begun about 3 weeks in advance of cardioversion and for 4 weeks after the procedure.[31] Patients with chronic atrial fibrillation and those with a previous history of embolism should receive anticoagulation with warfarin (International Normalized Ratio, or INR, of 2 to 3) unless there is a specific contraindication.

There are no randomized trials of surgery versus medical therapy. Roy and Gopinath's study[29] showed that in comparable patients, surgical commissurotomy was associated with a better survival than medical therapy in patients with class II symptoms as well as in those with class III and IV symptoms (Fig. 57-6).

Unless there is a contraindication, surgery should be recommended to an MS patient with functional class III or IV symptoms (Table 57-5). For younger patients with a pliable, noncalcified valve and without important mitral regurgitation, this means valve repair. The hemodynamic results of surgical commissurotomy are excellent.[9,32,33] Because of the low morbidity and mortality of mitral commissurotomy/valve repair,[9,32-34] surgery is also offered to those patients when functional class II symptoms are present. The results of successful commissurotomy are excellent; in experienced and skilled centers, surgical mortality is less that 1 percent. Late mortality at 10 years is less than 5 percent, the thromboembolism rate is 2 percent per year or less, and the reoperation rate ranges from 0.5 to 4.5 percent per year. The return of symptoms after commissurotomy/valve repair is usually the result of an incomplete operation, other valvular lesions, refusion of mitral commissures, or deterioration of myocardial function. In less developed countries, excellent results have been reported in a very high percentage of young patients for up to 25 years.[35]

Table 57-5: Indications for Interventional Therapy for Severe Mitral Stenosis

All severely symptomatic patients (functional classes III and IV)
All mildly symptomatic patients (functional class II)[a,b]
Asymptomatic patients[a,b]
Pulmonary artery hypertension
Episodic pulmonary edema
Atrial fibrillation (persistent or repeated episodes)
Thromboembolism (systemic/pulmonary)
Severe mitral stenosis (valve suitable for CBC/surgical valve repair)

[a]Catheter balloon commissurotomy (CBC)/surgery.
[b]Individualize depending on patient characteristics; suitability of patient for CBC/surgical valve repair versus valve replacement, skill and experience of interventional team.

SOURCE: Copyright by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C. (Ref. 10).

For the older patient with a stiff or calcified valve or when moderate mitral regurgitation is present, mitral valve replacement is usually performed. Valve replacement carries a higher operative mortality than does commissurotomy (up to 5 percent) and the morbidity associated with prostheses (see Chap. 60). Hemodynamic results of mitral valve replacement are often not ideal (Table 57-6).[36,37] Survival at 10 years after mitral valve replacement for functional class III and IV patients is better than 60 percent (see Chap. 60).

Catheter balloon commissurotomy (CBC) with use of the double balloon technique or the lnoue balloon produces immediate and 3-month hemodynamic and clinical results comparable to those obtained by surgical commissurotomy.[38-41] The mitral valve area increases from a mean of 1.0 to 2.0 cm^2.[26,32,38] There are reductions of LA and PA pressures at rest and on exercise and an increase of exercise capacity.[39] The immediate results of CBC are greatly influenced by the characteristics of the valve and its supporting apparatus, which are best determined by two-dimensional echocardiography (transthoracic and/or transesophageal).[22] Echocardiographic scores of ≤8 or of 0-1 determined by the two different methods provide a clue to the best immediate results. Repeat CBC or mitral valve replacement is needed in 20 percent of patients within 5 to 7 years. Late survival is poorer in those in whom functional class IV, higher echocardiographic score, higher LV end-diastolic pressure, or higher PA systolic pressure is present prior to the CBC.[42-47] In one study, the 7-year survival was 95 ± 1 percent and the event-free survival was 65 ± 6 percent.[47] The 7-year event-free survival ranged from 13 to 90 percent in various subgroups. The 7-year event-free survival was best predicted by the post-CBC mitral valve area (≥1.5 cm^2) and PA wedge pressure (18 mmHg); the 7-year event-free survival was 90 ± 6 percent.[47] In the appropriate patient and in centers with skilled and experienced staff, CBC is the procedure of first choice for relief of severe MS. Factors to be taken into account choosing between surgery and CBC in an individual patient are shown in Table 57-7.

Table 57-7: Some Factors to Be Considered in Choice of Type of Interventional Therapy for Mitral Stenosis[a]

Mitral valve morphology	
Low echo score:	Catheter balloon commissurotomy (CBC)
	Surgical valve repair
High echo score:	Surgery
	CBC in special circumstances
Mitral regurgitation	
≥3+:	Surgery
≤1+:	CBC
2+:	Individualize (CBC versus surgery)
Left atrial thrombus	
Surgery	

CBC in special circumstances	
Need for other cardiac surgery	
Surgery	
CBC in special circumstances	

[a]In centers with skilled and experienced interventional teams.

SOURCE: Copyright by S. H. Rahimtoola. M.B., F.R.C.P., M.A.C.P., M.A.C.C. (Ref. [10]).

The recommendations of the ACC/AHA Practice Guidelines are shown in Tables 57-8, 57-9, and 57-10.[48] Guidelines are *not* and should *not* be the law. Application of guidelines to clinical practice should be based on the following principles: (1) classes I and III apply to all patients in these classes unless there is a specific clinical circumstance contradicting this and (2) class II applies to patients in this class depending on the clinical condition of the patient and the skill and experience at the individual medical center.

Table 57-10: Recommendations for Mitral Valve Replacement for Mitral Stenosis

Indication	Class
1. Patients with moderate or severe MS (mitral valve area ≤1.5 cm^2)[a] and NYHA functional class III-IV symptoms who are not considered candidates for percutaneous balloon valvotomy or mitral valve repair	I
2. Patients with severe MS (mitral valve area ≤1 cm^2)[a] and severe pulmonary hypertension (pulmonary artery systolic pressure >60 to 80 mmHg) with NYHA functional class I-II symptoms who are not considered candidates for percutaneous balloon valvotomy or mitral valve repair	IIa

[a]The committee recognizes that there may be a variability in the measurement of mitral valve area and that the mean transmitral gradient, pulmonary artery wedge pressure, and pulmonary artery pressure should also be considered.

SOURCE: ACC/AHA Guidelines,[48] with permission.

Table 57-8: Recommendations for Percutaneous Mitral Balloon Valvotomy

Indication	Class
1. Symptomatic patients (NYHA functional class II, III, or IV), moderate or severe MS (mitral valve area ≤1.5 cm^2),[a] and valve morphology favorable for percutaneous balloon valvotomy in the absence of left atrial thrombus or moderate to severe MR	I
2. Asymptomatic patients with moderate or severe MS (mitral valve area ≤1.5 cm^2)[a] and valve morphology favorable for percutaneous balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure >50 mmHg at rest or 60 mmHg with exercise) in the absence of left atrial thrombus or moderate to severe MR	IIa
3. Patients with NYHA functional class III-IV symptoms, moderate or severe MS (mitral valve area ≤1.5 cm^2),[a] and a nonpliable calcified valve who are at high risk for surgery in the absence of left atrial thrombus or moderate to severe MR	IIa

4. Asymptomatic patients, moderate or severe MS (mitral valve area ≤1.5 cm^2)[a] and valve morphology favorable for percutaneous balloon valvotomy who have new onset of atrial fibrillation in the absence of left atrial thrombus or moderate to severe MR	IIb
5. Patients in NYHA functional class III-IV, moderate or severe MS (MVA ≤1.5 cm^2), and a nonpliable calcified valve who are low-risk candidates for surgery	IIb
6. Patients with mild MS	III

[a]The committee recognizes that there may be variability in the measurement of mitral valve area and that the mean transmitral gradient, pulmonary artery wedge pressure, and pulmonary artery pressure at rest or during exercise should also be taken into consideration.

SOURCE: ACC/AHA Guidelines,[48] with permission.

Table 57-9: Recommendations for Mitral Valve Repair for Mitral Stenosis

Indication	Class
1. Patients with NYHA functional class III-IV symptoms, moderate or severe MS (mitral valve area ≤1.5 cm^2),[a] and valve morphology favorable for repair if percutaneous mitral balloon valvotomy is not available	I
2. Patients with NYHA functional class III-IV symptoms, moderate or severe MS (mitral valve area ≤1.5 cm^2),[a] and valve morphology favorable for repair if a left atrial thrombus is present despite anticoagulation	I
3. Patients with NYHA functional class III-IV symptoms, moderate or severe MS (mitral valve area ≤1.5 cm^2),[a] and a nonpliable or calcified valve with the decision to proceed with either repair or replacement made at the time of the operation	I
4. Patients in NYHA functional class I, moderate or severe MS (mitral valve area ≤1.5 cm^2),[a] and valve morphology favorable for repair who have had recurrent episodes of embolic events on adequate anticoagulation	IIb
5. Patients with NYHA functional class I-IV symptoms and mild MS	III

[a]The committee recognizes that there may be a variability in the measurement of mitral valve area and that the mean transmitral gradient, pulmonary artery wedge pressure, and pulmonary artery pressure at rest or during exercise should also be considered.

SOURCE: ACC/AHA Guidelines,[48] with permission.

* Mitral stenosis section written by Dr. Rahimtoola. Mitral regurgitation section written by Drs. Enriquez-Sarano, Schaff, and Frye.

NEXT

Chapter 57: MITRAL VALVE DISEASE

NORMAL MITRAL STRUCTURE AND FUNCTION

The mitral valve is a complex structure formed by four elements[49,50]:

1. The annulus is asymmetrical, with a fixed portion (corresponding to the anterior leaflet) shared with the aortic annulus and a dynamic portion (corresponding to the posterior leaflet) that represents most of the circumference of the annulus.
2. The two leaflets are asymmetrical; the anterior has the greater length of tissue but occupies a smaller portion of the circumference of the annulus than the posterior.
3. The chordae join each papillary muscle to the corresponding commissure and the adjoining halves of both leaflets and maintain the two leaflets in a position allowing coaptation.
4. The two papillary muscles and the adjacent wall attach the mitral apparatus to the LV.

Mitral competence during systole is normally ensured, first, by a large area of coaptation between leaflets allowing high friction resistance to abnormal valve movement and, second, by the systolic position to the anterior leaflet parallel to the direction of blood flow. The mechanism of MR frequently combines abnormal function of more than one anatomic element, which fact underlines the complexity of conservative surgery for restoration of normal mitral function.

PREVIOUS | NEXT

Chapter 57: MITRAL VALVE DISEASE

MITRAL REGURGITATION

Mitral regurgitation (MR) is characterized by an abnormal reversed blood flow from the left ventricle (LV) to the left atrium (LA). The etiologic profile of MR is now dominated by degenerative and ischemic causes in developed countries. The development of noninvasive assessment with transesophageal echocardiography, color-flow imaging and Doppler methods of quantitation of regurgitation has transformed diagnostic approaches. With improved understanding of the impact of LV dysfunction on outcome, and most importantly with major advances in conservative surgery, the management of MR has become far more proactive.

Etiology and Mechanism (Table 57-11)

MR is often referred to as *organic* if there is an intrinsic valve disease or *functional* if the valve is structurally normal but leaks due to an extravalvular abnormality. Ischemic MR may be organic (ruptured papillary muscle) or functional (LV dysfunction). Nonischemic MR may be organic (e.g., rheumatic) or functional (e.g., cardiomyopathy).

RHEUMATIC DISEASE

Rheumatic MR is rarely pure, and in most cases is associated with stenosis and fusion of the commissures (Fig. 57-7, Plate 86). Severe rheumatic MR requiring surgical correction is still frequent in developing countries but is now rare in developed countries.[51] The underlying lesion is retractile fibrosis of leaflets and chordae, causing loss of coaptation. The secondary dilatation of the mitral annulus tends to further decrease the contract between leaflets. Elongated or ruptured chordae are infrequent.

DEGENERATIVE MITRAL REGURGITATION

These causes are often associated with valve prolapse, an abnormal movement of the leaflets into the LA during systole due to inadequate chordal support (elongation or rupture) and excessive valvular tissue. In western countries, mitral prolapse represents the most frequent causes leading to surgery for severe MR.[51] Degenerative MR can be separated in three categories:

- The mitral valve prolapse syndrome, characterized by diffuse myxomatous infiltration, discussed in detail in Chap. 58 (Fig. 57-8, Plate 87).
- The degenerative "primary" ruptured chordae, which involves the posterior more often than the anterior leaflet and occurs more often in men than in women. There is usually no excessive tissue, but enlargement of the annulus may occur as in any MR. The involved leaflet may present with a myxomatous infiltration, but the other leaflet usually remains normal. Calcification of the mitral annulus or systemic hypertension may precede the occurrence of the ruptured chordae. Isolated ruptured cord may occasionally be due to blunt thoracic trauma and endocarditis (secondary forms).
- Degenerative MR without prolapse, which is usually mild and due to valve sclerosis or isolated annular calcification; here regurgitation is secondary to deformation of the valves of annulus (Fig. 57-9, Plate 88).

INFECTIVE ENDOCARDITIS

Infective endocarditis accounts for about 5 percent of cases of severe MR. Vegetations may produce mild MR by interposition between leaflets. Severe endocarditic MR is usually related to ruptured chordae and less frequently to destruction of mitral tissue involving either the leaflet's edges or a perforation (Fig. 57-10, Plate 89).

ISCHEMIC AND FUNCTIONAL MITRAL REGURGITATION

Ischemic and functional MR-i.e., due to LV wall dysfunction secondary to ischemia, scarring, aneurysm, cardiomyopathy, or myocarditis-have in common the same mechanism: the coaptation of intrinsically normal leaflets is incomplete. Rupture of papillary muscle produces MR because of the flail leaflet and involves in 80 percent of cases the posteromedial papillary muscle and is most often associated with infarction of the adjacent ventricular wall.[53] It is the rarest form of heart rupture and of ischemic MR. Complete rupture is rapidly fatal without surgery, and partial or single-head rupture of the papillary muscle more often allows emergency surgery[53] (Fig. 57-11, Plate 90).

OTHER CAUSES OF MITRAL REGURGITATION

MR is observed very frequently with color-flow imaging, even in patients without cardiac disease. However, clinically significant MR may be found in (1) *connective tissue disorder,* Marfan syndrome, Ehlers-Danlos syndrome, pseudoxanthum elasticum, osteogenesis imperfecta, Hurler's disease, systemic lupus erythematosus, and anticardiolipin syndrome; (2) penetrating or nonpenetrating *cardiac trauma;* (3) *myocardial disease*-hypertrophic cardiomyopathy or sarcoidosis; (4) *endocardial lesions* due to hypereosinophilic syndrome, endocardial fibroelastosis, carcinoid tumors, ergot toxicity, radiation toxicity, diet or drug toxicity[54]; (5) *congenital* lesions such as cleft mitral valve isolated or associated with persistent atrioventricular canal, corrected transposition with or without Ebstein's abnormality of the left atrioventricular valve, and (6) *cardiac tumors*.

Pathophysiology

The abnormal coaptation of the mitral leaflets creates a *regurgitant orifice* during systole. The systolic pressure gradient between the LV and LA is the driving force of the regurgitant flow, which results in a *regurgitant volume*. This regurgitant volume represents a percentage of the total ejection of the LV and may be expressed as the *regurgitant fraction*. The regurgitant volume creates a volume overload by entering the LA in systole and the LV in diastole, modifying LV loading and function.

CHRONOLOGY OF REGURGITATION

The pressure gradient between the LV and atrium begins with mitral closure (simultaneous to S_1) and persists after closure of the aortic valve (S_2) until the mitral valve opens.[55] Thus, timing of regurgitant flow is determined by that of the regurgitant orifice and is most often holosystolic. Various dynamic changes in the regurgitant orifice can be observed depending on its cause.[56] With small regurgitant orifices, the regurgitant orifice declines with the ventricular volume tending to limit regurgitation to early systole.[55] Conversely, in valve prolapse, the regurgitant orifice appears or increases late in systole and variations of regurgitant flow throughout systole are the complex results of combined effects of changes of regurgitant orifice and gradient.[56,57]

DEGREE AND CONSEQUENCES OF REGURGITATION

The degree of volume overload depends on three factors, the area of the regurgitant orifice,[58] the regurgitant gradient, and the regurgitant duration. The volume overload is usually less severe in mitral than in aortic regurgitation, despite a usually larger regurgitant gradient and orifice.[58] Such differences are related to a shorter duration of MR during the cardiac cycle in mitral than in aortic regurgitation.[58]

The degree of MR is not fixed and may vary with interventions. Vasodilators may be beneficial,[59] but the change in regurgitant orifice area rather than that of ventriculoatrial gradient is the main mechanism of this effect. In functional[60] and organic MR,[61] the regurgitant orifice increases with increased afterload or ventricular volume and decreases with decreased afterload or improved contractility, but it is not influenced by changes in heart rate.[61]

The regurgitant energy produced by the LV translates into two components: the kinetic energy (regurgitant volume) and the potential energy (elevation of atrial pressure). The typical left atrial pressure change is the V wave,[62] which nevertheless, is not specific for MR. The height of the V wave and more generally left atrial pressure is mainly determined by left atrial compliance.[62] In acute MR, the LA is less compliant than in chronic MR and the MR produces a marked increase in LA pressure. The atrial V wave, in turn, decreases the ventriculoatrial gradient and, thus, for any effective regurgitant orifice,[58] tends to limit the regurgitant volume. When MR becomes chronic, the LA dilates, the V wave is less prominent, and it does not limit the regurgitant volume; the LA pressure may be normal even with severe MR.[63] At that stage, usually the cardiac output is decreased but the pulmonary pressures are often normal. Pulmonary hypertension in MR is poorly understood and mostly observed in elderly patients.

LEFT VENTRICULAR FUNCTION

With MR the LV is dilated, but less so than in aortic regurgitation of comparable degree.[64] LV end-diastolic volume and wall stress are increased,[64] and the ventricle's shape becomes spherical. End-systolic volume is increased in chronic MR but end-systolic wall stress is usually normal.[65] The myocardial mass is increased proportionately to LV dilatation.[66]

LV function is difficult to characterize because of the changes in preload and afterload. It has been suggested that normalization of ejection fraction (EF) to the preload would provide an appropriate assessment of LV function. Afterload is more difficult to assess because the MR may decrease the instantaneous impedance to ejection, but the measure of afterload provided by end-systolic wall stress is within the normal range.[65] However the usual inverse correlation between end-systolic wall stress and EF is also observed in MR.[67] Complex indices using the afterload-such as the end systolic wall stress,[68] or maximum elastance,[65] normalized to the LV volume-have been proposed and may be sensitive to subtle changes in function.

LV dysfunction is a frequent and dismal complication of MR.[69,70] The mechanism of LV hypertrophy is a reduction in protein degradation, but the mechanisms leading to interstitial fibrosis and LV dysfunction remain mysterious. Experimentally, LV dysfunction is not due to changes in coronary blood flow. The changes in myofiber contractility parallel those in LV function[71] and are associated with reduced myofiber content,[72] but the cause of the myofiber dysfunction and the explanation of its high incidence have not been clarified.

During diastole, LV relaxation is prolonged but chamber stiffness is reduced.[73] Age and decreased

systolic function[73] are associated with increased chamber stiffness. The significance of the diastolic abnormalities is unclear.

ISCHEMIC AND FUNCTIONAL MITRAL REGURGITATION

The pathophysiology of ruptured papillary muscles is poorly known. In chronic ischemic or functional MR, the primary disease involves the LV, which is often contracting poorly. However, MR may be determined more by localized LV deformation than by the systolic function. The apical and inferior traction on papillary muscles leads to leaflet tethering and tenting and subsequently to MR.[74,75] In ischemic or functional as opposed to organic (due to primary valvular disease) MR, the regurgitant volume is usually small,[76] and the LV and atrial dilatation is in excess to the degree of MR.[58] Nevertheless, MR is associated with elevated left atrial pressure[58] and poor outcome[77]; it is also a marker of sensitivity to vasodilators.

HORMONAL ACTIVATION

In organic MR, natriuretic peptides are elevated in experimental[78] and clinical[79] studies. The main determinant of elevation of atrial natriuretic peptide is the elevation of atrial pressures.[79] In our experience, brain natriuretic peptide is more a marker of LV remodeling than of altered hemodynamics. The value of natriuretic peptide levels as markers of hemodynamics, LV function, and prognosis is not established yet.

The activation of the renin-angiotensin system is not fully understood. In dogs with organic MR, systemic activation of the renin-angiotensin system is rare,[80] but tissue levels of angiotensin II are markedly elevated.[81,82] The role of angiotensin in the development of hypertrophy and fibrosis are not fully clarified.

Clinical Presentation

The sex distribution has changed in parallel to the changes in etiology of MR. With the decrease in rheumatic heart disease, severe MR is now predominantly seen in males (65 to 75 percent). The prevalence of MR increases with age[83]; therefore, patients with severe MR most often present in the sixth decade of life.[84]

The clinical presentation-including symptoms, physical findings, electrocardiographic and radiographic change-is determined by the degree, rapidity of development, and cause of MR and by LA and LV function and compliance.

SYMPTOMS

Patients with mild MR usually have no symptoms. Severe MR is diagnosed most often because of the murmur when no or minimal symptoms are present.[84] Fatigue and mild dyspnea on exertion are the most usual symptoms and are rapidly improved by rest. The administration of diuretics and progressive self-limitation of physical activity may prevent the occurrence of more severe symptoms. Severe dyspnea on exertion or, more rarely, paroxysmal nocturnal dyspnea, frank pulmonary edema, or even hemoptysis may be observed later in the course of the disease. Such severe symptoms may be triggered by a new onset of atrial fibrillation, or increase in degree of MR, the occurrence of endocarditis or ruptured chordae, or a change in LV compliance or function.

With severe MR of *acute onset*, symptoms are usually more dramatic-pulmonary edema or

congestive heart failure-but will progressively subside with administration of diuretic and increased LA compliance. A syndrome of sudden onset of atypical chest pain and dyspnea may occur with abrupt chordal rupture. Rupture of papillary muscle usually has a dramatic presentation, with cardiogenic shock or a severe pulmonary edema. Pulmonary edema may also be observed in transient severe papillary muscle dysfunction.

Sudden death as the initial presentation of MR is rare.[85]

PHYSICAL EXAMINATION

Blood pressure is usually normal. Carotid upstroke is brisk.

Cardiac palpation may show laterally displaced, diffuse, and brief apical impulse with enlarged LV. An apical thrill is characteristic of severe MR. The left sternal border lift is observed with right ventricular dilatation and may be difficult to distinguish from the left atrial lift due to the dilated, expansive LA, which is more substernal and lower.

S_1 is included in the murmur and is usually normal but may be increased in rheumatic disease. S_2 is usually normal but may be paradoxically split if the LV ejection time is markedly shortened. The presence of a third heart sound (S_3) is directly related to the volume of the regurgitation in patients with organic MR.[86] It is often associated with an early diastolic rumble due to the increased mitral flow in diastole even without mitral stenosis (Chap. 10). The S_3 and diastolic rumble are low-pitched sounds and may be difficult to detect without careful auscultation in the left lateral decubitus position. The S_3 increases with expiration. In ischemic-functional MR, S_3 corresponds more often to restrictive LV filling. An atrial gallop (S_4) is heard mainly in MR of recent onset and in ischemic/functional MR in sinus rhythm. Midsystolic clicks are markers of valve prolapse (Chaps. 10 and 11).

The hallmark of MR is the systolic murmur, most often holosystolic, including first and second heart sounds. If an opening snap or S_3 is mistakenly interpreted as S_2, the murmur may appear midsystolic. Only a careful examination beginning at the base of the heart to identify the second heart sound and progressing toward the apex will allow clear recognition of the nature of the murmur. The murmur is of the blowing type but may be harsh, especially in valve prolapse. The maximum intensity is usually at the apex, and it may radiate to the axilla in rheumatic or anterior leaflet prolapse, affecting primarily the anterior leaflet. In posterior leaflet prolapse, the jet is usually superiorly and medially directed and the murmur radiates towards the base of the heart.[87] The murmur may be heard in the back, in the neck, and sometimes on the skull. In the cases where the murmur radiates to the base, it may be difficult to distinguish from the murmur of aortic stenosis or obstructive cardiomyopathy, and pharmacologic maneuvers showing that the murmur decreases with amyl nitrite and increases with methoxamine strongly suggest MR. Murmur intensity does not increase with postextrasystolic beats and usually parallels the degree of MR,[88] but in myocardial infarction severe MR may be totally silent[89] (see Chap. 10).

Murmurs of shorter duration usually correspond to mild MR; they may be mid or late systolic in mitral valve prolapse or early systolic in functional MR.

ELECTROCARDIOGRAM

The most frequent feature of MR is atrial fibrillation which was found in approximately 50 to 60 percent of earlier series and is now present in approximately 50 percent of surgically corrected MR.[90] Patients in sinus rhythm may present with signs of left atrial enlargement (Fig. 57-

12). LV hypertrophy is more rarely seen and may be associated with secondary ST-T abnormalities.[91] Right ventricular hypertrophy is uncommon. The electrocardiogram, especially in acute MR, may be entirely normal. In ischemic MR, Q waves in the inferior leads or left bundle-branch block is often noted.

CHEST ROENTGENOGRAM

Cardiomegaly may be present in chronic MR or in ischemic/functional MR (Fig. 57-13). LA body and appendage dilatation is frequent but giant LA is rare and is usually seen in severe mixed valve disease. Although valvular calcifications are rare, annular calcification seen as a C-shaped density below the posterior leaflet is frequent. Because LA pressure is frequently normal even with severe MR, signs of pulmonary hypertension or pulmonary edema are rarely observed.

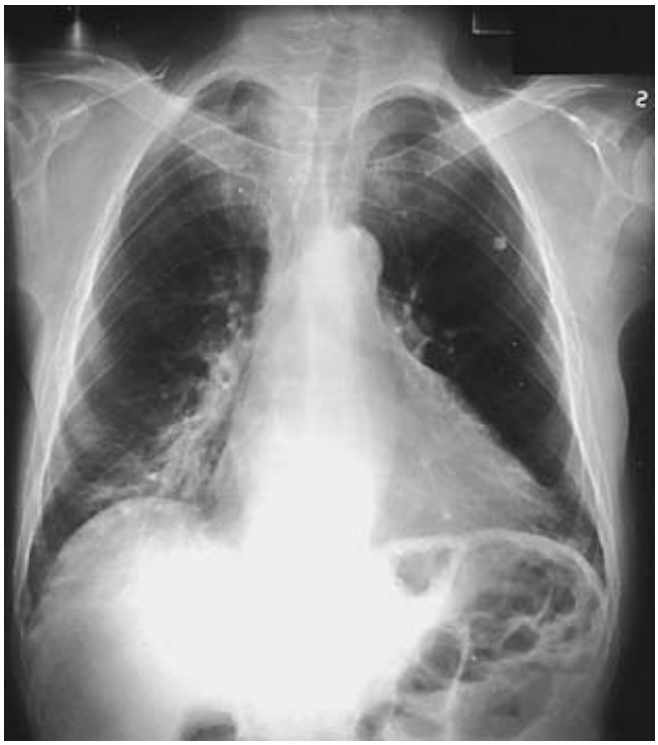

Figure 57-13: Chest roentgenogram of a patient with severe MR. Note the cardiomegaly and enlargement of the LA body and appendage.

CLINICAL SYNDROMES

The clinical presentation of patients with MR can be schematically separated in four syndromes, summarized in Table 57-12.

Table 57-12: Mitral Regurgitation: Clinical Presentations

	MVP Syndrome	Chronic MR	Acute MR	Ischemic/Functional MR
Symptoms	Chest pain	Fatigue	Pulmonary edema	CHF
Physical examination	Midsystolic click, murmur	Loud murmur S_3	Loud murmur S_4	Soft murmur S_3, S_4
Electrocardiogram	ST-T changes	Atrial fibrillation	Normal	Q waves, left bundle-branch block
Chest x-ray	Pectus excavatum	Cardiomegaly	Normal heart size, pulmonary edema	Cardiomegaly, pulmonary edema

Laboratory Tests

DOPPLER ECHOCARDIOGRAPHY

Doppler echocardiography has an important role in the assessment of MR using two-dimensional echocardiography with directed M-mode measurements, color-flow imaging, pulsed and continuous-wave Doppler, and transesophageal echocardiography (TEE). Quantitative measurements of flow and detailed hemodynamic assessment should be routinely performed. The goals of Doppler echocardiography are (1) to assess the mor phology of the mitral valve (etiology and mechanism), (2) to assess the degree of MR, and (3) to assess ventricular and atrial function (see also Chap. 13).

Morphology

The features of the most common causes are indicated below.

Rheumatic MR is characterized by thickening of the leaflets and chordae. The posterior leaflet has reduced mobility whereas the anterior leaflet may be doming if commissural fusion is associated. A valvular prolapse is usually not present unless a ruptured chordae or active rheumatic carditis are present. Similar lesions are observed in lupus or anticardiolipin syndrome, in which transesophageal echocardiography may also show small vegetations.

In *degenerative MR*, prolapse is observed with the passage of valvular tissue beyond the annulus plane in the long-axis view (Fig. 57-14). Some features are important:

- Myxomatous changes with diffusely thickened leaflets and excessive valvular tissue
- Localization of the leaflet involved (most often the posterior) confirmed by the initial direction of the jet
- The presence of mitral annular calcification, which may represent a limitation for conservative surgery if extensive and severe
- Flail segments appearing as complete eversion of the segment with or without the small floating echo of ruptured chordae (Fig. 57-15)

The usual mechanism in endocarditic MR, flail leaflets, is relatively easy to diagnose.[92] Perforations are more difficult to diagnose. Mitral annular abscesses are rare and are best detected by TEE. Vegetations can be seen on leaflets or on ruptured chords with superior sensitivity by TEE.[93]

In ischemic/functional MR, the finding of a dilated annulus[94,95] is nonspecific[76] and annular descent is reduced. The features of ischemic heart disease may be observed as regional wall motion abnormalities.[94] The leaflet tissue is normal. The mitral tenting due to the abnormal traction by the principal chordae on the anterior leaflet reduces the area of coaptation of the two leaflets and therefore allows for a central jet of MR.[94,95]

With papillary muscle rupture,[53] MR is due to the flail leaflet. The diagnosis is based on visualization of a small mass of muscle attached to chordae and floating freely during the cardiac cycle.

Assessment of Severity of Regurgitation (Table 57-13)

SEMIQUANTITATIVE METHODS

COLOR-FLOW IMAGING JET ANALYSIS

The origin and direction of the jet is related to etiology. Jet length and ratio of jet to left atrial area (or more simply jet area)[96] have been suggested as good indices of MR severity. Small jets consistently correspond to mild MR.[76] However, color-flow imaging has significant limitations, intrinsically related to the nature of regurgitant jets (Chap. 13). The extent of a jet is determined by its momentum and thus as much by regurgitant velocity as by regurgitant flow. Also, jets are constrained by the LA and expand more in large LAs.[76] The eccentric jets of valve prolapse[97] impinge on the LA wall and tend to underestimate MR[76] (Fig. 57-16, Plate 91). Central jets of functional MR expand markedly in the enlarged LA, and this tends to overestimate MR[76] (Fig. 57-17, Plate 92). TEE usually shows larger jets but does not suppress these limitations of color-flow imaging (Chap. 13).

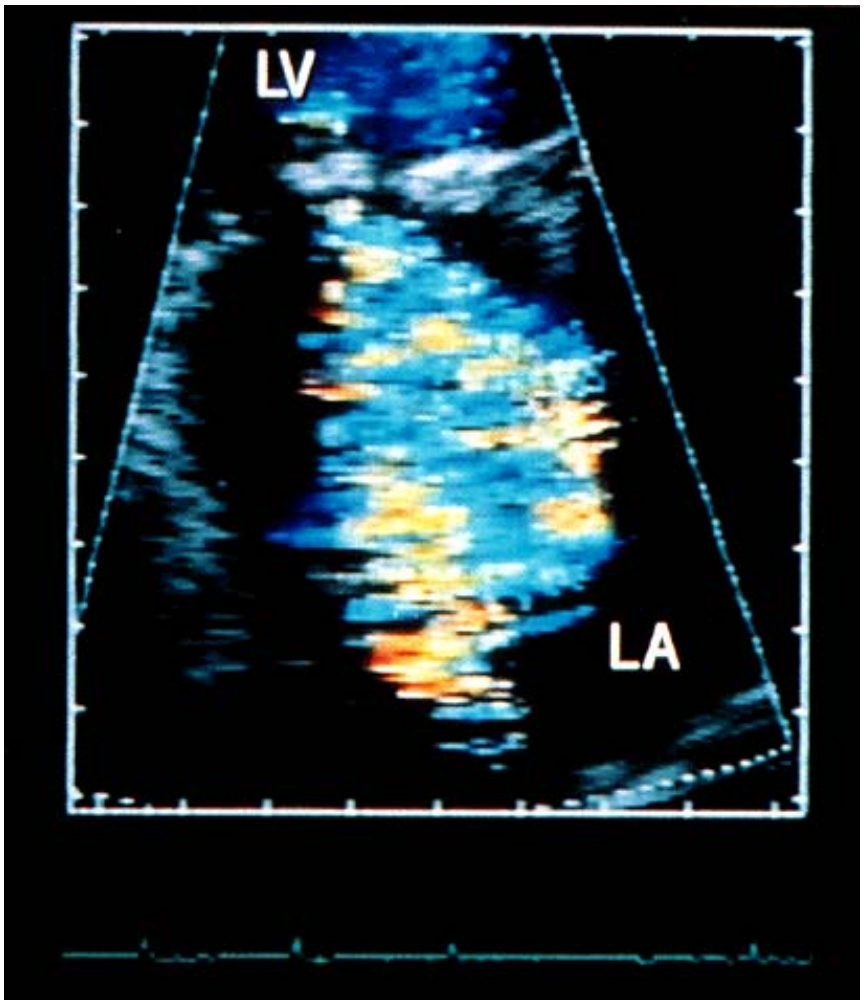

Figure 57-17: (Plate 92) Color flow imaging of a central jet of a functional mitral regurgitation by transthoracic echocardiography. Note that the jet is free, expands in the left atrium, and tends to overestimate this moderate regurgitation.

VENA CONTRACTA MEASUREMENT

The vena contracta is the region of the regurgitant flow immediately below the flow convergence through the regurgitant orifice.[98] Therefore, direct measurement of vena contracta width provides an index of the regurgitant orifice area. The vena contracta width appears superior to jet measurements and can be obtained either through transesophageal[98] or transthoracic echocardiography.[99]

The *pulmonary venous velocity profile* is useful to assess the degree of MR.[100] Systolic reversal in pulmonary veins is a strong argument for severe MR but is related not only to MR severity but also to jet direction and LA pressure.[101] Consequently, pulmonary venous reversal may be absent or asymmetric in severe MR[101] (Fig. 57-18).

QUANTITATIVE METHODS

The goal of quantitative methods is to measure the volume overload expressed as the regurgitant volume (difference between the total and forward stroke volume) or fraction (proportion of LV ejection volume regurgitated in the LA). The lesion's severity is expressed as the effective regurgitant orifice (ERO) area and calculated as follows[58,102]: ERO = regurgitant flow/regurgitant velocity or ERO = regurgitant volume/regurgitant TVI, where the TVI is the time velocity integral

of the regurgitant jet.

The *practical* quantitation of MR can be performed using various methods:

- *Quantitative Doppler* is based on the calculation of the mitral and aortic stroke volumes using pulsed-wave Doppler. The principle is simple and applicable in most cases, but the measurement of the mitral stroke volume is technically demanding, with a significant learning phase.
- *Quantitative two-dimensional echocardiography* is of similar principle but is based on measurement of LV volumes for total stroke volume calculation.
- The *proximal isovelocity surface area* (PISA) method, conversely, directly measures regurgitant flow by analyzing the flow convergence proximal to the regurgitant orifice (Fig. 57-19, Plate 93) and is based on the principle of conservation of mass. Because color-flow mapping allows precise determination of velocity in the flow-convergence region, the regurgitant flow can be calculated. Using regurgitant flow and velocity, regurgitant orifice and volume can be calculated. This method is simple and accurate if the assumptions are respected. (See also Chap. 13.)

Assessment of Left Ventricular and Atrial Function

The technique of guided M-mode diameters is used for assessment of LV size, mass, and wall stress.[90,105,106] LV volumes can be reliably measured by two-dimensional echocardiography. The EF can be calculated or estimated. M-mode diameter or volume can assess the LA size by two-dimensional echocardiography.

RADIONUCLIDE STUDIES

Radionuclide angiography can be used to estimate the LV end-diastolic and end-systolic volume as well as the right and LV EF. The detection of exercise-induced LV dysfunction is frequent. However the significance of such measurement on the long-term prognosis has not been analyzed in large series of patients. A comparison of the counts measured over the RV and LV allows the calculation of the regurgitant fraction.

CARDIAC CATHETERIZATION

Cardiac catheterization is utilized to assess hemodynamic status, the severity of MR, LV function, and coronary anatomy.

The major hemodynamic consequences of MR are reduction of cardiac output and elevation of pulmonary artery wedge pressure. Marked pulmonary hypertension is rarely present. The large V wave of the pulmonary wedge pressure is more frequent in acute than in chronic MR but can be observed in other disease such as ventricular septal defect or heart failure with reduced left atrial compliance without MR (Fig. 57-20).

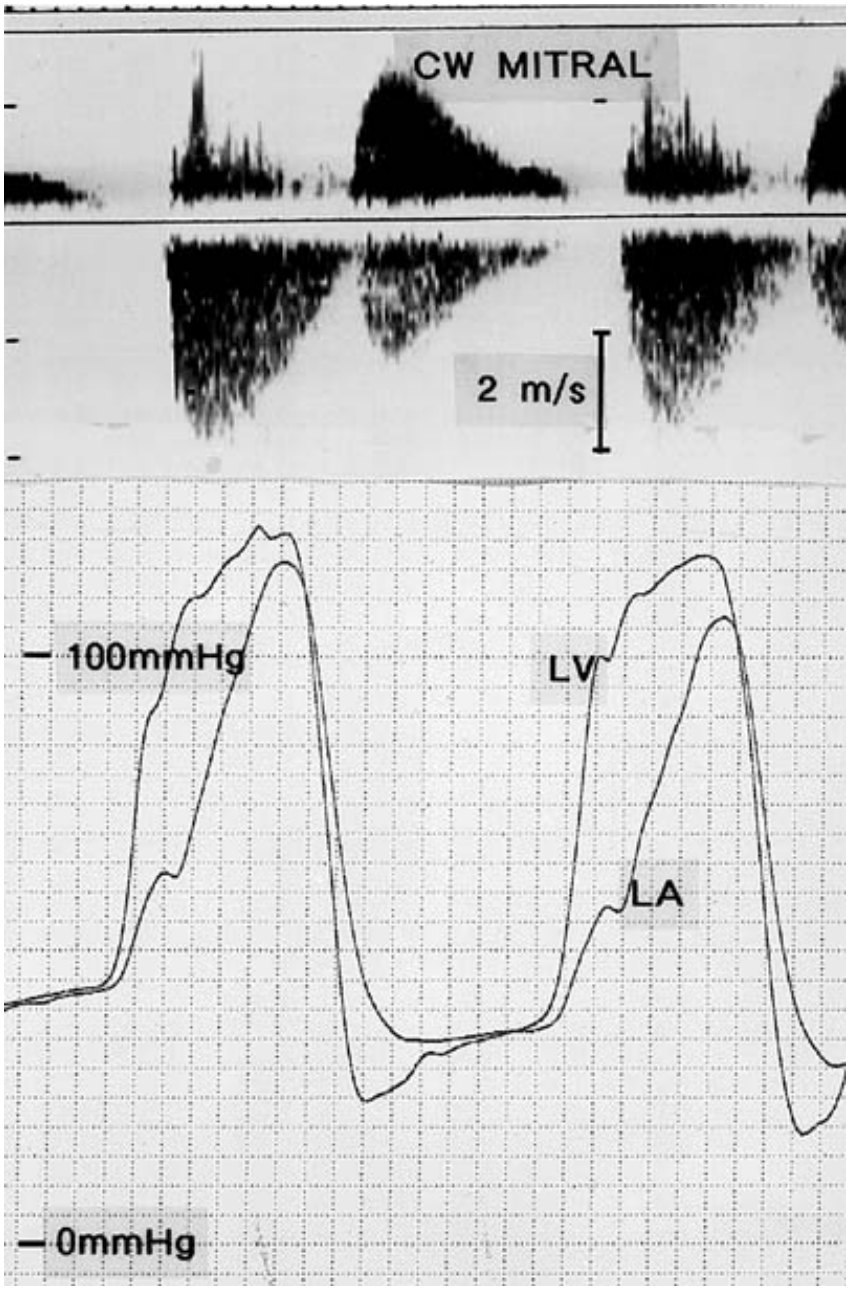

Figure 57-20: Simultaneous recording of LV and LA pressures and continuous-wave Doppler (CW) in a patient with severe MR. Note the large V wave on the left atrial pressure recording, with a triangular shape of the mitral regurgitant jet obtained by CW. (Courtesy of Dr. Rick Nishimura, Mayo Clinic.)

The assessment of MR degree can be obtained by LV selective angiography and can be qualitatively graded in three or four grades on the basis of the degree and persistence of opacification of the LA.[107] Although time-honored, this method has limitations, like all qualitative methods.[108] Quantitation of MR can be obtained by comparing the angiographic stroke volume to the forward stroke volume, calculated by the Fick or thermodilution methods,[109] to calculate the regurgitant volume and fraction. The angiographic stroke volume usually overestimates the true stroke volume and corrections have been used to minimize the overestimation of the regurgitant volume. Subtraction of two stroke volumes introduces a potentially high range of error, which cannot be verified by combined methods or by repeating the measurements; therefore this method is rarely utilized.

The assessment of LV function can be performed using quantitative angiography. LV volumes

correlate strongly to the regurgitant volume, duration and etiology of MR, and LV function. The most frequently utilized indices of LV function are end-systolic volume and EF, which are useful prognostic indices.[70,110] High-fidelity pressure recording with LV angiography allows calculation of more complex indices of LV distensibility in diastole[73] and of wall stress, maximum LV elastance, and LV systolic stiffness. The additional value of these complex measurements has been investigated in small groups of patients and remains to be defined in larger populations.

Selective coronary angiography allows definition of coronary anatomy. Obstructive coronary atherosclerosis continues to be frequent even in the absence of angina,[111] and coronary angiography is ordinarily performed in patients more than 40 to 50 years of age.

STRATEGY OF UTILIZATION OF LABORATORY TESTING

Not all the tests should be performed in all patients[112] (Fig. 57-21). Because transthoracic Doppler echocardiography confirms the diagnosis and degree of MR and of associated valvular diseases and provides a unique assessment of mitral lesions, it is performed in most cases for the initial diagnostic assessment, for follow-up, and for presurgical assessment. TEE provides superior imaging quality, but its incremental value is notable only when the transthoracic information is incomplete.[92] In our practice it is reserved preoperatively to the patients in whom a doubt persists regarding the lesions (especially if endocarditis is suspected) or regarding the severity of regurgitation, but it is utilized on a large scale intraoperatively to monitor the results of valve repair.[113]

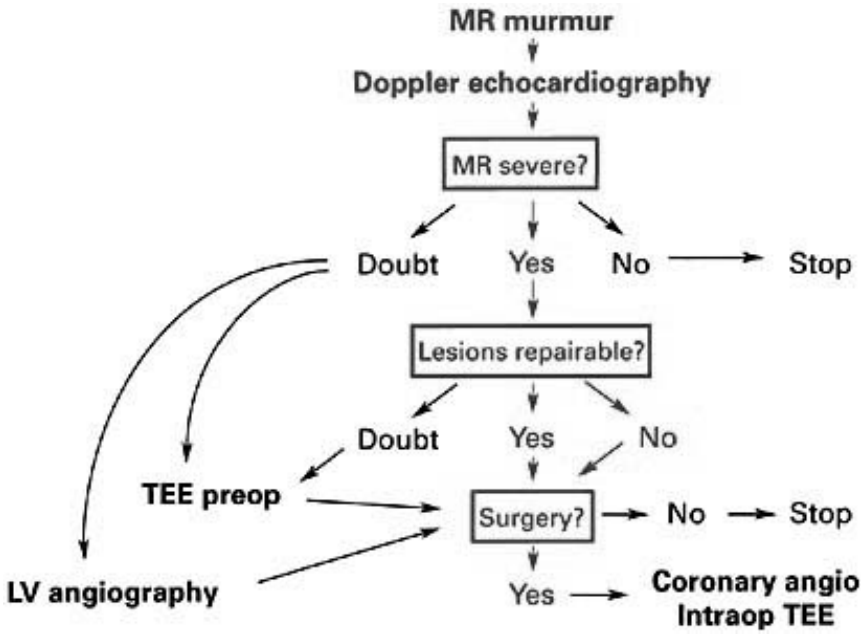

Figure 57-21: Strategy of utilization of tests in patients with mitral regurgitation.

Coronary angiography is indicated as a presurgical procedure depending on age. LV angiography is not required unless there is concern regarding validity of echocardiographic studies.[114] Although color-flow Doppler showed a significant number of discrepancies as compared to angiography,[115] the understanding of its pitfalls[76] and more recently introduced quantitative methods have reduced the need for redundant tests. Also, the analysis of LV function provided by routine LV angiography does not appear to add significant information to the noninvasive data.[90] However, the utilization of tests should be individualized based on the patient's characteristics and

the results of noninvasive studies.

Management

PRINCIPLES

Surgical treatment is reserved for patients with severe MR. Criteria most often used for severe MR are angiographic 4+ grade or color flow jet ≥8 cm^2,[96] with the intrinsic limitations of these definitions. Using quantitative techniques, thresholds for severe MR are 60 mL per beat for regurgitant volume, 50 percent for regurgitant fraction, and 40 mm^2 for effective regurgitant orifice.[116] Patients with severe MR will require surgery at some point during their follow-up. In these patients, the most relevant question is the timing of the surgical indication, which is influenced by the natural history of MR and by the outcome after surgical correction of MR. The determinants of outcome are listed in Table 57-14.

Table 57-14: Determinants of Outcome

Unoperated Patients	Operated Patients
Symptoms	Age
Pulmonary hypertension	Preoperative symptoms
LV end-diastolic volume	Coronary disease
AV-O_2 difference	End-systolic dimensions
Ejection fraction	Ejection fraction
	LA size?
	Valve repair

NATURAL HISTORY

Because of the qualitative and imprecise assessment of the degree of MR, the natural history of MR is ill defined. Patients with mild rheumatic MR appear to have a good prognosis,[117] whereas in those with more severe MR a higher mortality has been noted.[84,118] In patients with unoperated clinically significant MR, the late survival has been found as high 60 percent at 10 years[119] or as low as 46 percent[120] or even 27 percent[121] at 5 years. In our experience with flail mitral leaflets, at 10 years, survival was 57 percent, which represents an excess mortality as compared to the expected survival.[84]

The probability of sudden death is important to consider before delaying surgery. Such a devastating complication occurs more often if the ventricular function is decreased[84] but may also occur in patients with normal EF who are asymptomatic.[118] In our experience, sudden death in patients with MR due to flail leaflets occurs at a rate of 1.8 percent per year.[122] The rates are higher in patients with symptoms or reduced ejection fraction, but even in the absence of these risk factors the rate is 0.8 percent per year.[122]

Morbidity in patients with severe MR is also high. Of patients who are initially asymptomatic,

approximately 10 percent per year develop symptoms,[123] which may be hastened by atrial fibrillation. In patients with flail leaflets 10 years after diagnosis, heart failure occurred in 63 percent, and permanent atrial fibrillation in 30 percent of those initially in sinus rhythm[84] (Fig. 57-22). Also at 10 years, 90 percent of the patients had either died or undergone surgery,[84] confirming that in these patients surgery is almost unavoidable (Fig. 57-23).

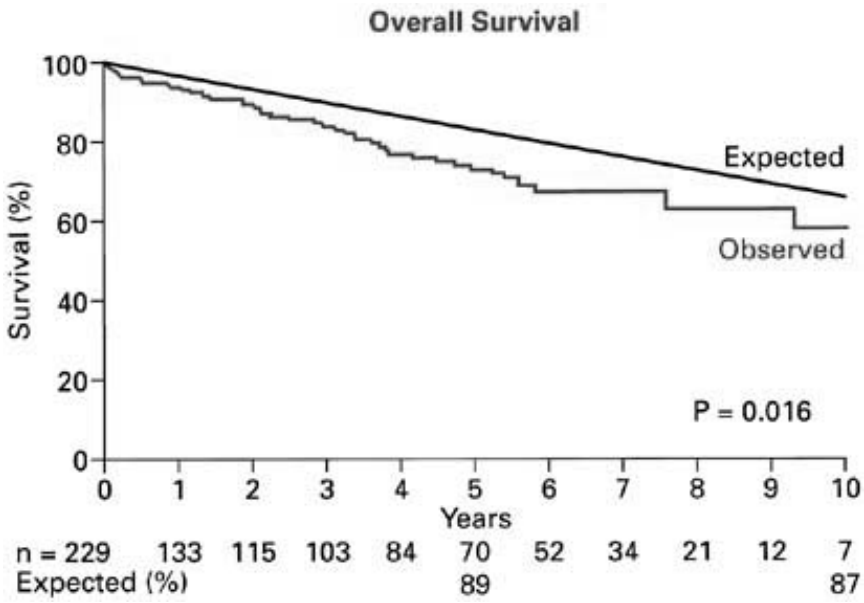

Figure 57-22: Survival with medical treatment of patients diagnosed with MR due to flail leaflets. Note the excess mortality in comparison to the expected survival. (Reprinted by permission of the *New England Journal of Medicine* from Ling LH, et al. 1996; 335:1417-1423. Copyright 1996, Massachusetts Medical Society.)

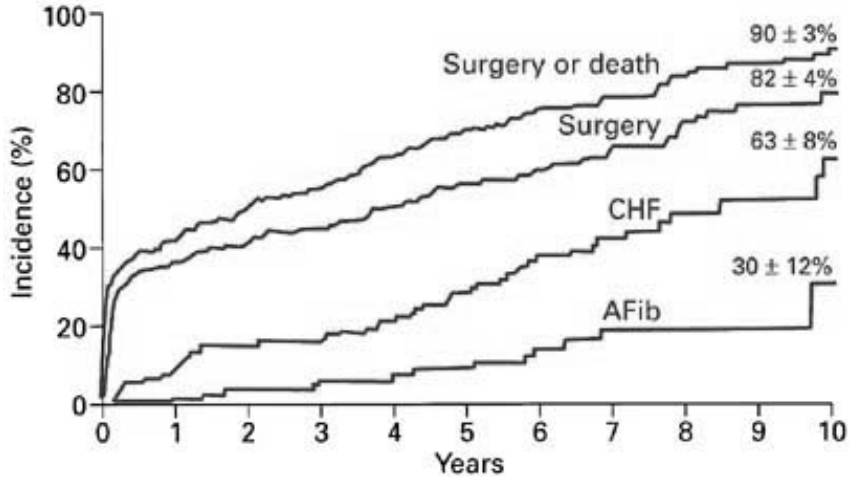

Figure 57-23: Cardiac morbidity with medical treatment in patients diagnosed with MR due to flail leaflets. CHF, congestive heart failure, Afib, atrial fibrillation. (Reprinted by permission of the *New England Journal of Medicine* from Ling LH, et al. 1996; 335:1417-1423. Copyright 1996, Massachusetts Medical Society.)

The predictors of poor outcome in patients medically treated are (1) severe symptoms (NYHA

classes III to IV),[120] even if the symptoms are transient,[84] (2) pulmonary hypertension, (3) markedly increased LV end-diastolic volume or arteriovenous difference in O_2,[124] and (4) reduced ejection fraction.[84] Comparison of prognosis in medically and surgically treated patients shows a trend in favor of the surgical treatment,[118] especially early surgery,[84] with definite improvement of outcome of patients with decreased systolic LV function.[124]

The progression of LV dysfunction in patients medically treated is not well defined. Progression of the degree of MR is usually slow, with progression of regurgitant volume of 8 mL/year, but it reaches 20 mL/year in patients with new flail leaflets.[125] The mechanism of progression of MR is an increase in regurgitant orifice without change in gradient. The major determinant of regression of MR is a reduction in afterload, whereas increase in annular size and new flail leaflet are major determinants of progression of MR.[125]

TREATMENT

Medical Treatment

Prevention of infective endocarditis using the appropriate prophylaxis is necessary in patients with MR.[126] Young patients with rheumatic MR should receive rheumatic fever prophylaxis. In patients with atrial fibrillation, rate control is achieved using digoxin and/or beta blockers. Long-term maintenance of sinus rhythm after cardioversion in patients with severe MR or enlarged LA is usually not possible in patients who are treated medically. However return to sinus rhythm after surgery is possible in patients with atrial fibrillation of short duration.[127] Oral anticoagulation should be used in patients with atrial fibrillation. Beta blockers are the drug of choice in patients with the mitral valve prolapse syndrome and palpitations or chest pain (Chap. 58). Diuretic treatment is extremely useful for the control of heart failure and for the chronic control of symptoms, especially dyspnea.

Acute afterload reduction may decrease the degree of MR.[59] This effect is achieved by reducing the LV systolic pressure but also by decreasing the effective regurgitant orifice area.[60] Acute utilization of sodium nitroprusside in unstable patients with severe MR, especially in the context of myocardial infarction, may be lifesaving in preparation for surgery.[60]

Chronic afterload reduction is more controversial. The hemodynamic effect of hydralazine,[128] has been demonstrated, but this drug is often poorly tolerated. The effect of angiotensin converting enzyme inhibitors has been analyzed in small series,[129-131] and their long-term efficacy is not defined. Furthermore, major discrepancies between series are noted regarding the effect on the degree of MR[132] and on LV remodeling.[133] Because of these uncertainties, vasoactive therapy is not recommended for chronic treatment of MR.[112]

Surgical Treatment

The approach to surgery can be the traditional median sternotomy or the more recently used "minimally invasive" approaches, which range from port-access surgery to small sternotomy to thoracotomy. These new techniques appear interesting but their long-term outcome remains uncertain. There are two main valvular surgical options: mitral valve reconstruction and mitral valve replacement.

MITRAL VALVE RECONSTRUCTION

Reconstruction of the incompetent mitral valve is almost always possible (approximately 90

percent of patients referred for primary correction of acquired MR at the Mayo Clinic). The frequency with which valve repair can be used varies with experience of the operating team and the spectrum of underlying valve disease; repair is more often feasible with degenerative valve disease than with rheumatic valvulitis or endocarditis.

The *valvular procedure* is as follows. With leaflet prolapse immobilization of this prolapsing section can be obtained by plicating or by excising it and then repairing the leaflet. This will overcome the problem of localized prolapse. However, the resulting reduction in area of the leaflet could reduce coaptation and induce residual MR; therefore, annuloplasty is a routine part of the repair. Resection or plication of prolapsing sections is most successful with posterior leaflet prolapse. With anterior leaflet prolapse the risk of residual MR is higher if the plication or resection is not combined with subvalvular procedures.[113] Other repairable leaflet abnormalities include congenital clefts and acquired perforation, which may be closed by using a patch of pericardium or synthetic material.

In the *subvalvular procedure,* chordal shortening may be necessary in patients with elongated chordae to ensure the appropriate coaptation of the leaflets, but the durability of this procedure has been criticized.[134] A major recent progress has been the introduction of transposition of chordae and of artificial chordae which have made the anterior leaflet prolapse as repairable as the posterior leaflet prolapse.[135,136]

Annular dilatation, almost constantly associated with MR, is treated by reduction of mitral circumference, i.e., *annuloplasty*. The annuloplasty should be placed in the region supporting the posterior leaflet to preserve the area of anterior leaflet. A cloth-covered rigid ring was originally developed by Carpentier. Recently, flexible annuloplasty rings have been developed to preserve the normal systolic contraction of the mitral annulus.[137] In general, results with the Carpentier ring annuloplasty have been favorable, but LV outflow obstruction associated with abnormal systolic anterior motion of the anterior mitral leaflet has been reported in 6 to 10 percent of patients.[138] This complication is mainly due to hypovolemia and excessive use of inotropes[113] but may be lower with flexible rings.[139]

It is important to assess the adequacy of mitral valve reconstruction before completion of the operation. When satisfactory repair cannot be achieved, it is preferable to replace the valve immediately. To assess adequacy of mitral repair (residual stenosis, regurgitation, or systolic anterior motion), TEE, which does not interfere with the surgical procedure, is performed routinely.[113]

Valve Replacement

When mitral reconstruction is considered impossible or is unsuccessful, replacement must be performed. The dilemma is the choice between a mechanical valve of excellent durability but with the hazard of thromboembolism and a biological valve with undefined long-term durability[140] but less tendency to cause thromboembolism. With atrial fibrillation, chronic anticoagulant therapy is necessary even with a bioprosthesis, so that avoiding anticoagulation is not relevant in choosing a prosthesis.

Postoperative Outcome

Valve repair, by preserving the normal valvular tissue, is preferable to valve replacement. Compared to prosthetic replacement, mitral valve reconstruction has a lower operative mortality.[141,142] Direct comparison of the results of valve repair and replacement is difficult[142] because the patients undergoing a valve repair are usually at a less advanced stage of the disease than patients undergoing valve replacement.[141] However, survival and LV function after valve

repair are better than after insertion of a prosthetic valve.[141] Better ventricular function with valvuloplasty may be due to preservation of chordae and papillary muscles.[143] Durability of valve repair for degenerative disease is excellent if no more than mild residual MR is accepted.[134] Valve repair has the same low rate of reoperation than valve replacement.[141] MR post-repair is due in two-thirds of the cases to new lesions and in one-third to an inadequate primary correction.[144] *Therefore valve repair should be the preferred procedure for surgical correction of MR* (Fig. 57-24).

Operative mortality has been reported between 5 and 12 percent[140] in earlier series, but most patients had prosthetic valve replacement rather than reconstruction. The operative risk is lower in the current era, around 1 to 2 percent in patients younger than 75 years with organic MR operated on at the Mayo Clinic whether they had valve repair or replacement.[90] LV function is not a predictor of operative mortality and patients with organtic MR even with markedly depressed function have a reasonable chance of surviving surgery.[90] Age symptoms and coronary disease are the most important predictors of operative mortality.[90] Some important points should be noted: First, the risk of surgery has become progressively similar in patients 65 to 75 years old as compared to younger patients. Second, operative mortality has decreased recently in patients 75 and older but remains relatively high, around 5 percent. Third, in ischemic MR the operative mortality remains high, around 10 percent.

Postoperative survival has considerably improved and in our recent experience, with a population of mean age 62, the 5- and 10-year survivals were 83 and 68 percent after valve repair and 69 and 52 percent after valve replacement. Remarkably, the survival after valve repair is not different from the expected survival, whereas it represents 77 percent of the expected survival after valve replacement.[141]

A large majority of long-term survivors after mitral valve replacement for MR show a symptomatic improvement by at least one functional class and some become asymptomatic. However, with time postoperative heart failure and symptomatic deterioration tend to occur at a progressively increasing rate (38 percent at 10 years in operative survivors) and is most often (in two thirds of the cases) due to residual LV dysfunction.[145] Valvular or prosthetic dysfunction explain the heart failure in approximately one-third of the cases.[145] Postoperative congestive heart failure has a dismal prognosis and should be prevented as much as possible[145] by early correction of the MR.

The most frequent cause of mortality after surgical correction of MR is LV dysfunction[90] due to chronic irreversible myocardial damage.[66,69,70] LV dysfunction occurs, in our experience in 40 percent of patients overall and 32 percent of those with organic MR.[69] The majority of patients demonstrate a decrease in EF after successful valve replacement.[66,69] This decline may be the result of several factors: cumulative permanent myocardial damage, occasional myocardial insult sustained at the time of operation, diminished preload, and probably increase in impedance to ejection after elimination of the MR. However, the relationships between pre- and postoperative LV function[65,66,69,70,110] and between preoperative LV function and postoperative survival[68,90,105] underline the fact that LV dysfunction is most often already present preoperatively. Because of the modified loading conditions, multiple and complex indices of LV function have been proposed.[65,67,68] Despite these altered loading conditions preoperative EF is an acceptable independent predictor of postoperative EF[66,69,70] and survival.[90] In general, one can estimate that the postoperative EF likely will decrease by approximately 10 percent early after valve replacement.[66,69,70] However, there is a significant individual variation and more decline is observed with markedly increased end-systolic diameter,[69,105] volume,[70,110] or wall stress[69] or in

patients with severe symptoms, prolonged duration of MR or coronary disease.[69] A markedly reduced preoperative EF (<50 percent) is associated with a high late mortality,[90] but nevertheless surgery provides a better outcome than medical treatment.[124] Even a "borderline" EF (50 to 60 percent) is associated with an excess late mortality.[90] Therefore, *currently the widely accepted signs of overt LV dysfunction in MR are LV diameter* ≥45 *mm or ejection fraction* <60 *percent.*[112] Nevertheless, the end-systolic diameter rarely and belatedly reaches 45 mm and the best outcome of surgery is obtained in patients with both end-systolic diameter <45 mm and ejection fraction ≥60 percent[69,90] (Fig. 57-25).

Figure 57-25

Figure 57-25: Survival after surgical correction of organic mitral regurgitation. Note the excess mortality in patients with preoperative ejection fraction above 50 percent but also in patients with preoperative ejection fractions of 50 to 60 percent. (From Enriquez-Sarano M, Tajik A, Schaff H, et al. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation* 1994; 90:830-837, with the authorization of the American Heart Association.)

Another issue, which has been controversial, has been the impact on postoperative outcome of preoperative symptoms. Patients with severe preoperative symptoms, NYHA class III or IV, incur an excess postoperative mortality independently of all baseline characteristics, in particular age, EF, and the type of surgery performed.[146] Importantly, patients preoperatively in class I or II incur a very low operative risk,[146,147] and an excellent long term survival, identical to the expected survival.[146] These data suggest that *in centers and patients at low operative risk, timing of surgery when there are no or minimal symptoms offers distinctive advantages*.

Atrial fibrillation when present preoperatively usually persists postoperatively, unless of brief duration[127] but the excess risk due this arrhythmia appears modest,[90,127] although it requires anticoagulation. Conversely, the association of a Maze procedure to mitral valve repair can be accomplished with minimal risk.[148]

Late risk of thromboembolism after mitral replacement for MR is not different from it as in other mitral valve diseases. Differences in thromboembolic risk after valve repair and valve replacement have been variably estimated[141,142] but appear to favor valve repair. In addition, because following valve repair, anticoagulation is recommended permanently only if atrial fibrillation persists, the occurrence of bleeding is less common than following prosthetic replacement.[141]

Indications for Surgery

Based on the most recent data regarding the natural history of MR treated with and without surgery, the indications for surgery have evolved[112] and can be outlined as follows:

TRADITIONAL INDICATIONS

Patients with severe symptoms (functional NYHA class III or IV). Patients with transient severe symptoms even if they markedly improve with medical treatment should be considered at high risk and offered surgery within that category.

ADVANCED INDICATIONS

These apply to patients with NYHA class II symptoms and to patients with no symptoms (class NYHA I) but with either signs of overt LV dysfunction (LV ejection fraction <60 percent, end-systolic diameter ≥45 mm) or with pulmonary hypertension or with atrial fibrillation.

EARLY INDICATIONS

Patients with no symptoms (NYHA class I) and no sign of LV dysfunction (ejection fraction ≥60 percent). These patients can expect the best results of surgery and in particular, after the immediate postoperative phase, a survival identical to the expected survival.[90,146] Therefore, the authors consider surgery to be a reasonable option in this subgroup. However because surgery in these patients is justified neither by symptoms nor by LV dysfunction certain conditions should be fulfilled:

- *Low operative risk:* Both the operative mortality in the institution where such an indication is contemplated and the operative risk for the individual patient involved should be minimal (1 to 2 percent).
- *Reparability:* The valvular lesions as determined by echocardiography should be in all probability repairable and the surgeon performing the intervention should have a high degree of experience with all forms of valve repair.
- *Intraoperative TEE should be performed* by experienced physicians to monitor the repair procedure and help with decisions warranted by an imperfect result.
- *Quantitation of MR should be performed* systematically in these patients preoperatively using multiple noninvasive techniques to determine objectively the degree of MR and affirm that surgery is warranted.

Therefore, despite the considerable progress recently accomplished, currently *not all patients and not all institutions* are candidates for these early indications of surgical correction of MR, but surgery should be considered early in the course of MR when severe MR has been thoroughly documented.

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Chapter 57: MITRAL VALVE DISEASE

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Chapter 57: MITRAL VALVE DISEASE

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Figure 57-1: Pathophysiology of mitral stenosis. Mitral stenosis results in a diastolic pressure gradient from the LA to the LV. The actual gradient is dependent on the mitral valve area and the mitral valve *flow per diastolic second*. As a result, there is an elevation of LA pressure and therefore also of pulmonary venous pressure. Physiologic and pathologic changes-such as tachycardia and atrial fibrillation (which shorten diastole and may also result in loss of effective atrial contraction) or pregnancy, volume loading, and left-to-right shunts (at ventricular and aortopulmonary levels), which increase pulmonary venous flow-will increase the mitral valve gradient as well as LA and pulmonary venous pressures. An increased LV diastolic pressure will also result in further increase of LA pressure. An elevated LA pressure has several important effects; these include enlargement of the left atrium, atrial arrhythmias, and an increase of pulmonary venous pressure. Pulmonary venous hypertension may result in pulmonary edema and pulmonary arterial hypertension. PA hypertension and RV ventricular hypertension results in RV hypertrophy and may result in tricuspid regurgitation and RV enlargement. All of these changes contribute to producing symptoms. In addition, a fixed or even reduced cardiac output will also contribute to the symptomatic state of the patient. [Copyright by S. H. Rahimtoola. M.B., F.R.C.P., M.A.C.P., M.A.C.C. (Ref. [10]).]

Figure 57-2: Auscultatory signs of MS in patients in sinus rhythm are illustrated. These include a presystolic murmur, loud first heart sound (S_1), an opening snap (OS), and a middiastolic murmur (low-pitched, decrescendo diastolic rumble, rumbling murmur). These signs may be accentuated or at times may be heard only by placing the patient in the left lateral decubitus position. Importantly, these signs are helpful in assessing the severity of the MS; as the MS becomes more severe, the S_2-OS interval is shortened and the length of the middiastolic rumble is increased. In mild OS, the S_2-OS interval is long and the diastolic murmur is short. In moderate MS, the S_2-OS interval is shorter, and although the diastolic murmur is longer at rest, there is usually a gap between the end of the murmur and the onset of the presystolic murmur. In severe MS, the S_2-OS interval is short (usually 0.04 to 0.06 s) and the diastolic murmur is a full-length murmur. With PA hypertension, P_2 is increased in intensity. In the presence of a rigid mitral valve (with or without calcification), S_2 is soft and the OS is usually not heard. A holosystolic murmur of mitral regurgitation may be present. (Adapted and modified from Kawanishi DT, Rahimtoola SH. Mitral stenosis. In: Rahimtoola SH, ed. *Valvular Heart Disease II*. St. Louis: Mosby; 1996:8.1-8.24. Copyright by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C.)

Figure 57-3: Auscultatory signs of MS in atrial fibrillation are illustrated. The presystolic murmur is absent. The loud S_1 and the OS are still heard. In the short cycles, the duration of diastole is short and the middiastolic rumble occupies the whole of diastole (*left panel*). In the long cycles (*right panel*), the length of middiastolic murmur is related to the severity of MS. As the MS becomes more severe, the length of this murmur is increased. In atrial fibrillation, with a slow ventricular response and very long R-R intervals, the middiastolic rumble may not occupy the whole diastolic period and the presystolic murmur is usually absent. Thus, one may get the impression that the MS is moderate rather than severe. Increasing the heart rate-for example, with brief physical exertion-may produce more characteristic auscultatory findings. Alternatively, when the ventricular rate in atrial fibrillation is rapid or in short cycles, the auscultatory findings may suggest a more severe degree of MS than is really the case (*left panel*). (Adapted and modified from Kawanishi

DT, Rahimtoola SH. Mitral stenosis. In: Rahimtoola SH, ed. *Valvular Heart Disease. II.* St. Louis: Mosby; 1996:8.1-8.24. Copyright 1996 by S. H. Rahimtoola, M.B., F.R.C.P., M.A.C.P., M.A.C.C.)


Figure 57-4: This figure depicts the survival of patients with MS who initially where asymptomatic or had mild symptoms and were treated medically. In the 1960 study of Rowe and coworkers[30] (*dashed lines*), 52 percent of 250 patients with "auscultatory MS" who presented between 1925 and 1947 were asymptomatic; their 10-year survival was 84 percent. The lower dashed line represents the survival in the 42 percent of patients who had mild symptoms on clinical presentation; their 10-year survival was 42 percent.[30] The data of Olesen, 1962[27] (*upper solid curve connecting solid symbols*), show the survival in the 21 percent of 271 symptomatic MS patients who had class II symptoms. Their 10- and 20-year survival was 34 and 14 percent, respectively. The data of Roy and Gopinath, 1968[29] (*lower solid curve connecting open symbols*), also show the survival in patients with class II symptoms. (From Kawanishi DT, Rahimtoola SH. Mitral stenosis. In: Rahimtoola SH, ed. *Valvular Heart Disease. II.* St. Louis: Mosby; 1996:8.1-8.24.)


Figure 57-5: Survival of patients with MS and moderate or advanced (severe) symptoms is shown. Patients who were in NYHA functional class IV (Olesen, class IV, 1962)[28] had a 42 percent 1-year survival and all patients had died within 8 years. The other four survival curves are of patients who were in functional classes II to IV, and their survival curves are similar, with 5-, 10-, and 15-year approximate survivals of 60, 40, and 20 percent, respectively; at 20 years, less than 10 percent of the patients were still alive.[28-30] Thus, the survival in this group of patients with more advanced symptoms is much worse than that of patients who were initially asymptomatic or minimally symptomatic (see Fig. 57-4). (From Kawanishi DT, Rahimtoola SH. Mitral stenosis. In: Rahimtoola SH, ed. *Valvular Heart Disease. II.* St. Louis: Mosby; 1996:8.1-8.24.)


Figure 57-6: Comparison of survival of patients with class II symptoms (*left panel*) and class III and IV symptoms due to MS (*right panel*).[29] Survival of patients treated medically (unoperated) is indicated by the broken line and with surgical closed mitral commissurotomy (operated) by the solid line. In patients treated by surgical commissurotomy, there were no operative or late deaths in those with mild symptoms and no late deaths in those with class III and IV symptoms. There is a clear improvement in survival in operated patients. The 5-year mortality with medical treatment alone in those with class III and IV symptoms approaches 50 percent (also see Fig. 57-5); with surgery, there is no appreciable mortality following recovery from the procedure. [From Roy SB, Gopinath N. Mitral stenosis. *Circulation* 1968; 38(suppl v):68-76.]


Figure 57-7: (Plate 86) Anatomic example of rheumatic MR. Note the thickening of the leaflet and chordae and the retraction of the mitral tissue. (Courtesy of Dr. W. D. Edwards.)


Figure 57-8: (Plate 87) Anatomic example of MR due to mitral valve prolapse seen from the atrial view (the mitral orifice is on the left of picture). Note the redundancy of the leaflets with excess tissue. (Courtesy of Dr. W. D. Edwards.)


Figure 57-9: (Plate 88) Anatomic example of a flail posterior leaflet with ruptured chord. On the right of the picture, closeup view of the ruptured chord. Otherwise the left atrium is enlarged and the valvular tissue normal. (Courtesy of Dr. W. D. Edwards.)


Figure 57-10: (Plate 89) Anatomic example of MR due to endocarditis. Note the vegetations of the anterior leaflet and the ruptured chords. (Courtesy of Dr. W. D. Edwards.)


Figure 57-11: (Plate 90) Anatomic example of a ruptured posterior papillary muscle. Note the normal valvular tissue otherwise. (Courtesy of Dr. W. D. Edwards.)


Figure 57-12: Electrocardiogram of a patient with severe MR. Note LA enlargement, as indicated by notched p waves (lead I and rhythm strip lead II).


Figure 57-13: Chest roentgenogram of a patient with severe MR. Note the cardiomegaly and enlargement of the LA body and appendage.

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Chapter 57: MITRAL VALVE DISEASE

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Part 9: VALVULAR HEART DISEASE
Chapter 58:

MITRAL VALVE PROLAPSE SYNDROME

Author: Robert A. O'Rourke

The syndrome of mitral valve prolapse (MVP) is the most common form of valvular heart disease, occurring in 2 to 6 percent of the population, thus being more common than a bicuspid aortic valve. The incidence varies depending on the criteria used for its diagnosis.[1,2] MVP is commonly detected by cardiac auscultation, with one or more systolic clicks and/or a mid to late-systolic murmur detected on a careful physical examination. Often the auscultatory complex is the only clinical manifestation of cardiac disease, and many patients are asymptomatic.

Midsystolic clicks were first described in the late nineteenth century and originally were attributed to a pericardial or extracardiac etiology. Subsequently, late-systolic murmurs were recognized to be present in apparently healthy people and were associated with a benign natural history. Thus the murmur also was considered to be extracardiac in origin.

In 1961, Reid[3] suggested that the midsystolic click and the late-systolic murmur were due to mitral regurgitation. In 1963, Barlow et al.[4] confirmed this hypothesis by left ventricular (LV) cineangiography. Subsequently, intracardiac phonocardiogram studies documented the mitral valve origin of a systolic click and late-systolic murmur.

During the past four decades, considerable new data obtained from pathologic studies, echocardiography, and cineventriculography have demonstrated that this common syndrome is associated with prolapse of one or both mitral valve leaflets into the atrium during LV systole.

Recognition of MVP (also known as the *systolic click-late systolic murmur syndrome*) is often difficult because of the extreme variability of its clinical manifestations. It is, however, an important cause of incapacitating chest pain and refractory arrhythmias in certain patients. The abnormal components of the mitral valve apparatus are a potential site for endocarditis, and some patients, particularly males in their sixties and seventies, can develop severe mitral regurgitation (MR) due to ruptured chordae tendineae.

DEFINITION, ETIOLOGY, AND TIMING

MVP refers to the systolic billowing of one or both mitral leaflets into the left atrium, with or without MR. MVP often occurs as a clinical entity with no or only mild MR, and it is frequently associated with unique clinical characteristics when compared with the other causes of MR.[5-9] Nevertheless, MVP is the most common cause of significant MR and the most frequent substrate for mitral valve endocarditis in the United States. The mitral valve apparatus is a complex structure composed of the mitral annulus, valve leaflets, chordae tendineae, papillary muscles, and the supporting left ventricle, left atrium, and aortic walls[10] (Fig. 58-1). Disease processes involving any one or more of these components may result in dysfunction of the valvular apparatus and prolapse of the mitral leaflets toward the left atrium during systole when LV pressure exceeds left atrial (LA) pressure.

The complexity of the mitral valve apparatus provides an explanation for the presence of secondary prolapse in many conditions that affect one or more of the components of the apparatus (e.g., ruptured mitral chordae). There is, however, considerable evidence that a disorder of the mitral valve leaflets exists in which there are specific pathologic changes causing redundancy of the mitral leaflets and their prolapse into the left atrium during systole. This is the primary form of MVP (Table 58-1).

Table 58-1: Classification of Mitral Valve Prolapse

Primary mitral valve prolapse
Familial
Nonfamilial
Marfan ssyndrome
Other connective tisue diseases
Secondary mitral valve prolapse
Coronary artery disease
Rheumatic heart disease
Cardiomyopathies
'Flail' mitral valve leaflet(s)
Normal variant
Inaccurate auscultation
'Echocardiographic heart disease'

In *primary* MVP, there is interchordal hooding due to leaflet redundancy that involves both the rough and clear zones of the involved leaflets[6] (Fig. 58-2). The height of the interchordal hooding usually exceeds 4 mm and involves at least one-half of the anterior leaflet or at least two-thirds of the posterior leaflet. The basic microscopic feature of primary MVP is marked proliferation of the *spongiosa*, the delicate myxomatous connective tissue between the *atrialis* (a thick layer of collagen and elastic tissue forming the atrial aspect of the leaflet) and the *fibrosa*, or *ventricularis*, which is composed of dense layers of collagen and forms the basic support of the leaflet.[6] In primary MVP, myxomatous proliferation of the acid mucopolysaccharide-containing spongiosa tissue causes focal interruption of the fibrosa. Secondary effects of the primary MVP syndrome include fibrosis of the surfaces of the mitral valve leaflets, thinning and/or elongation of chordae tendineae, and ventricular friction lesions. Fibrin deposits often form at the mitral valve-left atrial angle.

The primary form of MVP may occur in families, where it appears to be inherited as an autosomal dominant trait with varying penetrance.[11,12] No consistent chromosomal abnormalities have yet been identified in patients with MVP, which also often occurs in isolated cases.[13,14] Primary MVP has been found with increasing frequency in patients with Marfan syndrome, where it is almost always present, and in other heritable connective tissue diseases such as Ehlers-Danlos

syndrome,[15] pseudoxanthoma elasticum,[16] and osteogenesis imperfecta.[17] Marfan syndrome also has an autosomal dominant mode of inheritance. It is possible that some genetic studies of MVP may have been tracking a more general connective tissue disorder such as Marfan syndrome (see also Chap. 76).

Many observers have speculated that primary MVP syndrome represents a generalized disorder of connective tissue. Thoracic skeletal abnormalities such as straight thoracic spine and pectus excavatum are commonly associated with this syndrome.[18] The mitral valve undergoes differentiation between the thirty-fifth and forty-second days of fetal life, when the vertebrae and thoracic cage are beginning chondrification and ossification.[19] Any adverse factors in this period may affect both the mitral valve and the bones of the thoracic cage. Of possible relevance, rats fed a diet containing large amounts of peas of the genus *Lathyrus* develop both bony abnormalities and myxomatous changes in their valve leaflets. Therefore, it has been postulated that the MVP syndrome is a connective tissue disorder resulting from fetal exposure to toxic substances during the early part of pregnancy.[20,21]

Others have suggested that MVP is a result of defective embryogenesis of cell lines of mesenchymal origin. The increased prevalence of primary MVP in patients with von Willebrand disease and other coagulopathies, primary hypomastia, and various connective tissue diseases has been used to support this concept.[21]

In *secondary* forms of MVP (see Table 58-1), myxomatous proliferation of the spongiosa portion of the mitral valve leaflet is absent. Tei et al.[22] were able to produce de novo echocardiographic evidence of MVP, often with MR, in closed-chest dogs undergoing transient coronary artery occlusion; MVP was attributed to relative displacement of ischemic papillary muscles. Also, serial studies in patients with known ischemic heart disease occasionally have documented unequivocal MVP following an acute coronary syndrome that was previously absent.[23] In most patients with coronary artery disease (CAD) and MVP, however, the two entities are coincident but unrelated.

More recent studies[24-26] indicate that MR caused by MVP may result from postinflammatory changes, including those following rheumatic fever. In histologic studies of surgically excised valves, fibrosis with vascularization and scattered infiltration of round cells, including lymphocytes and plasmacytes, was found *without myxomatous proliferation* of the spongiosa.[24] With rheumatic carditis, the anterior mitral leaflet is more likely to prolapse.[26]

MVP has been observed in patients with hypertrophic cardiomyopathy, in whom posterior MVP may result from a disproportionately small LV cavity, altered papillary muscle alignment, or a combination of factors.[21] The mitral valve leaflet is usually normal, but occasionally, the changes of primary MVP are present. Since LV segmental wall motion abnormalities and sometimes depressed global LV function occur in certain patients with echocardiographic and auscultatory evidence of MVP and MR, nonhypertrophic cardiomyopathy has been listed as a cause of mitral prolapse.[27] This is probably not the case; the ventricular wall motion abnormalities usually disappear when the mitral valve is repaired or replaced. In MVP patients, atrial septal defects, pulmonary hypertension, anorexia nervosa, dehydration, or straight-back syndrome may be secondary to the relatively small size of the left ventricle in this disorder, resulting in a mitral apparatus that is relatively large and redundant.[21,28] However, atrial septal defect may be associated with primary MVP.[16] Patients with primary and secondary MVP must be distinguished from those with normal variations on cardiac auscultation or echocardiography; these variations can result in an incorrect diagnosis of MVP, particularly in patients who are hyperkinetic or dehydrated during the physical examination or two-dimensional (2-D) echocardiography. Other auscultatory findings may be misinterpreted as midsystolic clicks or late-systolic murmurs.[8,21]

Patients with mild to moderate billowing of one or more nonthickened leaflets toward the left atrium with the leaflet coaptation point on the ventricular side of the mitral annulus and no or minimal MR by Doppler echocardiography are probably normal. Unfortunately, many such patients with neither a nonejection click nor murmur of MR are frequently overdiagnosed as having the MVP syndrome.[1,2,29]

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Chapter 58: MITRAL VALVE PROLAPSE SYNDROME

PATHOPHYSIOLOGY

In patients with MVP, there is frequently LA enlargement and LV enlargement, depending on the presence and severity of MR.[30] The supporting apparatus is often involved, and in patients with connective tissue syndromes such as Marfan syndrome, the mitral annulus is usually dilated, sometimes calcified, and does not decrease its circumference by the usual 30 percent during LV systole. The hemodynamic effects of mild to moderate MR are similar to those from other causes of MR.

Many studies suggest an increased prevalence of autonomic nervous system dysfunction in patients with primary MVP. In 1979, Gaffney et al.[31] reported a reduced heart rate slowing with intravenous phenylephrine and an abnormal diving reflex heart rate response in patients with MVP as compared with age-matched controls. Patients with MVP had a lesser lower extremity pooling of blood in response to lower body negative pressure. Increased vagal tone and prolonged QT intervals on the electrocardiogram (ECG) are more common in patients with MVP. Measurements of serum and 24-h urine epinephrine and norepinephrine levels are often increased in patients with symptomatic MVP as compared with controls.[32] Patients with MVP often have an increased heart rate and contractility response to intravenous isoproterenol.[33] An increased incidence of high-affinity beta receptors in the lymphocytes of patients with MVP has been reported, as well as greater than usual increases in cyclic adenosine monophosphate with isoproterenol stimulation as compared with normal individuals.[33] Patients with MVP often have postural phenomena such as orthostatic tachycardia and hypotension. Low intravascular volume and/or an abnormality in the renin-aldosterone axis may contribute to the orthostatic changes.[7,34]

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Chapter 58: MITRAL VALVE PROLAPSE SYNDROME

ASSOCIATED CONDITIONS

Tricuspid valve prolapse, with similar interchordal hooding and histologic evidence of mucopolysaccharide proliferation and collagen dissolution, occurs in about 40 percent of patients with MVP.[6] Pulmonic valve prolapse and aortic valve prolapse occur in approximately 10 and 2 percent of patients with MVP, respectively.[6] The frequent findings of thoracic skeletal abnormalities in patients with MVP were noted earlier. There is an increased incidence of secundum atrial septal defect in patients with MVP and an increased incidence of MVP in patients with atrial septal defects that cannot be explained by a chance occurrence and does not represent only stretching of a patent fossa ovalis (see also Chaps. 63 and 64). An increased incidence of left-sided atrioventricular bypass tracts and supraventricular tachycardias also occurs in patients with MVP.[6,35]

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Chapter 58: MITRAL VALVE PROLAPSE SYNDROME

CLINICAL MANIFESTATIONS

Symptoms

The diagnosis of MVP is most commonly made by cardiac auscultation in asymptomatic patients or by echocardiography being performed for some other purpose. The patient may be evaluated because of a family history of cardiac disease or occasionally may be referred because of an abnormal resting ECG. Some patients consult their physicians because of one or more of the common symptoms that occur in patients with this syndrome. The most common presenting complaint is *palpitation*. The source of palpitation is usually ventricular premature beats, but various supraventricular arrhythmias are also frequent, and the most common sustained tachycardia is paroxysmal reentry supraventricular tachycardia (see Chap. 24). Ventricular tachycardia occurs in some patients, and others have had symptomatic bradyarrhythmias. Palpitation is often reported by patients at a time when continuous ambulatory ECG recordings show no arrhythmias.

Chest pain is a frequent complaint in patients with MVP. It is atypical in most patients without coexisting ischemic heart disease and rarely resembles classic angina pectoris. Occasionally, it is recurrent and can be incapacitating. The etiology of the chest pain is unknown; sometimes it may represent true myocardial ischemia produced by abnormal tension on the papillary muscles and supporting ventricular wall by the prolapsing mitral leaflets.[36] Coronary artery spasm has been reported in patients with MVP, but it is unlikely to be the cause of most episodes of atypical chest pain.[37]

Dyspnea and *fatigue* are frequent symptoms in patients with MVP, including many without severe MR. Objective exercise testing often fails to show impaired exercise tolerance, and some patients exhibit distinct episodes of hyperventilation. Neuropsychiatric complaints occur in certain patients with MVP. Some have panic attacks (see Chap. 80), and others have frank manic-depressive syndromes. Transient cerebral ischemic episodes occur with increased incidence in patients with MVP, and some develop stroke syndromes.[38-42] One recent study showed no association between MVP and stroke.[43] Reports of amaurosis fugax, homonymous field loss, and retinal artery occlusion have been made; occasionally, the visual loss persists.[44] These signs likely are due to embolization of platelets and fibrin deposits that occur on the atrial side of the mitral valve leaflets.[45] *It is important to note that both MVP and panic attacks occur relatively frequently. Accordingly, the occurrence of the two syndromes in the same individual would be expected to occur frequently by chance, rather than panic attacks necessarily being part of the primary MVP syndrome.*

Physical Examination

The presence of thoracic skeletal abnormalities may suggest the diagnosis of MVP, the most common being scoliosis, pectus excavatum, straightened thoracic spine, and narrowed anteroposterior diameter of the chest.[16] Some patients with MVP may show signs, such as arachnodactyly, more typical of Marfan syndrome.

The principal cardiac auscultatory feature of this syndrome is the midsystolic click, a high-pitched sound of short duration (see Chap. 10). The click may vary considerably in intensity and location in systole according to LV loading conditions and contractility. It results from the sudden tensing of the mitral valve apparatus as the leaflets prolapse into the left atrium during systole. Multiple systolic clicks may be generated by different portions of the mitral leaflets prolapsing at varying times during systole.[46] The major differentiating feature of the midsystolic click of MVP from that due to other causes (e.g., aneurysm of the ventricular septum, atrial myxomas, or pericarditis) is that its timing during systole may be altered by maneuvers that change hemodynamic conditions (Table 58-2).

Table 58-2: Response of the Murmur of Mitral Valve Prolapse to Interventions

Intervention	Timing	Intensity
Standing upright	←	↑
Recumbent	→	↓ or 0
Squatting	→	↓ or 0
Hand-grip	←	±
Valsalva	←	±
Amyl nitrite	±	↑

NOTE: ↑ = increase; ↓ = decrease; 0 = no change; ± = variable; ← = earlier; → = later.

The midsystolic click is frequently followed by a late-systolic murmur, usually medium- to high-pitched and most audible at the apex. Occasionally, the murmur has a musical or honking quality. The character and intensity of the murmur also vary under certain conditions, from brief and almost inaudible to holosystolic and loud (Fig. 58-3).

Dynamic auscultation is often useful for establishing the clinical diagnosis of the MVP syndrome.[21] Changes in the LV end-diastolic volume lead to changes in the timing of the midsystolic click and murmur. When end-diastolic volume is decreased, the critical volume is achieved earlier in systole, and the click-murmur complex occurs shortly after the first heart sound (Fig. 58-4). In general, any maneuver that decreases the end-diastolic LV volume, increases the rate of ventricular contraction, or decreases the resistance to LV ejection of blood causes the MVP to occur early in systole, and the systolic click and murmur to move toward the first heart sound (see Table 58-2). By contrast, any maneuver that augments the volume of blood in the ventricle, reduces myocardial contractility, or increases LV afterload lengthens the time from the onset of systole to the initiation of MVP, and the systolic click and/or murmur move toward S_2. Maneuvers causing the click and/or murmur to occur earlier in systole include standing from the supine position, submaximal isometric handgrip exercise, the Valsalva maneuver, and amyl nitrite inhalation. Those which cause the click and murmur to move toward S_2 include squatting from the upright position and maneuvers that slow the heart rate.

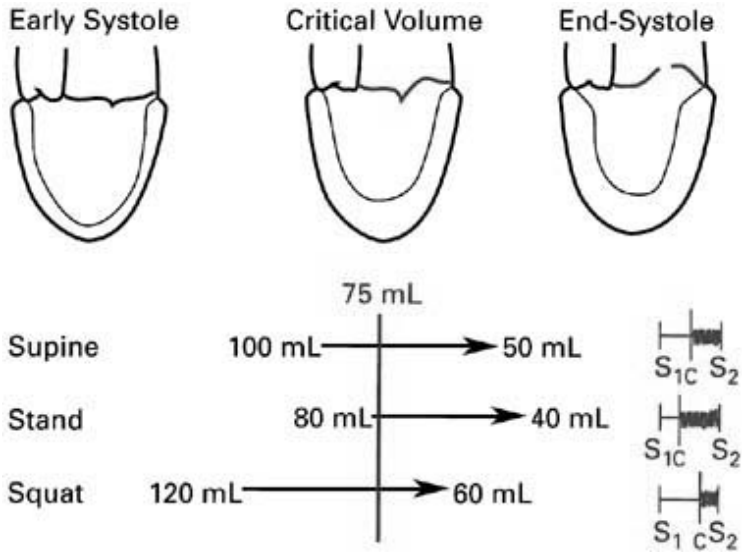

Figure 58-4: The effect of LV volume on the timing of MVP and the accompanying murmur. In the upper panel, three phases of LV systole are illustrated. In early systole, there is coaptation of the leaflets and no prolapse; when a critical ventricle volume of 75 mL is reached, valve prolapse commences and progresses until the end of systole. In the lower panel, three body positions are indicated; the corresponding change in volume and timing of the click-murmur are shown. The critical volume for prolapse remains constant. When the critical volume occurs earlier, the onset of the click-murmur is earlier. When the critical volume occurs later, the onset of the click-murmur is later. (From Crawford MH, O'Rourke RA. In: Isselbacher KJ et al., eds. *Harrison's Principles of Internal Medicine*, 9th ed. New York: McGraw-Hill; 1980:91-105. Reproduced with permission from the publisher, editors, and authors.)

Electrocardiogram

The ECG is usually normal in patients with MVP. The most common abnormality noted is the presence of ST-T-wave depression or T-wave inversion in the inferior leads (III, aV_F)[47] (Fig. 58-5). These changes may reflect ischemia of the inferior wall due to traction on the posteromedial papillary muscle by the prolapsing mitral leaflets. Sometimes ST-T-wave changes are present only during interventions that induce prolapse earlier in systole, as discussed earlier. More unusual electrocardiographic changes include prominent U waves, peaked T waves in the midprecordial leads, and prolongation of the QT interval.

MVP is associated with an increased incidence of false-positive exercise electrocardiographic results in patients with normal coronary arteries, especially females. Myocardial perfusion imaging with thallium or technetium sestamibi has been useful for differentiating false from true abnormal exercise electrocardiographic findings in patients with MVP (see Chap. 16).

Although arrhythmias may be observed on the resting ECG or during treadmill or bicycle exercise, they are detected more reliably by continuous ambulatory electrocardiographic recordings (see Chap. 13). The reported incidence of documented arrhythmias is higher in patients with MVP, ranging from 40 to 75 percent.[48] Most of the arrhythmias detected, however, are not life-threatening. Patients with ST-T-wave changes in the inferior electrocardiographic leads appear to have a higher incidence of serious ventricular arrhythmias on ambulatory recordings.[20]

Echocardiography

Echocardiography (see Chap. 13) is the most useful noninvasive test for defining MVP. The M-mode echocardiographic definition of MVP includes 2 mm or more of posterior displacement of one or both leaflets or holosystolic posterior "hammocking" of more than 3 mm (see Fig. 58-3). On 2-D echocardiography, systolic displacement of one or both mitral leaflets, particularly when they coapt on the LA side of the annular plane, in the parasternal long-axis view indicates a high likelihood of MVP[49] (see Fig. 58-5). There is disagreement concerning the reliability of an echocardiographic diagnosis of

MVP when observed only in the apical four-chamber view. The diagnosis of MVP is even more certain when the leaflet thickness is greater than 5 mm during ventricular diastole. Leaflet redundancy is often associated with an elongated mitral annulus and elongated chordae tendineae. On Doppler velocity recordings, the presence or absence of MR is an important consideration, and MVP is more likely when the MR is detected as a high-velocity jet midway or more posterior in the left atrium.[29]

At present, there is no consensus on the 2-D echocardiographic criteria for MVP. Since echocardiography is a tomographic cross-sectional technique, no single view should be considered diagnostic. The parasternal long-axis view permits visualization of the medial aspect of the anterior mitral leaflet and middle scallop of the posterior leaflet. If the findings of prolapse are localized to the lateral scallop in the posterior leaflet, they would be best visualized by the apical four-chamber view.[49,50] All available echocardiographic views should be used, with the provision that anterior leaflet billowing alone in the four-chamber apical view is not evidence of prolapse; however, a displacement of the posterior leaflet or the coaptation point in any view including the apical views suggests the diagnosis of prolapse. The echocardiographic criteria for MVP should include structural changes such as leaflet thickening, redundancy, annular dilatation, and chordal elongation.

Patients with echocardiographic criteria for MVP but without evidence of thickened/redundant leaflets or definite MR are more difficult to classify. If such patients have auscultatory findings typical of MVP, the echocardiogram confirms the diagnosis. On the other hand, a patient with typical auscultatory findings but a negative echocardiogram likely also has MVP; in the past, as many as 10 percent of patients with MVP have had a nondiagnostic echocardiographic study. Currently, this percentage is lower because of more careful and complete echocardiographic studies. In clinical practice, a false diagnosis of MVP occurs too frequently. The use of echocardiography as a screening test for MVP in patients with and without symptoms who have no systolic click or murmur on serial, carefully performed auscultatory examinations *is not recommended*. The likelihood of finding a prolapsing mitral valve in such patients is extremely low. Most patients with or without symptoms who have negative dynamic cardiac auscultation and "mild mitral valve prolapse" by echocardiography should not be diagnosed as having MVP. Recommendations for echocardiography in MVP are listed in Table 58-3.[51]

Table 58-3: Recommendations for Echocardiography in Mitral Valve Prolapse

Indication	Class
1. Diagnosis, assessment of hemodynamic severity of MR, leaflet morphology, ventricular compensation in patients with physical signs of MVP.	I
2. To exclude MVP in patients who have been given the diagnosis where there is no clinical evidence to support the diagnosis.	I
3. To exclude MVP in patients with first-degree relatives with known myxomatous valve disease.	IIa
4. Risk stratification in patients with physical signs of MVP with no or mild regurgitation.	IIa
5. To exclude MVP in patients in the absence of physical findings suggestive of MVP a positive family history.	III
6. Routine repetition of echocardiography in patients with MVP with no MR and no changes in clinical signs or symptoms.	III

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a proce-dure or treatment.

Class IIa: Weight of evidence/opinion is in favor ofusefulness/efficacy.

Class IIb: Usefulness efficacy is less well established byevidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

SOURCE: From ACC/AHA clinical practice guidelines for valvular heart disease. *J Am Coll Cardiol* 1998; 32:1486-1588.

Echocardiography is useful for defining LA size, LV size and function, and the extent of mitral leaflet redundancy, as well as for detecting associated lesions such as secundum atrial septal defect. Doppler echocardiography is helpful for the detection and semiquantitation of MR as well. Serial echocardiograms are often useful for following patients with murmurs, especially holosystolic murmurs, since quantitation of MR by examination alone is more difficult. In a carefully performed study comparing auscultatory findings with echocardiographic results in patients with clinical evidence of MVP, the amount of billowing of one or both mitral leaflets into the left atrium, the level of the leaflets' coaptation point, and the presence or absence of moderate or severe MR were each important considerations in deciding on the likelihood of MVP.[29]

Chest Roentgenogram

Posteroanterior and lateral chest x-ray films usually show normal cardiopulmonary findings. The skeletal abnormalities described earlier can be seen.[19] When severe MR is present, both LA and LV enlargement often results. Various degrees of pulmonary venous congestion are evident when left-sided heart failure results. Acute chordal rupture with a sudden increase in the amount of MR may present as pulmonary edema without obvious LV or LA dilatation. Calcification of the mitral annulus may be seen, particularly in adults with Marfan syndrome (see Chap. 12).

Myocardial Perfusion Scintigraphy

Exercise myocardial perfusion imaging with thallium or technetium sestamibi has been recommended as an adjunct to exercise ECG for determining the presence or absence of coexistent myocardial ischemia in patients with MVP.[52] Most MVP patients *with clinical evidence of CAD* have an abnormal exercise scintigram. On the other hand, a negative scintigram in these patients does not exclude ischemia as the basis for the chest pain, nor does it completely exclude CAD as the etiology (see Chap. 16).

Cardiac Catheterization

Cardiac catheterization is rarely used as a diagnostic technique for MVP. Also, contrast ventriculography is unnecessary for determining LV function because it usually can be quantitated by 2-D echocardiography or radionuclide ventriculography. While contrast cineventriculography is often useful for assessing the severity of MR, cardiac catheterization and angiography are used most commonly in patients with MVP to exclude the possibility of CAD.

Intracardiac pressures and cardiac output are usually normal in uncomplicated MVP; however, these measurements become progressively more abnormal as MR becomes more severe.

LV cineangiography usually confirms the presence of prolapse of the mitral valve.[5,8] The right anterior oblique projection is best for observing prolapse of the three scallops of the posterior leaflet. The left anterior oblique view is necessary for the adequate evaluation of prolapse of the anterior leaflet.

LV wall motion is usually normal in patients with primary MVP, but some patients show abnormal

contraction patterns in the absence of CAD.[5,27] These contraction abnormalities usually represent indentation of the left ventricle at the point of attachment of the papillary muscles; it is thought to be due to abnormal traction on the papillary muscles and buckling of the ventricular wall. Patients with the most severe prolapse more commonly exhibit misshapen ventricular cavities during systole, and wall motion abnormalities frequently disappear after successful mitral valve replacement or repair.[27]

Coronary arteriography is usually normal in patients with primary MVP, and no congenital anomalies of the coronary vessels have been associated with this syndrome.

Electrophysiologic Testing

The indications for electrophysiologic testing in a patient with MVP are similar to those in other patients (i.e., recurrent unexplained syncope, sudden death survivors, symptomatic complex ventricular ectopy, and the presence of the preexcitation syndromes) (see Chap. 26). Upright tilt studies with monitoring of blood pressure and rhythm may be valuable in patients with light-headedness or syncope and in diagnosing autonomic dysfunction (see Chap. 32).

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Chapter 58: MITRAL VALVE PROLAPSE SYNDROME

NATURAL HISTORY, PROGNOSIS, AND COMPLICATIONS

In most patient studies, the MVP syndrome is associated with a benign prognosis[6,53-60] (Fig. 58-6). The age-adjusted survival rate for both males and females with MVP is similar to that in patients without this common clinical entity. The gradual progression of MR in patients with mitral prolapse, however, may result in progressive dilatation of the left atrium and ventricle. LA dilatation often results in atrial fibrillation, and moderate to severe MR eventually results in LV dysfunction and the development of congestive heart failure. Pulmonary hypertension may occur with associated right ventricular dysfunction. In some patients with an initially prolonged asymptomatic interval, the entire process may enter an accelerated phase as a result of LA and LV dysfunction, atrial fibrillation, and in certain instances, ruptured mitral valve chordae. The latter occurs more commonly in males and with increasing age.[6,7]

Several long-term prognostic studies suggest that complications occur most commonly in patients with a mitral systolic murmur, thickened redundant mitral valve leaflets, or increased LV or LA size[30,57,58,62] (Fig. 58-7 and Table 58-4).

In a prospective follow-up study of 237 asymptomatic or minimally symptomatic patients with MVP documented by echocardiography, sudden death occurred in 6 patients.[55] In a multivariant analysis of the echocardiographic findings, the presence or absence of redundant mitral valve leaflets by M-mode echocardiography was the only variable associated with sudden death. Ten patients sustained a cerebral embolic event, six of whom were in atrial fibrillation with LA enlargement. Marks et al.[49] confirmed these data in a retrospective 2-D echocardiographic study from 456 patients with MVP. Two groups of patients were compared; those with thickening and redundancy of the mitral valve leaflet and those without leaflet thickening. Complications or a history of complications was more prevalent in those with leaflet thickening and redundancy compared with those without leaflet thickening. The incidence of stroke, however, was similar in the two groups. Long-term follow-up studies in patients with MVP associated with a floppy, myxomatous mitral valve permit several conclusions.[7] Serious complications occur in some patients with MVP, predominantly in those with diagnostic auscultatory findings. Also, redundant mitral valve leaflets and increased LV size are associated with a frequency of serious complications. Finally, men and those over 50 years of age are at increased risk of complications, including severe MR requiring surgery.

Sudden death is the least common but obviously the most severe complication of MVP (Table 58-5). While infrequent, the highest incidence of sudden death has been reported in the familial form of MVP. Some of these patients have been noted to have QT-interval prolongation. Also, patients with MVP with severe autonomic dysfunction and excessive vagotonia resulting in bradyarrhythmias and asystole have been reported.[63,64] Therefore, arrhythmias are likely to be the usual cause of sudden death in patients with MVP, so it seems prudent to limit ambulatory electrocardiographic recordings to those patients at highest risk. Many believe that patients with electrocardiographic ST-T-wave changes are more likely to have complex ventricular arrhythmias.[6,7] Certainly, any patients with symptoms suggestive of arrhythmia or who have arrhythmias noted during physical examination or on the resting ECG should be evaluated further (see Chap. 24).

Table 58-5: Mitral Valve Complications in 102 Hearts with Mitral Valve Prolapse

	No.	Percent
Sudden death	0	0
Primary rupture of chordae	7	7
Bacterial endocarditis	7	7
Mitral valve regurgitation	18	18
Primary rupture of chordae	(7)	-
Bacterial endocarditis	(4)	-
Severe prolapse	(4)	-
Entrapped chordae	(3)	-
Fibrin deposits	4	4

SOURCE; Modified from Lucas RV Jr, Edwards JE. The floppy mitral valve. *Curr Probl Cardiol* 1982; 7:1-48.

Infective endocarditis is a serious complication of MVP, and MVP is the leading predisposing cardiovascular diagnosis in most series of patients reported with endocarditis.[6,7,65] Since the absolute incidence of endocarditis is extremely low for the entire MVP population, there has been much discussion concerning the risk of endocarditis in MVP.[66] While there is general agreement that MVP patients with murmurs and/or thickened redundant valves confirmed by echocardiography or cineangiography should receive antibiotic prophylaxis, some authorities state that patients with isolated systolic clicks and no murmurs do not need antibiotic prophylaxis for endocarditis.[67] The dynamic nature of MVP, with variable physical findings on different examinations, makes it difficult to make judgments on the basis of the presence or absence of a systolic murmur. With the increasing use of color-flow echo-Doppler studies, MR often has been observed in patients in whom no murmur is heard.[68] Recommendations for antibiotic endocarditis prophylaxis for patients with MVP undergoing procedures associated with bacteremia are listed in Table 58-6.

Table 58-6: Recommendations for Antibiotic Endocarditis Prophylaxis for Patients with Mitral Valve Prolapse Undergoing Procedures Associated with Bacteremia

Indication	Class
1. Patients with characteristic systolic click-murmur complex.	I
2. Patients with isolated systolic click and echo evidence of MVP and MR.	I
3. Patients with isolated systolic click, echo evidence of high-risk MVP.	IIa
4. Patients with isolated systolic click and no or equivocal evidence of MVP.	III

SOURCE: From ACC/AHA guidelines for the clinical application of echocardiography. *Circulation* 1997; 95:1686-1744.

As indicated earlier, progressive MR occurs frequently in patients with long-standing MVP. Fibrin emboli are responsible in some patients for visual problems consistent with involvement of the ophthalmic or

posterior cerebral circulation. Several studies have indicated an increased likelihood of cerebral vascular accidents of various types in patients under age 45 who have MVP than would have been expected in a similar population without MVP. Therefore, it has been recommended that antiplatelet drugs such as aspirin be administered to patients who have MVP and suspected cerebral nervous system emboli; however, neither antiplatelet drugs nor anticoagulants should be prescribed routinely for patients with MVP because the incidence of embolic phenomena is very low. Recommendations for aspirin and oral anticoagulants in MVP are listed in Table 58-7. *It is important to avoid the incorrect diagnosis of MVP syndrome. This mistake is especially likely to occur in patients with neuropsychiatric symptoms, in whom an incorrect diagnosis of MVP is made from the ECG. Such an improper diagnosis can form the foundation of a chronic, often disabling cardiac neurosis. Even if the diagnosis of MVP is properly made, it is not necessarily correct to attribute neuropsychiatric symptoms to the MVP* (see also Chap. 80).

Table 58-7: Recommendations for Aspirin and Oral Anticoagulants in Mitral Valve Prolapse

Indication	Class
1. Aspirin therapy for cerebral transient ischemic attacks (TIAs).	I
2. Warfarin therapy for patients in atrial fibrillation with age ≥65 yr, hypertension, MR murmur, or history of heart failure.	I
3. Aspirin therapy for patients in atrial fibrillation <65 years old with no history of MR, hypertension, or heart failure.	I
4. Warfarin therapy for poststroke patients.	I
5. Warfarin therapy patients for TIAs despite aspirin therapy.	IIa
6. Aspirin therapy in poststroke patients with contraindications to anticoagulants.	IIa
7. Aspirin therapy for patients in sinus rhythm with echocardiographic evidence of high-risk MVP	IIb

SOURCE: From ACC/AHA guidelines for the clinical application of echocardiography. *Circulation* 1997; 95:1686-1744.

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Chapter 58: MITRAL VALVE PROLAPSE SYNDROME

TREATMENT

The majority of patients with MVP are asymptomatic and lack the high-risk profile described earlier. These patients with mild or no symptoms and findings of milder forms of prolapse should be assured of a benign prognosis. A normal lifestyle and regular exercise are encouraged.[5,7] For most patients in whom the *diagnosis of MVP is definite*, we recommend antibiotic prophylaxis for the prevention of infective endocarditis while undergoing procedures associated with bacteremia. Patients with MVP and palpitation associated with sinus tachycardia or mild tachyarrhythmias and those with chest pain, anxiety, or fatigue often respond to therapy with beta blockers.[5,7,69] In many cases, however, the cessation of catecholamine stimulants such as caffeine, alcohol, cigarettes, and certain drugs may be sufficient to control symptoms.

Orthostatic symptoms are best treated with volume expansion, preferably by liberalizing fluid and salt intake. Mineralocorticoid therapy may be needed in severe cases, and wearing support stockings may be beneficial.[7] In sudden death survivors and those patients with symptomatic complex arrhythmias, specific antiarrhythmic therapy should be guided by monitoring techniques, including electrophysiologic testing when indicated[7] (see Chap. 26).

Daily aspirin therapy (80-325 mg/day; see Table 58-7) is recommended for MVP patients with documented focal neurologic events. Such patients also should avoid cigarettes and oral contraceptives. Some clinicians use long-term anticoagulant therapy with warfarin in poststroke patients with prolapse, particularly when symptoms occur on aspirin therapy (see also Chap. 89).

Restriction from competitive sports is recommended when moderate LV enlargement, LV dysfunction, uncontrolled tachyarrhythmias, long QT interval, unexplained syncope, prior sudden death survival, or aortic root enlargement is present, individually or in combination.[7]

The familial occurrence of MVP should be explained to the patient and is particularly important in those with associated disease, who are at greater risk for complications. Screening relatives can uncover high-risk individuals and potentially prevent some complications. There is no contraindication to pregnancy based on the diagnosis of MVP alone.

Patients with severe MR with symptoms and/or impaired LV systolic function require cardiac catheterization studies and evaluation for mitral valve surgery.[70] The thickened, redundant mitral valve often can be repaired rather than replaced, with a low operative mortality and excellent long-term results.[71-79] Follow-up studies also suggest lower thromboembolic and endocarditis risk than with prosthetic valves.

Asymptomatic patients with MVP and no significant MR can be evaluated clinically every 2 to 3 years. Echocardiography has been suggested every 5 years in such patients to help determine the natural history and the likelihood of complications. Patients with MVP who have high-risk characteristics, including those with moderate to severe MR, should be followed more frequently, even if no symptoms are present.

Surgical Considerations

Management of the patient with MVP may require valve surgery, particularly in those patients who develop a flail mitral leaflet due to rupture of chordae tendineae or their marked elongation.[79] Most such valves can be repaired successfully by surgeons experienced with mitral valve repair, especially when the posterior leaflet valve is predominantly affected. Symptoms of heart failure, the severity of MR, the presence or absence of atrial fibrillation, LV systolic function, LV end-diastolic and end-systolic volumes, and pulmonary artery pressure (rest and exercise) all influence the decision to recommend mitral valve surgery. Recommendations for surgery in patients with MVP and MR are the same as for those with other forms of nonischemic severe MR and include class III-IV symptoms, LV ejection fraction less than 60 percent, and/or marked increases in LV end-diastolic and end-systolic volumes. If mitral repair is likely to be successful, severe MR with class II symptoms or atrial fibrillation may be an appropriate reason for surgical referral.[51]

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Chapter 58: MITRAL VALVE PROLAPSE SYNDROME

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Chapter 58: MITRAL VALVE PROLAPSE SYNDROME

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Chapter 58: MITRAL VALVE PROLAPSE SYNDROME

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Part 9: VALVULAR HEART DISEASE
Chapter 59:

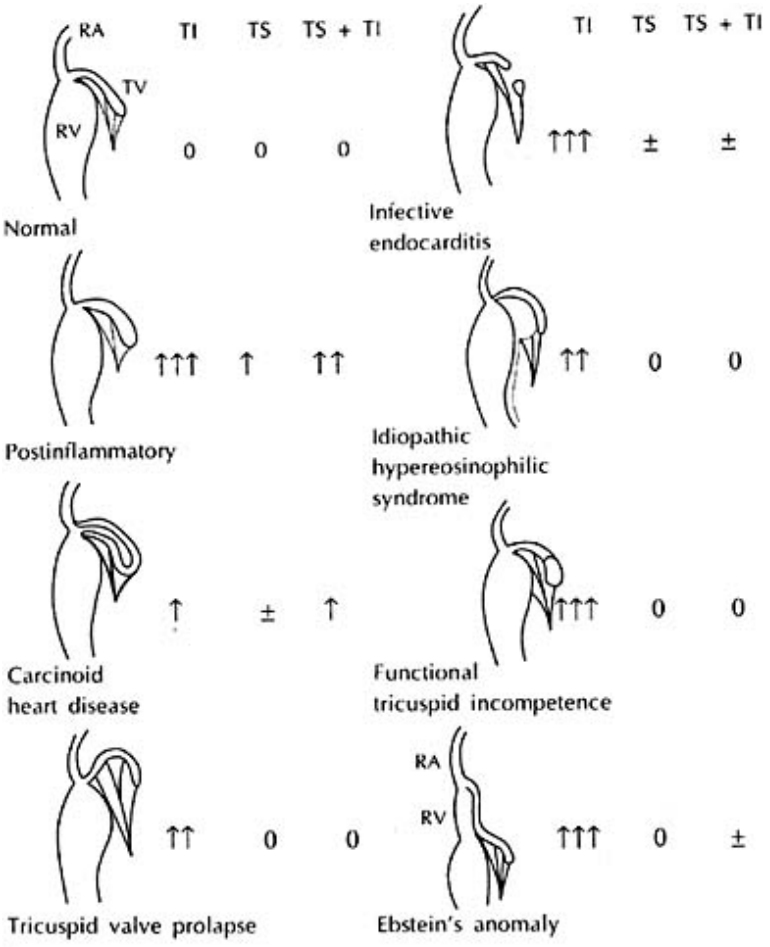
TRICUSPID VALVE, PULMONIC VALVE, AND MULTIVALVULAR DISEASE

Author: Robert A. O'Rourke

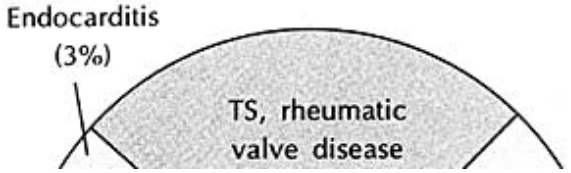
DEFINITION, ETIOLOGY, AND PATHOLOGY

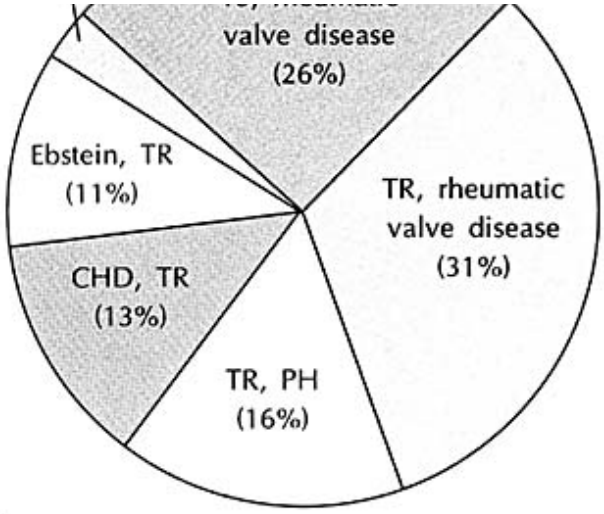
Tricuspid Valve Disease

Tricuspid valve dysfunction can occur with normal or abnormal valves.[1] When normal tricuspid values develop dysfunction, the resulting hemodynamic abnormality is almost always pure regurgitation. Tricuspid regurgitation (TR) occurs when the tricuspid valve allows blood to enter the right atrium (RA) during a right ventricular (RV) contraction. Tricuspid stenosis (TS) results from obstruction to diastolic flow across the valve during filling of the RV. A diagrammatic illustration of tricuspid valve disease and the prevalence of various pathologic etiologies are shown in Fig. 59-1*A* and *B*.



A





B

Figure 59-1: *A.* Tricuspid valve (TV) disease. Diagrammatic illustration of TV; TI, tricuspid insufficiency; TS, tricuspid stenosis; RA, right atrium; RV, right ventricle. *B.* Pathologic findings in TV. TR, tricuspid regurgitation; TS, tricuspid stenosis. [From Virmani R et al. Pathology of valvular heart diseases. In: Rahimtoola SH, ed. Philadelphia: Mosby (Current Medicine, Inc.), 1997:116, with permission.]

Diseases causing TR are more numerous than those causing TS. It is important to note that the normal tricuspid valve often does not completely coapt in systole, as is shown by the frequent occurrence of TR jets on Doppler ultrasound. Usually the volume of regurgitant blood is so small that the TR is silent; this finding occurs in 24 to 96 percent of normal individuals by Doppler ultrasound and thus must be considered a variant of normal.[2-4] Pathologic TR is most commonly due to diseases that cause RV dilatation and failure;[5] left ventricular (LV) failure and/or pulmonary hypertension can result in tricuspid regurgitation (Table 59-1). Primary diseases of the tricuspid valve apparatus, which includes the tricuspid annulus, the leaflets, the chordae, the papillary muscle, and the RV wall, also cause TR (Table 59-1).[6-8] The most common etiology of isolated TR is infective endocarditis in drug addicts[9] (see Chap. 73). Less common causes include myocardial infarction, trauma, carcinoid, leaflet prolapse, and such congenital abnormalities as atrial septal defect and Ebstein's anomaly[10-15] (see Chap. 63). TR also occurs in patients with rheumatoid arthritis, radiation therapy, and Marfan's syndrome.[6] Primary involvement of the tricuspid valve due to rheumatic fever results in TS, usually in association with TR (Fig. 59-2).

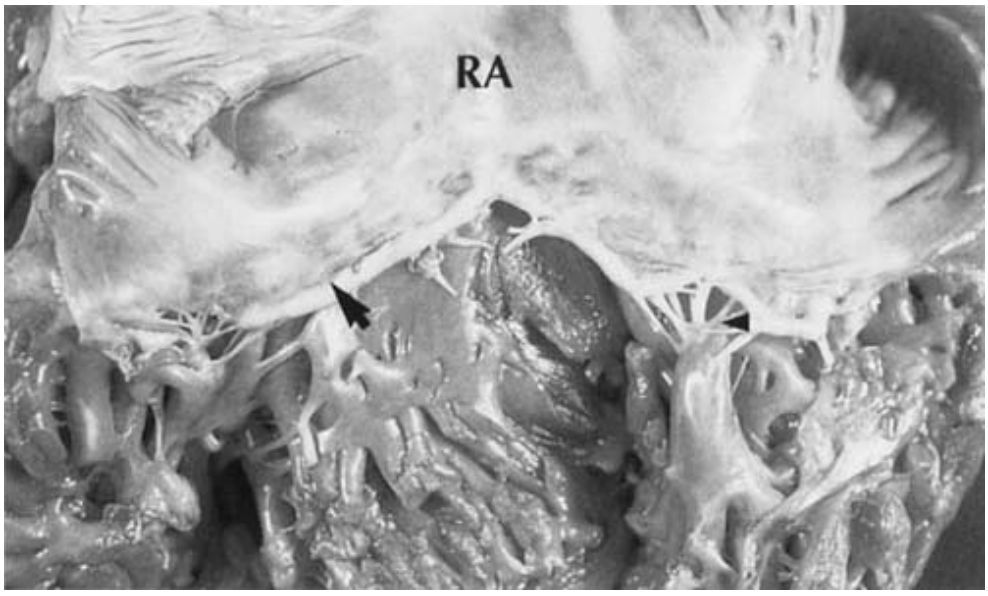


Figure 59-2: Heart displaying a tricuspid valve with fused, shortened chordae and rolled, thickened, fibrotic edge, consistent with chronic rheumatic heart disease. Isolated rheumatic TR or TS is very rare; it occurs almost always in the presence of concomitant MS. RA, right atrium. [From Farb A et al. Anatomy and pathology of the right ventricle (including acquired tricuspid and pulmonic valve disease). *Card Clin North Am* 1993; 10:1-2, with permission.]

Table 59-1: Diseases Causing Acquired Tricuspid Valve Regurgitation

DISEASE CAUSING PULMONARY HYPERTENSION
❍ All LV diseases with LV failure
❍ Mitral stenosis or mitral regurgitation
❍ Pulmonary venous obstruction
❍ Diseases causing an increase in pulmonary vascular resis- tance
❍ Primary pulmonary hypertension
❍ Acquired pulmonary vascular disease (atrial septal defects), ventricular septal defects, and patent ductus arteriosus
❍ Intrinsic pulmonary disease (chronic obstructive pulmonary disease, pulmonary fibrosis, and pulmonary resection)
❍ Collagen vascular diseases
❍ Pulmonary emboli, acute and chronic
PRIMARY DISEASES OF THE TRICUSPID VALVE
❍ Rheumatic heart disease
❍ Rheumatoid arthritis
❍ Trauma, penetrating and nonpenetrating
❍ Radiation therapy
❍ Carcinoid heart disease
❍ RA myxoma
❍ Infective endocarditis
❍ Eosinophilic myocarditis
❍ Prosthetic and bioprosthetic valve malfunction, including thrombosis and calcification
❍ RV myocardial infarction
❍ Myxomatous tricuspid valve (tricuspid valve prolapse)

SOURCE: Modified from Cheitlin and MacGregor,[22] with permission.

The most common cause of TS is rheumatic fever. This is usually associated with concomitant mitral stenosis (MS). Isolated TS can be seen with the carcinoid syndrome, infective endocarditis, endocardial fibroelastosis, endomyocardial fibrosis, and systemic lupus erythematosus, among other conditions[6-8] (Table 59-2). It has also been reported to occur in patients with Fabry's disease, or Whipple's disease and in patients receiving methysergide therapy.[6] Mechanical obstruction of the valve can be due to a RA myxoma, tumor metastases, and thrombi in the RA, each resulting in the hemodynamic abnormalities of TS.[16,17] In addition, RV inflow tract obstruction can result from thrombosis endocarditis, degeneration, or calcification affecting a prosthetic tricuspid valve.

Table 59-2: Diseases Causing Acquired Tricuspid Valve Stenosis

- Rheumatic heart disease (usually with mitral stenosis)
- Carcinoid heart disease
- Fabry's disease
- Whipple's disease
- Endocardial fibroelastosis
- Endomyocardial fibrosis
- Methysergide therapy
- Systemic lupus endocarditis
- RA myxoma or thrombus
- Prosthetic valve thrombosis
- Prosthetic valve infective endocarditis
- Paraprosthetic valve degeneration and calcification

SOURCE: Modified from Cheitlin and MacGregor,[22] with permission.

In rheumatic tricuspid valve disease, alterations in the valve are characterized by fibrosis, with contracture of the leaflets and commissural fusion. The former leads to TR and the latter to TS.[18] The stenotic component of rheumatic tricuspid valve disease is often minor and would go unrecognized clinically if it were not for the high flow across the valve caused by the coexistent regurgitation. Whenever the tricuspid valve is affected by rheumatic disease, there is also involvement of left-sided valves.[19] Flammang and associates observed that 9.5 percent of cases requiring surgical replacement of *both* the mitral and aortic valves also had rheumatic involvement of the tricuspid valve.[20]

Carcinoid heart disease is present in up to 53 percent of patients with malignant carcinoid tumor (usually originating in the ileum) with extensive metastases[15] (see Chap. 77). Carcinoid usually causes TR and TS and, less often, pulmonic stenosis (PS) and pulmonic regurgitation (PR).[21,22] Changes include deposits of fibrous tissue on the surfaces of these valves. Fibrous plaques can also develop on the endocardial surfaces of the RA and RV as well as on the intima of the coronary sinus and the pulmonary artery.[23] The hemodynamic effects result from the rigidity and contracture of the fibrous tissues deposited on the valves. Although TS may result, the major functional abnormality is usually TR.

The most common type of TR is the secondary type that results from the enlargement of the orifice and annulus secondary to congestive heart failure with RV dilation due to LV disease (Table 59-1). TR may diminish when the heart failure is treated successfully but can be permanent with long-standing dilatation of the RV.[24-26] In infective endocarditis, the TR results from improper coaptation of the leaflets because of interposed vegetations (Table 59-1). Major degrees of regurgitation may be due to rupture of chordae tendineae of the RV or perforation of the valve leaflets.

Until recently, myocardial infarction was not considered a common cause of TR except when secondary to chronic congestive heart failure.[27] Rare cases have been described from rupture of an RV papillary muscle.[28,29] Currently, RV infarction is being recognized more often and is frequently associated with TR, as documented by echocardiography (see Chap. 42).

Various degrees of tricuspid valve prolapse are commonly present in the general population and may occur in 3 to 54 percent in patients with mitral valve prolapse[22] (see Chap. 58). The reported incidence of *severe* TR from prolapse is low.[30]

External blunt trauma, most often in motor vehicle accidents, is a classic cause of TR. Isolated instances of rupture of a tricuspid papillary muscle have been described from external cardiopulmonary resuscitation.[31] Traumatic TR usually results from rupture of one or more of the components of the tensor apparatus, with disruption of the papillary muscle occurring more often than rupture of the chordae.[13] Less frequently, there

is a laceration of leaflet tissue.[32,33] Occasionally, traumatic TR and ruptured ventricular septum coexist[34] (Chap. 79). TR can also occur from iatrogenic trauma produced during an endomyocardial biopsy.[35,36] Mild TR often results when a pacemaker is placed across a normally functioning tricuspid valve or after extraction of permanent pacemaker leads.[37]

Tolerance to traumatic TR varies, with up to 39 years of survival reported.[38-40] Patients with rupture of a papillary muscle tend to tolerate the TR less well than do those in whom the trauma resulted in rupture of chordae.[39] Among reported cases of TR resulting from the rupture of the chordae, a traumatic etiology is more common than is infective endocarditis.[41] Primary congenital lesions of the tricuspid valve that cause regurgitation are Ebstein's malformation and valvular dysplasia, as discussed in Chap. 64.

Pulmonic Valve Disease

Acquired lesions of the pulmonic valve generally cause PR (Table 59-3). On rare occasions, an inflammatory process can create stenosis and regurgitation of the valve. Pulmonary hypertension from any cause, such as MS, chronic lung disease, or pulmonary emboli, can produce PR. Inflammatory diseases, such as endocarditis, rheumatic fever, and, rarely, tuberculosis, can result in PR.[42-45]

Table 59-3: Acquired Lesions of the Pulmonic Valve

- Pulmonary hypertension with pulmonic regurgitation
- Mitral stenosis
- Chronic lung disease
- Pulmonary emboli
- Inflammatory lesions
- Endocarditis
- Rheumatic fever
- Tuberculosis
- Tumors
- Sarcoma
- Myxoma
- Previous surgery or angioplasty for congenital lesions
- Mediastinal lesions
- Tumor
- Aneurysm
- Constrictive pericarditis
- Miscellaneous
- Carcinoid syndrome

PS is created by obstruction of systolic flow across the valve and is most commonly congenital (Fig. 59-3; see Chaps. 63 and 64). Sarcomas and myxomas can sometimes extend to the pulmonic valve, causing PS.[46] Previous cardiac surgery on a congenital pulmonic valve lesion can result in PR. The carcinoid syndrome with cardiac involvement can create mild PS and associated PR[44] (Fig. 59-4). Compression of the pulmonary artery can stimulate valvular stenosis and is rarely produced by tumor, aneurysm, or even constrictive pericarditis.

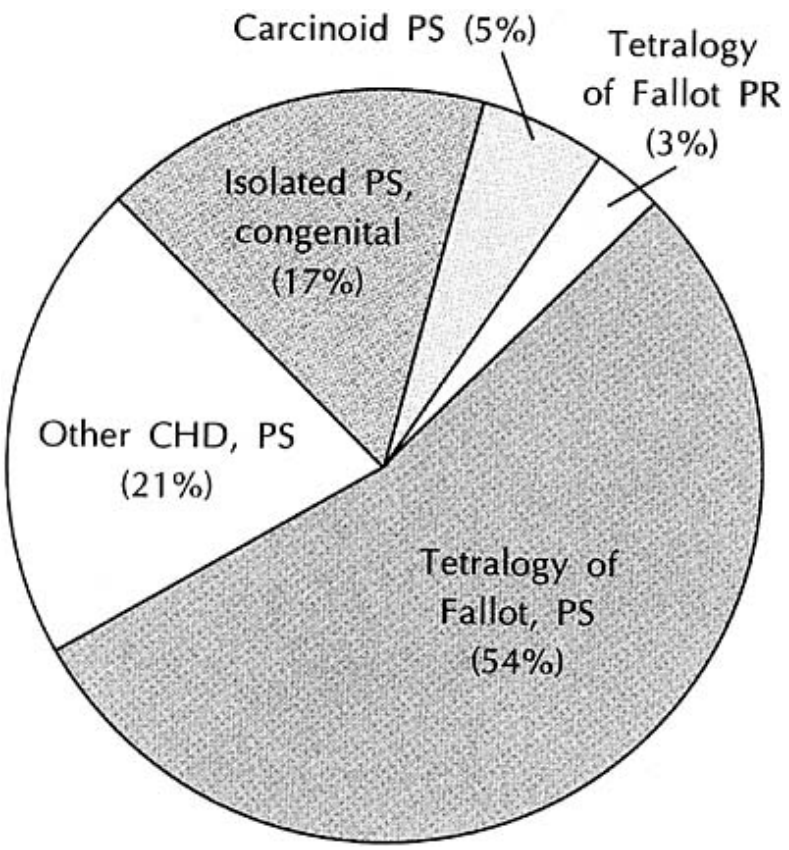


Figure 59-3: Pathologic findings in pulmonary valve (PV) replacement. CHD, congenital heart disease; PH, pulmonary hypertension; PR, pulmonary regurgitation; PS, pulmonary stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis. (Adapted from Altricher PM et al. Surgical pathology of the pulmonary valve; a study of 116 cases spanning 15 years. *Mayo Clin Proc* 1989; 64:1352-1360, with permission.)

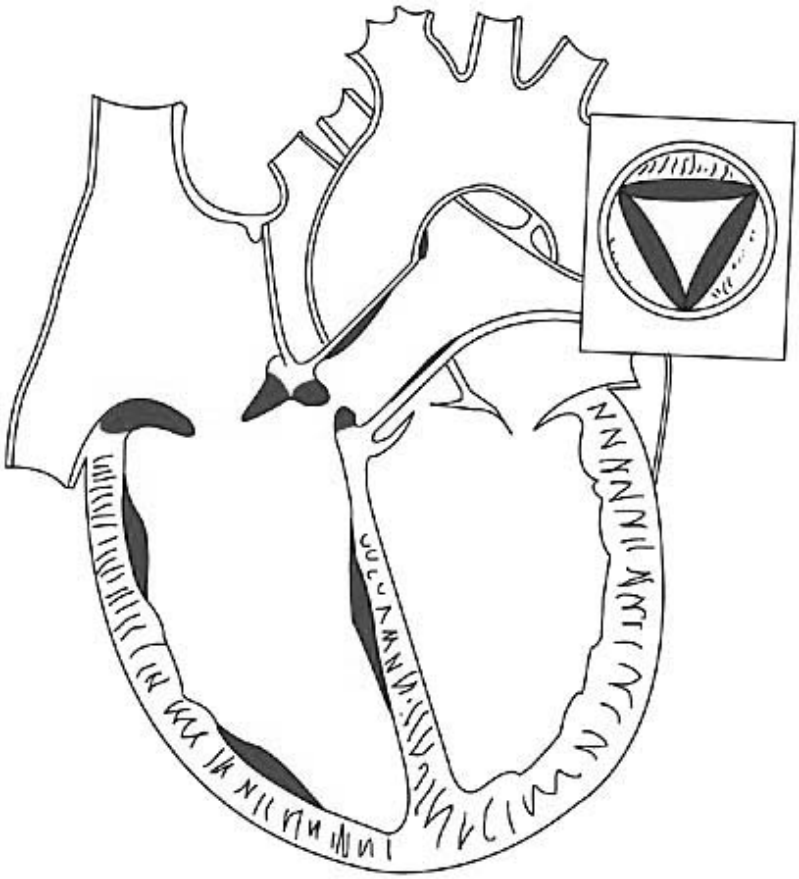


Figure 59-4: Carcinoid heart disease. The insert shows PS. The leaflets of the tricuspid valve are thickened. The valve is predominantly incompetent and causes PR. Fibrous plaques are deposited on the lining of the right ventricle and pulmonary trunk. (From Edwards JE. Effects of malignant noncardiac tumors upon the cardiovascular system. *Cardiovasc Clin* 1971; 4:282. Reproduced with permission from the publisher and author.)

Multivalvular Disease

Multivalvular disease includes mixed single valve disease [e.g., aortic stenosis (AS) plus aortic regurgitation (AR)] or combined disease affecting two or more values (e.g., MS plus TR). Rheumatic fever remains an important cause of combined disease of the mitral and aortic valves. Primary involvement of the tricuspid valve in the rheumatic process is unusual, and more commonly TR results from RV failure secondary to LV decompensation in valvular heart disease. A high prevalence of anatomic lesions involving two or more valves is present when the characteristic Aschoff body is observed at necropsy.[47] Connective tissue diseases (see Chap. 76) can affect both the aortic and the mitral valves. For example, in Marfan's syndrome mitral valve prolapse, resulting in MR, often occurs together with the frequently observed changes in the aortic valve and ascending aorta. In the aging patient, calcification can develop in the aortic valve and the mitral valve apparatus as well as in the mitral annulus. Finally, infective endocarditis of the aortic or mitral valve can extend to the adjacent valve apparatus. In an autopsy series, combined aortic and mitral valve disease was observed in 33 percent of 996 patients with rheumatic fever.[48] In a 30-year follow-up of 1042 children with a history of rheumatic fever, multiple-valve involvement became apparent in 50 percent of the individuals.[49] Bland and Jones followed 699 patients with cardiac involvement due to rheumatic fever for 20 years; 99 percent eventually exhibited aortic and mitral valve abnormalities.[50]

Rheumatic fever, myxomatous proliferation and prolapse, calcification in the aged, and infective endocarditis can impair both the aortic and mitral valves. The inflammatory process of rheumatic fever thickens and scars valve leaflets, which leads to fusion, fibrosis, and calcification (Fig. 59-5).

Myxomatous proliferation and valvular prolapse occur in the aortic, tricuspid, and pulmonic valves as well

as in the mitral valve (Fig. 59-6). Fusiform aneurysms of the aortic sinus and ascending aorta can develop in Marfan's syndrome; a dilated annulus, prolapse, ruptured chordae, and annular calcification can affect the mitral valve (Fig. 59-7). Annular dilatation, with or without prolapse, is a major cause of mitral regurgitation (MR) in Marfan's syndrome,[51] and most of the patients with Marfan's syndrome have mitral valve prolapse (see Chaps. 60 and 76).

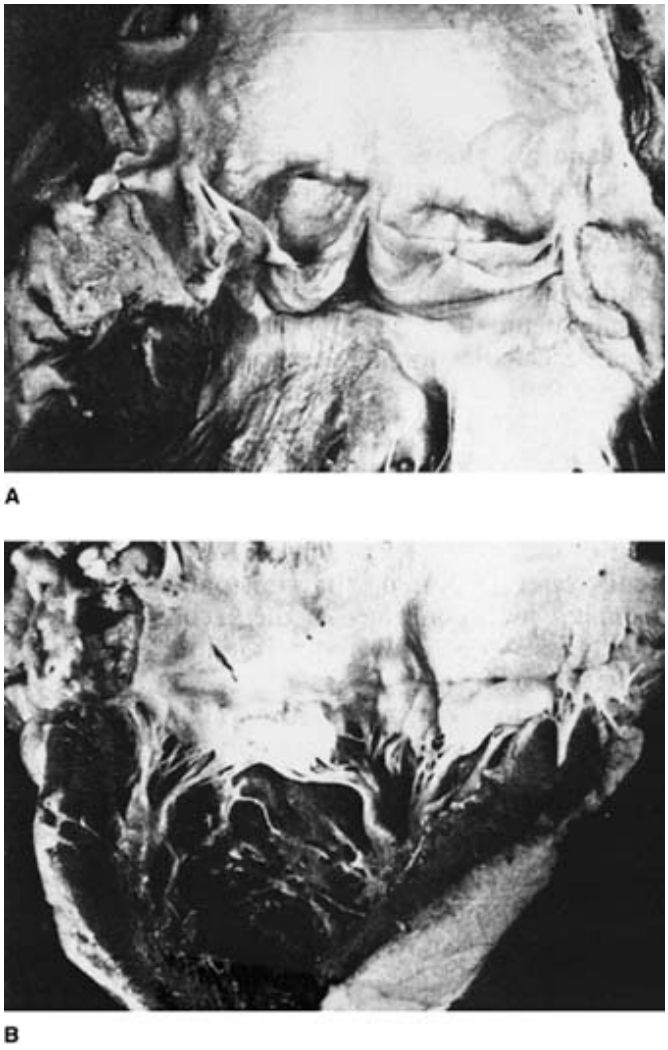
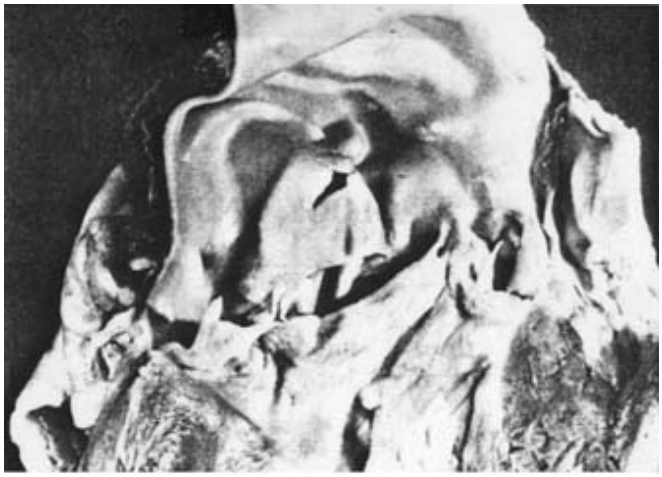


Figure 59-6: Prolapsed mitral valve and prolapsed aortic valve. *A.* Specimen of aortic valve from a 61-year-old man. The aortic valve shows redundance or prolapse of its right cusp. *B.* Specimen of mitral valve from a 73-year-old woman. The mitral valve shows prominent evidence of prolapse involving the posterior leaflet (right) and the posterior half of the anterior leaflet.



A

B

Figure 59-7: Floppy mitral valve and limited dissecting aneurysm of the ascending aorta, leading to aortic regurgitation, in a specimen from a 60-year-old man. *A.* Ascending aorta and aortic valve. The ascending aorta exhibits a laceration leading to a false channel within the aortic wall in which a hematoma is present (seen on each side of the opened aorta). Secondary distortion of the aortic valvular mechanism caused aortic regurgitation. *B.* Mitral valve, LA, and a portion of the LV. The posterior leaflet of the mitral valve (right) shows several areas of prolapse.

In aging patients, calcification can involve the aortic and mitral valves. Aortic stenosis is common, whereas mitral annular calcification usually creates regurgitation (Fig. 59-8). Infective endocarditis can extend from either the aortic or the mitral valve to the adjacent valve through the inflammatory process (Fig. 59-9).

NEXT

Last modified: September 12, 2001 .

Chapter 59: TRICUSPID VALVE, PULMONIC VALVE, AND MULTIVALVULAR DISEASE

PATHOPHYSIOLOGY

Tricuspid Valve Disease

In TR, the systolic blood flow into the RA elevates the mean RA pressure.[52] Regurgitant flow produces a prominent *cv* wave reflected through the venous system. Diastolic volume overload of the RV causes further dilatation of the RV and movement of the intraventricular septum toward the LV during diastole. RV failure further raises the mean RA and vena caval pressures and results in systemic venous congestion and signs of RV failure.[22]

TR decreases diastolic flow across the valve, elevates the RA pressure, and reduces the cardiac output.[1,53,54] With TS, there is stiffening of the valve by fibrosis and commissural fusion, both of which narrow the effective valvular orifice.[1,22] Flow from systemic veins or RA into the RV is obstructed, and a pressure gradient develops in diastole between the RA and RV. The normal area of the tricuspid valve is 7 cm^2, and impairment of RV filling occurs when the valve area is reduced to less than 1.5 cm^2. Elevation of the mean RA pressure above 10 mmHg usually results in peripheral edema. Development of atrial fibrillation produces a higher RA pressure in TS than when sinus rhythm and normal RA contraction are present. The hemodynamic abnormalities in TS can be further influenced by coexisting MS. Reduced RV flow in tricuspid valve obstruction has been proposed as a mechanism for protection against severe pulmonary hypertension.

Pulmonic Valve Disease

Pulmonic regurgitation is the most frequently acquired lesion of the pulmonic valve (Table 59-3). Regurgitation may be secondary to pulmonary hypertension or may be caused by primary abnormalities in the leaflets. PR imposes a volume overload on the RV, and if pulmonic hypertension preexists, the overload is superimposed on hypertrophied myocardium. Volume overload of the RV may cause an increase in diastolic volume of the chamber, an increase in RV stroke volume, and subsequent RV failure, resulting in TR.[1,22] Fortunately, isolated PR can usually be tolerated for a long time without cardiac decompensation.[55]

Multivalvular Disease

Multiple valve diseases affecting the mitral and aortic valves can produce a pressure overload, volume overload, or combinations of the two.[1,22] In the presence of combined valvular lesions, the pressure overload will cause concentric LV hypertrophy, even if myocardial failure develops.[1,23] An LV volume overload will result from AR and MR, and further dilatation will follow, with development of heart failure.[1,22] The combination of MS and AR usually results in a volume overload on the LV associated with LV pressure-volume work and myocardial oxygen consumption.[56,57]

Important physiologic considerations in combined valvular disease are the predominance of a single valvular lesion in altering hemodynamics and the potential failure to identify the presence of a second abnormal valve. MS produces left atrial (LA) and pulmonary venous hypertension,

with eventual pulmonary hypertension and RV failure, even though aortic stenosis may also be present. Despite the presence of MS, concomitant AS can create pressure overload and hypertrophy of the LV. When MR accompanies AS, the pressure and volume overloads create both LV dilatation and hypertrophy. LA enlargement and elevation of pulmonary artery pressure eventually accompany this condition. In regurgitation of both mitral and aortic valves, severe LV dilatation develops, accompanied by compensatory LV hypertrophy.[58] LV compliance increases in MR and AR, resulting in small elevations of end-diastolic pressure in the LV and LA for larger end-diastolic volumes.[59] Abnormalities in both early and late diastolic filling can accompany valvular regurgitation.[60]

In all combinations of aortic and mitral valve lesions, pulmonary congestion and elevated pulmonary capillary pressure usually follow significant depression of the contractile state of the LV. LA enlargement produced by either MS or MR is often associated with atrial fibrillation. Alterations in pulmonary blood flow and cardiac rhythm commonly accompany the LV pressure-volume overload in combined mitral and aortic valve disease.

TR usually accompanies RV dilatation secondary to pulmonary hypertension from any combination of mitral or aortic valve diseases. TS almost invariably is accompanied by disease of the mitral valve and can create significant elevations of the RA and central venous pressures.

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Chapter 59: TRICUSPID VALVE, PULMONIC VALVE, AND MULTIVALVULAR DISEASE

CLINICAL MANIFESTATIONS

Symptoms

TRICUSPID VALVE DISEASE

Since TR generally accompanies LV failure or MS, presenting symptoms include dyspnea, orthopnea, and peripheral edema.[61] Even though LV failure is usually present, paroxysmal nocturnal dyspnea is often absent. TR under these conditions may occasionally ameliorate the pulmonary symptoms and provide a physiologic basis for the alleviation of left-sided heart failure by the development of right-sided heart failure. Some patients also have less pulmonary edema due to the development of pulmonary arteriolar disease. If the TR is produced by infective endocarditis, symptoms of febrile illness may be accompanied by fatigue and peripheral edema.

The most frequent symptoms in TS are dyspnea and fatigue. When MS coexists, the development of significant TS can diminish the paroxysmal symptoms of dyspnea, pulmonary congestion, and pulmonary hypertension.[16,17] Occasionally, patients with TS complain of prominent pulsations in the neck veins, which may precede the development of peripheral edema.

PULMONIC VALVE DISEASE

Clinical manifestations of acquired pulmonic valvular lesions depend on the severity of the hemodynamic impairment as well as on the extent of the underlying disease. Isolated PR can be tolerated without symptoms. Severe pulmonary hypertension may cause syncope in addition to shortness of breath and fatigue. With inflammatory lesions of the pulmonic valve, febrile manifestations and pulmonary infection may be present. The carcinoid syndrome is characterized by episodes of facial flushing, increased intestinal activity, diarrhea, and bronchospasm (see Chap. 77). Tumors involving the pulmonic valve may exert pressure from expansion and metastases that affect the heart and lungs.

MULTIVALVULAR DISEASE

Dyspnea is the most frequent complaint of patients with combined mitral and aortic valve disease.[1,22,62] With combined MS and AS, chest discomfort, palpitations, and syncope are frequent clinical manifestations. Symptoms of heart failure result from pulmonary congestion and usually include fluid retention. Although angina pectoris is uncommon in patients with predominant MR, this symptom is more frequent with regurgitation of both the aortic and mitral valves. Also, syncope is rare in predominant MR but may develop when AR and MR coexist; palpitations are present in the majority of patients.

Angina, dizziness, syncope, and palpitations are common symptoms in AS when it is associated with MR. Angina may also be a symptom when AR and MS are the predominant lesions; but the more frequent symptoms, dyspnea and fatigue, are attributed to pulmonary congestion and heart failure (see Chaps. 56 to 58).

Physical Examination

TRICUSPID VALVE DISEASE

In patients with primary TR not due to pulmonary hypertension, there are large *v* waves in the jugular venous pulse (JVP). There is a dilated RV with a precordial lift and right-sided third or fourth heart sounds. There is usually a long systolic murmur in the third and fourth intercostal space at the left sternal border that increases with inspiration. The murmur is often confined to early and mid-systole or may not be heard at all when there is small gradient between the RV and RA during systole and a large regurgitant orifice (see Chap. 10). When a large amount of blood returns to the RV in diastole, a short diastolic rumble along the left sternal border may be heard. All of these findings are increased with inspiration (Rivero Carvallo's sign).[63] When RV failure occurs, the mean central venous pressure becomes elevated, and the jugular veins are pulsatile and engorged. When TR is due to pulmonary hypertension, there is an accentuated P_2, and a high-pitched decrescendo diastolic murmur of PR is often heard that is louder during inspiration in the second and third left intercostal spaces. In patients with TR and atrial fibrillation, there is a prominent *cv* wave in the jugular veins, produced by the regurgitant flow into the RV (see Chap. 10). The characteristic physical finding of TR due to pulmonary hypertension is a holosystolic murmur at the left sternal border that increases during inspiration; there is a RV-RA pressure gradient throughout systole. Although the murmur of MR may also be present, respiration exerts a predominant influence on the TR murmur (see Chap. 10).

Tricuspid stenosis is frequently associated with lesions of the mitral and aortic valves. When sinus rhythm is present, the JVP will display the prominent *a* wave indicative of impaired RV diastolic filling with atrial systole. The *a* wave in the neck may be of moderate height and sometimes reaches the mandible. Auscultation of the heart is required to confirm that the rise of the venous *a* wave is simultaneous with the first heart sound. The *cv* wave is small, and the *y* descent is slow and insignificant (see Chap. 10).

PULMONIC VALVE DISEASE

If RV failure and TR have developed as a result of PR, a prominent *cv* wave will be present in the JVP. Increased RV activity may be visible and palpable along the left sternal border. If pulmonic hypertension is present, the pulmonic second sound will be accentuated over the left upper sternal border. The murmur of acquired PR is a high-pitched diastolic blow along the left sternal border. Thus, the murmur may be difficult to differentiate from the murmur of AR, but the absence of peripheral findings of AR is useful in identifying regurgitation of the pulmonic valve as the source of the diastolic murmur. Congenital PR characteristically is associated with a low-pitched, decrescendo murmur along the left sternal border, the peak of the murmur occurring shortly after P_2 (see Chap. 10).

MULTIVALVULAR DISEASE

In combined MS and AS, the LV apical impulse may not be displaced, but a palpable parasternal RV systolic lift is usually present. A mitral diastolic rumble is audible in most patients and can vary from grade I to III in intensity (on scale of I to VI). The aortic systolic murmur is usually loud, but occasionally may be faint with severe MS. A mitral opening snap may not be audible, and in some patients the diastolic rumble of MS cannot be heard.

When both AR and MR exist, the diastolic arterial blood pressure is usually less than 70 mmHg. In those with a diastolic blood pressure above 70 mmHg, there is usually a loud holosystolic

mitral murmur. If AR is the dominant lesion, the early diastolic murmur is usually prominent, whereas when MR prevails, the aortic murmur becomes less intense. MR may diminish the AR due to the increased LV diastolic filling from the enlarged LA. Depending on the contractile state of the myocardium, loud regurgitant murmurs may be associated with mild regurgitation, whereas faint murmurs may accompany severe valvular regurgitation if myocardial failure has developed. A diastolic "flow murmur" across the mitral valve is heard in the majority of patients with combined MR and AR. If AR is important, a systolic murmur produced by the large forward flow across the aortic valve often is present (see Chap. 10).

When AR and MS are both present, the LV impulse is also displaced, sustained, and forceful. The early diastolic murmur at the apex may be prominent and may be accentuated by the AR flow striking the anterior leaflet of the stenotic mitral valve. Although the low-pitched diastolic murmur of MS and the diastolic flow murmur with AR are usually reliable diagnostic parameters, neither murmur correlates with the hemodynamic measurements when the two lesions coexist.

When AR is combined with MS, the systemic pulse pressure does not necessarily reflect the severity of AR. A prominent apical impulse in apparently pure MS indicates the likelihood of associated AR but may not indicate its severity. Finally, the intensity of the aortic diastolic murmur is of little value in predicting the severity of AR in the presence of MS (Chap. 10).

In the presence of AS and possible MR, an apical holosystolic murmur is reasonable evidence for associated MR, but the intensity of the murmur is not a reliable indicator in estimating severity.

While the murmur of TR often increases with inspiration, distinction from a concomitant MR murmur may be difficult. Identification of the rumble of TS requires careful auscultation during inspiration at the left lower sternal border. Detection by auscultation is more difficult because of the frequent association of MS and TS.

Electrocardiogram

TRICUSPID VALVE DISEASE

Atrial fibrillation is frequent in patients with TR. When TR results from myocardial infarction, acute or chronic electrocardiographic (ECG) changes will be seen in the inferior leads, and ST-segment elevation indicating RV infarction may be present in the right-sided precordial leads. The characteristic ECG finding in TS is a large P wave of RA enlargement in the absence of RV hypertrophy[1,22,64] (see Chap. 11).

PULMONIC VALVE DISEASE

Although there are no characteristic changes with pulmonic valvular lesions, preexisting pulmonary hypertension will produce RV hypertrophy, right-axis deviation, and changes in the *p* wave, suggesting RA enlargement. If pulmonary hypertension is secondary to mitral stenosis, P mitrale, with characteristic notches, will be present in lead II (see Chap. 11).

MULTIVALVULAR DISEASE

In combined MS and AS, ECG evidence of LV hypertrophy, LA enlargement, and atrial fibrillation is often present. Similar findings are observed in MR and AR, with a high likelihood of LA and LV enlargement along with atrial fibrillation. With AS and MR, LV hypertrophy is accompanied by a moderate incidence of atrial fibrillation. MS with severe AR also produces LV

hypertrophy.

Chest Roentgenogram

TRICUSPID VALVE DISEASE

TR may produce some degree of RA enlargement, but there will usually be accompanying RV enlargement.[61] In TS, the most characteristic radiographic finding is prominence of the RA without significant pulmonary arterial enlargement or changes due to pulmonary hypertension[1,22] (see Chap. 12).

PULMONIC VALVE DISEASE

Patients with PR have pulmonary artery prominence along with an increase in RV dimensions. If PS is acquired, there may be poststenotic dilatation or prominence of the main pulmonary artery.

MULTIVALVULAR DISEASE

With combined MS and AS, the LA is always enlarged. LV chamber size may be significantly enlarged; however, prominent RV dimensions are usually present. Valvular calcification at either site is relatively uncommon. In AS accompanied by MR, heart size is increased, with both LV and LA enlargement. In MS with AR, marked LV enlargement is often present.

Echocardiogram

TRICUSPID VALVE DISEASE

With TR, there may be echocardiographic evidence of systolic prolapse, rupture of the chordae or papillary muscle, or vegetative lesions on the valve.[65] Increased RV dimensions indicate impaired RV function and the likelihood of secondary TR (see Chap. 13). Contrast echocardiography with peripheral venous injection can identify the back-and-forth flow across the valve.[66] The echo-Doppler technique can estimate the severity of the regurgitation and the systolic pressure in the RV[67] (Fig. 59-10). Color-flow Doppler imaging can delineate the patterns and sites of regurgitation across the valve apparatus[71] (see Chap. 13).

Figure 59-10

Figure 59-10: A continuous echo-Doppler recording in a patient with tricuspid valve disease illustrates TR in the lower portion and TS in the upper portion of the tracing. (Reproduced with permission from and courtesy of Dr. Pamela Sears-Rogan.)

A characteristic pattern of TS can often be recorded with the echocardiogram. Fibrosis and calcification of the valve can be identified. Obstructive lesions, such as myxoma, thrombus, or other tumors, can be recognized echocardiographically. The two-dimensional echocardiogram of a patient with carcinoid syndrome with both TR and TS is shown in Fig. 59-11*A* and *B*. The echo-Doppler technique can be used to estimate the diastolic gradient across the valve with generally good accuracy (see Chap. 13).

Figure 59-11

Figure 59-11: *A.* Two-dimensional echocardiogram of a 40-year-old patient, with carcinoid tumor of the testes without metastases. He presented with a testicular mass and was found to have a grade III/VI pansystolic murmur and grade III/VI diastolic murmur; both increased with inspiration. This four-chamber view shows a thickened stenotic tricuspid valve (TV) in diastole. The RA is enlarged, and the atrial septum bulges to the left, indicating a higher RA than LA pressure, which is consistent with tricuspid stenosis. The liver was normal because the humoral products of the carcinoid tumor bypassed the liver by the testicular venous drainage flowing directly to the inferior vena cava and renal veins. Carcinoid tumors arise from neuroendocrine cells known as enterochromaffin cells, which are found in organs derived from the embryonic gut. Because the liver detoxifies the humoral products of the carcinoid tumor, which most often arises in the ileum, it is extremely rare to see carcinoid heart disease in the absence of liver metastases, making this case extremely unusual.4,5 Only about 20% of patients with carcinoid tumors develop cardiovascular symptoms. RV, right ventricle; SL, septal leaflet. *B.* Two-dimensional echocardiogram in diastole. This is from the same patient as in (*A*). Note the thickened tricuspid valve (TV) and the lack of excursion of the TV from diastole to systole. This washer-like, thickened TV is characteristic of carcinoid heart disease. It is common for a carcinoid TV to be both stenotic and insufficient. With carcinoid TV disease the valve becomes thickened, and its mobility and flexibility are reduced. RA, right atrium; RV, right ventricle. (From Cheitlin and MacGregor,[22] with permission.)

PULMONIC VALVE DISEASE

Echocardiography can delineate the anatomy of the pulmonic valve as well as intrinsic or extrinsic lesions impinging on the valve apparatus. Sometimes a vegetative lesion or tumor can be detected in the pulmonic valve area. The echo-Doppler technique can estimate both the severity of both the regurgitation and the stenosis of the valve,[68] and analysis of echo-Doppler recordings can provide estimates of pulmonary artery pressure[69-71] (Fig. 59-12). Color-flow imaging can further confirm the patterns of regurgitation in the RV outflow tract (see Chap. 13).

Figure 59-12

Figure 59-12: An echo-Doppler continuous tracing in a patient with TR. By employing the equation, the systolic gradient across the tricuspid valve can be calculated, and the addition of 10 mmHg yields an estimate of the pulmonary systolic pressure. Thus, in this patient, the level of pulmonary hypertension could be estimated from the echo-Doppler tracing of the TR. (Reproduced with permission from and courtesy of Dr. Pamela Sears-Rogan.)

MULTIVALVULAR DISEASE

Echocardiography provides information on valve anatomy, chamber dimensions, pressure gradients, valve size, patterns of regurgitation, and estimates of ventricular function. MS and AS produce characteristic echoes (see Chap. 13). Prolapse of mitral, aortic, and tricuspid valves can be characteristically recognized with echocardiography.[72] The number of aortic cusps can be identified, as can the presence of calcium in the aortic or mitral valve apparatus. Dimensions of the LA, LV, and RV, together with LV wall thickness measurements and determinations of mass, are useful in estimating the extent of volume and pressure overload. Two-dimensional and Doppler echocardiographic techniques can assess the orifice size of the aortic and mitral valves and estimate the valve gradients accurately.[73,74] Even in the presence of AR, appropriate

modifications in the mathematical analysis of the pressure gradient can yield reasonably accurate estimates of the aortic valve gradients (see Chap. 13). Color-flow Doppler readings can identify patterns and sites of valvular-regurgitation across the aortic and mitral valves.[75,76] Also, thrombus formation in the LA and LV can be detected with various echocardiographic methods. Transesophageal echocardiography can accurately assess prosthetic valve function and valvular repair during the operative procedures.

Nuclear Techniques

A radionuclide ventriculogram (RNV) can delineate dimensions of the RA and RV, which may help differentiate between TS and TR (see Chap. 16). RV size and function can be evaluated in stenotic and regurgitant lesions of the pulmonic valve. Myocardial perfusion imaging techniques are useful in detecting RV infarction as a cause of TR as well as in providing estimates of RV function. RV size and function can be evaluated in stenotic and regurgitant lesions of the pulmonic valve.

Quantitative information on LV function at rest and during exercise can be provided by RNV (see Chap. 16). Segmental wall motion can be assessed at rest and during exercise and may assist in the recognition of underlying coronary artery disease. Since combined lesions of the aortic and mitral valves often create pulmonary hypertension and RV dysfunction, RNV is useful in estimating the RV ejection fraction[77] (see Chap. 16).

Cardiac Catheterization

TRICUSPID VALVE DISEASE

Accurate angiographic documentation of TR is difficult to obtain because the catheter overrides the tricuspid valve, and ventricular irritability with an RV injection can induce TR. A prominent *cv* wave in the RA suggests TR, and an intracardiac phonocardiogram may record a regurgitation murmur in the absence of Rivero Carvallo's sign.[78]

If TS is clinically suspected, simultaneous pressures should be recorded in the RA and in the RV in order to measure the gradient across the valve accurately.[59] Since the normal gradient across the tricuspid valve is less than 1 mmHg, small gradients may not be detected if pullback pressure is recorded from the RV to the RA. The area of the tricuspid valve in TS is usually less than 1.5 cm^2; in severe TS, it is less than 1 cm^2.

PULMONIC VALVE DISEASE

PR is not readily demonstrated angiographically, but a right-sided injection can outline the pulmonary valve as well as show poststenotic dilatation. An aortic root injection can be helpful in the elimination of AR as the etiology of a diastolic murmur along the left sternal border. Nevertheless, this distinction is usually best made by echo-Doppler studies.

MULTIVALVULAR DISEASE

Cardiac catheterization is appropriate for most patients with combined valvular heart disease in order to calculate the stenotic and regurgitant status of each valve as well as to identify the predominant valvular lesion. Gradients across the valve can be measured with precision and the valve area calculated. Pulmonary hypertension is commonly present in these patients, and LV end-diastolic pressure is often elevated despite the presence of MS (see Chap. 15).

In MR plus AR, the LV end-diastolic pressure is elevated in most patients, and the central aortic pressure is generally greater than 40 mmHg. As noted, however, in approximately one-third of the patients the central aortic diastolic pressure may be above 70 mmHg. The *v* wave of MR can be recorded in the wedge position, and capillary and pulmonary arterial pressures are abnormally elevated in most of these patients.

In AS with MR, LV end-diastolic and pulmonary artery pressures are elevated; however, the extent of pressure elevation does not necessarily reflect the severity of the MR. When it is severe, forward cardiac output may be reduced; thus, a spuriously small pressure gradient may be recorded across a significantly stenotic aortic valve. In MS with AR, the LV end-diastolic pressure is abnormal and the central aortic diastolic pressure is usually less than 70 mmHg.

In combined valvular lesions, the measurement of total angiographic LV stroke volume is useful in calculating the regurgitant volume across each valve.[1,22] When both valves are regurgitant, it is more difficult to calculate the regurgitant volume across each valve.

Assessment of ventricular function is important in patients with combined valvular lesions; yet the ejection fraction may be spuriously normal or elevated in MR and, to a lesser extent, in AR. Measurements of LV end-systolic pressure, volume, and wall thickness permit calculation of end-systolic wall stress.[79] This parameter has been particularly helpful in pressure and volume overload conditions, since the end-systolic pressure-volume wall stress calculation is relatively independent of loading conditions.

Finally, coronary arteriography should be performed at the time of cardiac catheterization in patients above the age of 35, since coronary artery disease may be present without symptoms and may contribute to LV dysfunction. Coronary artery bypass grafting at the time of valve surgery is an important consideration.

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Chapter 59: TRICUSPID VALVE, PULMONIC VALVE, AND MULTIVALVULAR DISEASE

USUAL STRATEGY OF WORKUP

Tricuspid Valve Disease

The history should identify underlying conditions, such as rheumatic fever, systemic disorders, and left-sided heart failure, as etiologies for tricuspid valve disease. The physical examination should carefully define the waveforms in the JVP. The auscultatory changes of systolic and diastolic murmurs at the left lower sternal border during the respiratory cycle should be carefully evaluated. In addition, physical findings of left-sided valvular abnormalities, particularly MS or evidence of LV failure, should be observed. Peripheral edema as evidence of impaired right-sided filling should be identified.

Echocardiography is the most useful noninvasive technique for identifying the presence, severity, and potential etiologies of TS and/or TR (see Chap. 13). If the patient undergoes cardiac catheterization for assessment of left-sided heart disease, right-sided hemodynamics should be recorded and, if clinically indicated, simultaneous pressures recorded in the RA and the RV (see Chap. 15).

Pulmonic Valve Disease

The clinical history is important in delineating causes of left-sided heart failure that can lead to pulmonary hypertension and PR. Symptoms of the carcinoid syndrome, tumors, or infectious etiologies involving the pulmonic valve should be determined. The physical examination is important in evaluating the venous pulsations in the neck veins as well as the pulmonic murmurs. RV prominence should be carefully evaluated, as should concomitant left-sided valve lesions and evidence of heart failure. Although an ECG and chest x-ray should be obtained to assess the pulmonic artery, RV outflow tract, and body of the RV, the most useful noninvasive technique is echocardiography. The anatomy, competence of the valve, extent of the regurgitation, and stenosis can be recognized and assessed by an echo-Doppler sudy. In addition, other valve lesions affecting the left side of the heart can be documented. Since PR can be relatively well tolerated, this specific lesion does not require such frequent follow-up, but underlying mechanisms for pulmonary hypertension or left-sided heart failure should be monitored closely.

Multivalvular Disease

Symptoms of dyspnea, exercise intolerance, chest discomfort, or syncope should be elicited during a carefully taken clinical history. On physical examination, special attention should be directed to the peripheral and central arterial pulses and the JVP. Heart size, precordial movement, and auscultatory findings should be carefully noted. A 12-lead ECG and posterior-anterior and lateral chest films should be obtained. Echocardiography is indicated to delineate valve anatomy, measure valve gradients, recognize regurgitant patterns, calculate orifice size, and estimate ventricular function and wall motion (see Chap. 13). A limited exercise test with or without radionuclide studies may help determine the exercise capacity as well as detect functional deterioration, chest pain, arrhythmias, deterioration of ventricular ejection fraction, or segmental wall motion abnormalities. If symptoms are atypical and the extent of valvular or LV function cannot be satisfactorily evaluated by noninvasive techniques, cardiac catheterization is indicated.

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Chapter 59: TRICUSPID VALVE, PULMONIC VALVE, AND MULTIVALVULAR DISEASE

NATURAL HISTORY AND PROGNOSIS

Tricuspid Valve Disease

With TR due to RV hypertension, the symptoms and clinical course are primarily related to the left-sided heart conditions that produce a pressure-volume overload on the RV. TR virtually always develops with severe RV failure. In infective endocarditis of the tricuspid valve, the type of organism may significantly influence the course and the response to antibiotics (see Chap. 73).

With TS, the symptoms are usually those of MS, and the absence of pulmonary congestion in the presence of peripheral edema should raise the possibility of underlying TS. Significant TS may slow the development of characteristic symptoms of MS and result in an underestimation of the severity of mitral valve obstruction.

Pulmonic Valve Disease

In pulmonic valve lesions, the course will be more prolonged if there is chronic pulmonary hypertension due to mitral stenosis or chronic lung disease. Inflammatory conditions and tumors that affect the valve usually result in a much shorter clinical course.

Multivalvular Disease

When combined aortic and mitral valve disease are due to rheumatic fever, 10 years or more may elapse before the development of significant murmurs, and an additional decade (or more) may elapse before symptoms become manifest. If lesions of the aortic and mitral valves are due to degenerative collagen changes, symptoms may develop later in life. When combined lesions are due to calcific changes in the aortic valve and annulus as well as the mitral valve annulus, symptoms develop much later in life. There may, however, be rapid progression of degenerative aortic calcific stenosis over a 2- to 3-year period (see Chap. 56).

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Chapter 59: TRICUSPID VALVE, PULMONIC VALVE, AND MULTIVALVULAR DISEASE

MEDICAL MANAGEMENT

Tricuspid Valve Disease

With TR, treatment of RV failure requires digitalis and diuretics, and vasodilating agents are also required for the management of LV failure (see Chap. 21). If failure of the right side of the heart is caused by MS, early intervention to enlarge or replace the mitral valve is appropriate (see Chap. 57).

In TS, the usual precautionary measures of antibiotic coverage and prevention of endocarditis apply. Peripheral edema may not respond well to administration of digitalis, diuretics, and vasodilator therapy, thus emphasizing the clinical importance of detecting underlying TS. Tricuspid balloon valvuloplasty has been used successfully in patients with predominant TS.[80]

Pulmonic Valve Disease

Patients with congenital pulmonic valve stenosis are usually best treated by catheter balloon valvotomy (see Chaps. 63 and 64).

Prophylaxis and Medical Therapy

Antibiotic prophylaxis against endocarditis (see Chap. 73) is appropriate for patients with either tricuspid or pulmonic valve lesions. If pulmonary emboli contribute to the pulmonary hypertension, anticoagulation is indicated (see Chap. 53). Furthertreatment of pulmonary hypertension may require managementof left heart failure, correction of MS, or the use of vasodilating agents that can lower pulmonary artery pressure. Vasodilating agents are often ineffective in treating primary pulmonary hypertension (see Chap. 52).

If rheumatic fever is the likely etiology of combined aortic and mitral valve disease, prophylactic penicillin should usually be continued until age 35 years (see Chap. 55). Dental prophylaxis with antibiotic coverage, using either amoxicillin or erythromycin, should be provided in all patient groups prior to dental procedures. For genitourinary or other abdominal procedures, gram-negative antibiotic coverage should be provided (see Chap. 82).

Atrial Fibrillation

If atrial fibrillation develops, chronic anticoagulation with low-dose warfarin [International Normalized Ratio (INR) 2.0 to 3.0] is warranted, since the accompanying incidence of systemic and cerebral emboli is estimated at 10 to 20 percent (see Chap. 61).

The early development of atrial fibrillation associated with hemodynamic deterioration warrants an initial attempt at electrical cardioversion. If this is successful, digitalis as well as antiarrhythmic preparations should be administered thereafter for prophylaxis against recurrence (see Chap. 24). Chronic atrial fibrillation should be controlled with digitalis, beta blockers, and calcium blockers as indicated. The development of symptoms, particularly dyspnea, limited exercise activity, chest

pain, and syncope, warrants consideration for surgery. It is usually recommended for New York Heart Association (NYHA) class III symptoms despite adequate medical therapy.

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SURGICAL MANAGEMENT

Tricuspid Valve Disease

The decision to proceed with valvular heart surgery is usually based on the severity of the aortic and mitral valve disease, rather than on the severity of the disease of the tricuspid valve. The usual decisions to be made regarding the tricuspid valve are (1) whether a procedure should be added to the mitral and/or aortic valve procedures and, (2) if so, which procedure-annuloplasty or valve replacement-should be performed. Patients may present with mild mitral valve disease but severe tricuspid valve dysfunction. Such patients may require an operation on the tricuspid valve only.

The severity of the symptoms and clinical signs of tricuspid valve disease are used to determine the indications for tricuspid valve surgery. If there are signs of TS and, particularly, if stenosis is demonstrated by cardiac catheterization and two-dimensional echocardiography, the tricuspid valve is directly visualized at operation with the anticipation of performing commissurotomy or valve replacement. Tricuspid valve balloon valvulotomy has been advocated for[80-84] TS of various etiologies.[82] However, severe TR is a common consequence of this procedure, and results are poor when severe TR develops.

When there are signs of severe TR secondary to MS, it is important to document the duration of the regurgitation and the severity and duration of pulmonary artery hypertension. If the TR is severe and long-standing and if there is chronic pulmonary artery hypertension, it is unlikely to resolve in the early postoperative period after mitral valve surgery alone. In this circumstance, tricuspid valve surgery is usually indicated. In contrast, if TR and pulmonary artery hypertension are of short duration, mitral valve replacement will usually reduce pulmonary artery pressure in the early postoperative period, and this will result in a decrease in the TR. Occasionally, severe TR will be present with only modest elevation of pulmonary artery pressure. In this circumstance, the tricuspid valve leaflets are usually deformed and valve replacement is necessary.[83]

The appearance of the heart at the time of surgery is helpful in assessing the severity of tricuspid valve disease. A thinned-out RA wall together with moderate to marked enlargement of the RA and venae cavae are indications of significant disease. The degree of stenosis and regurgitation can be estimated by palpation through the RA appendage. Intraoperative transesophageal echocardiography (see Chap. 13) provides more precise information as to the degree of residual valvular regurgitation after repair. The ACC/AHA guidelines recommendations for surgery for TR are listed in Table 59-4.

Table 59-4: Recommendations for Surgery for Tricuspid Regurgitation

Indication	Class
Annuloplasty for severe TR and pulmonary hypertension in patients with mitral valve disease requiring mitral valve surgery	I
Valve replacement for severe TR secondary to diseased or abnormal tricuspid valve leaflets not amenable to annuloplasty or repair	IIa
Valve replacement of annuloplasty for severe TR with mean pulmonary artery pressure <60 mmHg when symptomatic	IIa
Annuloplasty for mild TR in patients with pulmonary hypertension secondary to mitral valve disease requiring mitral valve surgery	IIb
Valve replacement or annuloplasty for TR with pulmonary artery systolic pressure <60 mmHg in presence of a normal mitral valve in asymptomatic patients or in symptomatic patients who have not received a trial of diuretic therapy	III

TS may be treated successfully by commissurotomy, which is usually performed under direct vision. The procedure may be combined with annuloplasty to correct valve regurgitation. Valve replacement is occasionally necessary if the changes in the leaflets and subvalvular structures are advanced or if severe TR cannot be relieved by annuloplasty. For TR, three basic reconstructive techniques have been described. The first procedure is used widely and consists of plication of the posterior leaflet,[84,85] thus converting the tricuspid valve into a functionally bicuspid valve.[84,85] De Vega described a second type of annuloplasty that narrows the annulus along the anterior and posterior leaflets with a pursestring suture.[86,87] The third major technique, described by Carpentier et al., consists of placing a carefully sized semiflexible ring along the anterior and posterior aspects of the annulus.[88] It draws in and supports the tissue evenly. Follow-up studies have shown that annular dilatation occurs in these areas rather than along the leaflets.[89]

When the leaflets and subvalvular apparatus are severely deformed as a result of rheumatic fever, reconstruction may not be feasible. In such cases, replacement is performed with either a mechanical or tissue valve. Anticoagulation with warfarin (see Chap. 52) is generally advisable in patients with tricuspid valve replacement, and therefore the major advantage of a bioprosthetic valve is negated. If a mechanical valve is preferred and the cavity of the RV is not capacious, a low-profile, tilting disk-type prosthesis seems appropriate. Usually, however, if TR is severe, a ball-cage prosthesis functions better.

Mild TR does not seem to increase the risk of surgery involving the mitral valve or both aortic and mitral valves. When the TR is moderate to severe, however, the risk of operation is significantly increased. Although long-term improvement in TR after mitral valve replacement alone has been documented, a tricuspid procedure is generally employed in the setting of moderate to severe TR to enhance cardiac function in the critical early days after operation.[90] Mitral valve replacement alone does not invariably decrease TR, even several months after operation.[91]

In general, the early and late results of tricuspid annuloplasty have been superior to those of valve replacement, and valve replacement should be avoided when possible. There is a significant incidence of thrombosis with tricuspid prostheses, and the long-term functional results have been less favorable than those of aortic and mitral valve replacements.[92] Good early results have been obtained with all three methods of annuloplasty.[93-97] When tricuspid valve replacement is necessary, the 30-day perioperative mortality increases to 15 to 20 percent. Two preoperative

factors-severity of edema and mean pulmonary artery pressure-as important predictors of long-term survival.[98] A variety of prostheses have been used for tricuspid valve replacement with variable results.[98-103]

Infective endocarditis of the tricuspid valve is relatively common because of the increased incidence of drug abuse. In general, the treatment of tricuspid valve endocarditis is medical. When septic pulmonary embolization occurs despite intensive antibiotic treatment, tricuspid valve surgery is indicated. Excision of the valve without replacement has been recommended, and reinfection of the new valve in intravenous drug users is an important risk.[104] Nevertheless, since valvulectomy alone carries an important risk of heart failure, tricuspid valve replacement has been recommended by others.[105]

The cardiac output is often marginal after tricuspid valve surgery, a reflection of persistent pulmonary arterial hypertension and long-standing RV dysfunction. Measurements of cardiac output and pulmonary artery pressure are used to guide postoperative care. If annuloplasty is performed, a pulmonary artery catheter can be used for such measurements (see Chap. 15). Nitroglycerin infused through a central venous catheter is a valuable adjunct in reducing pulmonary artery pressure. Prostaglandin E_1, in combination with pressor agents, may also be employed to treat severe postoperative pulmonary hypertension.[106] Intravenous dopamine and dobutamine may be used to enhance myocardial contractility. If cardiac output remains marginal, an intraaortic balloon pump may be used to reduce left-sided pressures. Pulmonary artery balloon counterpulsation has been employed for acute RV failure.[107] The use of a temporary circulatory assist device, such as a centrifugal pump, to bypass the RV may sustain adequate circulation when RV failure is unresponsive to other measures.

Digitalis and diuretics are usually employed for several months after tricuspid valve surgery. For patients with tricuspid valve replacement, warfarin and dipyridamole are used as anticoagulants.[108] The additional use of antiplatelet agents in this setting may improve the long-term results.[109] A serious late complication of tilting disk valves in the tricuspid position is thrombosis. Thrombolytic therapy with streptokinase has been used successfully to restore valve function.[110] Prophylaxis against infective endocarditis is also required (see Chap. 73).

Pulmonic Valve Disease

Pulmonic valve surgery for acquired disease is performed infrequently. PS on an acquired basis is rare. Although there are a variety of causes of PR, this hemodynamic condition is relatively well tolerated if pulmonary vascular resistance is normal. Pulmonic valve replacement may be performed for acquired conditions, such as carcinoid heart disease and infective endocarditis, but it usually is limited to cases where RV dysfunction has become severe after congenital heart disease surgery[111,112] (see Chaps. 63 and 64). In general, bioprosthetic valves have been preferred because of the tendency for mechanical valve thrombosis in this position. Pulmonic valve surgery is currently being performed earlier and more commonly, since studies indicate that RV dysfunction may be present in asymptomatic postoperative patients with PR.[113]

Infective endocarditis involves the pulmonic valve in about 1 percent of cases seen at autopsy. Isolated pulmonic valve infective endocarditis is even more uncommon but may be the cause of metastatic pulmonary infections. In a review of 28 cases of this entity, the overall mortality rate was 24 percent, with all those treated by operation surviving.[114] Valvulectomy in combination with antibiotic therapy is sometimes the most effective treatment (see Chap. 77).

Multivalvular Disease

Many patients with clinical evidence of combined disease of the mitral and aortic valves have severe and progressive symptoms. Experience indicates that both valves can be replaced, with a hospital mortality rate that is now between 5 and 10 percent.

Commonly, in the presence of aortic and mitral valve disease, repair, rather than replacement, of the stenotic or regurgitant mitral valve can be accomplished (see Chap. 57). Disease of the aortic valve in adults usually requires valve replacement. The combination of aortic valve replacement with mitral valve repair probably decreases early mortality rates and improves long-term survival. There have been marked subjective and objective improvements in surviving patients. When tricuspid valve replacement is added, the risk of the operation is higher (up to 20 percent), but even then the long-term results are considerably better than the life history of surgically untreated patients with triple-valve disease. The use, when possible, of tricuspid annuloplasty rather than replacement has greatly improved the early results of operation in this group of patients.

When hemodynamic derangement is significant at both mitral and aortic valves, the decision to repair or replace both is easily made, and the principles of surgical treatment are the same as when one valve alone requires operation.[115,116]

MULTIVALVULAR SURGERY

Combined MS and AR

When mechanical correction is anticipated in predominant MS, balloon mitral valvotomy followed by aortic valve replacement (AVR) obviates the need for double-valve replacement, which has a higher risk of complications than does single-valve replacement.[117] In most cases, it is advisable to perform mitral valvotomy first and then follow the patient for symptomatic improvement. If symptoms disappear, correction of AR can be delayed.

Combined MS and TR

If the mitral valve anatomy is favorable for percutaneous balloon valvotomy and there is concomitant pulmonary hypertension, valvotomy should be performed regardless of symptom status. After successful mitral valvotomy, pulmonary hypertension and TR almost always diminish.[118]

If mitral valve surgery is performed, concomitant tricuspid annuloplasty should be considered, especially if there are preoperative signs or symptoms of right-heart failure, rather than risking severe, persistent TR, which may necessitate a second operation. However, TR that seems severe on echocardiography but does not cause elevation of RA or RV diastolic pressure will generally improve greatly after mitral valve replacement (MVR). If intraoperative assessment suggests that TR is functional without significant dilatation of the tricuspid annulus, it may not be necessary to perform an annuloplasty.

Combined MS and AS

If the degree of AS appears to be mild and the mitral valve is acceptable for balloon valvotomy, this should be attempted first. If mitral balloon valvotomy is successful, the aortic valve should then be reevaluated.

Combined AS and MR

Noninvasive evaluation should be performed with two-dimensional and Doppler

echocardiography to evaluate the severity of both AS and MR. Attention should be paid to LV size, wall thickness and function, LA size, right-heart function, and pulmonary artery pressure. Patients with severe AS and severe MR (with abnormal mitral valve morphology) with symptoms, LV dysfunction, or pulmonary hypertension should undergo combined AVR and MVR or mitral valve repair. However, in patients with severe AS and lesser degrees of MR, the severity of MR may improve greatly after isolated AVR, particularly when there is normal mitral valve morphology. Intraoperative transesophageal echocardiography and, if necessary, visual inspection of the mitral valve should be performed at the time of AVR to determine whether additional mitral valve surgery is warranted in such patients.

In patients with mild to moderate AS and severe MR in whom surgery on the mitral valve is indicated because of symptoms, LV dysfunction, or pulmonary hypertension, preoperative assessment of the severity of AS may be difficult because of reduced forward stroke volume. If the mean aortic valve gradient is greater than 30 mmHg, AVR should be performed. In patients with less severe aortic valve gradients, inspection of the aortic valve and its degree of opening on two-dimensional or transesophageal echocardiography as well as visual inspection by the surgeon may be important in determining the need for concomitant AVR.

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Figure 59-9: Bacterial endocarditis in specimens from a 36-year-old man. *A.* Aortic valve. The base of the aortic valve shows major destruction of a cusp with extension of inflammation onto the subjacent mitral valve. Near the free edge of the mitral valve, its ventricular aspect shows an ostium of a nonruptured mycotic aneurysm. *B.* Mitral valve, LA, and LV. The lobulated mycotic aneurysm of the mitral valve lies near its free edge.

Figure 59-10: A continuous echo-Doppler recording in a patient with tricuspid valve disease illustrates TR in the lower portion and TS in the upper portion of the tracing. (Reproduced with permission from and courtesy of Dr. Pamela Sears-Rogan.)

Figure 59-11: *A.* Two-dimensional echocardiogram of a 40-year-old patient, with carcinoid tumor of the testes without metastases. He presented with a testicular mass and was found to have a grade III/VI pansystolic murmur and grade III/VI diastolic murmur; both increased with inspiration. This four-chamber view shows a thickened stenotic tricuspid valve (TV) in diastole. The RA is enlarged, and the atrial septum bulges to the left, indicating a higher RA than LA pressure, which is consistent with tricuspid stenosis. The liver was normal because the humoral products of the carcinoid tumor bypassed the liver by the testicular venous drainage flowing directly to the inferior vena cava and renal veins. Carcinoid tumors arise from neuroendocrine cells known as enterochromaffin cells, which are found in organs derived from the embryonic gut. Because the liver detoxifies the humoral products of the carcinoid tumor, which most often arises in the ileum, it is extremely rare to see carcinoid heart disease in the absence of liver metastases, making this case extremely unusual.4,5 Only about 20% of patients with carcinoid tumors develop cardiovascular symptoms. RV, right ventricle; SL, septal leaflet. *B.* Two-dimensional echocardiogram in diastole. This is from the same patient as in (*A*). Note the thickened tricuspid valve (TV) and the lack of excursion of the TV from diastole to systole. This washer-like, thickened TV is characteristic of carcinoid heart disease. It is common for a carcinoid TV to be both stenotic and insufficient. With carcinoid TV disease the valve becomes thickened, and its mobility and flexibility are reduced. RA, right atrium; RV, right ventricle. (From Cheitlin and MacGregor,[22] with permission.)

Figure 59-12: An echo-Doppler continuous tracing in a patient with TR. By employing the equation, the systolic gradient across the tricuspid valve can be calculated, and the addition of 10 mmHg yields an estimate of the pulmonary systolic pressure. Thus, in this patient, the level of pulmonary hypertension could be estimated from the echo-Doppler tracing of the TR. (Reproduced with permission from and courtesy of Dr. Pamela Sears-Rogan.)

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Part 9: VALVULAR HEART DISEASE
Chapter 60:

CLINICAL PERFORMANCE OF PROSTHETIC HEART VALVES

Authors: Gary L. Grunkemeier, Albert Starr, Shahbudin H. Rahimtoola

A heart valve functions as a check valve: opening to permit forward blood flow and closing to prevent retrograde flow, about 40 million times per year. Heart valve prostheses consist of an orifice, through which blood flows, and an occluding mechanism that closes and opens the orifice. There are two classes of heart valves: *mechanical prostheses*, with rigid, manufactured occluders, and *biological* or *tissue valves*, with flexible leaflet occluders of animal or human origin. Among the mechanical valves there are three basic types, depending on whether the occluding mechanism is (1) a reciprocating ball, (2) a tilting disk, or (3) two semicircular hinged leaflets. The biological valves include those whose origin is from (1) the patient, (2) another human, or (3) another species. For each type there are several models available from different manufacturers. Selected frequently used valves are described.

PROSTHETIC HEART VALVES

Mechanical Valves

Ball valves appeared in the early 1960s, disk valves in the early 1970s, and bileaflet valves predominantly during the 1980s.

BALL VALVES

The first successful valve replacement devices, which led to long-term survivors and a design that has endured until today, used a ball-in-cage design.[1,2] Several modifications of this design have been used, but only the *Starr-Edwards* valve (Fig. 60-1, Plate 94) has endured; it has been used about 200,000 times.

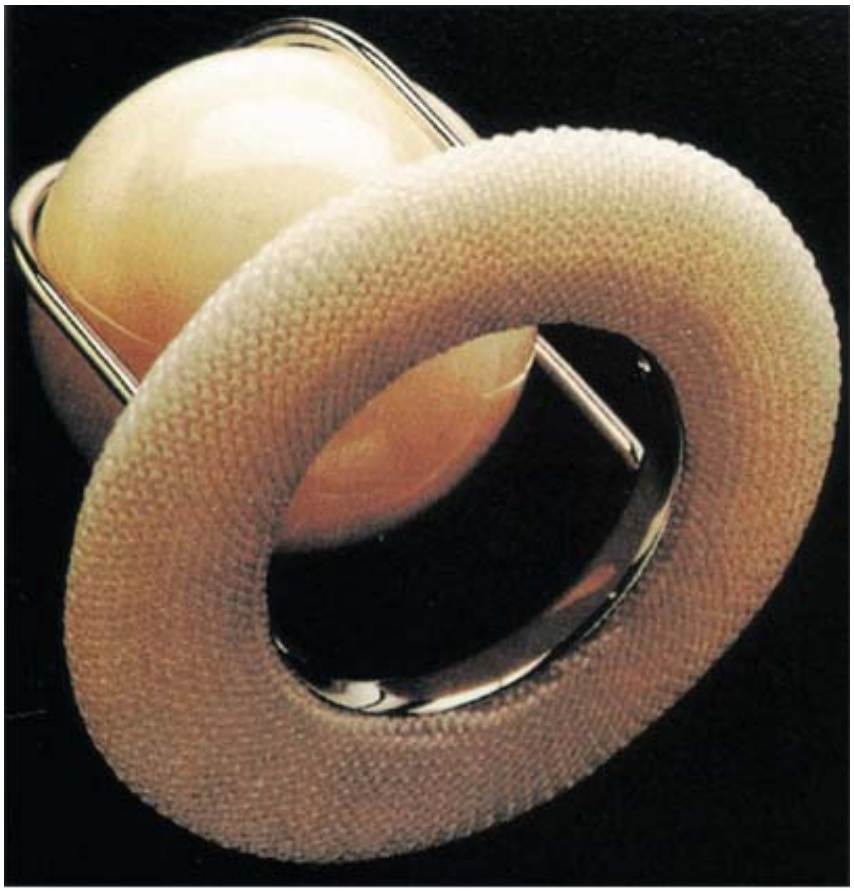


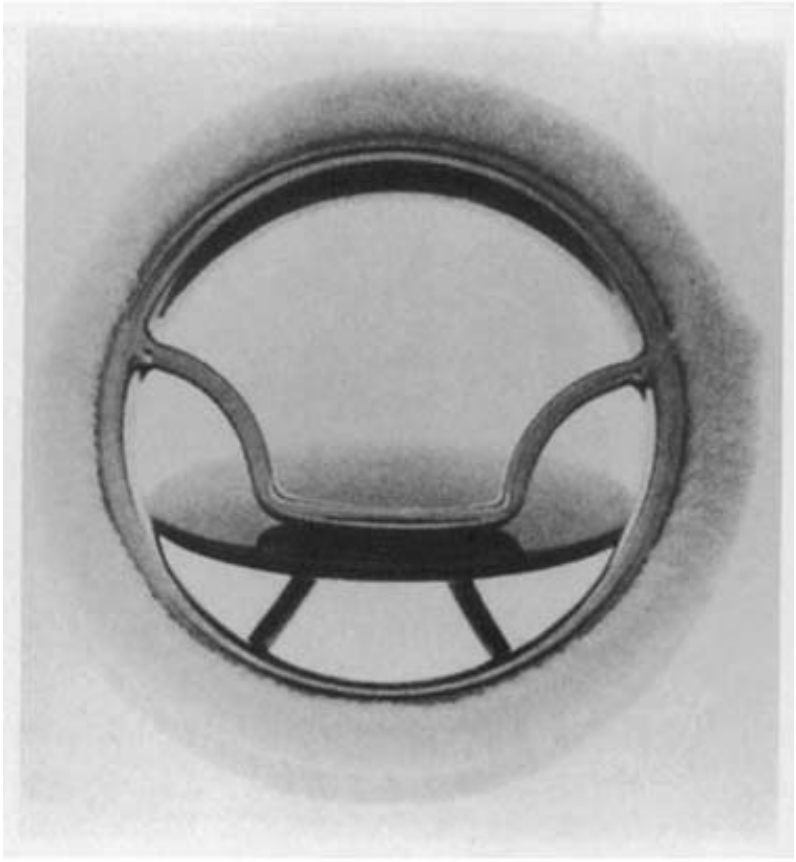
Figure 60-1: (Plate 94) Starr-Edwards caged ball valve. The ball is a silicone rubber polymer, impregnated with barium sulfate for radiopacity, which oscillates in a cage of cobalt-chromium alloy. When the valve opens, blood flows through the circular primary orifice and a secondary orifice between the ball and the housing. In the aortic position, there is a tertiary orifice between the ball and the aortic wall.

DISK VALVES

Improvement on the clinical success of the ball valves was sought by developing designs with reduced height. The first successful low-profile design was the *Björk-Shiley* tilting-disk valve, introduced in 1969.[3] It evolved through several design refinements,[4] and about 360,000 valves were implanted. These refinements also introduced a structural failure mode caused by strut fracture in the Convexo-Concave model. Some results with the discontinued Björk-Shiley models are included because many patients are still alive with these valves. Tilting-disk valves employ a circular disk as an occluder. It is retained by wirelike arms or closed loops that project into the orifice. The disks are graphite with a coating of pyrolytic carbon, and the housings are stainless steel or titanium. With the disk open, the primary orifice is separated into two unequal (major and minor) orifices. The *Medtronic Hall* valve has been used clinically since 1977.

BILEAFLET VALVES

Current development in mechanical valves is based on the bileaflet design, introduced by St. Jude Medical in 1977. Unlike the free-floating occluders in ball and disk valves, the two semicircular leaflets of a bileaflet valve are connected to the orifice housing by a hinge mechanism. The leaflets swing apart during opening, creating three flow areas: one central and two peripheral. The *St. Jude* bileaflet valve (Fig. 60-2, Plate 95) has been used over 900,000 times and the *Carbomedics* valve has been used about 300,000 times since its clinical introduction in 1986.



A

B

Figure 60-2: (Plate 95) Bileaflet valves. The St. Jude Medical valve (*A*) has leaflets that open to an angle of 85 degrees from the plane of the orifice and travel from 55 to 60 degrees to the fully closed position, depending on valve size. The original version, whose housing did not rotate within the sewing ring, has been supplemented by a model that does rotate for intraoperative adjustment. The Carbomedics valve (*B*) has flat leaflets that open to 78 to 80 degrees and close at

an angle of 25 degrees with the horizontal and has a carbon-coated surface on the sewing ring to inhibit thrombus formation.

Biological Valves

Biological valves include as wide a variety of models, as do mechanical valves:

1. An *autograft* valve is one that is translocated within the same individual-e.g., the pulmonary valve in the aortic valve position.
2. A *homograft* (or allograft) valve is one that has been transplanted from a donor of the same species-when, for example, a donor's aortic or pulmonary valve has been placed in a recipient's aortic or pulmonary position.
3. *Heterograft* (or xenograft) valve is a transplant from another species, either an intact valve (e.g., a porcine aortic valve) or a valve fashioned from heterologous tissue (e.g., bovine pericardium).

The point of using biological valves is to reduce the complications associated with thromboembolism and the need for anticoagulation. The first successful biological valves were homografts, pioneered by Ross[5] and Barratt-Boyes[6] in 1962.

AUTOGRAFT

The pulmonary autograft procedure consists of an autotransplant of the pulmonary valve to the aortic position; the pulmonary valve is then replaced by an aortic or pulmonary homograft. This operation was first described in 1967[7] and is called the Ross procedure; it is currently undergoing increased popularity,[8-12] but this operation involves a double valve replacement, with the attendant early and late risks. This procedure uses double valve replacement to solve a single valve problem; however, subsequent problems with pulmonary valve replacement may be easier to remedy and those related to autograft will be similar to those of aortic valve re-replacement.

HOMOGRAFT

The homograft valve is considered to be a preferred substitute for aortic valve replacement, especially in younger patients. It achieves excellent hemodynamics; there is no need for anticoagulation and it has low thrombogenicity. The drawbacks are a more technically demanding operation and a low availability; however, the latter drawback has been alleviated by its commercial availability from cryopreservation services. Several methods of procurement, sterilization, and preservation have been used.[13] Three surgical techniques are used for aortic valve replacement: (1) replacement of the valve only into the subcoronary position, (2) complete aortic root replacement with reimplantation of the coronary arteries, and (3) miniroot replacement with part of the donor aortic wall inserted within the host aorta.

PORCINE HETEROGRAFT

Glutaraldehyde sterilizes valve tissue, renders it bioacceptable by destroying antigenicity, and stabilizes the collagen cross-links for durability. The use of glutaraldehyde for tissue preservation was pioneered by Carpentier,[14] who introduced the term *bioprosthesis*[15] for nonviable valves of biological origin, such as the *Hancock II* and *Carpentier-Edwards SupraAnnular* (SAV) porcine valves (Fig. 60-3, Plate 96).

Figure 60-3: (Plate 96) Stented porcine valves. The Carpentier-Edwards SupraAnnular Valve is designed to be implanted above rather than within the aortic annulus. It has low-pressure fixation and a cone-shaped stent which flares out at the top to improve leaflet durability.

Most porcine valves are mounted on rigid or flexible stents, to which the leaflets and the sewing ring are attached. Unstented versions have also been devised by several manufacturers.[16-20] Their goal is to achieve some of the potential benefit of a homograft valve, especially hemodynamics and perhaps durability, with an easily available commercial product. The valve, however, is porcine and can be expected to have the same problems of primary valve failure as the stented porcine valve. As with homografts, there are potentially three ways of implanting a stentless porcine valve (valve only, aortic root replacement, and cylinder inclusion). The St. Jude Medical Toronto SPV (Fig. 60-4, Plate 97) and the Medtronic Freestyle (Fig. 60-5, Plate 98) stentless porcine valves were approved for marketing by the FDA in 1997.

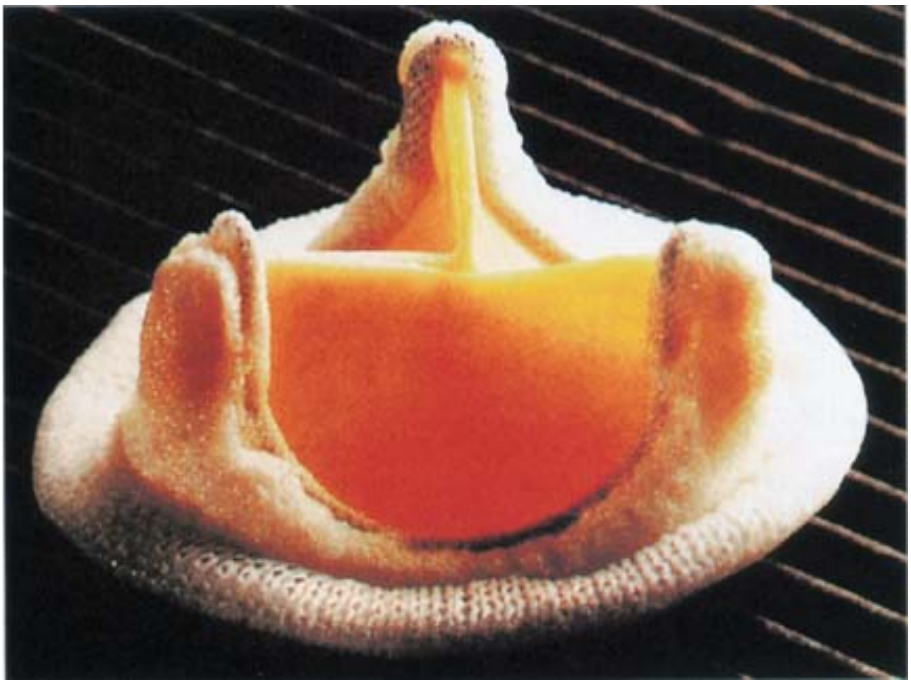


Figure 60-5: (Plate 98) The Carpentier-Edwards Perimount pericardial bioprosthesis uses a method of mounting the leaflets to the stent, which does not depend on retaining stitches passed through the pericardium-a design weakness of previous pericardial valves. Instead, the leaflets are anchored behind the stent pillars.

BOVINE PERICARDIAL VALVE

Pericardial valves that are tailored and sewn into a valvular configuration using bovine pericardium as a fabric result in a valve that opens more completely than a porcine valve, providing better hemodynamics. They might also be expected to have better durability, because there is extra tissue to allow for shrinkage and a higher percentage of collagen to be cross-linked during fixation. Unfortunately, the lonescu-Shiley, the first commercially available pericardial valve, did not bear out this promise and was taken off the market, as was the Hancock pericardial valve. These failures were due to aspects of the design, however, rather than to an intrinsic problem with pericardial tissue. The Carpentier-Edwards Perimount pericardial bioprosthesis (Fig. 60-6) has a method of construction that overcomes these design issues. It has been used clinically since 1982 and received FDA approval, for the aortic position only, in 1991.

Repair

When possible, valve repair[21-23] is generally preferable to replacement (see discussion below).

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Chapter 60: CLINICAL PERFORMANCE OF PROSTHETIC HEART VALVES

GUIDELINES FOR REPORTING CLINICAL RESULTS

The analytic aspects of the reporting of clinical results of heart valves have evolved consistently since the first successful implants in 1960. As late (posthospital) experience accumulated near the end of the first decade of implants, the need to analyze time-related events resulted in the introduction of actuarial analysis,[24] which had previously been used to analyze the results of cancer therapy.[25] Later, the use of linearized (constant hazard) rates,[26,27] Cox regression,[28] and multivariable parametric models[29] was advocated. The effectiveness of these refined statistical methods in comparing results from different series, however, was limited by the lack of standardization in definitions and follow-up methods.

AATS/STS Guidelines for Clinical Reporting

In 1988, standards that specified which complications should be collected and how they should be defined were proposed by the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity, a joint committee of the American Association for Thoracic Surgery (AATS) and the Society of Thoracic Surgeons (STS).[30] These guidelines were revised in 1996.[31,32] The complications that were determined to be of critical importance by these guidelines are as follows:

1. *Structural valvular deterioration*, or any change in function of an operated valve resulting from an intrinsic abnormality that causes stenosis or regurgitation.
2. *Nonstructural dysfunction*, a composite category that includes any abnormality that results in stenosis or regurgitation of the operated valve that is not intrinsic to the valve itself, exclusive of thrombosis and infection. This includes inappropriate sizing, also called *prosthesis-patient mismatch*.[33]
3. *Valve thrombosis* is any thrombus, in the absence of infection, attached to or near an operated valve that occludes part of the blood flow path or that interferes with the function of the valve.
4. *Embolism* is any embolic event that occurs in the absence of infection after the immediate perioperative period (when anesthesia-induced unconsciousness is completely reversed). These include any new, temporary or permanent, focal or global neurologic deficits and peripheral embolic events; emboli proven to consist of nonthrombotic material are excluded.
5. *Bleeding event*is any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g., vision loss) or requires transfusion. The complication "bleeding event" applies to all patients, whether or not they are taking anticoagulants or antiplatelet drugs.
6. *Operated valvular endocarditis* is any infection involving an operated valve. Morbidity associated with active infection-such as valve thrombosis, thrombotic embolus, bleeding event, or paravalvular leak-is included under this category but is not included in other categories of morbidity.

The *consequences* of the above morbid events include reoperation, valve-related mortality, sudden unexpected unexplained death, cardiac death, total deaths, and permanent valve-related impairment.[31,32]

FDA Guidelines for New Valve Approvals

In 1976, medical devices including prosthetic heart valves came under the jurisdiction of the FDA,[34] which subsequently issued various guidelines for submission of premarket approval (PMA) applications for heart valves. The FDA issued a guidance document in December 1993[35] that used the analytical approach to clinical studies adapted from the work of Gersh et al.[36] These authors proposed a method for premarket clinical testing of heart valves that emphasizes confidence interval estimation and comparisons to objective performance criteria (OPC). *OPC are linearized rates for critical complications, representing averages achieved by the best currently used valves*. A *linearized rate* is calculated as the number of events divided by total patient-years and multiplied by 100 to convert it to units of "events per 100 years" or "percent per year."[27]

To determine OPC for contemporary use, the FDA screened the literature plus data submitted by clinical investigators of approved devices and identified OPC for the major morbidity categories.[35] They determined that these rates were similar for aortic and mitral positions but varied for some complications between mechanical and biological valves. The OPC for complications are given in Table 60-1 for mechanical and biological replacement heart valves. Several observations on these data are significant.

The category *Structural deterioration* was not included in the list of OPC because the clinical PMA investigation is not designed to detect intrinsic valve failure. Structural durability should be evaluated by in vitro testing, and the clinical realization of structural failure should be so small (mechanical valves) that the clinical study is of insufficient size or so long-term (tissue valves) that the clinical study is of insufficient duration to assess it adequately.

From the *Nonstructural dysfunction* category, the FDA included only leak, the most common and the most frequently reported subcategory, and derived OPC for major leaks ("as defined by AATS/STS, 1988")[30] and for all leaks.

The FDA separated *Thromboembolism* into the separate categories of valve thrombosis and thromboembolism, as had been strongly advocated,[37,38] and the FDA derived OPC both for major *Anticoagulant-related hemorrhage* events ("as defined by AATS/STS, 1988")[30] and for all bleeding events.

Based on the OPC values given in Table 60-1, the FDA has set the minimum amount of follow-up required for a PMA study at 800 valve-years.[39] The assumption of constant risk for heart valve complications, as embodied by the OPC formulation, is only an approximation; but if operative events are excluded (the intent of the FDA guidelines) and maximum follow-up is in the 2- to 3-year range, this assumption may be acceptable, at least for the purpose of sample size estimation.

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Chapter 60: CLINICAL PERFORMANCE OF PROSTHETIC HEART VALVES

VALVE-RELATED COMPLICATIONS

Actuarial valve failure-free curves[25] are used to describe tissue valve durability, and linearized rates[27] are used for all other complications.

Structural Deterioration

This category, the first one considered in the guidelines for reporting, virtually always results in death or valve explant. There is a dual standard with regard to this complication: for biological valves, structural deterioration is probably inevitable if the patient lives long enough; whereas for mechanical valves, the only acceptable rate is a very low one (near zero).

MECHANICAL VALVES

The durability of currently used mechanical valves is remarkable, given the harsh biological environment in which the valve must perform. For example, the current Starr-Edwards ball valve, now in use for 35 years and in over 200,000 patients, has had fewer than a dozen structural problems reported to the manufacturer, most of which did not cause clinical problems. Even the discontinued Björk-Shiley Convexo-Concave valve, whose strut fracture failures have been highly publicized, had fewer than 1 percent failures reported after 15 years of experience.[40] The Medtronic Hall valve had three leaflet fractures in a version that is not used in the United States. The problem was determined to be related to unequal coatings of pyrolytic carbon on the two faces of the leaflet and to be limited to a very small subset of valves. Since the manufacturing specifications were changed to ensure more equal coatings, the problem has not recurred. The St. Jude valve has had only 12 reported postoperative fractures of the disk or housing, which resulted in leaflet escape reported to the FDA-an excellent record considering that over 900,000 valves have been implanted.

BIOLOGICAL VALVES

Data on freedom from structural deterioration for several series of aortic porcine and pericardial bioprostheses and homografts are shown in Fig. 60-6. The mean age of patients in these older series is around 50 years. The current series of porcine valves, together with the tendency to select older patients,[41-44] should have improved durability. Design changes in some porcine valves,[45,46] such as stentless configurations,[16-20] may possibly improve durability.

Although the Carpentier-Edwards pericardial valve has been available for over 15 years, relatively few long-term results on the valve are available. Those that have been reported, however, show improved durability in the aortic position, as compared with the previously discontinued lonescu-Shiley pericardial valve. The durability of the Carpentier-Edwards pericardial valve also compares favorably with that of porcine valves (Fig. 60-6; Table 60-2). The patients in the Carpentier-Edwards pericardial valve series were older than patients in previous series of pericardial and porcine valves, however, and it is unknown to what extent this has resulted in apparent improvement in the durability of the Carpentier-Edwards pericardial valve.

Table 60-2: 14-Year Results with Carpentier-Edwards Pericardial Valve

		FDA-Mandated Patients[a] (*n* = 267) Actuarial (%)
Thromboembolism/thrombosis		19 ± 4
Anticoagulant-related bleeding		6 ± 2
Endocarditis/sepsis		7 ± 2
Valve dysfunction		70 ± 4
Explant due to structural valve deterioration:	Total	15 ± 3
	≤65 years of age	24 ± 5
	>65 years of age	4 ± 2
Mortality:	Total	60 ± 3.1
	Valve-related	21 ± 3.2

[a]FDA approval was based on 719 patients at 7 years. Data from FDA-mandated longer follow-up of selected patients are from Frater et al.[85]

Structural durability is considered to be better with *homografts* than with other bioprostheses. From various published reports[13] for homografts used primarily in the aortic position, it is apparent that the variation among series is wide, the current methods of sterilization/preservation provide better results than those which have been discontinued, and the results do not appear better than those for porcine bioprostheses (Fig. 60-6).

The pulmonary autograft is considered an excellent aortic valve substitute, especially for young patients[10] and in the treatment of patients with endocarditis.[47] Freedom from reoperation has been reported as 100 percent in 33 patients from 8 to 47 years old followed to a maximum of 48 months[11] and 93 percent at 5.5 years in 51 patients from 2 to 21 years old.[10] Data from one center showed 48.5 percent freedom from reoperation at 19 years[47] and, after excluding patients from three hospitals, 85 percent freedom from reoperation at 20 years.[48] To evaluate complications of this procedure fully, problems with the valve used to replace the pulmonary valve must be combined with complications of the pulmonary autograft itself.

VALVE REPAIR

Mitral valve repair is considered preferable to replacement, when practicable. It has been shown to improve ejection fraction[49] and to provide good results for treating bacterial endocarditis[50] and valve problems in elderly patients.[51,52] It has been strongly suggested that it improves survival; however, there are problems associated with the comparisons.[53]

The weakness of valve repair is durability. The 10-year actuarial reoperation rate has been reported to be 15

percent in nonrheumatic mitral disease.[54] The reoperation rate for patients with rheumatic mitral disease varies from 25 percent reoperation at 5 years[55] to 17 percent at 10 years in a large series in which calcium debridement[56] and anterior leaflet procedures were performed.[57] The reoperation rate at 10 years was 24 percent for patients less than 20 years of age and 9 percent at 10 years for patients over 20 years of age.[58]

Early results of aortic valve repair have been published,[23,59,60] but further follow-up is needed to assess the long-term results.

Other Valve-Related Complications

Linearized rates are often used to describe the complications required by the AATS/STS guidelines for reporting.[30-32] The use of such rates assumes that the risks are constant, which is usually only approximately true. A review of a large number of published reports of the performance of prosthetic heart valves reveals a wide spread of results for every complication for every valve. In 172 series of heart valves covering 335,485 valve-years accumulated by 63,531 valves of 20 different models implanted in two positions (aortic, mitral), the linearized event rates ranged from 0 to 7.5 percent per year for thromboembolism, 0 to 0.6 percent per year for thrombosis, 0 to 9.3 percent per year for bleeding, 0 to 1.7 percent per year for infection, and 0 to 2.8 percent per year for paravalvular leak.[61] Caution must be exercised in directly comparing event rates among valves for many reasons, including the simplifications involved in the use of linearized rates, varying definitions of complications (many of these reports predate the standardized definitions), and differences in patient characteristics between series.[53,62]

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Chapter 60: CLINICAL PERFORMANCE OF PROSTHETIC HEART VALVES

DIFFICULTIES IN MAKING COMPARISONS BETWEEN PUBLISHED SERIES

As noted above, there is wide variation in the reported complication rates of series using the same valves. Figures 60-7, 60-8, 60-9 and 60-10 illustrate the wide range of embolism with use of the same heart valve in different series. This variation must be due to variations between series other than the *valve model*. These include factors associated with the following:

1. *Patients*-age, ventricular function, comorbidities, etc.
2. *Reporting center*-surgical variables, postoperative medical management, method, frequency and thoroughness of follow-up, definitions of complications, etc.
3. Problems with *data analysis*[63,64]-many patient-related factors are known to influence thromboembolism,[53,65] stroke rates in patients with atrial fibrillation and in the elderly are equal to those observed in prosthetic valve series,[66] and standardized definitions[30-32] were not in effect or were not employed when many of the available series were reported, etc.
4. *Published data*-these reports describe only a small fraction of the valves implanted and are probably not a representative subset.

Several types of bias can affect reported results. As examples, selection bias occurs in the collection and analysis of data and the decision to report them;[63] publication bias describes the fact that published series tend to be those with the best (or worst, but not typical) results.[67] If a random allocation of valves had been made among patients within a center, statistical methods could theoretically assess the effect on complication rates due to valve model. For logistic, financial, and ethical reasons, however, the number of randomized studies of valves is small, and the available studies are usually of insufficient size to show differences among valves. Although randomized studies provide the best internal validity or valve-specific comparison within centers, they may lack external validity or generalizability to patients outside of the study.[68]

A theoretically preferable way to answer this bias is to allocate patients randomly to different treatments (valves). Randomized trials, however, also have difficulties,[69] and as noted, there are logistic, financial, and ethical arguments against randomization of patients to different heart valves.[70] Consequently, the number of randomized studies of valves is small, and those that exist are usually of insufficient size to add to the knowledge already obtained from careful observational studies except for comparison of survival data with use of different types of prosthesis.

Major Randomized Trials

The two major randomized clinical trials that have been reported are the Edinburgh Heart Valve Trial[71] and the Veterans Administration (VA) Cooperative Study on Valvular Heart Disease.[72] Both studies compared mechanical valves to porcine bioprostheses.

The Edinburgh trial compared the Björk-Shiley Standard valve to porcine valves-initially the Hancock and later the Carpentier-Edwards.[71] It contains actuarial comparisons at 5 and 12 years for the 211 aortic and 261 mitral valve patients. The authors concluded that survival with a mechanical valve was better than with the bioprosthetic valve, but that this was somewhat offset by the increased risk of bleeding.

The VA trial compared the standard Björk-Shiley valve to the Hancock Modified Orifice (size 21 to 23 mm aortic) or Hancock Standard (other sizes) porcine valves.[72] Table 60-3 contains actuarial comparisons of the endpoint variables at 15 years. The principal long-term findings of this randomized trial[73] are: (1) Use of a mechanical valve resulted in a lower mortality and a lower reoperation rate after aortic valve replacement (AVR); (2) The mortality after mitral valve replacement (MVR) was similar with

use of the two prosthetic valve types; (3) There were virtually no primary valve failures with use of a mechanical valve; (4) Primary valve failure after AVR and MVR occurred more frequently in patients with a bioprosthetic valve especially in patients aged <65 years; (5) The primary valve failure rate between bioprosthesis and mechanical valve was not significantly different in those aged ≥65 years; (6) Use of a bioprosthetic valve resulted in a lower bleeding rate; and (7) There were no significant differences between the two valve types with regard to other valve related complications including thromboembolism, and all complications.

Comparison of the 12-year actuarial event rates between these two trials[72] showed that the bleeding and thromboembolism rates were higher in the VA study but that reoperation rates were higher in the Edinburgh study. These differences could be partially accounted for by the composition of the two patient populations: The Edinburgh patients (1) were younger and less heavily anticoagulated, (2) included women and those with double valve replacements, and (3) had a higher percentage of porcine valves in the mitral position. Late results show a better survival with mechanical valves than with bioprostheses in the mitral position with the original valve in the Edinburgh trial (42 versus 24 percent, $p < .05$), probably because of the high rate of bioprosthetic degeneration, and in the aortic position in the VA trial (23 versus 0 percent; $p = 0.0001$).

VALVE SELECTION CRITERIA

Because of the wide variation in results among and between various valve models, it is impossible to rank valves within valve types on the basis of complication rates. Some general recommendations, however, can be made with regard to valve selection (Table 60-4).[74]

Table 60-4: Recommendations for Valve Replacement with a Mechanical Prosthesis

Indication	Class
1. Patients with expected long life spans	I
2. Patients with a mechanical prosthetic valve already in place in a different position than the valve to be replaced	I
3. Patients in renal failure, on hemodialysis, or with hypercalcemia	II
4. Patients requiring warfarin therapy because of risk factors[a] for thromboembolism	IIa
5. Patients ≤65 years for AVR and ≤70 years for MVR[b]	IIa
6. Valve rereplacement for thrombosed biological valve	IIb
7. Patients who cannot or will not take warfarin therapy	III

[a]Risk factors: atrial fibrillation, severe LV dysfunction, previous thromboembolism and hypercoagulable condition.
[b]The age at which patients may be considered for bioprosthetic valves is based on the major reduction in rate of structural valve deterioration after age 65 and the increased risk of bleeding in this age group.

SOURCE: ACC/AHA Guidelines,[74] with permission.
ABBREVIATIONS: AVR = aortic valve replacement; LV = left ventricle; MVR = mitral valve replacement.

A biological valve should be used when the patient cannot or will not take anticoagulants or has a short life expectancy. Its use in relation to subsequent pregnancy is controversial (see Chap. 61). A mechanical valve should be used if the patient needs anticoagulant therapy (e.g., because of atrial fibrillation), has a

mechanical valve in another position, previously had a stroke, requires double valve replacement, or has a long life expectancy. Mechanical valves should be considered for double valve replacement because the risk of structural deterioration for two porcine valves is additive,[75] whereas the thromboembolic risk of two mechanical valves is not additive.[76]

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Chapter 60: CLINICAL PERFORMANCE OF PROSTHETIC HEART VALVES

MANAGEMENT OF PATIENTS WITH PROSTHETIC HEART VALVES

Patients who have undergone valve replacement are *not* cured but still have serious heart disease. They have exchanged native valvular disease for prosthetic valvular disease and must be followed with the same care as patients with native valvular disease.[77] The clinical course of patients with prosthetic heart valves is influenced by several factors.[78]

Ventricular Dysfunction

Despite relief of valvular obstruction or regurgitation, some patients fail to improve after valve replacement or even deteriorate because of ventricular dysfunction. The cause of dysfunction may be carditis associated with rheumatic disease, myocardial degeneration and fibrosis from long-standing pressure or volume overload, ischemic damage at the time of valve replacement, coronary artery disease, or other associated diseases such as systemic hypertension or idiopathic dilated cardiomyopathy. Perioperative myocardial damage is an important cause of postoperative ventricular dysfunction. The importance of myocardial protection at the time of valve surgery is now recognized, and current operative techniques reduce myocardial oxygen consumption by hypothermic cardioplegia and use a variety of means for maintaining adequate myocardial perfusion and protection.

Other Cardiac Lesions

Cardiac diseases affecting primarily one valve often affect other valves, the conduction system, the coronary arteries, and the pulmonary vasculature. With the exception of pulmonary hypertension and functional tricuspid regurgitation, these disorders usually do not improve after isolated valve replacement. Rheumatic disease typically affects both mitral and aortic valves but not necessarily with the same severity at the same time. Therefore, patients who have mitral valve replacement may subsequently, years later, require aortic valve replacement, or vice versa. Calcification of the aortic and mitral valve annuli may extend to the conduction system. High-degree or complete atrioventricular block may occur at the time of surgery or during the late postoperative period, requiring pacemaker implantation. Coronary artery disease is very common in the age range of patients requiring valve replacement. Preoperative coronary arteriography should be performed in all patients with myocardial ischemic pain, in those with left ventricular dysfunction, in those with risk factors for coronary artery disease, and in those about 35 years of age or older.[78,79] Coronary bypass surgery of technically suitable vessels should be performed at the time of valve surgery if the patients have associated significant coronary artery disease.

Prosthesis-Related Problems

The incidence of problems with each prosthesis (see Tables 60-5 and 60-6) was discussed earlier. *Operative mortality* is related to older age of patient, New York Heart Association functional class III or IV, increased left ventricular size, left ventricular dysfunction, heart failure, pulmonary hypertension, low cardiac output, and presence of associated diseases such as systemic arterial hypertension, diabetes mellitus, peripheral and cerebral vascular disease, prior heart surgery, prior myocardial infarction, chronic obstructive pulmonary disease, and renal and hepatic failure. Coronary bypass surgery performed at the same time as valve replacement increases the operative mortality modestly (from 1.4 to 4.0 percent), but associated coronary artery disease, if not bypassed, significantly increases the operative mortality to 9.4 percent and the 10-year mortality to 64 percent.[80] Other very important factors include the occurrence of perioperative myocardial infarction, the duration of the operation, aortic cross-clamp time, and whether or not the patient needed reoperation within 1 to 2 weeks after the initial operation, and on an elective or emergency basis.

Table 60-5: Recommendations for Valve Replacement with a Bioprosthesis

Indication	Class
1. Patients who cannot or will not take warfarin therapy	I
2. Patients ≥65 years[a] needing AVR who do not have risk factors for thromboembolism[b]	I
3. Patients considered to have possible compliance problems with warfarin therapy	IIa
4. Patients >70 years[a] needing MVR who do not have risk factors for thromboembolism[b]	IIa
5. Valve rereplacement for thrombosed mechanical valve	IIb
6. Patients <65 years[a]	IIb
7. Patients in renal failure, on hemodialysis, or with hypercalcemia	III
8. Adolescent patients who are still growing	III

[a]The age at which patients should be considered for bioprosthetic valves is based on the major reduction in rate of structural valve deterioration after age 65 and increased risk of bleeding in this age group.
[b]Risk factors: atrial fibrillation, severe LV dysfunction, previous thromboembolism, and hypercoagulable condition.

SOURCE: ACC/AHA Guidelines,[74] with permission.
ABBREVIATION: AVR = aortic valve replacement; LV = left ventricle; MVR = mitral valve replacement.

Table 60-6: Major Complications of Valve Replacement

1. Operative mortality
2. Perioperative myocardial infarction
3. Prosthetic endocarditis
4. Prosthetic dehiscence
5. Prosthetic dysfunction
    a. Obstruction: Usually thrombotic, occasionally due to item 3, 4, or 8
    b. Regurgitation
    c. Hemolysis
    d. Structural failure
6. Thromboemboli
7. Hemorrhage with anticoagulant therapy
8. Valve prosthesis-patient mismatch
9. Prosthetic replacement often caused by item 3, 4, or 5, occasionally caused by item 6, 7, or 8
10. Late mortality, including sudden, unexplained death

SOURCE: Rahimtoola.[64] Reproduced with permission of the publisher and author.

The risk of *prosthetic endocarditis* is about 3 percent in the first year and 0.5 percent in subsequent years. Infections in the early postoperative period (up to 2 to 12 months) are due to hospital-based organisms. Despite therapy, the infections are difficult to cure and have a high mortality (about 80 percent);[81,82] early reoperation is usually recommended. The mortality rate from late (2 to 12 months or later) postoperative infection is approximately 40 percent;[81,82] about half the patients can be treated successfully with medication alone. The infected valve should be replaced in patients who do not respond to medical

treatment or who have evidence of heart failure, annular invasion, embolism, prosthetic dysfunction, unstable prosthesis, or gram-negative, staphylococcal, or fungal infection.[64] The importance of adequate antibiotic prophylaxis for the prevention of endocarditis cannot be overemphasized; the prevention and treatment of prosthetic valve endocarditis are discussed in Chap. 82.

Long-term anticoagulant therapy is associated with *bleeding* episodes. The incidence of minor bleeding is about 2 to 4 percent per year or less. The incidence of major bleeding is about 1 to 2 percent per year or less, with a mortality rate of about 0.5 percent per year or less. The incidence of these complications is lower in patients who take their medications reliably, in those in whom smooth long-term anticoagulation can be achieved, and in those who receive low-dose warfarin therapy (INR 2 to 3 versus >3). With oral anticoagulants, low- or mid-dose warfarin therapy is combined with low-dose aspirin. Higher degrees of anticoagulation increase the incidence of bleeding without reducing the incidence of thromboembolism. The management of antithrombotic therapy is discussed in Chap. 68.

Prosthetic dehiscence is the result of sutures pulling out of the cardiac tissues. It may result from infection, inadequate surgical technique, or diseased cardiac tissue (e.g., edema, necrosis, calcification).

Because of the continued proliferation of new types and models of prostheses and their relatively brief history of clinical use, the natural history of *structured valve deterioration* is incompletely determined. Although some mechanical prostheses had initial problems with component failure, the most common cause for dysfunction of mechanical prosthetic valves is thrombotic obstruction. The incidence of thrombotic obstruction with the Björk-Shiley spherical occluder valve is higher than that seen with the Starr-Edwards or St. Jude valves, particularly in the mitral position. Failure of biological valves is more common than failure of mechanical prostheses because of leaflet deterioration or calcification; progressive prosthetic regurgitation and/or stenosis is the rule. Bioprosthesis failure is greater in younger patients, in older patients with chronic renal insufficiency, and in the mitral position. In younger patients (average age <60 years), failure of mitral prostheses usually starts at 5 to 8 years and of aortic prostheses at 8 to 10 years. It is unlikely that the tissue valves currently in use will be able to provide the long-term performance demonstrated by the ball-valve mechanical prosthesis.

Red cells are fractured by turbulence and contact with foreign surfaces. Some degree of *hemolysis* is present with all mechanical prostheses but not with bioprostheses. Important hemolysis, however, may occur with a perivalvular leak or severe prosthetic obstruction regardless of prosthesis type. Serum lactic dehydrogenase (LDH) is usually the simplest and most reliable index of hemolysis to follow in patients with prosthetic valves. A sudden increase in LDH may indicate prosthesis dysfunction, perivalvular leak, or cloth tear. Iron and folate therapy usually correct the anemia. Valve rereplacement may be required for severe, refractory hemolytic anemia.

Important *systemic embolization* is an unfortunate complication of prosthetic valve replacement. Anticoagulation is recommended for all patients with mechanical prostheses. *Despite long-term anticoagulation, patients with prosthetic valves face an embolic rate from aortic prostheses of 1 to 2 percent or less per year and from mitral prostheses of 3 to 4 percent or less per year*.

No prosthesis currently employed has an effective orifice as large as that of the native valve, and valve prosthesis-patient mismatch[33] may occur. *All patients with prosthetic heart valves have mild to moderate stenosis*. Patients with aortic valve prostheses have obstruction to left ventricular outflow (aortic stenosis), and patients with mitral valve prostheses have obstruction to left atrial emptying (mitral stenosis). This is most important in a large patient in whom a prosthesis that is considered "small" in relation to body size must be placed for technical reasons. The resulting patient-prosthesis mismatch[33] contributes to incomplete relief of symptoms. The long-term effect of intrinsic prosthetic stenosis on survival and ventricular dysfunction is unknown but may lead to long-term effects similar to those of aortic or mitral stenosis.[83] The presence of intrinsic prosthetic stenosis must be considered when patients with prosthetic heart valves are being advised concerning activity.

Reoperation to replace a prosthetic heart valve is a serious complication. It is usually required for moderate to severe prosthetic dysfunction and dehiscence, prosthetic valve endocarditis, and occasionally recurrent thromboembolism, severe recurrent bleeding from anticoagulant therapy, or valve prosthesis-patient mismatch.

Late cardiac death may result from ventricular dysfunction, other cardiac lesions, or prosthesis-related causes. Late, sudden death is not uncommon. It may result from a bradyarrhythmia; a tachyarrhythmia that is often associated with ventricular dysfunction, prosthetic dysfunction, or mismatch; coronary artery disease; or a combination of these.

Management

All patients with prosthetic valves need appropriate antibiotics for prophylaxis against infective endocarditis (Chap. 82). Patients with rheumatic heart disease continue to need antibiotics as prophylaxis against the recurrence of rheumatic carditis (Chap. 62). Adequate antithrombotic therapy is needed for appropriate patients (Chap. 68).

During the first 4 to 6 weeks after surgery, the physician and surgeon jointly manage the patient, directing their attention toward relieving postoperative discomfort, readjusting cardiac medications, and instituting anticoagulation if not contraindicated. A graduated plan of activity is started that, in most cases, enables the patient to return to full activity in 4 to 6 weeks.

Several syndromes are peculiar to the postoperative period. The *postperfusion syndrome* usually appears in the third or fourth postoperative week. It is characterized by fever, splenomegaly, and atypical lymphocytes; it is benign and self-limited. The *postpericardiotomy syndrome* is characterized by fever and pleuropericarditis. It usually develops in the second or third postoperative week but can appear as late as 1 year after surgery and sometimes recurs. Although this syndrome is usually self-limited, most patients benefit from taking anti-inflammatory drugs, such as aspirin or indomethacin; a short course of glucocorticoids is also occasionally required.

Even though the pericardium is left open at the end of surgery, *cardiac tamponade* has been known to occur during the first 6 weeks. The fact that a critically ill patient may improve promptly with pericardial drainage underscores the need to consider this uncommon postoperative complication. Usually, anticoagulants have been given and the fluid is hemorrhagic.

The *4- to 6-week postoperative visit* is critical, because by this time the patient's physical capabilities and expected improvement in functional capacity can usually be assessed. At this time, the physician should assemble essential records and data for the subsequent office follow-up, including the preoperative history, physical examination, chest roentgenogram, electrocardiogram (ECG) and indication for surgery, preoperative echocardiographic/Doppler ultrasound and cardiac catheterization/angiographic reports, surgeon's operative report, postoperative complications, and hospital discharge summary. The prosthesis model, serial number, and size should be recorded.

The workup on this visit should include an interval or complete initial history and physical examination, ECG, chest x-ray, echocardiography/Doppler ultrasound, complete blood count, and measurement of electrolytes, LDH, and international normalized ratio (INR) if indicated (Table 60-7). The examination's main focus is on physical signs that relate to functioning of the prosthesis or suggest the presence of a myocardial, conduction, or valvular disorder. The auscultatory findings to expect with some normally functioning prostheses have been described.[84] Severe perivalvular mitral regurgitation can be inaudible on physical examination, a fact to remember when considering possible causes of functional deterioration in a patient.

Table 60-7: Recommendations for Follow-up Strategy of Patient with Prosthetic Heart Valves

Indication	Class
1. History, physical exam, ECG, chest x-ray, echocardiogram, complete blood count, serum chemistries, and INR (if indicated) at first postoperative outpatient evaluation[a]	I
2. Radionuclide angiography or magnetic resonance imaging to assess LV function if result of echocardiography is unsatisfactory	I
3. Routine follow-up visits at yearly intervals with earlier reevaluations for change in clinical status	I
4. Routine serial echocardiograms at time of annual follow-up visit in absence of change in clinical status	IIb
5. Routine serial fluoroscopy	III

[a]This evaluation should be performed 3 to 4 weeks after hospital discharge. In some settings, the outpatient echocardiogram may be difficult to obtain: if so, an inpatient echocardiogram may be obtained before hospital discharge.

SOURCE: ACC/AHA Guidelines,[73] with permission.
ABBREVIATIONS: INR = international normalized ratio; LV = left ventricle.

The interval between routine follow-up visits depends on the patient's needs. Anticoagulant regulation usually does not require office visits.

Multiple noninvasive tests have emerged for assessing valvular and ventricular function. Fluoroscopy can reveal abnormal rocking of a dehiscing prosthesis or limitation of the occluder if the latter is opaque as well as strut fracture of a Björk-Shiley valve. Radionuclide angiography, which is useful for determining whether or not functional deterioration is the result of reduced ventricular function, is performed if the same data cannot be obtained by echocardiography.

Echocardiography/Doppler ultrasound is the most useful noninvasive test. It provides information about prosthesis stenosis/regurgitation, valve area, assessment of other valve disease(s), pulmonary hypertension, atrial size, left ventricular hypertrophy, left ventricular size and function, and pericardial effusion/thickening. It is essential at the first postoperative visit because it allows an assessment of the effects and results of surgery and serves as a baseline for comparison should complications and/or deterioration occur later. Subsequently, it is performed as is needed in both symptomatic and asymptomatic patients at 1- to 2-year intervals. We recommend that in patients with a bioprosthesis in the mitral position, echocardiography/Doppler ultrasound should be performed annually after 5 years and in the aortic position annually after 8 years because of the increasing incidence of bioprosthetic structural valve deterioration.

"Heart failure" after valve replacement may be the result of (1) preoperative left ventricular dysfunction that improved partially or not at all, (2) perioperative myocardial damage, (3) progression of other valve disease, (4) complications of prosthetic heart valves, and (5) associated heart disease such as coronary artery disease and systemic arterial hypertension.

Any patient with a prosthetic heart valve who does not improve after the surgery or who later shows deterioration of functional capacity should undergo appropriate testing to determine the cause. Such studies are also usually necessary for patients who require reoperation for endocarditis or repeated embolism to determine the hemodynamics and anatomy.

The indications for reoperating on a patient with prosthetic valve endocarditis have already been discussed. A patient in stable condition, without prosthetic valve endocarditis, can usually undergo reoperation with only slightly greater risk than that of the initial surgery. For the patient with catastrophic dysfunction, surgery is clearly indicated and urgent. The patient without endocarditis or severe dysfunction requires careful hemodynamic evaluation; the decision about reoperation should then be based on the hemodynamic abnormalities, the symptoms, ventricular function, and current knowledge of the natural history of the

particular prosthesis.

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Figure 60-9: Embolism rates for biological aortic valves. For explanation of symbols, see Fig. 60-7. Valve model abbreviations: HA = Hancock I and Modified Orifice porcine; H2 = Hancock II porcine; IN = Intact porcine; CE = Carpentier-Edwards porcine; FS = Freestyle stentless porcine; BC = Biocor stentless porcine; CP = Carpentier-Edwards Perimount pericardial; MF = Mitroflow pericardial; HG = homograft. (From Grunkemeier et al.[61] Reproduced by permission of the publisher and authors.)

Figure 60-10: Embolism rates for biological mitral valves. For explanation of symbols, see Fig. 60-7. Valve model abbreviations: see Fig. 60-9. (From Grunkemeier et al.[61] Reproduced by permission of the publisher and authors.)

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Part 9: VALVULAR HEART DISEASE
Chapter 61:

ANTITHROMBOTIC THERAPY FOR VALVULAR HEART DISEASE

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INTRODUCTION

The most important reason to address the issue of protection against thromboemboli in every patient with valve disease is the risk of a stroke. In addition, the consequences of valve thrombosis and of emboli to other organs make the risk of antithrombotic therapy reasonable to assume in many patients with valve disease. Treatment has to be individualized, but some issues and principles are widely applicable (Table 61-1).[1,2] Although some recommendations are appropriate for affluent American communities, the risk, benefit, and cost ratio may not be applicable in poorer areas, where the resources are simply not available. Thromboemboli are not ignored, but alternative therapy-for example, a greater use of antiplatelet agents, in particular aspirin-may, on balance, be more appropriate.

Table 61-1: Valve Disease and Antithrombotic Therapy[a,b]

1. Prevention of thromboemboli should be addressed each time a patient with valve disease is seen.
2. Lifelong antithrombotic therapy is required in patients with atrial fibrillation (paroxysmal or persistent) (Table 61-2).
3. Warfarin therapy is required in all patients with a mechanical prothesis (Table 61-3).
4. Antithrombotic therapy should be started early after valve surgery.
5. Warfarin should be avoided in the first trimester of pregnancy.
6. Antithrombotic therapy should be individualized during noncardiac surgery and cardiovascular procedures (Table 61-5).

[a]See text for discussion.
[b]In general, whenever warfarin/aspirin therapy is recommended it is assumed that there is no specific contraindication to its use.

Intracardiac thrombosis most often presents as an embolic cerebrovascular event in over 80 percent of cases. Rarely, thrombosis becomes manifest by causing valve dysfunction. The physical examination should include careful attention to the peripheral pulses and to the skin, fundi, and soft tissues (mouth, conjunctiva), looking for clues of an embolus. A detailed neurologic assessment for focal deficits is essential. Although thrombosis most often occurs without any change in the cardiac examination, auscultation to assess for a change in a murmur or in the quality of heart sounds is important. Intracardiac thrombosis often is first diagnosed when cardiac catheterization or echocardiography is performed for other reasons.

Thrombus is the most common but not the exclusive cause of an embolus. Infective endocarditis must be considered and excluded as a cause, particularly in individuals with valve disease. Disruption of a vascular plaque in the ascending aorta, arch, or descending aorta and in the cerebral vessels may be a common cause of peripheral and cerebral emboli in patients with atherosclerotic disease. Intracardiac tumors or calcified emboli from the heart or aorta are other rare causes.

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Chapter 61: ANTITHROMBOTIC THERAPY FOR VALVULAR HEART DISEASE

NATIVE VALVE DISEASE

The risk of thromboembolism in patients with native valve disease is most directly related to certain risk factors, including atrial fibrillation, a history of thromboembolism, left ventricular (LV) dysfunction, and known hypercoagulability. The risk is increased by the presence of certain types of native valve disease (e.g., mitral stenosis) and with prosthetic heart valves, particularly mechanical prostheses, which put a patient at risk even without other associated risk factors (Fig. 61-1).

Risk Factors for Thromboemboli with Native Valve Disease

ATRIAL FIBRILLATION

Most is known about the stroke risk with atrial fibrillation, which is common even without valve disease. Six recent large prospective randomized trials have assessed the value of antithrombotic therapy for primary prevention in patients with nonvalvular atrial fibrillation.[3-8] The term *nonvalvular* is not completely accurate, as at least some patients with aortic valve disease and with mitral regurgitation were included in the studies if the valve lesions were considered hemodynamically "insignificant."

In these trials, the embolic rate (essentially the rate of a stroke in untreated patients with nonvalvular atrial fibrillation) ranged from 3 to 8 percent per year. This was true whether the atrial fibrillation was constant or paroxysmal. Importantly, these trials indicated that warfarin therapy reduced the stroke rate to approximately 0.5 to 2 percent per year. One study, SPAF II,[7] demonstrated equal protection against an adverse neurologic event when aspirin (325 mg daily) was compared to warfarin. In SPAF III,[8] the aspirin was less protective if atrial fibrillation occurred in association with LV dysfunction or uncontrolled hypertension, if the patient was a woman over age 75, and most importantly, if the patient had had a previous thromboembolic event. Warfarin is indicated in these patients if they are reasonable candidates for the drug, with particular emphasis on its role in those who have had a previous embolic event, as secondary prevention;[6,8] the International Normalized Ratio (INR) should be in the 2.0 to 3.0 range (see also Chap. 44).

The exclusion of mitral stenosis in these prospective trials implies that the risks of emboli and the benefits of warfarin in these patients with associated atrial fibrillation are well understood; however, these are not thoroughly documented or proven. Retrospective assessment, however, suggests that such patients may have an embolic rate >5 percent per year. Until the role of warfarin is better defined, the authors recommend its use in patients with mitral stenosis and one or more risk factors.

LEFT VENTRICULAR DYSFUNCTION

Systemic or pulmonary thromboemboli occur at a rate of over 5 percent per year in patients with LV dysfunction. The type and degree of dysfunction indicating risk are not well defined, but LV systolic abnormalities have been related to emboli most often. However, antithrombotic therapy is of unproven value in preventing or reducing the embolic rate.[9,10] Still, the risk is sufficient that, with or without valve disease, consideration should be given to treatment. One approach (including the authors') is to use warfarin if the LV ejection fraction (EF) $\leq$0.30 and the patient is a reasonable candidate for this treatment.

PREVIOUS THROMBOEMBOLI

In other clinical situations (e.g., in patients with atrial fibrillation[6,8] or with a prosthetic valve[11-13]), a thromboembolic event defines patients at high risk for having an embolic event-i.e., a recurrent event. It is unclear whether this is true in patients with native valve disease, but we recommend lifelong warfarin

therapy.

HYPERCOAGULABLE CONDITIONS

Reasons to consider anticoagulant therapy are the presence of protein C, protein S, or antithrombin III deficiencies; the anticardiolipin antibody syndrome; resistance to activated protein C; or an associated malignancy. This is also true in patients with native valve disease (see also Chap. 44).

Screening for Patients at High Risk for Thromboemboli

The risk factors described above define patients requiring antithrombotic therapy. Transthoracic (TTE) and transesophageal echocardiography (TEE) are often performed in patients with valvular heart disease and in those who have had a systemic embolic episode. The use of these procedures in determining which patients are at risk of thromboemboli is not yet well defined; left atrial (LA) thrombi, a patent foramen ovale, an atrial septal aneurysm, or spontaneous echo contrast are occasional findings of concern, but the value of treatment is unproven. Until more is known, it may not be appropriate to screen patients with native valve disease who do not have one of the obvious clinical risk factors listed above.

Antithrombotic Treatment for Native Valve Disease

Antithrombotic therapy is not required in patients with native valve disease (Table 61-2) unless there is an associated risk factor.[2-14] Theoretically, the risk of thrombosis is greater with mitral valve disease as compared to aortic valve disease: there is more blood stasis, the LA may be larger, and the frequency of atrial fibrillation is greater. Still, the presence of mitral valve stenosis or regurgitation by itself is not a reason to initiate antithrombotic therapy. If there is a risk factor, antithrombotic therapy should be considered as defined in Table 61-2. If the patient is a reasonable candidate for warfarin therapy, the use of warfarin (maintaining an INR of 2 to 3) is appropriate if a patient with valve disease has atrial fibrillation (constant or paroxysmal) in combination with reduced LV function (heart failure or LV EF ≤0.30) or with associated severe hypertension or if there is a history of thromboemboli. There is a suggestion that women over the age of 75 with atrial fibrillation might be better protected by warfarin than aspirin,[8] but the bleeding rate on warfarin is significant in this patient population; treatment should be individualized and the INR more closely monitored. If a patient with atrial fibrillation has reasonable LV function, has not had a previous thromboembolism, and does not have other risk factors, aspirin (325 mg/day) is just as likely as warfarin to be protective against thromboemboli, without the associated expense and risk of warfarin therapy.[7-15] Unrelated to atrial fibrillation, warfarin therapy is recommended if a patient has had a previous thromboembolism or has LV dysfunction (heart failure and an ejection fraction ≤0.30).

Table 61-2: Antithrombotic Therapy-Native Valve Disease

I. *No therapy* if no thrombosis risk factor
II. *Therapy* if thrombosis risk factor present
    A. *Atrial fibrillation*
        1. Warfarin (INR 2-3) if congestive heart failure, hypertension, or previous thromboembolism
        2. Warfarin (INR 2-3) if valve lesion is mitral stenosis
        3. Aspirin (325 mg/day) or warfarin (INR 2-3) if valve lesion other than mitral stenosis
    B. *Previous thromboembolism*-warfarin (INR 2-3)
    C. *LV dysfunction* (ejection fraction ≤0.30-warfarin (INR 2-3)
    D. *Hypercoagulable state*-warfarin (INR 2-3)

Abbreviation: INR = International Normalized Ratio.

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Chapter 61: ANTITHROMBOTIC THERAPY FOR VALVULAR HEART DISEASE

PROSTHETIC HEART VALVES

All patients with mechanical valves require warfarin therapy. Even with the use of warfarin, the risk of thromboemboli in these patients is 1 to 2 percent per year;[16-19] the risk is *considerably higher* without treatment with warfarin.[11] The risk of an embolus in patients with biological valves in sinus rhythm has been approximately 0.6 to 0.7 percent per year, and most of those patients were not on warfarin therapy.[16,17,19-21] Almost all studies have shown that the risk of embolism is greater with a valve in the mitral position (mechanical or biological) as compared to a valve in the aortic position;[11,16] however, this was not found in one study.[17] With either type of prosthesis or valve location, the risk of emboli is probably higher in the first few days and months after valve insertion,[20] before the valve is fully endothelialized.

Antithrombotic Treatment for Prosthetic Valves (Table 61-3)

MECHANICAL VALVES

All patients with mechanical valves require warfarin, and the INR should be maintained between 2.0 and 3.5.[16,17,22-24] In patients with an aortic prosthesis without risk factors for emboli the INR should be between 2.0 and 3.0; in those with risk factors and in those with a mitral prosthesis the INR should be between 2.5 and 3.5.[2] Some valves are thought to be more thrombogenic than others (particularly the tilting-disk valves), and a case could be made for increasing the INR to between 3 and 4.5, but this would be associated with an increased risk of bleeding.[22,25,26] The addition of low-dose aspirin (50 to 100 mg/day) to warfarin therapy may further decrease the risk of thromboembolism.[27,28] The authors recommend the addition of aspirin (50 to 100 mg/day) to warfarin unless there is a contraindication to the use of aspirin (i.e., bleeding or aspirin intolerance). This combination is particularly appropriate in patients who have had an embolus while on warfarin therapy and/or who are known to be particularly hypercoagulable; for example, it is recommended by a committee addressing antithrombotic therapy in women during pregnancy.[29] It is important to note that the thromboembolic risk increases early after the insertion of the prosthetic valve; this is a reason to initiate heparin therapy within the first 24 to 48 h of surgery, with maintenance of the *activated partial thromboplastin time* (aPTT) at a "therapeutic effect" level (Table 61-4) until warfarin therapy has achieved the recommended INR level.

Table 61-4: 'Therapeutic Effect' of Heparin

Unfractionated heparin	An aPTT at 8 h after a dose that has been calibrated[a] to reflect a heparin level of 0.35 to 0.70 anti-Xa units
Low-molecular-weight heparin	An aPTT at 8 h after a dose that has been calibrated[a] reflect a heparin level of 0.7 to 1.1 anti-Xa units
During pregnancy	A heparin level of 0.6 to 0.7 anti-Xa units with unfractionated heparin or 0.10 to 0.11 anti-Xa units with low-molecular-weight heparin[b] (aPTT measurements do not accurately reflect heparin levels during pregnancy)

[a]Calibration of aPTT to heparin levels is performed in each clinical laboratory; thus the time (number of seconds) of the aPTT reflecting the 'therapeutic effect' levels will vary.
[b]*Important Note:* Although low-molecular-weight heparin is increasingly being utilized in many disorders, it is reemphasized here (see text) that its value in protecting against thromboemboli in patients with valve disease has *not* been proven. Therefore its use in patients with valve disease *cannot* be recommended at the present time.

BIOLOGICAL (TISSUE) VALVES

Because of an increased risk of thromboemboli during the first 3 months after implantation of a biological prosthetic valve, anticoagulation with warfarin is indicated.[20] The risk is particularly high in the first few days after surgery, and heparin therapy should be started within 24 to 48 h, with maintenance of the aPTT at a "therapeutic effect" level (Table 61-4) until an INR of 2.0 to 3.0 is achieved with warfarin. After 3 months, the tissue valve can be treated like native valve disease (see Table 61-2), and warfarin can be discontinued in approximately two-thirds of patients with biological valves.[16,17,20,30] Associated atrial fibrillation or an LV EF ≤0.30 are reasons for lifelong warfarin therapy.

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Chapter 61: ANTITHROMBOTIC THERAPY FOR VALVULAR HEART DISEASE

SPECIAL CLINICAL SITUATIONS

Altered Native Valves

Valve disease is increasingly being treated by interventional catheter techniques or surgical valve repair. It is difficult to give firm recommendations about antithrombotic therapy in these patients, but the recommendations given for treatment of native valve disease would seem most applicable in patients who have had surgical valve repair or catheter valve procedures (see Table 61-2).

Pregnancy

Pregnancy makes decisions regarding antithrombotic therapy for valve disease more difficult. Warfarin should be avoided in the first trimester of pregnancy, particularly in weeks 6 through 12.[29,31-32] It crosses the placental barrier and is associated with, and is the clear cause of, an embryopathy manifest in the live born as mental impairment, ocular atrophy, and facial and digital abnormalities. Therefore, warfarin should be discontinued immediately when pregnancy is recognized and heparin therapy should be initiated. The value of switching from warfarin to heparin *before* conception is uncertain. We suggest this when pregnancies are planned, since little is known about the consequences of warfarin taken in the first 6 weeks of pregnancy; however, this is often not clinically practical or feasible. Currently, the estimated risk of an embryopathy in well-managed warfarin therapy is ≤5 percent. While a return to warfarin during the second and third trimesters is recommended, there is concern that this drug may continue to endanger the fetus.

Heparin does not cross the placenta. While not devoid of problems (maternal bleeding, heparin-initiated thrombocytopenia, an increased risk of osteoporosis when used for longer than 1 month), successful pregnancies have occurred when adequate doses of the drug are administered subcutaneously at home throughout gestation.[33] Thromboembolic complications have occurred with heparin use during pregnancy in women with a mechanical prosthesis.[34,35] To minimize this, it is important to give a dose that will result in high "therapeutic effect" heparin levels (Table 61-4) prior to the next dose (this usually requires 15,000 to 30,000 units every 12 h).[29,36] Activated PTT measurements do not accurately reflect heparin levels during pregnancy.

Low-molecular-weight heparin (LMWH) is currently approved *only* for treatment of venous thrombosis. Still, there is no reason to suspect that it will not result in effective anticoagulation in patients with valve disease. It has been used safely in pregnancy,[37,38] does not cross the placenta, can be given once or twice daily, does not require regular blood test monitoring, and is associated with less thrombocytopenia and osteoporosis. More studies are needed.[39] Since there are *no* data about use of LMWH in patients with native valve disease or with prosthetic heart valves, LMWH cannot be recommended in such patients at this time.

Aspirin crosses the placenta and has been implicated as a cause of abortion and fetal growth retardation,[40] but it has been used so frequently without problems and has even been considered for use in all pregnant women as prophylaxis against preclampsia[41] that, when required for valve disease (see Table 61-2), it should be continued.

The concern about the use of antithrombotic therapy during pregnancy makes the decision about management of valve disease more difficult in women of childbearing age. If valve surgery is required, commissurotomy or valve repair is preferable because subsequent antithrombotic therapy is not required unless the woman has one of the risk factors for thrombosis (see Fig. 61-1). If a prosthetic valve is required in a woman of childbearing age, the advantage of a mechanical prosthesis is its durability. On the other hand, it obligates the woman of childbearing age to anticoagulation with warfarin because aspirin

therapy itself does not offer adequate protection against thromboembolism. The theoretical advantage of a biological prosthesis is that, except for the first 3 months after valve replacement, warfarin therapy is not required. However, as many as one-third of patients with biological valves have associated atrial fibrillation and require warfarin antithrombotic therapy. In addition, the rate of degeneration of biological valves accelerates dramatically in young patients and thus also in women of childbearing age.[42] Furthermore, some data suggest that the rate of structural valve degeneration is increased in pregnant women. The choice of a prosthesis should be individualized. A young woman capable of safely using warfarin when not pregnant and warfarin/heparin during pregnancy is best treated with a mechanical valve. If a woman's social situation or attention to her health is questionable in regard to the safe use of anticoagulation therapy, a biological valve may be considered. In young women needing aortic valve replacement, the Ross procedure should be considered (see also Chap. 60).

Surgery and Dental Care (Table 61-5)

The risk of increased bleeding during a procedure performed with a patient on antithrombotic therapy has to be weighed against the increased risk of a thromboembolism caused by stopping the therapy.

Table 61-5: Antithrombotic Therapy at the Time of Surgery

I. Usual approach
   A. If patient on warfarin
      Stop 72 h before procedure
      Restart on day of procedure or after control of active bleeding
   B. If patient on aspirin
      Stop 1 week before procedure
      Restart the day after procedure or after control of active bleeding
II. Unusual circumstances
   A. Very high risk of thrombosis if off warfarin[a]
      Stop warfarin 72 h before procedure
      Start heparin 48 h before procedure[b]
      Stop heparin 6 h before procedure
      Restart heparin within 24 h of procedure and continue until warfarin can be restarted and the INR is 2-3
   B. Surgery complicated by postoperative bleeding
      Start heparin as soon after surgery as deemed safe and maintain aPTT of 60-80 s until warfarin restarted and the INR is 2-3
   C. Very low risk from bleeding[c]
      Continue antithrombotic therapy

[a]Clinical judgment: consider this approach if recent thromboembolus or if three risk factors are present.[b]Heparin can be given in outpatient setting before and after surgery.[c]For example, local skin surgery, dental prophylaxis, and treatment for caries.
Abbreviation: aPTT = activated partial thromboplastin time.

The risk of stopping warfarin can be estimated and is relatively low if the drug is withheld for only a few days. As an example, and using a *worst case* scenario (e.g., a patient with a mechanical prosthesis with previous thromboemboli), the risk of a thromboembolus off warfarin could be as high as 10 to 20 percent per year. Thus, if the therapy were stopped for 3 days, the risk of an embolus would be 3/365 times 0.10 to 0.20, which equals 0.08 to 0.16 percent. There are theoretical concerns that stopping the drug and then reinstituting it might result in hypercoagulability-with a thrombotic "rebound." An increase in markers for activation of thrombosis with abrupt discontinuation of warfarin therapy has been observed,[43] but it is not clear that these increase the clinical risk of thromboembolism.[44] In addition, when reinstituting warfarin therapy, there are theoretical concerns of a hypercoagulable state caused by suppression of proteins C and S before the drug affects the thrombotic factors. Although the risks are only hypothetical, this is a reason to treat individuals at very high risk with heparin therapy until the INR returns to the desired range.

Although antithrombotic therapy must be individualized, some generalizations apply (see Table 61-6). For procedures where bleeding is unlikely or would be inconsequential if it occurred, antithrombotic therapy should not be stopped. This can apply to surgery on the skin, dental prophylaxis, or simple treatment for dental caries. Eye surgery, in particular surgery for cataracts or glaucoma, is usually associated with very little bleeding; when bleeding is likely or its potential consequences are severe, antithrombotic treatment should be altered. If a patient is on aspirin, it should be discontinued 1 week before the procedure and restarted as soon as it is considered safe by the surgeon or dentist.

Table 61-6: Antithrombotic Therapy at the Time of a Thromboembolic Event

I. Acute management
   A. *No* antithrombotic treatment for 72 h
   B. CT scan at 72 h
      1. *No (or little) hemorrhage* on CT:
         a. Heparin: aPTT in low 'therapeutic effect' (Table 61-4)
         b. Warfarin: continue heparin until INR in desired range[a]
      2. *Hemorrhage* on CT:
         a. No treatment until bleed stabilized or treated (7-14 days), then heparin and warfarin as above

II. Chronic management
   A. If embolus occurred *off* antithrombotic therapy:
      1. Treat with warfarin[a]
   B. If embolus occurred *on* antithrombotic therapy:
      1. If patient was on aspirin, switch to warfarin[a]
      2. If patient was on warfarin but INR was low, increase dose until INR in high desired range[a]
      3. If patient was on warfarin and INR was in desired range, add aspirin 80-325 mg/day
      4. If recurrent embolus or bleed on warfarin plus aspirin, assess valve for possible surgery

[a]See Tables 61-2 and 61-3.
Abbreviation: CT = computed tomography.

For most patients on warfarin, the drug should be stopped 48 to 72 h before the procedure to ensure the INR is ≤1.5 and restarted within 24 h after a procedure; admission to the hospital or a delay in discharge to give heparin is usually unnecessary.[2,27,44-47] Deciding who is at very high risk of thrombosis and thus should require heparin until warfarin can be reinstated may be difficult; clinical judgment is required. Heparin can usually be reserved for those who have had a recent thrombosis or embolus (arbitrarily within 1 year), those with demonstrated thrombotic problems when previously off therapy, and those with three or more risk factors. When used, unfractionated heparin should be started 24 h after warfarin is stopped (i.e., 48 h before surgery) and stopped 4 to 6 h before the procedure. The heparin should be restarted as early after surgery as bleeding stability allows and the aPPT maintained at a "therapeutic level" (Table 61-4) until warfarin is restarted and the desired INR can be achieved. Home administration and management of heparin (and warfarin) can be arranged to minimize time in the hospital. LMWH is even more easily utilized outside of the hospital (see also Chap. 48); however, there are no data with its use in patients with valve disease.

Cardiac Catheterization and Angiography

Antiplatelet therapy or heparin need not be stopped for these procedures. Protamine can be given to the patient on heparin if bleeding occurs. In an emergent or semiemergent situation, cardiac catheterization can be performed with a patient on warfarin, but, preferably, the drug should be stopped 72 h before the procedure and restarted the day of the procedure. This is also true for most patients with prosthetic heart valves (mechanical as well as biological). If a patient is at very high risk of thromboembolism, heparin should be started 48 h before the procedure and continued until warfarin is restarted and the desired INR is

achieved. If the catheterization procedure is to include a transseptal puncture (especially in a patient who has not had previous opening of the pericardium), patients should be off all antithrombotic therapy and the INR should be <1.2-the same is also true if an LV puncture is to be performed.[48]

Therapy at the Time of an Active Thromboembolic Event

VALVE THROMBOSIS

Thrombosis of a valve, usually a prosthetic valve, can result in severe hemodynamic compromise. If recognized (TEE can be diagnostic[49]), this complication may be treated with thrombolytic therapy, although the risk of bleeding and of emboli at the time of treatment is high.[50,51] Thrombolytic therapy is most effective for a "young thrombus." Many valves, however, have pannus formation and tissue ingrowth on the valve, which is not amenable to thrombolytic therapy. Therefore, we recommend emergency surgery rather than thrombolytic therapy in the patient with severe hemodynamic compromise. If a patient is not a surgical candidate, thrombolysis should be attempted.[2,52] Streptokinase or urokinase should be initiated but stopped at 24 h if there is no improvement by Doppler echocardiography and at 72 h even if hemodynamic recovery is incomplete.[2] This should be followed by heparin until high INR levels are achieved with concomitant warfarin therapy (INR 3 to 4 for aortic prostheses or 3.5 to 4.5 with mitral prostheses).

THROMBOEMBOLIC EVENT

An embolic event often indicates inadequate therapy for that patient's circumstances. Data and opinions about optimal timing for initiating or continuing anticoagulants in patients in whom an embolus is the presumed cause of a stroke are conflicting.[2,53-55] Ideally, treatment would be started early to prevent recurrent emboli, but the early use of heparin (within 72 h) is associated with a 15 to 25 percent chance of converting a nonhemorrhagic into a hemorrhagic stroke.[54] While a case can still be made for immediate use of heparin,[53,54] the early recurrence of an embolus in patients with valve disease while off anticoagulants has not been clearly documented. Data are insufficient to provide definitive treatment outlines, but the authors' practice is listed in Table 61-6.

ACUTE MANAGEMENT OF AN EMBOLIC EVENT

Antithrombotic therapy should be withheld or stopped for 72 h. If a computed tomography (CT) scan at that time reveals little or no hemorrhage, heparin should be administered to maintain an aPPT at the lower end of the therapeutic level (Table 61-4) until warfarin, started at the same time, results in the desired INR (see Tables 61-2 and 61-3). If the CT scan demonstrates significant hemorrhage, antithrombotic therapy should be withheld until the bleed is treated or has stabilized (7 to 14 days). Anticoagulation can then be started as just described.

LONG-TERM MANAGEMENT

If the embolic event occurs when a patient is *off* antithrombotic therapy, long-term warfarin therapy is required (see Tables 61-2 and 61-3). An exception may be those with mitral valve prolapse; aspirin (325 mg/day) is recommended for those who are judged to have had a minor event. If the embolic event occurs while the patient is *on* antithrombotic treatment, therapy should be individualized. Those who are on warfarin but in whom the INR was low at the time of the embolus should have the dose increased into the high end of the desired range (see Tables 61-2 and 61-3). If the embolus occurs in a patient despite an INR in the desirable range, aspirin (50 to 100 mg/day) should be added to the warfarin. Embolism recurring with this combination should lead to consideration of possible valve surgery if the valve is the likely source of the thrombus.

Therapy at the Time of a Bleed

With significant bleeding, antithrombotic therapy should be stopped and, if the patient is at risk, drug effects should be reversed. If possible, the site of bleeding should be corrected and antithrombotic therapy restarted as soon as possible. If this is not possible, treatment decisions are difficult. In patients with a

mechanical prosthesis or multiple risk factors for thromboemboli, acceptance of intermittent bleeding with acute management for the bleeds may be necessary. In valve patients who are at lower risk of emboli or in whom the role of antithrombotic treatment is less clear (e.g., LV dysfunction), it may be optimal to withhold chronic therapy or, if a patient is on warfarin, to switch to aspirin. In some patients with mechanical valves, consideration should be given to replacing the mechanical valve with a biological valve, for example, in those who have had multiple, large life- or organ-threatening bleeds.

Antithrombotic Therapy in the Patient with Endocarditis

If a patient with valve disease develops endocarditis, antithrombotic therapy should be continued.[2,56] If the patient presents with or develops an embolic event involving the central nervous system, therapy should be as described above for acute embolic events. Additionally, the issue of whether or not the embolus is due to thrombus or infected vegetation should be addressed. If thrombus is likely, the chronic anticoagulation program will also require alteration.

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Part 10: CONGENITAL HEART DISEASE
Chapter 62:

CARDIOVASCULAR DISEASES DUE TO GENETIC ABNORMALITIES

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Genetic factors play a significant role in the pathogenesis of many if not all cardiovascular disorders. Malformations of the heart and blood vessels account for the largest number of human birth defects, occurring in about 1 percent of all live births; among stillbirths, the prevalence is estimated to be tenfold higher.[1,2] In conjunction with cytogenetics (the study of chromosomes and their abnormalities), molecular genetics provides an opportunity to decipher the genetic basis of cardiovascular diseases. Genetic diagnosis and screening for genetic disorders will soon be incorporated into standard practice.[3] The goal of the Human Genome Project[4] is to identify all of the genes by the year 2001 (see Chap. 7).[5] The challenge for the clinical and investigative cardiologist is to link these genes to their specific physiologic or pathologic function.[6] It is thus imperative that the cardiologist understand the basis for genetic disorders so as to have a better appreciation of the medical, ethical, and moral implications.[7]

BASIS FOR GENETIC TRANSMISSION

All hereditary information is transmitted through DNA, a linear polymer composed of purine (adenine, guanine) and pyrimidine (cytosine, thymine) bases (see Chap. 4). The basic hereditary unit is the gene, which consists of a distinct fragment of DNA that encodes for a specific polypeptide (protein). It is estimated there are only about 100,000 genes, although there is enough DNA to code for several hundred thousand genes. However, less than 5 percent of the DNA is used to code for genes. Each individual has two copies of each gene-called alleles. The genes are localized in linear sequence along 23 pairs of chromosomes, the rod-shaped bodies derived from the parents of each individual. Each parent contributes one member of each chromosome pair (the pair is referred to as *homologous chromosomes*) and thus one copy of each gene. The site at which a gene is located on a particular chromosome is called the *genetic locus*. A given gene always resides at the same specific locus on a particular chromosome, so the loci on homologous chromosomes are identical but the alleles residing at these loci may be the same or different. When the same loci on two homologous chromosomes have identical alleles, the individual is homozygous. When the two genes differ (i.e., two different alleles present at the locus), the individual is heterozygous at that locus. Each individual is homozygous at some loci and heterozygous at others, and, based on present knowledge, at least one-third of human genes have polymorphic forms. The gene, transmitted to each offspring during the union of sperm and ova, passes on the genetic information to the offspring (genotype), which, through the synthesis of their corresponding proteins, determines the observable characteristics of an individual (phenotype). The genetic information carried in the gene's DNA is coded by the sequence of the four bases. Translation of this information into protein is through a translational code passed on through messenger ribonucleic acid (mRNA), whereby each specific amino acid is encoded by three bases referred to as a *codon* (Chap. 4). The mRNA transcribed from the gene serves as the template that determines which amino acids are included and their sequence in the resulting polypeptide. Although it is true each gene encodes for a unique protein, it is preferable to use polypeptide, since many proteins are single polypeptides and other proteins consist of several polypeptides which may be from a single gene or multiple genes. The 23 pairs of chromosomes include 22 pairs of autosomes (chromosomes 1 to 22) and one pair of sex chromosomes, X and Y. Females have two X chromosomes, while males carry one X and one Y chromosome. Both autosomal alleles are

potentially active in specifying RNA copies of their DNA sequences, but the expression of each gene depends on the cell type, developmental stage, and regulatory molecules that interact with promoter sequences, and enhancer sequences that control gene transcription. In cells that carry two X chromosomes, whether these are derived from normal females or XXY individuals with Klinefelter syndrome, only one X is active after early embryogenesis.

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ORIGIN OF GENETIC DISEASE

The three broad categories of inherited diseases are chromosomal abnormalities, single gene disorders, and polygene disorders (Table 62-1). Thus, hereditary and congenital diseases may be due to chromosomal abnormalities or mutations within a single gene or multiple genes. A mutation is a stable, heritable alteration in DNA caused by a number of factors, including environmental agents such as radiation, chemicals, and viruses as well as baseline changes in the fidelity of transfer of sequences. Since offspring typically resemble their parents, it is assumed that the DNA nucleotide sequences remain stable. Base sequence changes do occur, however, albeit at a slow rate compared to the overall life span of humans, and these changes occur by a number of different mechanisms. Mutations can involve a visible alteration at the level of the chromosome, such as deletion or translocation of a portion of the chromosome, whereby often several genes are eliminated or altered. Chromosome alterations (discussed later), especially those involving too many or too few chromosomes (called an euploidy), are quite common in human development. The sequence of each codon determines the amino acid, and the linear sequence of the codons in the mRNA is collinear with the linear sequence of the amino acids in the protein. A change in even one amino acid, if critical to the function of the protein, will result in altered function or lack of function, with a concomitant change in the phenotype. Since proteins are the working molecules derived from genes, mutations in genes exert their deleterious effects via structural alteration of the proteins, whether they be enzymes, regulatory proteins, or structural proteins. On the average, a mutation occurs every 106 cell divisions, and, obviously, only mutations occurring in the gametes are transmitted. On the average, a gene undergoes one mutation per 200,000 years.

Table 62-1: Inherited Disorders

Chromosomal abnormalities	Polygene disorders
Single-gene disorders	

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GENETICS OF SINGLE-GENE DISORDERS

Inherited disorders due to a single abnormal gene are transmitted to offspring in a predictable fashion termed *mendelian transmission*. These inheritance patterns produce phenotypes that are inherited according to Mendel's laws of inheritance. As previously noted, in each individual there exists two copies of each gene, referred to as alleles, one obtained from the mother and one from the father. Mendel's first law states that each of the two alleles located on separate chromosomes segregates independently and is passed unchanged into different gametes at the formation of the next generation. Thus, the odds of getting the mother's allele versus the father's are by chance alone, namely, 50 percent. Mendel's second law states that genes on the same chromosome also assert themselves independently through the process of crossover between chromosomes (discussed below). The greater the distance between two loci, the more likely they are to be separated during genetic transmission. As a result of gene mutations, abnormal genes located on any of the 22 autosomal pairs or the two sex chromosomes may produce phenotypes inherited by simple patterns classified as autosomal (dominant or recessive) or X-linked, respectively. When different genes induce the same phenotype, it is referred to as *genetic heterogeneity*, and most diseases in humans exhibit genetic heterogeneity. The same disease may be due to multiple mutations in the same gene (*allele heterogeneity*) or it may be due to a single or multiple mutations in two or more genes (*locus heterogeneity*). Within any one family, however, the gene and the mutation responsible for the disease are the same and only rarely would two genes be transmitted for the same disease. A good example is familial hypertrophic cardiac myopathy (HCM), in which eight different genes have been recognized with multiple mutations in each. Genetic heterogeneity is to be distinguished from polygenic disorders, such as atherosclerosis, which are due to the interaction of several genes. As noted above, mutations can involve a microscopically visible alteration, such as deletion or translocation of a portion of the chromosome, or they can involve a minute change in one purine or pyrimidine base in the DNA sequence of a single codon. Mutations involving only a single nucleotide are known as point mutations and are responsible for 70 percent or more of all adult single gene disorders (Table 62-2). A point mutation may be a substitution of one nucleotide for another, resulting in a different amino acid being encoded (missense mutation); or it may change the codon from encoding for an amino acid to that of a stop codon, which will truncate the protein (truncated mutant); or it may eliminate a stop codon so the protein is elongated (elongated mutant). Finally, a nucleotide may be deleted or added, which results in a frame shift, and the gene is read entirely differently (nonsense mutation), resulting in a nonfunctioning protein. If a purine nucleotide is substituted for a pyrimidine, the mutation is referred to as a *transversion*, while if purine or pyrimidine substitutes for another purine or pyrimidine, respectively, it is called a *transition*. Other mutations may result from deletion or addition of several nucleotides. An example of the latter is the defect responsible for myotonic dystrophy, where a triplet repeat of several thousand nucleotides in length is inserted into the 3′ end of the gene. Another type of mutation is known as *gene conversion*, where two genes interact and part of the nucleotide sequence of one gene becomes incorporated into the other. Mutations in genes exert their deleterious effects via structural alteration of enzymes, regulatory proteins, or structural proteins. The terms *dominant inheritance* and *recessive inheritance* refer to characteristics of the phenotype and are not characteristics of the gene per se. Dominant inheritance implies that a person with one copy of a mutant allele and one copy of the normal allele develops a phenotype of the mutant allele. Recessive traits, on the other hand, require both alleles to be mutant to develop a phenotype. This situation usually occurs when the patients are consanguineous, with each carrying mutant alleles, or when the mutant allele is common in the population, as is seen in sickle cell anemia.

Table 62-2: Single-Gene Disorders

Alteration of a single nucleotide (point mutation)
Missense
Truncated
Elongated
Nonsense
Synonomous
Deletion of several nucleotides
Addition of several nucleotides

Genetic Penetrance and Expressivity

The percentage of individuals with a disease-related gene who have one or more features of the disease is referred to as *penetrance*. Penetrance is an all-or-none phenomenon, and any manifestation, however minute, indicates that the gene has full penetrance in that individual. Nonpenetrance refers to lack of any observable phenotype. This feature is to be distinguished from *expressivity*, which refers to the variable nature of the clinical features. Thus, by definition, to have expressivity, the trait must be penetrant. Numerous genetic and environmental factors can affect expression of a gene, making it nearly impossible to determine which factor is most important in a specific individual or specific disease. These factors include (1) genetic background, (2) age-dependency, (3) sex influence and sex limitation, (4) exogenous factors, (5) maternal factors, (6) modifying loci, and (7) gene alterations.

Patterns of Inheritance

AUTOSOMAL DOMINANT INHERITANCE

Dominant disorders are those that have phenotypic manifestations (disease) in heterozygous individuals-persons carrying only one abnormal allele, with the other allele on the homologous chromosome being normal. In autosomal dominant disorders, both males and females can be affected, and since alleles segregate independently at meiosis, there is a 50-50 chance that the offspring of an affected heterozygote will inherit the mutant allele. Not all affected individuals, however, must have an affected parent because, in all autosomal dominant diseases, a certain proportion of cases occur due to a new mutation (i.e., they are sporadic). The parent whose germ cells contain the new mutation will be clinically normal, since the mutation affects only a single germ cell, but will transmit the disease-causing allele to half of his or her offspring. Autosomal dominant inheritance can be misdiagnosed as sporadic if there is low expressivity in the phenotypically normal parent carrying the mutant allele or if extramarital paternity has occurred. The following features are characteristic of autosomal dominant inheritance (Fig. 62-1): (1) each affected individual has an affected parent unless the disease occurred due to a new mutation or the heterozygous parent has low expressivity; (2) equal proportions (i.e., 50-50) of normal and affected offspring are likely statistically to be born to an affected individual; (3) normal children of an affected individual bear only normal offspring; (4) equal proportions of males and females are affected; (5) both sexes are equally likely to transmit the abnormal allele to male and female offspring, and male-to-male transmission occurs; and (6) vertical transmission through successive

generations occurs. Two other features are characteristically seen in autosomal dominant diseases that help to differentiate this type of inheritance from autosomal recessive disorders: delayed age of onset and variable clinical expression. The former is commonly seen in such disorders as familial HCM, while the latter may occur in Holt-Oram syndrome, in which the patient may present with an atrial septal defect (ASD) and skeletal abnormality of the upper extremity in combination or with either of these abnormalities individually. Examples of autosomal dominant primary heart disease include HCM and Romano-Ward long-QT syndrome.

AUTOSOMAL RECESSIVE INHERITANCE

Autosomal recessive phenotypes are clinically apparent when the patient carries two mutant alleles (i.e., is homozygous) at the locus responsible for the disease state. The disease-causing gene is found on one of the 22 autosomes, and thus both males and females will be equally affected. Clinical uniformity is typical, and disease onset generally occurs early in life. Recessive disorders are more commonly diagnosed in childhood than are dominant diseases. Only one in four children (25 percent) on average, will be affected. The following are characteristics of autosomal recessive disorders (Fig. 62-1): (1) parents are clinically normal heterozygotes; (2) alternate generations are affected, with no vertical transmission; (3) both sexes are affected with equal frequency; and (4) each offspring of heterozygous carriers has a 25 percent chance of being affected, a 50 percent chance of being an unaffected carrier, and a 25 percent chance of inheriting only normal alleles. Examples of autosomal recessive disorders affecting the heart include Jervell and Lange-Nielsen long-QT/deafness syndrome and Pompe's (type II glycogen storage) disease.

X-LINKED INHERITANCE

X-linked inherited disorders are caused by genes located on the X chromosome; therefore the clinical risk and severity of disease differ between the sexes. Since a female has two X chromosomes, she may carry either one mutant allele (heterozygote) or two mutant alleles (homozygote); the trait may therefore display dominant or recessive expression. Males have a single X chromosome (and one Y chromosome); therefore they are expected to display the full syndrome whenever they inherit the abnormal gene from their mother. This development of the trait occurs regardless of whether the mother carrying the mutant allele exhibits a recessive (i.e., clinically silent) or dominant (i.e., clinically apparent) trait. Hence, the terms *X-linked dominant* and *X-linked recessive* apply only to the expression of the gene in females. Since males must pass on their Y chromosome to all male offspring, they cannot pass on mutant X alleles to their sons; therefore no male-to-male transmission of X-linked disorders can occur. On the other hand, males must contribute their one X chromosome to all daughters. All females receiving a mutant X chromosome are known as *carriers*, and those who become affected clinically with the disease are known as *manifesting female carriers*. The characteristic features of X-linked inheritance (Fig. 62-1) include (1) no male-to-male transmission; (2) all daughters of affected males are carriers; (3) sons of carrier females have a 50 percent risk of being affected, and daughters have a 50 percent chance of being carriers; (4) affected homozygous females occur only when an affected male and carrier female have children; and (5) the pedigree pattern in X-linked recessive traits tends to be oblique because of the occurrence of the trait in the sons of normal carriers sisters of affected males (i.e., uncles and nephews affected). Examples of X-linked disorders of the heart include X-linked cardiomyopathy, X-linked cardioskeletal myopathy (Barth's syndrome) and those X-linked diseases in which the heart is affected, such as muscular dystrophy (MD) (e.g., Duchenne/Becker and Emery-Dreifuss MD).

MITOCHONDRIAL INHERITANCE

Another inheritance pattern described in patients with cardiovascular anomalies occurs because of abnormalities of the mitochondrial genome. Generation of energy is dependent on the oxidative

phosphorylation process within the mitochondria. Within many mitochondria is a single chromosome that encodes for a number of the enzymes of oxidative phosphorylation (i.e., encodes for 13 of the 69 proteins required for oxidative metabolism) and the transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) required for their translation. The remaining enzymes of the oxidative-phosphorylation pathway are encoded by genes on the nuclear chromosomes, and the resultant proteins are transported into the mitochondrion. Genetic defects of oxidative phosphorylation, therefore, can be due either to gene mutations within the X chromosome or autosomes (i.e., nuclear chromosomes), resulting in diseases that behave as Mendelian recessive traits, or to mitochondrial genome defects that cause diseases with nonmendelian traits. These differences may be explained by events of conception, since the spermatocyte contributes few or no mitochondria to the zygote (Fig. 62-2). The entire mitochondrial complement present in a fetus must therefore be derived from the mitochondria already present in the cytoplasm of the oocyte. Thus, phenotypes due to mitochondrial DNA mutations demonstrate maternal inheritance only. The characteristic features of mitochondrial inheritance of disease (Fig. 62-1) include (1) equal frequency and severity of disease for each sex; (2) transmission through females only, with offspring of affected males being unaffected; (3) all offspring of affected females may be affected; (4) extreme variability of expression of disease within a family (may include apparent nonpenetrance); (5) phenotypes may be age-dependent; (6) organ mosaicism is common. An example of mitochondrial inherited cardiac disease is the cardiomyopathy of Kearns-Sayre syndrome.

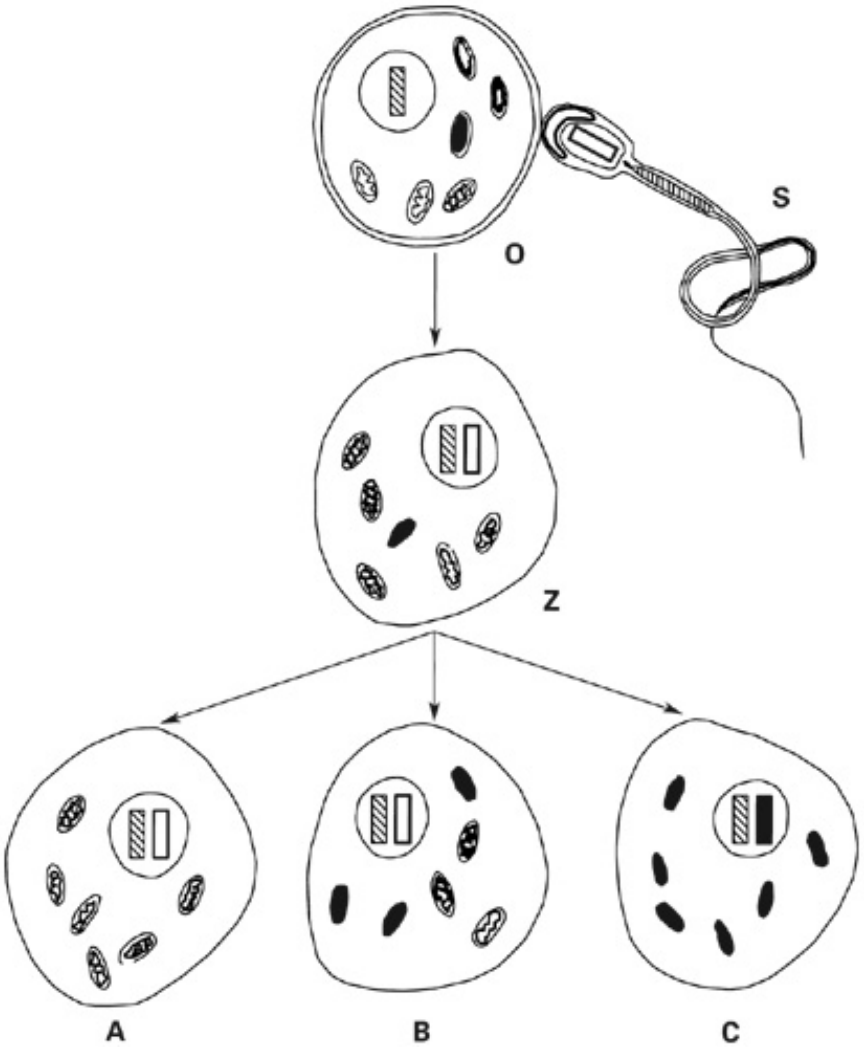

Figure 62-2: Cartoon (not to scale) illustrating maternal inheritance of mtDNA, compared with

biparental inheritance of nuclear genes, and the random distribution of normal and mutant mitochondrial genomes in daughter cells of the zygote. It is assumed for simplicity that individual mitochondria contain either normal (open mitochondria) or mutant (filled mitochondria) mtDNA, not both. O = oocyte; S = sperm; Z = zygote; A, B, C = daughter cells of zygote, representing stem cells of different tissues. (Reprinted with permission from DiMauro S et al. Mitochondrial encephalomyopathies. *Neurol Clin* 1990; 8:494.)

POLYGENIC INHERITANCE OF CARDIAC DISEASE

Disorders such as hypertension or ischemic heart disease are believed to require concomitant mutations in several genes-i.e., they are polygenic hereditary disorders (discussed in Chap. 7). The genes responsible for polygenic hereditary disorders are difficult to map, since computational methods to describe their mode of inheritance are only now being explored.[8] Over the past two decades, this type of inheritance has been invoked for a large number of disorders, including coronary artery disease and congenital heart disease. In multifactorial, or polygenic, genetic diseases, multiple genes interact in a cumulative fashion to induce the disease or provide an increased risk of developing the disease. This multifaceted process is illustrated by coronary artery disease, in which one common phenotype is myocardial infarction due to thrombosis superimposed on atherosclerosis. There are many single-gene disorders that alter plasma lipoproteins and contribute to atherosclerosis (see Chaps. 7, 35, and 38). Several other genetic risk factors have been identified that predispose to atherosclerosis, such as the paraoxonase gene or homocysteine gene.[9] The phenotype of acute myocardial infarction is more likely if the individual, in addition to atherosclerosis, has a mutant form of fibrinogen[10] or mutant forms of other clotting factors, discussed in detail in Chap. 7.

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Chapter 62: CARDIOVASCULAR DISEASES DUE TO GENETIC ABNORMALITIES

OVERVIEW OF CHROMOSOMAL MAPPING AND IDENTIFICATION OF A DISEASE-RELATED GENE

Identification of a disease-causing gene, in the setting where the protein is unknown, was until the 1980s nearly impossible. Familial hypercholesterolemia and some of the thalassemias are disorders in which genes were isolated and cloned, knowing the protein. For the majority of diseases, however, neither the defect nor the protein is known. Technical advances[11] aiding chromosomal mapping include (1) computerized linkage analysis, (2) development of highly informative DNA markers, and (3) detection of markers by polymerase chain reaction (PCR).[11] The 46 chromosomes of the human genome contain 3 billion base pairs (bp). To locate a particular gene, one must first map the chromosomal location and its relative position. This process requires certain chromosomal landmarks. Identification of a particular locus is made possible by showing that the disease-related gene of interest is on the same chromosome and in close proximity to one of these landmarks, a method referred to as *genetic linkage analysis*. This technique requires a family with a disease that is transmitted over at least two generations (and preferably three) with at least 10 affected individuals, although even 6 or 7 affected individuals may be adequate, depending on the structure of the family. A landmark, referred to as a DNA or chromosomal *marker*, is a polymorphic sequence of DNA, the chromosomal position of which is known and can be detected by analyzing an individual's DNA (discussed in detail below). A major limitation until recently was the lack of markers evenly distributed across each of the chromosomes. Today there is a marker available at least every 1 million base pairs on all chromosomes.[12,13] Genetic distance is measured in terms of centimorgans (cM), named after the geneticist T. H. Morgan, and 1 cM approximates 1 million bp. Markers, like genes, have two alleles and are transmitted to offspring according to Mendel's law, with the individual being heterozygous or homozygous for that marker. If a marker is homozygous, it is not informative for genetic linkage. Hence, several markers in the same region may have to be analyzed to find one that is heterozygous in that individual. When all of the markers are placed together on each chromosome and the genetic distance between them is estimated, a *genetic map* is produced. A map of over 5000 highly informative markers has been developed, which has significantly accelerated the mapping of disease-related genes-an achievement that provides the foundation for genetic linkage analysis.[13] Each gene, allele, or marker is transmitted independently; thus, the odds of any two genes (or a marker and a gene) being coinherited are by chance alone (50 percent), even though they are on the same chromosome. The homologous pairs of chromosomes are assorted, and one from each parent is transmitted to the offspring by chance. Genetic diversity from homologous chromosomes segregating independently would produce 223 types of gametes; in other words, the probability of an offspring inheriting a set of chromosomes identical to those of a parent is one in 8,388,608.[14] If this were the only mechanism for diversity, all of the genes on a particular chromosome would be coinherited in the next progeny. This does not happen. Genes on the same chromosome are transmitted independently unless they are in close physical proximity to each other. Genes on the same chromosome are transmitted independently by the mechanism of crossover between homologous chromosomes (Fig. 62-3), which provides continual mixing of the genes during every meiosis and is the predominant reason why no two individuals have the same genotype unless they are identical twins. Prior to meiosis, the two homologous chromosomes come together and form bridges (*chiasmata*) such that segments of equal proportion are exchanged between them, giving rise to crossover of various genes. There is no net loss of chromosomal material or genes, but crossover leads to a constant intermixing of the chromosomes such that no two offspring will ever be identical. Crossovers occur only between homologous chromosomes. The loci occupy the same chromosomal position on the homologous chromosome

on which they are combined as they had on their original homologous chromosome. On average there are 33 crossovers between homologous chromosome pairs per meiosis.[14] In genetic parlance, crossing over is referred to as recombination.

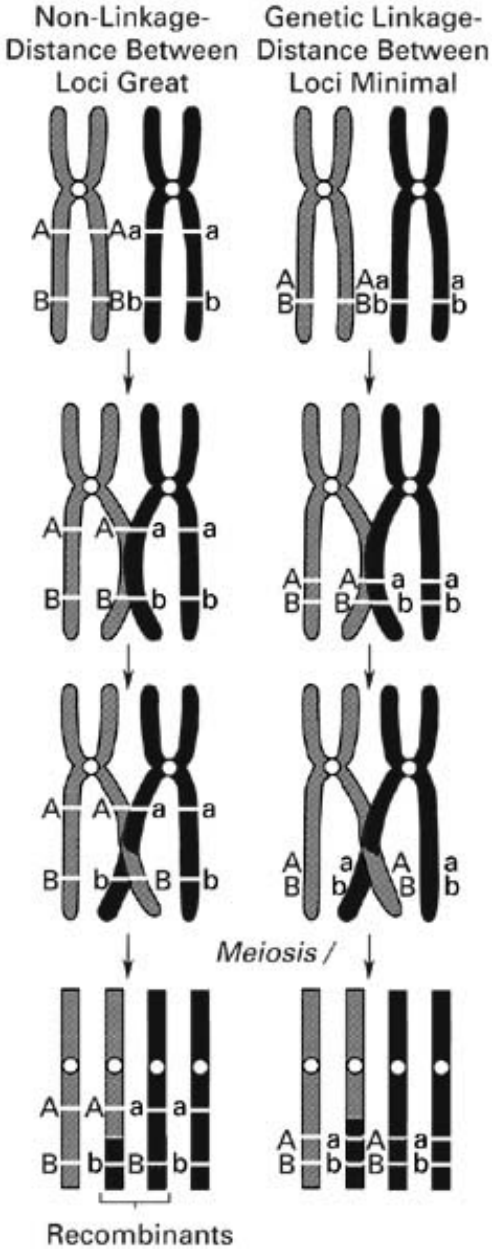

Figure 62-3: Comparison of nonlinked genes (*left*) and linked genes (*right*). In nonlinkage, the distance between loci is large, allowing crossing over to occur and resulting in recombinants after meiosis. The distance between linked genes is comparatively small, thereby minimizing the chance for recombinants.

Concept of Genetic Linkage Analysis

Despite the independent assortment of chromosomes and genes, the genes (alleles) on two or more loci are often coinherited because they are so close together that the chance of a chiasmatic bridge forming between them is less likely. Thus, breakage and recombination of the chromosomes does not occur and they tend to be coinherited more often than by chance alone; by definition this means the two loci are in genetic linkage. Any two loci coinherited more than 50 percent of the

time are said to be genetically linked.[15] To map the chromosomal locus responsible for a disease-related gene, one selects DNA markers that are evenly distributed across the chromosomes. DNA is collected from all the members of a family (normal and affected) and analyzed for these markers. If one or more DNA markers is coinherited in more than 50 percent of the affected individuals, the locus where the marker resides is on the same chromosome and in close physical proximity to the locus of the gene responsible for the disease. This is referred to as *genetic linkage* between the disease (gene) and the marker. Once a disease is linked to a marker of known chromosomal locus, it follows that the disease locus is on the same chromosome and in close proximity. The concept of linkage analysis is illustrated in Fig. 62-3. Shown in the panel at the right is an illustration of genetic linkage between a locus for a DNA marker and that of a disease that is inherited in a mendelian dominant fashion. The locus, designated with an "A," carries the allele responsible for the disease. The corresponding locus, "a," on the homologous chromosome has the allele that codes for the same protein but has not undergone a mutation and is thus the normal allele. The loci designated "B" and "b" represent alleles of a DNA marker of known location that has nothing to do with the disease. In the panel on the right, the disease and the marker loci are so close that they tend to be coinherited within the family, whereas in the panel on the left, the DNA marker of known location is so far from the locus carrying the disease allele it is not coinherited but separate by chance. The calculation necessary to prove definitively that genetic linkage exists between a marker and a disease-related locus is sophisticated and requires advanced computer programs. The odds for and against linkage are calculated, and linkage exists if the odds in favor of linkage are at least 1000:1. To avoid the cumbersome ratio (1000:1), the logarithm to base 10 is derived, which is 3 (i.e., 10^3), and is referred to as the LOD score (log of the odds). If the LOD score is -2 (i.e., 10^{-2} or 100:1 odds against linkage), it excludes linkage. The likelihood of two genes being separated by recombination increases in proportion to the distance between them. The distance between a marker and a disease-causing gene when genetically linked is quite variable and may be anywhere from 1000 kilobase pairs (kbp) to 50,000 kbp but is usually within 1000 to 10,000 kbp.[16] The inherent resolution of genetic linkage analysis is never better than 1000 kbp. It is possible on the basis of linkage analysis alone to construct a chromosomal map of all the markers, with the distance between the various markers estimated in centimorgans. This is a complex calculation derived from the number of recombinations between the markers during meioses. The recombination frequency between two markers, two genes, or a gene and a marker is the ratio of the number of crossover events to the total number of meioses. The lower the recombination frequency between the locus of a marker and that of a disease-related gene, the closer those two must be in physical distance on the chromosome. Even though the locus of the marker and that of the disease-related gene are in close enough proximity to be genetically linked, recombination may occur, and the extent to which recombination does occur reflects roughly the physical distance between the two loci. The recombination fraction (or *theta*) is used to develop a means of estimating the genetic distance (in centimorgans) between genetically linked loci. A recombination frequency or crossover of 1 percent between two loci, whether occupied by two genes or one gene and a marker, reflects a physical distance between them of approximately 1 million bp (1 cM).[16] For a marker and a gene separated by 1 cM, this means the chance of a crossover between them during meiosis is only 1 percent; thus, the chance of being coinherited is 99 percent. This is a statistically derived genetic map, however, and the distances are only approximate. The correlation between the percent crossover and the physical distance in base pairs varies somewhat from chromosome to chromosome and from region to region even on the same chromosome. For example, recombination is more frequent in the telomeric than in the centromeric portion of the chromosome and is also more frequent in females. If the marker locus and the disease-related locus are close, such as 5 to 10 cM, then a single crossover may be uncommon and a double crossover rare. Two loci may be 20 to 40 cM apart, however, and a double crossover occurs, which recombines the locus with the original chromosome and leads to coinheritance of the two (linkage of the two loci). When this occurs, the genetic distance is misleading and represents a gross underestimation of the true physical distance between the two loci.

Chromosomal Markers and Their Identification

A chromosomal marker (as defined above) is any DNA sequence of known chromosomal location that is polymorphic for the population (two or more alleles). The greater the number of alleles, the more informative the marker. When compared between individuals in the population, the DNA of the human genome shows a difference in the nucleotide sequence (polymorphism) every 300 to 500 bp. Polymorphisms occur more frequently in the sequence of the unexpressed DNA (intron) than in DNA coding for proteins (exon). Until recently, the most common chromosomal marker was that of restriction fragment length polymorphism (RFLP)[17] identified by Southern blotting. These markers have been replaced by what are referred to as short tandem repeat polymorphisms (STRP),[18] which occur more frequently, are more informative, and are more conveniently and rapidly detected than are RFLPs[19] (Fig. 62-4). Distributed throughout the human genome are repeats of dinucleotides, trinucleotides, or tetranucleotides that are repeated in tandem (microsatellites) and may vary anywhere from 60 to 300 repeats. The number of tandem repeats of STRPs, which provide for marked polymorphism, occur about every 500 bp throughout the human genome. The dinucleotide repeats of cytosine-adenosine are more common than trinucleotide or tetranucleotide repeats. A major advantage of STRPs is rapid and convenient detection by PCR rather than requiring Southern blotting, as is necessary for RFLPs. PCR requires only a nanogram of DNA as opposed to a milligram for RFLPs, and results are available in only 1 to 24 h as opposed to 9 to 10 days for Southern blotting. The resolution of STRPs detected by PCR is much better than by Southern blotting and, since STRPs have multiple alleles (as opposed to RFLPs, which have only two alleles), they are much more informative for genetic linkage. A more recent marker is that of single nucleotide polymorphism, which may represent the markers of the future.[17-19]

Identification of the Gene

Once the chromosomal location of a gene has been mapped, the first technique in attempting to identify the gene is referred to as the *candidate gene approach*. Over 5000 loci have now been mapped for human genes and over 1000 genes recorded in a gene bank. In addition, there are over 50,000 expressed sequenced tags (ESTs) mapped. The ESTs are unique DNA sequences of 100 to 200 bp, each of which is believed to represent a unique gene.[20] These genes and ESTs are entered through a worldwide network of databases[21] in the United States, Europe, and Japan that is updated on a daily basis. Once a locus is identified on a chromosome, genes previously known to be localized to that region become candidate genes for the newly mapped locus. These genes are amplified, usually by PCR, to determine if there is a mutation that segregates with the disease. If none of the candidate genes in the region is shown to have a mutation that cosegregates with the disease, it may be necessary to clone the region. This approach is referred to as *positional cloning*, so named because a region is cloned knowing only its position relative to the genetically linked marker. Positional cloning is usually not attempted unless the region (containing the gene) between the flanking markers is 1 cM or less. To reduce the region for cloning, it is necessary to expand the family with the hope of finding crossovers such that markers common to all affected would span only a short distance (<1 cM). This collection of markers in a region would represent the haplotype being inherited by the affected individual and contains the responsible gene. To prove that the gene causes the disease, the mutation must be identified and shown to cosegregate with the disease and not with the unaffected members in the family. The remaining task would be to determine the gene product (protein) and the pathophysiology of how the mutation induces the disease. In attempting to decipher the pathophysiology, one may transfect cells in culture with normal and mutant forms of the gene and compare the resulting phenotype. The other definitive approaches for determining causality are to overexpress the gene as a transgene in animals such as mice or to do homologous knockout, replacing the normal with the mutant gene to determine whether the disease phenotype is induced as have been done for familial hypertrophic cardiomyopathy (FHCM).[22-24] Chromosomal mapping of hereditary diseases by linkage analysis

and subsequent isolation of the gene[25] are summarized in Table 62-3.

Table 62-3: Chromosomal Mapping and Identification of a Gene

1. Identification of a family with a familial disease
2. Collection of clinical data from the family
3. Clinical assessment to provide an accurate diagnosis of the disease using a consistent and objective criterion to separate normal individuals from those affected and from those that are indeterminate or unknown
4. Collection of blood samples for immediate DNA analysis and development of lymphoblastoid cell lines for a renewable source of DNA
5. Development of a family pedigree
6. DNA analysis for markers of known chromosomal loci that span the human genome in an attempt to find a marker locus linked to the disease
7. Identification of the gene
8. Identification of mutation(s) causing the disease
9. Demonstration of a causal relationship between the mutant gene and the disease
10. Development of a convenient test to screen for the mutations

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Family History and Evaluation

The most important part of an evaluation for genetic disease is the family history. First, the family history may give clues to the diagnosis of a particular disorder, information about possible inheritance patterns within an individual family, and information about conditions for which family members may be at an increased risk. An individual's ethnic background may, for instance, suggest the need for specific types of genetic screening such as for hemoglobinopathies in individuals of African or Mediterranean ancestry or for Tay-Sachs disease in individuals of eastern European (Ashkenazi) Jewish ancestry. The individual with the medical problem who brought the family to the attention of the physician is referred to as the *proband*, or *propositus* (proposita for females). Information generally should be collected on all individuals who are first-, second-, or third-degree relatives of the proband. First-degree relatives of the proband are the parents and children. Second-degree relatives are aunts and uncles, grandparents, and grandchildren of the proband. Third-degree relatives are first cousins, great aunts and uncles, great-grandparents, and great-grandchildren. A pedigree chart (as shown in Fig. 62-1) is useful in this task. This information should include medical problems and pregnancies. If relatives are deceased, the age at death and the cause of death should be recorded. With a pedigree chart and specific family information, more general questions are asked, including whether other family members have the same or similar problems. Information about various types of birth defects, mental retardation, early infant deaths, miscarriages, stillbirths, or other diseases or handicaps in the family is sought. With some disorders, there may be a variability of a particular condition (i.e., clinical heterogeneity), even within a family. For example, with a possible diagnosis of FHCM, one should ask about premature death or syncope. A pregnancy history may provide information to support a possible teratogenic exposure. The date of the last menstrual period, whether the pregnancy was planned, whether contraception was used immediately prior to pregnancy, the time when the pregnancy was recognized, and when the mother sought prenatal care should be noted. Problems during the pregnancy, such as bleeding, spotting, cramping, fevers, rashes, or illnesses; drug exposures (both prescribed and nonprescribed), alcohol intake, or "recreational" drug use; and exposures to potent chemicals in the workplace or while involved in various hobbies should be explored. Pregnancy and family histories can then be used in conjunction with the findings on physical examination to derive a potential etiologic diagnosis and to plan for further diagnostic studies. The term *etiologic diagnosis* should suggest whether a specific cardiac defect is familial

(by family history), genetic but not familial (sporadic), teratogenic (by pregnancy history), or multifactorial. Prognosis and recurrence risk are linked strongly to an accurate diagnosis and its probable etiology.

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Chapter 62: CARDIOVASCULAR DISEASES DUE TO GENETIC ABNORMALITIES

GENETIC COUNSELING PRINCIPLES

Genetic counseling should provide information about the diagnosis, its possible etiology, and its prognosis. In addition, psychosocial issues, reproductive options, and the availability of prenatal diagnosis should be discussed. Genetic counseling should be nondirective, providing information in a nonjudgmental, unbiased manner. The family should then be able to make decisions based on medical information in the context of their religious, moral, cultural, and social backgrounds and their financial situation. Although a genetic counselor may occasionally feel frustrated with a specific couple's decision, an effective counselor does not let personal biases interfere with the counseling role. Conflicts leading to major ethical issues and disputes may arise, however, and may be particularly apparent regarding issues of nonpaternity, sex selection, pregnancy termination, and selective nontreatment of malformed infants. Couples have many reproductive options, but not all may be acceptable religiously or culturally. Nevertheless, potential options should be mentioned in a sensitive manner. A common misunderstanding among families in genetic counseling is the issue of prenatal diagnosis and its relationship to abortion. Prenatal diagnosis does not imply that a parent should or would terminate the pregnancy. In many circumstances, the information from prenatal diagnosis may help to reassure a couple that their risk of having another handicapped child is in fact much lower than expected. Conversely, if defects are found, the subspecialist may use more diagnostic approaches to make rational decisions about medical management of the infant prior to or immediately after delivery.

Genetic Diagnosis and Health Insurance

The accelerated pace of gene discovery, molecular medicine, and molecular diagnostics has begun to allow for improved genetic counseling and portends the possibility of future genetic therapy. As knowledge about the genetic basis of disease grows, however, so does the potential for health insurance coverage discrimination to be used to exclude individuals at risk or to change prohibitively high rates on the basis of predetermined illness. For this reason, planners of the Human Genome Project recognized the need to protect individuals who volunteered for genetic study as well as those diagnosed by molecular methods in the future. Also for this reason, the National Institutes of Health-Department of Energy (NIH-DOE) Working Group on Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project was developed. The Congress has passed a bill prohibiting companies from using DNA analysis to assess genetic risk as a basis for hiring. Only 11 states, however, prohibit the use of DNA analysis to determine who should get medical insurance or whether they qualify for high- or low-risk premiums.[7]

Chapter 62: CARDIOVASCULAR DISEASES DUE TO GENETIC ABNORMALITIES

CARDIOVASCULAR DISEASE DUE TO SINGLE-GENE MUTATIONS

Compensatory Response of the Heart Is Limited to Hypertrophy, Dilatation, or a Combination

The heart responds to stimuli, physiologic or pathologic, which may be inherited or acquired, with hypertrophy, dilation, or a combination of the two.[26] The same mechanisms mediate the growth response to pressure overload, volume overload, or loss of contractile mass (myocardial infarction). In FHCM, hypertrophy occurs without altered workload. In familial dilated cardiomyopathy (DCM), the heart responds predominantly by dilatation, generally in association with diffuse loss of myocytes and fibrosis. Most inherited defects are associated with hypertrophy. Several mutations in the mitochondrial genome have been associated with cardiac hypertrophy or dilatation.[27,28] In mitochondrial DNA mutations, HCM or DCM is usually part of a general phenotypic expression of a systemic disease that is characterized by metabolic disorders and involving the central nervous and the skeletal muscle systems. Three clinical categories of primary cardiomyopathies exist: (1) hypertrophic, (2) dilated, and (3) restrictive forms. Most of the cardiomyopathies other than those caused by infection have a genetic basis, although many of the mutations may occur de novo and are not necessarily familial. Only when a genetic defect is present in the germline and transmitted to one or more generations is it familial. For a detailed discussion of the clinical features, diagnosis, and treatment of the cardiomyopathies refer to Chaps. 64 to 69.

Familial Hypertrophic Cardiomyopathy (FHCM)

GENETIC BASIS

Familial HCM is an autosomal dominant disorder characterized by myocardial hypertrophy with a wide spectrum of symptoms, including dyspnea, chest pain, and syncope. The annual mortality rate of 2 to 4 percent is primarily due to sudden death, which often occurs in asymptomatic individuals (see Chap. 67). This disorder is the leading cause of sudden death in the young and in athletes. The annual incidence of sudden death is higher in younger patients with FHCM (about 6 percent) than in the elderly (1 percent). The diagnosis is based on typical clinical features and the demonstration of unexplained left ventricular, right ventricular, or biventricular hypertrophy on two-dimensional echocardiography. The left ventricular hypertrophy is commonly asymmetrical, localized to the septum, but it may involve the entire ventricle in a concentric pattern. Isolated right ventricular hypertrophy occurs in fewer than 5 percent. Isolated apical hypertrophy is rare except in Japan, where it is claimed to account for 20 to 30 percent of the cases. Dynamic outflow tract obstruction occurs in about 30 percent.[29,30] Histologically, the myocardial hypertrophy consists of myocyte hypertrophy, cellular and myofibrillar disarray, and myocardial fibrosis. The literature suggests that the hallmark of FHCM is myocyte and myofibrillar disarray (see Chap. 66). The disorder exhibits marked variability of expressivity, even in the same family. FHCM was the first primary cardiomyopathy to yield to molecular genetics. Jarcho et al. in 1989 showed genetic linkage of the disease to the chromosomal locus of 14q1 in a large French/Canadian family.[31] The 14q1 locus subsequently was shown to be involved in FHCM in several families throughout North America.[32] The β-myosin heavy chain (βMHC) gene was identified as the responsible gene (Fig. 62-5), and over 50 mutations have been detected.[11,33,34] A total of eight genes have now been identified responsible for FHCM and a brief description of the loci and

the proteins they encode, together with their function, is summarized in Table 62-4. Mutations in the βMHC gene may account for 30 to 50 percent of the families with FHCM.[33] While it remains to be determined for certain, these eight genes probably account for 80 to 90 percent of the disease of FHCM. Two other loci have been identified, one in a family with HCM and Wolff-Parkinson-White (WPW) syndrome mapped to 7q3[35] and the other to chromosome 11q in a Japanese family.[36] Since all of the genes identified to date involve the sarcomere, it has been proposed that FHCM is a disease of the sarcomere and perhaps should be referred to as *sarcomeropathy*.[34]

The βMHC is the most common gene for FHCM and over 50 mutations have been described. Almost all of the mutations are point mutations (a single base nucleotide) that result in substitution of one amino acid for another and are located in the globular head of the myosin molecule. These mutations appear to arise independently.[37] The frequency of each particular mutation is low. Two hot spots, codons 403 and 719, have been identified for mutations in the βMHC in patients with HCM.[38,39] Mutations in the rod region of the βMHC molecule have also been described but are uncommon and appear to induce a mild phenotype.[40]

PROGNOSIS FROM GENOTYPE-PHENOTYPE CORRELATIONS

The hypertrophy of FHCM is markedly variable in its degree, distribution, and age at onset as well as in the type and severity of its associated clinical manifestations.[41-43] The natural course of FHCM in certain families is riddled with sudden cardiac death, whereas in others, sudden cardiac death is almost absent and the life span is essentially normal.[34] None of the clinical features are reliable predictors of sudden death. Hypertrophy, while present in all individuals, since it is required for the clinical diagnosis, does not correlate with the incidence of sudden death. FHCM due to mutations in the troponin T gene is associated with a high incidence of sudden death, yet there is often minimal hypertrophy.[44] The occurrence of palpitations, arrhythmias, or syncope are poor predictors of sudden death. A family history of sudden death usually indicates that the affected individuals in the family are at risk for sudden death. Several studies have now been performed correlating the genotype to the phenotype and several interesting observations have evolved pertinent to the diagnosis and treatment and future genetic screening. Results of these studies[45] have shown that the majority of families with the βMHC mutations $Arg^{403}Gln$, $Arg^{453}Cys$, and $Arg^{719}Trp$ are associated with a poor prognosis and a high incidence of sudden cardiac death[34,42,43,46] (Fig. 62-6). In contrast, the βMHC mutations $Leu^{908}Val$, $Gly^{256}Glu$, and $Val^{606}Met$ are associated with near-normal life expectancy, and mutations $Glu^{930}Lys$ and $Arg^{249}Gln$ are associated with an intermediate risk of sudden cardiac death.[47] The incidence of premature death in affected individuals with $Arg^{403}Gln$ is approximately 50 percent,[34] and the mean age of sudden cardiac death is 33 years. The life expectancy of affected individuals with the βMHC mutation $Arg^{719}Gln$ appears to be about 38 years and in those with $Arg^{453}Cys$ about 30 years. In contrast, the mutation $Leu^{908}Val$ is associated with low penetrance, a benign course, and a low incidence of sudden cardiac death.[46] The cumulative survival rate at 60 years of age was 92 percent with this mutation. Similarly, the $Gly^{256}Glu$ and $Val^{606}Met$ mutations are associated with a relatively benign course, with most individuals having a near-normal life span. In contrast, the two mutations $Glu^{930}Lys$ and $Arg^{249}Gln$[46,47] show an intermediary prognosis, with an average age of onset of cardiac failure and severe symptoms around 49 years. These correlations must be interpreted with caution, however, as the number of families studied remains too small for definitive generalizations to be made. Although most individuals affected with FHCM due to the βMHC mutation manifest the disease in the second or third decade of life, those with FHCM due to myosin-binding protein C mutations frequently do not develop any evidence of the disease until the fourth or fifth decade.[48] This is a striking example of age-dependent penetrance based on 16 families involving over 500 individuals. However, once the disease develops, the particular

mutation is highly predictive of risk for sudden death. Mutations in the essential light chain (3p) and the regulatory light chain of myosin (12q23-q24.3) of patients is associated with a peculiar form of HCM in which mid-left ventricular chamber thickening occurs due to massive hypertrophy of the papillary muscles and adjacent ventricular tissue, resulting in mid-cavitary obstruction.[49] In addition to the cardiac abnormalities described, the skeletal muscles of these patients were histologically abnormal and appeared as ragged-red fibers.

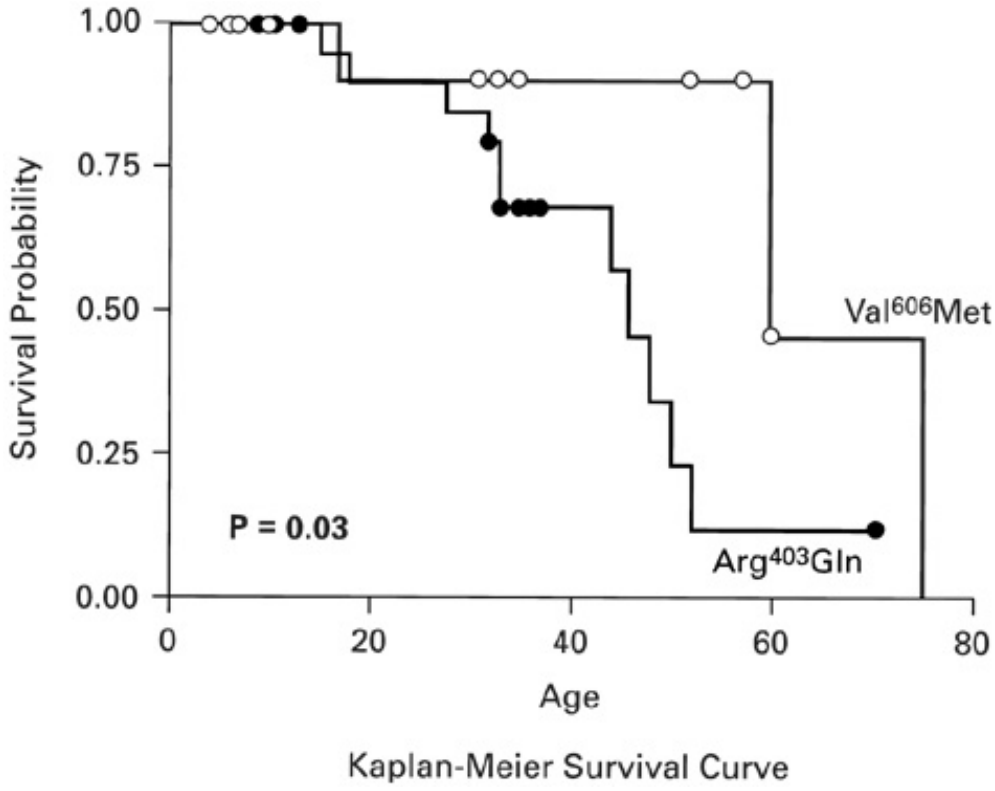

Figure 62-6: Kaplan-Meier survival curve in patients with hypertrophic cardiomyopathy depending on myosin heavy chain mutation.

INFLUENCE OF OTHER GENES AND THE ENVIRONMENT

While a single-gene mutation appears to be the primary cause of the disease, there remain significant environmental and other genetic influences that determine whether or not the phenotype develops (penetrance) and its expressivity. A striking example of the influence of environment on FHCM is the observation that hypertrophy seldom develops in the right ventricle, yet the defective genes and their mutations are present to the same extent in the right as in the left ventricles.[34] Presumably, the increased workload and pressure in the left ventricle stimulate the development of the hypertrophy and phenotypic expression. There also appears to be more hypertrophy in males than females who have FHCM. βMHC is the major myosin and contractile unit of many skeletal muscles, yet the latter do not appear to be affected by this disease, again emphasizing the influence of either the environment or other genes.[50] Another example of presumably environmental or other genetic influences is the marked variability of the extent and degree of left ventricular hypertrophy that occurs even within the same family with the same mutation. In addition, there is a significant effect from other genes that predispose to features such as hypertrophy. An example of the influence of another gene on FHCM is afforded by the angiotensin converting enzyme (ACE) DD genotype. Patients with FHCM who also have the ACE DD genotype have a much higher incidence of sudden death[51] and more extensive hypertrophy,[52]

which may be mediated through the mitogenic effect of angiotensin II. Individuals with FHCM who participate in combative reports seem to be more prone to develop hypertrophy and sudden death.[53] A similar effect is observed if they have a variance of the endothelin I gene.[54] It is not surprising that the phenotype of cardiac hypertrophy requires the coordination of probably hundreds of genes, and thus it is highly likely that other genes in addition to ACE will exert a minimal, yet significant influence on either the penetrance or expressivity of the primary genetic defect.

ELUCIDATION OF THE PATHOGENESIS FROM GENETIC MODELS

Based on in vitro and in vivo studies in genetic animal models of HCM, it now appears that the primary defect is impaired contractility. Analysis of a human heart from a patient with the $Arg^{403}Gln$ mutation showed the ratio of myosin to actin was normal,[55] indicating there is no deficiency of the βMHC protein. All of the responsible mutant genes encode for a sarcomeric protein and appear in some way to impair systolic contraction or diastolic relaxation. In feline adult cardiac myocytes, in which βMHC is the predominant myosin form, expression of human mutant βMHC gene, $Arg^{403}Gln$, was associated with sarcomere disassembly.[56] Expression of the human mutant troponin T in this model also induced sarcomere disassembly and was associated with impaired rate of cell shortening as detected by laser.[24] Furthermore, it was shown the expressed mutant protein was incorporated into the sarcomere. In a transgenic mouse, expression of troponin T gene (cTnT-Gln^{92})[57] exhibited sarcomere disarray, increased fibrous tissue, and sudden death, but only minimal hypertrophy. In this model it was also shown that increased expression of the mutant protein was associated with a more severe phenotype, confirming the mutant protein has a dominant-negative effect as expected. These results have been confirmed by several investigators.[56,58-60] Expression of the mutant myosin heavy chain gene or the troponin gene in the mouse has, in general, been associated with less hypertrophy than expected.[57] Recently, a transgenic rabbit model (rabbit has βMHC as its cardiac myosin) has been developed expressing the βMHC ($Arg^{403}Gln$) mutation, which exhibits sarcomere disarray, hypertrophy, and increased fibrous tissue virtually identical to that observed in humans.[61] Thus, the overall postulated pathogenesis of FHCM may be summarized briefly as follows: The mutant protein is incorporated into the sarcomere and acts as a poison peptide which impairs contractility of that particular cell which, in turn, provides the stimulus for the mitogenic response (probably several growth factors) of compensatory hypertrophy. The growth stimulus, as in acquired disorders, appears highly localized and mediated by autocrine or intracrine factors, given that the hypertrophy is localized in many patients, primarily to the interventricular septum. The growth factors also stimulate fibroblast proliferation and increased matrix formation. The relationship between the hypertrophy and increased fibrous tissue response to sudden death and arrhythmias remains to be determined. It is postulated that the fibrous tissue leads to delayed electrical conduction and predisposes to arrhythmias and sudden death.[62,63] The future elucidation of the molecular basis for the pathogenesis of this disease, however, must provide a rationale for three puzzling, consistent features of the pathology of FHCM: (1) predominance of hypertrophy in the septum, (2) sarcomere and myocyte disarray, and (3) the supernormal systolic function. The diastolic stiffness or decreased compliance is expected with hypertrophy, whether it is primary or compensatory, but these other features are not seen in compensatory hypertrophy associated with myocardial infarction or pressure overload.

IMPLICATIONS FOR FUTURE THERAPIES

Based on clinical studies and experimental genetic models, certain important observations have evolved. FHCM is seldom manifested before puberty and when due to certain genes may not be manifested until the fourth or fifth decade. This provides a window for future therapeutic intervention as therapies become available. The observation that the DD genotype increases the extent of hypertrophy and the risk for sudden death in individuals with FHCM is of considerable

therapeutic interest.[51] ACE inhibitors have been shown to either induce regression or prevent progression of hypertrophy due to pressure overload, in part due to a direct effect on the growth response. Therefore, it would be intriguing to know whether or not ACE inhibitors induce regression of hypertrophy in patients with FHCM and, perhaps more importantly, prevent hypertrophy in children genetically affected who are identified by genetic testing prior to the development of hypertrophy. There is no evidence to recommend such therapy for FHCM at this time. Elucidation that the hypertrophy is secondary and similar to the hypertrophy developed in response to pressure overload also has important implications; hence, therapies shown to be effective in FHCM would be expected to be effective in acquired hypertrophy. Thus, HCM, as a model, may be a paradigm for the evaluation of known therapies and the development of more specifically targeted therapies. It is evident that genotyping could provide risk stratification of therapeutic and prognostic significance. Genotyping will also have a major diagnostic impact since it is not always possible to make a diagnosis with conventional methods, particularly in the elderly. It will be essential for genetic screening of asymptomatic individuals within families with the disease. Despite the observation that not all of the genes responsible for FHCM have been identified, it must be realized that the first gene was not identified until 1990. Screening for mutations in individuals from a family affected with FHCM is feasible for known mutations but is tedious and expensive. In a family in which the disease is not due to a known mutation, chromosomal mapping and subsequent identification of the gene are required. It is expected, however, that the techniques for mass genetic screening, such as the DNA chip array, will make it possible to do routine genetic screening.[64] Ultimately, if gene therapy becomes available, genotyping will, of course, be essential. It is conceivable that regression of cardiac hypertrophy can be induced by inhibiting transcription of the mutant allele or translation of the mutant mRNA, thus abolishing synthesis of the mutant peptide. Thus, not only genetic diagnosis but also curative therapy may be possible. Since the heart, even in an adult, is renewed every 2 to 3 weeks, there is a tremendous potential for a cure with subsequent remodeling to normal.

Pompe's Disease (Type II Glycogen Storage Disease)

Genetic deficiency of acid α-1,4-glucosidase production results in a wide clinical spectrum ranging from the rapidly fatal infantile-onset of type II glycogen storage disease (GSD) to a slowly progressive adult-onset myopathy. The infantile-onset form (Pompe disease) typically manifests during the first months of life and patients usually die before their second year.[65] This rare inborn error of glycogen metabolism occurs in less than 1 per 100,000 persons. Massive glycogen accumulation occurs, leading to the clinical findings of enlarged tongue, striking hepatomegaly, hypotonia with decreased deep tendon reflexes, and hypertrophic cardiomyopathy[65] with cardiac failure (Table 62-5). The diagnosis may be predicted from the electrocardiogram (ECG), which demonstrates striking QRS complex voltage.[65] The diagnosis can also be made by analysis of α-glucosidase in blood lymphocytes or skin fibroblasts. Recently, urinary oligosaccharide identification using matrix-assisted laser desorption ionization time-of-flight mass spectrometry has been shown to allow facile and sensitive identification of the pathognomonic oligosaccharidiuria of this disorder.[66] The disease has autosomal recessive inheritance and is caused by mutations in this lysosomal gene found on chromosome 17q23-q25. Recently, the lysosomal-associated membrane protein (LAMP-1) was shown to be elevated in Pompe disease, which occurs due to altered trafficking and turnover of LAMP-1.[67]

Table 62-5: Cardiovascular Anomalies Associated with Selected Autosomal Recessive Syndromes

Syndrome	Cardiovascular Anomaly
Carpenter's syndrome	Patent ductus arteriosus
Cockayne's syndrome	Atherosclerosis
Cutis laxa	Pulmonary hypertension
Cystic fibrosis	Cor pulmonale
Ellis-van Creveld syndrome	Atrial septal defect
Friedreich's ataxia	Hypertrophic cardiomyopathy
Homocystinuria	Thromboses
MPS IH (Hurler's syndrome)	Coronary artery disease, aortic and mitral insufficiency, hypertrophic cardiomyopathy
MPS IS (Scheie's syndrome)	Aortic valve disease
MPS IV (Morquio's syndrome)	Aortic valve disease
MPS VI (Maroteaux-Lamy syndrome)	Aortic valve disease
Pompe's disease (GSD II)	Hypertrophic cardiomyopathy
Pseudoxanthoma elasticum	Coronary artery disease, mitral insufficiency
Refsum disease	Arrhythmias
Smith-Lemli-Opitz syndrome	Ventricular septal defect, patent ductus arteriosus
Thrombocytopenia-absent radii (TAR) syndrome	Atrial septal defect, tetralogy of Fallot

In an attempt to better understand this metabolic disorder, animal models have been developed using targeted disruption of the murine acid α-glucosidase gene.[68,69] This model closely mimics the human disorder, particularly the cardiac phenotype. Also, using animal models such as quail and rat, gene therapy using recombinant α-glucosidase has been shown to correct the enzyme levels and clinical phenotype, suggesting that enzyme replacement by this method is promising therapy in humans.[70-72]

Beckwith-Wiedemann Syndrome (BWS)

The combination of macroglossia, exophthalmos, and visceromegaly has been designated the BWS.[73-74] Multiple other abnormalities have also been described, including fetal adrenocortical cytomegaly, hypoglycemia due to pancreatic islet hyperplasia, transverse linear creases of the ear lobules, hemihypertrophy, and accelerated osseous maturation. Infants with this syndrome are at particularly high risk, cumulatively estimated at between 5 and 20 percent, for development of Wilms' tumor, adrenocortical carcinomas, hepatoblastomas, and rhabdomyosarcomas.[75] The cardiovascular system is also commonly affected with the development of HCM. The BWS occurs with an incidence of 1 in 13,700 live births. Cases (about 85 percent) are generally sporadic, but familial disease (15 percent) has been described. Most of these familial cases have apparent autosomal dominant inheritance,[76] albeit with reduced, sex-dependent penetrance and variable

expressivity. A variety of structural abnormalities of chromosome 11 have been shown, including partial duplication of 11p13, duplication of 11p15 only, deletion of 11p11-13, or deletion of 11p11. The extra chromosomal material is usually of paternal origin. The breakpoints found in BWS patients with balanced chromosomal translocation or inversion involving chromosome 11 lie in two regions: (1) close to the insulin/insulin-like growth factor II (INS/IGF2) genes in 11p15.5 or (2) proximal to β-hemoglobin (HBB). The recombinant chromosome was shown to be of maternal origin. Family studies showed that the gene responsible for familial BWS mapped to 11p15.5. For sporadic BWS, uniparental paternal disomy for 11p15.5 markers was found in approximately 20 percent of cases analyzed. Mutations in p57KIP2, a potent tight-binding of several G1 cyclin/cyclin-dependent kinase complexes, have been identified in cases of BWS,[77-80] and mice lacking this gene have been shown to have a phenotype similar to that seen in humans.[81] Clinical heterogeneity exists, however; potential mechanisms include a possible role for genomic imprinting (i.e., an epigenetic chromosomal modification in the gamete or zygote causing preferential expression of a specific parental allele in the somatic cells of the offspring) in 11p15, and this was later shown to occur with KVLQT1, a cardiac potassium channel gene known to cause long-QT syndrome when mutated.[82,83] This region of 11p15.5 has a cluster of imprinted genes, in fact, such as insulin-like growth factor II (IGF2),[84] HI9,[85] LIT1,[86] and p57KIP2.[77-80] Animal models have been created using these as transgenes.[84]

Leopard Syndrome

This rare autosomal dominant disorder is characterized by the cardinal features leading to the pneumonic L (lentigenes), E (ECG conduction defects), O (ocular hypertelorism), P (pulmonic valve stenosis), A (abnormalities of genitals), R (retardation of growth), and D (deafness, sensorineural). Cardiac abnormalities are common and include both anatomic as well as conduction defects. Anatomically, PS is the most frequent, followed by HCM and endocardial fibroelastosis (Table 62-6). The most common ECG defects include first-degree AV block, left anterior hemiblock, and complete heart block. No cytogenetic or molecular genetic abnormalities have been identified.

Table 62-6: Cardiovascular Anomalies Associated with Selected Autosomal Dominant Syndromes

Syndrome	Cardiovascular Anomaly
Albright's hereditary osteodystrophy	Cardiomyopathy
Ehlers-Danlos syndrome	Rupture of large vessels
Holt-Oram syndrome	Atrial and ventricular septal defects
Leopard syndrome	Pulmonic stenosis, hypertrophic cardiomyopathy, prolonged PR interval
Marfan syndrome	Aortic aneurysm, aortic insufficiency, mitral valve prolapse
Myotonic dystrophy	Dilated cardiomyopathy, conduction abnormalities
Neurofibromatosis	Coarctation of the aorta, renal artery
	Stenosis

Treacher Collins syndrome	Atrial and ventricular septal defects, patent ductus arteriosus
Tuberous sclerosis	Myocardial rhabdomyoma, Wolff-Parkinson-White syndrome
Noonan's syndrome	Pulmonic stenosis, hypertrophic cardiomyopathy, atrial septal defect, aortic stenosis

Friedreich's Ataxia (FA)

FA is the most common of the hereditary spinal cerebellar degenerations, with an incidence of 1 in 50,000 and carrier frequency of 1 in 110.[87] This autosomal recessive form of spinocerebellar degeneration is characterized by progressive limb ataxia, loss of deep tendon reflexes, sensory abnormalities, and musculoskeletal deformities. The symptoms of FA usually appear insidiously during childhood or early adolescence. Progressive weakness of the upper and lower extremities gradually becomes obvious. Gait difficulties are often the first symptom; they progress slowly, followed by unsteadiness in the arms and hands. Difficulty in writing and handling eating utensils subsequently becomes apparent.

Cardiac involvement[87] occurs in 50 to 90 percent of patients. The most common abnormality is hypertrophic cardiomyopathy (Table 62-5); dilated cardiomyopathy occurs rarely. Thus, the most common cardiac symptoms relate to cardiac failure and arrhythmias. Left ventricular outflow tract obstruction due to asymmetrical septal hypertrophy may be evident, and approximately 50 percent of patients die of cardiac disease. Patients are followed for development of arrhythmias and the signs and symptoms of cardiac failure. Treatment consists primarily of conventional drugs to relieve the symptoms and signs of heart failure.

Involvement of the heart is readily detected by electrocardiography and echocardiography. The electrocardiographic abnormalities are found in 90 percent of patients and include repolarization abnormalities manifesting as inverted or biphasic T waves in the inferior limb leads and left precordial leads, a short PR interval, left and right ventricular hypertrophy, as well as left and right axis deviation. Premature atrial contractions, atrial flutter/fibrillation, and premature ventricular contractions are common. Echocardiography detects cardiac involvement in 60 to 100 percent of patients with the most common finding of concentric hypertrophy, but asymmetrical septal hypertrophy accompanied by systolic anterior motion (SAM) of the mitral valve is also common. Left ventricular chamber diameter may be normal or decreased and fractional shortening or ejection fraction is usually normal, although dilated cardiomyopathy (left ventricular dilation and reduced contractility) is seen occasionally (see Chap. 10). There is no specific treatment for the cardiac manifestations except symptomatic treatment if cardiac failure ensues (see Chap. 23).

Friedreich's ataxia is inherited as an autosomal recessive disorder, and parental consanguinity has been noted in some cases. The gene was initially mapped to chromosome 9q13-31.1,[88] and in 1996 the gene was identified.[89] This gene is 40 kb, contains five exons, has a 1.3-kb transcript, and encodes a 210-amino acid protein called frataxin. The highest level of expression is within the heart, while intermediate levels are seen in liver, skeletal muscle, and pancreas; minimal levels are identified in other tissues, including the brain. Although a few affected patients were found to have a point mutation of frataxin, the majority (about 95 percent) are homozygous for an unstable GAA trinucleotide expansion in the first intron.[89] The remainder of patients are compound heterozygotes for the expansion. In patients homozygous for the expansion, there is a correlation between the number of GAA repeats on the smaller allele, age of onset, disease progression, and cardiomyopathy,[87,90-93] confirming that the expansion is the primary cause of disease. The

expansion results in severely reduced levels of mature frataxin mRNA.[89]

Campuzano et al.[94] demonstrated that frataxin is localized to the mitochondria associated with the mitochondrial membranes and crests using immunocytofluorescence and immunocytoelectron microscopic evaluation. They suggested that reduction in frataxin results in oxidative damage. Subsequently, Rotig and colleagues[95] suggested that frataxin regulates mitochondrial iron transport and that deficiency of iron-sulfur cluster-containing subunits of mitochondrial respiratory complexes I and II and the iron-sulfur protein aconitase occurs. Hence, it appears that Friedreich's ataxia is a mitochondrial disorder.[96,97] As these patients have HCM, diabetes, ataxia, and apparent free radical toxicity, the mitochondrial basis of this disorder clarifies the clinical features.

Dilated Cardiomyopathy

IDIOPATHIC DILATED CARDIOMYOPATHY

Idiopathic DCM (DCM) is a disease of unknown etiology characterized by increased ventricular chamber size, decreased wall thickness, and impaired systolic ventricular function. The prevalence of idiopathic DCM has been estimated to be approximately 40 cases per 100,000.[98] The diagnosis of DCM is typically made by echocardiography (see Chap. 65), and symptoms usually are those of sudden death and heart failure. Familial DCM (FDCM) is estimated to account for 30 percent of patients with idiopathic DCM. In a large family with idiopathic DCM, an autosomal dominant pattern was determined and the disease was linked to chromosome 1q32.[99] Three other chromosomal loci have been identified: 9q13,[100] 2q31,[101] and 10q21-23.[102] Three additional chromosomal loci have been mapped-to 1p1-1q1,[103] 3p22-25,[104] and 6q23[105]-in families having DCM in association with conduction defects and 6q23 also has limb girdle dystrophy. In the family mapped to 1p1-1q1, transient arrhythmias, which presented in the second or third decade, become sustained and commonplace by the third or fourth decade. The abnormal rhythms included second- or third-degree AV block, atrial fibrillation, or marked bradycardia, commonly requiring a pacemaker. DCM usually developed in the fourth or fifth decade, generally out of proportion to the severity of the rhythm disturbance. Sudden death commonly occurred in the late stages of the disease. On autopsy, marked right and left ventricular dilatation, interstitial fibrosis, myocyte degeneration characterized by cytoplasmic vacuolization, and AV nodal cell replacement by fibrous tissue were noted. The gene and its characteristics have recently been described as lamin A/C, the same gene identified for autosomal dominant Emery-Dreifuss muscular dystrophy. None of the other genes residing at these loci responsible for FDCM have yet been identified. However, two genes have now been identified responsible for FDCM-actin[106] and desmin.[107] Three missense mutations have been identified in actin. Actin, in addition to forming the thin filaments of the sarcomere, essential to the generation of force, is also an important cytoskeletal protein involved in structural integrity and the transmission of force. Mutations in actin responsible for FDCM are located in the domain which is immobilized and attached to the Z-band or intercalated disk and involved with transmitting force. In contrast, it was recently shown that mutations in the actin domain affecting the myosin cross bridges and the generation of force (sarcomere) give rise to FHCM.[108] Desmin is the specific intermediate filament for muscle and an essential cytoskeletal protein for maintaining cardiac structure and for the transmission of force and other signals to the cytoplasm and the nucleus of the cell. Desmin stretches from its attachment to the sarcomere Z-band to the nuclear membrane and other organelles.[109] Mutations in desmin have been shown to be associated with cardiac and skeletal abnormalities.[110] A missense mutation ($Ile^{451}Met$) was recently found to be responsible for DCM in a family without any skeletal or smooth muscle abnormalities. Mutations leading to combined skeletal and cardiac abnormalities have all been in the rod region of desmin. In contrast, the $Ile^{451}Met$ mutation responsible for the restricted cardiac phenotype of DCM encodes for the tail domain of human

desmin, located in codon 451 with cytosine substituting for guanine. This would suggest a possible unique cardiac function for the domain in this region. Elimination of the desmin gene in a knockout mouse was associated with a phenotype of DCM exhibiting impaired cardiac function and myocyte necrosis.[110] It is of note that DCM associated with musculoskeletal disorders such as Duchenne muscular dystrophy are due to dystrophin, α-dystroglycan, and α-sarcoglycan, all of which are cytoskeletal proteins[111] (Fig. 62-7). There is thus the strong suggestion that familial DCM may be a disease of the cytoskeletal proteins[107,112-114] analogous to HCM being a disease of the sarcomere. This has been termed by Towbin as the "final common pathway hypothesis"[113,114] (Fig. 62-8).

X-LINKED DILATED CARDIOMYOPATHY (XLCM)

Berko and Swift[2] reported a five-generation kindred with DCM and no clinical evidence of skeletal myopathy. Males presented in their teens or early twenties with clinical evidence of mitral regurgitation and an echocardiographic diagnosis of DCM. Episodes of ventricular tachycardia were noted in several patients. The males progressed rapidly (within 1 or 2 years) to death or cardiac transplantation. Manifesting female carriers developed mild cardiomyopathy in the fourth or fifth decade and progressed slowly. Right ventricular endomyocardial biopsy revealed minimal interstitial fibrosis, while postmortem evaluation showed marked dilatation, widespread patchy fibrosis (worst in the posterior wall), and normal mitochondria on electron microscopy. There were no pathognomonic findings differentiating this cardiomyopathy from other dilated forms except for the apparent X-linked inheritance and elevation of the muscle isoform of creatine kinase (CK-MM) in the serum of affected males and female carriers.

Towbin and colleagues[115] demonstrated linkage of XLCM to the dystrophin locus at Xp21 (i.e., the gene responsible for Duchenne and Becker muscular dystrophy) in the family described above as well as in a second family. Evaluation of the protein defect in XLCM showed absence (or low abundance) of the *N*-terminal and rod portion of the dystrophin protein, while skeletal muscle total protein was normal.[115] The 156-kDa dystrophin-associated glycoprotein (known as α-dystroglycan),[116,117] a membrane-bound constituent of the dystrophin-associated glycoprotein complex, was decreased in cardiac tissue as well.[116] This was later confirmed.[118] Diverse mutations leading to XLCM have been shown by Towbin and Ortiz-Lopez,[119,120] Yoshida et al.,[121] Muntoni et al.,[122] and Milasin et al.,[123] with most mutations residing in the 5′ portion of the gene. It appears that the DCM occurs due to mechanical destablization of the muscle membrane. Recently, novel mutations in the 5′ end of dystrophin, including a transposon[124] insertion and an *Alu*-rearrangement[125] were found to result in XLCM. Treatment of congestive heart failure and ventricular arrhythmias is necessary and transplantation is common (see Chap. 23).

X-LINKED CARDIOSKELETAL MYOPATHY (BARTH SYNDROME)

Neustein et al.[126] and Barth and coworkers[127] described an X-linked recessive disease characterized by the triad of DCM with endocardial fibroelastosis, neutropenia, and skeletal myopathy. All affected males died in infancy or early childhood from cardiac decompensation or septicemia. There were no affected females. Ultrastructural abnormalities were detected in mitochondria from cardiac and skeletal muscle as well as in neutrophil bone marrow cells. Furthermore, respiratory chain abnormalities were observed and isolated skeletal muscle mitochondria demonstrated diminished cytochrome concentrations. Lactic acidemia not provoked by prolonged fasting, increased plasma and muscle carnitine concentrations, growth retardation, and increased levels of urinary 3-methylglutaconic acid and 2-ethyl-hydracrylic acid have also been seen.

The locus was mapped by linkage to Xq28.[128] The gene G4.5 codes for a novel protein known as

taffazin, whose function is unclear.[129] Tafazzin belongs to a family of proteins ranging from 129 to 292 amino acids in length. Direct sequencing of genomic DNA indicated different mutations in G4.5, which interfere with translation of the putative protein. Mutations in G4.5 have also been shown to cause other infantile cardiomyopathies, including isolated left ventricular noncompaction[130-132] and dilated hypertrophic cardiomyopathy. Treatment is that for cardiac failure (see Chap. 23).

FAMILIAL ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)

Arrhythmogenic right ventricular dysplasia is characterized by fatty infiltration of the right ventricle, fibrosis, and ultimately thinning of the wall with chamber dilatation.[133] It is the most common cause of sudden cardiac death in the young in Italy[134] and is said to account for about 17 percent of sudden death in the young in the United States.[135] Rampazzo et al.[136] mapped this disease in two families, one to 1q42-q43, and the other on chromosome 2q32; a third locus was mapped to 14q12.[137] A large Greek family with arrhythmogenic right ventricular dysplasia and Naxos disease was recently mapped to 17q.[138] Two loci responsible for ARVD in North America were recently mapped at 3p23[139] and the other at 10p12.[140] This is a very devastating disease, since the first symptom is often sudden death. Electrocardiographic abnormalities include inverted T waves in the right precordial leads, late potentials, and right ventricular arrhythmias with left bundle-branch block (LBBB). This is compounded by the great difficulty in making the diagnosis even when the condition occurs in a family with a history of the disease. Since the disease affects only the right ventricle, it is difficult to detect.[106] There is no definitive diagnostic standard. The right ventricular biopsy is definitive when positive but often produces a false-negative result, since the disease initiates in the epicardium and spreads to the endocardium of the right ventricular free wall, making it inaccessible to biopsy. Consensus diagnostic criteria was developed that include right ventricular biopsy, magnetic resonance imaging (MRI), echocardiography, and electrocardiography.[141] Identification of the gene will have tremendous diagnostic impact and hopefully will provide an explanation as to why ARVD is restricted to the right ventricle. Is it a specific right ventricular chamber gene? Is there a stimulus that is unique or predominates in the right ventricle that precipitates the phenotype? What is the stimulus? There are data suggesting that apoptosis is the process leading to the development of fat and fibrosis in ARVD. Discovery of a gene should shed light on the apoptosis pathway.

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Chapter 62: CARDIOVASCULAR DISEASES DUE TO GENETIC ABNORMALITIES

RESTRICTIVE CARDIOMYOPATHY

In the western countries, restrictive cardiomyopathy (RCM) is the least common of the three major categories of cardiomyopathy (see Chap. 75). The most common cause of secondary restrictive cardiomyopathy in adults is myocardial amyloid. Patients manifest exercise intolerance due to their inability to increase cardiac output by tachycardia without further compromising ventricular filling. Weakness and dyspnea are often prominent, and chest pain may also occur. At end stage, the findings are those of cardiac failure with anasarca. Mutations in the transthyretin (TTR) gene[142,143] which codes for the TTR serum protein, has been found associated with RCM. This protein contains four subunits, each with 127 amino acids, encoded by four exons within a 7-kb gene. Many TTR point mutations cause TTR to form amyloid, which occurs primarily in the heart, leading to heart failure. The diagnosis is suspected by echo and confirmed by genetic analysis. Treatment is that of cardiac failure.

Familial forms of restrictive cardiomyopathy have also been seen. One such family was found to have mutations in the desmin gene[144] and mice have been created with desmin mutations that have a similar phenotype as the clinical condition.[110]

Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) are a group of diseases caused by deficiency of lysosomal enzymes involved in the degradation of glycosaminoglycans.[145] Undegraded glycosaminoglycans accumulate in lysosomes and affect tissue function. MPS have been divided into seven major types. The classification (types I to VII) is based on the deficient enzyme responsible for the disorder. These disorders carry such eponyms as *Hurler*, *Scheie*, *Hurler-Scheie*, *Hunter*, *Sanfilippo*, *Morquio*, *Maroteaux-Lamy*, and *Sly*. They share many clinical features, including multiple system involvement, organomegaly, dysostosis multiplex, facial abnormalities, loss of hearing and vision, joint involvement, cardiac involvement, and central nervous system (CNS) involvement. Cardiac disease includes myocardial hypertrophy, pulmonary and systemic hypertension, valvular disease, coronary occlusion, and myocardial infarction. Congestive heart failure and sudden death are relatively frequent. The most common mucopolysaccharidosis with cardiac involvement is MPS I (Hurler syndrome). Valvular disease is prominent in the Scheie's syndrome (late-onset form). Less commonly, heart disease has been noted in Sanfilippo A syndrome with aortic regurgitation, as well as in severe Maroteaux-Lamy syndrome with valvular heart disease (Table 62-5). The diagnosis for either of these disorders is made by assaying the enzyme activity in cultured skin fibroblasts or leukocytes.

Hurler's Syndrome

Hurler's syndrome (MPS-I) is an autosomal recessive trait found on chromosome 22 (22q11), which occurs in approximately 1 of 40,000 people. It is caused by a deficiency of α-iduronidase (IDUA), which is required for the degradation of both heparan sulfate and dermatan sulfate.[146] The result is similar to that of Hunter's syndrome, with both dermatan and heparan sulfate in high concentrations in the urine. Myocardial infarction occurs in childhood (Table 62-5). *Severe* (Hurler, MPS-IH), *intermediate* (Hurler/Scleie, MPS-IH/S), and *mild* (Scheie) clinical subtypes of MPS-I occur.[145] MPS-IH patients usually present within the first year of life and progress with a

combination of hepatosplenomegaly, skeletal deformities, corneal clouding, and severe mental retardation. Obstructive airway disease, respiratory infection, and cardiac complications usually result in death before age 10 years. Dangel[147] reported on 64 children with mucopolysasccharidoses, noting 72 percent with cardiac disease (valvular lesions, cardiomyopathy). Mitral valve thickening with regurgitation or stenosis, hypertrophic cardiomyopathy, aortic stenosis, and EFE were most common. MPS-IH/S is characterized by little neurologic involvement but most of the somatic involvement described for MPS-IH develops early in the teenage years, causing considerable loss of mobility. MPS-IS patients, those with the mildest symptoms, have little or no neurologic involvement, normal stature, and normal life span but do develop stiff joints, mild hepatosplenomegaly, aortic valve disease, and corneal clouding.[145] Diagnosis is confirmed in MPS-I by demonstration of mucopolysaccharidiuria and absence of IDUA activity in leukocytes and fibroblasts. Biochemical differentiation between subtypes is difficult. Gene identification[148] has allowed for mutation analysis; the broad range of clinical phenotypes is related to the types of mutations in the IDUA gene.[149] Allogenic bone marrow transplantation is the most effective treatment for Hurler's syndrome[150] and gene transfer is being evaluated.[151] Animal models are now available[152154] for study.

Hunter's Syndrome

Hunter's syndrome, an X-linked disorder mapped to the Xq26-Xq28 region, is found in approximately 1 of 30,000 people.[145] It is caused by a deficiency of the enzyme iduronate sulfatase and results in excessive urinary excretion of dermatan and heparan sulfate and accumulation of mucopolysaccharides, which can result in coronary obstruction and subsequent myocardial infarction in childhood. Most patients die before the third decade. Mutations in this gene are heterogeneous, ranging from small microlesions to gross deletions and inversions[155-157] and, in some cases, involves neighboring genes. Therefore, wide clinical variation is common. Gene therapy has been reported.[158-160]

Morquio's Disease

Morquio's disease (MPS-IVA), an autosomal recessive disorder caused by a genetic deficiency in *N*-acetyl-galactosamine-6sulfatase, is a prototypical chondroosteodystrophy.[145] The disorder is characterized by specific spondyloepiphyseal dysplasia, short-trunk dwarfism, coxa valga, odontoid hypoplasia, corneal opacities, normal intelligence, and excessive urinary excretion of keratan sulfate and chondroitin 6-sulfate. The deficient *N*-acetyl-galactosamine-6-sulfatase results in progressive accumulation of mucopolysaccharides in lysosomes of various tissues, leading to vertebral involvement and cardiac disease (Table 62-5) in the second decade of life. Tomatsu et al.[161] isolated and characterized the full-length cDNA of the gene and it was localized to chromosome 16q24.[162] This gene is approximately 50 kb in size and has 14 exons; mutations have been described.[163,164]

Maroteaux-Lamy Disease

The Maroteaux-Lamy syndrome is caused by the deficiency of the enzyme arylsulfatase B, which is required for degradation of the glycosaminoglycans, dermatan sulfate, and chondroitin 4-sulfate.[165] It is associated with aortic valve disease. This gene, located on 5q13-q14,[165] has been isolated and characterized.[166] Mutations have been identified, and different mutations cause different clinical phenotypes.[167] The clinical features are quite variable, occurring in infancy and consist of growth retardation, coarse facies, corneal clouding, and multiple skeletal changes, together with dilated cardiomyopathy and aortic or mitral value stenosis or insufficiency. Cardiac manifestations usually appear after the neurologic features but are usually present by adolescence. Molecular diagnosis is currently available. Bone marrow transplants are currently the treatment of

choice.[150] All of these disorders can be diagnosed prenatally by enzyme assay in at-risk pregnancies.

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Chapter 62: CARDIOVASCULAR DISEASES DUE TO GENETIC ABNORMALITIES

MUSCULAR DYSTROPHIES WITH CARDIAC INVOLVEMENT

The muscular dystrophies are a heterogeneous group of diseases, the primary manifestations of which include progressive muscle wasting secondary to intrinsic defects of the muscle fiber. These defects have a wide spectrum of clinical expression and include Duchenne's muscular dystrophy, Becker's muscular dystrophy, Emery-Dreifuss muscular dystrophy, the limb-girdle muscular dystrophies, and myotonic dystrophy. Cardiac disease, especially DCM, is central to the morbidity and mortality associated with these disorders (Table 62-7).

Duchenne Muscular Dystrophy (DMD)

DMD is an X-linked disorder characterized by the early onset of progressive, generalized muscle weakness and "pseudohypertrophy" of certain muscle groups.[168] The incidence of DMD is estimated to be 1 in 3300 live male births with little ethnic variation, and the calculated mutation rate of 10^4 is an order of magnitude higher than for most other genetic diseases. About one-third of cases arise by spontaneous mutation, with the remaining two-thirds occurring by inheritance of the disease-causing gene from the carrier mother. Female carriers of DMD are usually asymptomatic but occasionally have a slowly progressive myopathy of moderate severity. This "manifesting female carrier" state occurs in approximately 8 percent of carriers and is thought to occur due to random X-inactivation. The disease may also be expressed in females with Turner syndrome having a single X chromosome and in females with X-autosome translocations that disrupt the DMD gene. In the latter case, the translocation not only disrupts the DMD gene but also causes the nonrandom inactivation of the normal allele on the other X chromosome, resulting in the expression of the disease phenotype.

Although evidence of skeletal muscle disease in boys with DMD is evident in the neonatal period, as seen by high serum muscle enzymes (particularly CK-MM), clinical disease is not. There may be mild developmental delay, walking later than expected, but weakness is usually not appreciated until at least 2 or 3 years of age. Early symptoms reported by parents include difficulty in running or climbing stairs, frequent falling, and enlargement of calf muscles. Pelvic-girdle weakness is more obvious than shoulder-girdle weakness in the early stages. The gait becomes lordotic and waddling, and the child usually walks with the heels raised slightly off the ground (i.e., toe walking). As pelvic girdle weakness increases, the child has increasing difficulty rising from a seated position. In order to rise from the floor to a standing position, the child must brace the arms against the front of the thigh and climb up the legs, the so-called Gowers sign. Muscle pseudohypertrophy usually appears by 5 to 6 years of age, with muscle enlargement most commonly occurring in the calf muscles; the quadriceps, infraspinatus, deltoid, and gluteal muscles may also be involved, however. The upper and lower extremities become progressively weaker with age, and joint contractures may appear due to uneven weakness of agonist and antagonist muscles. Contractures of the hip flexors, iliotibial bands, and heel cords develop in 70 percent of patients between 6 and 10 years of age. Most patients are wheelchair-bound by the end of the first decade of life. After ambulation is lost, fixed contractures occur and paraspinal muscle weakness leads to progressive kyphoscoliosis. Significant weakness of the respiratory muscles occurs early in the second decade and is a common cause of demise.

Although most cases of DMD can be recognized on the basis of the patient's history and clinical

signs alone, laboratory evaluation is important to confirm the diagnosis.[168] As previously noted, extremely high levels of CK-MM are found in the early stages of disease, as early as birth, and precede evidence of clinical involvement. Other muscle enzymes-including aldolase, SGOT, lactic dehydrogenase (LDH), and pyruvate kinase-are also grossly elevated. In the end stages of the disease, enzyme levels fall but do not reach normal values. Electromyographic examination may also be useful, demonstrating the characteristic features of a myopathy. Insertional activity is normal or increased initially but decreases in the advanced stages of the disease, when fibrosis replaces muscle fibers. Fibrillation potentials and positive sharp waves occur in the early stages of the disease due to the splitting of muscle fibers. The motor unit potentials are small and polyphasic, and an early recruitment pattern with minimal effort is present. Mild intellectual impairment is common in patients with DMD. The retardation is present at an early age, is nonprogressive, and does not correlate well with the stage of the disease. Approximately one-third of patients have IQs below 75, characterized primarily by impaired verbal ability.

The heart is commonly involved in DMD, with electrocardiographic abnormalities and dilated cardiomyopathy being most typical.[168] Cardiac symptoms, however, are unusual before the terminal stages of the disease. Congestive heart failure tends to occur. A midsystolic click and late systolic murmur associated with mitral valve prolapse are also common. In addition, an S3 or S4 gallop, sinus tachycardia, and a mitral regurgitation murmur are usually heard; cardiomegaly and increased pulmonary vascular markings appear at this stage, and bilateral diaphragmatic elevations may be seen owing to diaphragmatic dystrophy. Unlike the late-onset findings of dilated cardiomyopathy, the electrocardiogram is abnormal early in the course of DMD, with a tall R-wave and an abnormally increased R/S ratio in the right precordial chest leads and a deep, narrow Q-wave in leads I, aV_L, V_5, and V_6. These abnormalities progress over time and are attributed to the finding of that the greatest dystrophic myocardial changes in the posterobasal and contiguous lateral left ventricular myocardium. In addition, P waves with negative terminal deflections in V_1 exceeding 20 ms and 0.1 mV appear in 20 to 45 percent of patients and, in the absence of left atrial enlargement on echocardiogram, are attributed to an intrinsic disorder of left atrial or intraatrial conduction. A short PR interval may be seen in up to 50 percent of patients but is not thought to be due to a bypass tract, as seen in Wolff-Parkinson-White syndrome. Infranodal conduction abnormalities, however, may be seen in patients with DMD, and these include complete or incomplete bundle-branch block, and left anterior or posterior fascicular block. Atrial and ventricular premature beats and atrial flutter are seen in some patients.

Echocardiography reveals left ventricular dilatation and dysfunction, with significantly reduced ejection fraction, and LV hypokinesis of the posterobasal ventricular wall is identified. Doppler and color Doppler commonly demonstrate mitral regurgitation, either secondary to the dilated cardiomyopathy or to the associated mitral valve prolapse, which occurs secondary to papillary muscle dysfunction. In some patients systolic function appears normal but diastolic dysfunction is present.

Histopathologic abnormalities of the heart and skeletal muscle are universal in patients with DMD, and those of skeletal muscle are widespread even in the early stages of disease.[168] Typical findings are rounding of the muscle fibers, increased variability in fiber size, increased central nucleation, and fiber splitting. Necrotic and regenerating fibers are present along with large, round hyaline fibers. In the late stages, muscle may be virtually replaced by fat and fibrous tissue. In the heart, degenerative changes in muscle fibers and areas of fibrosis in the ventricles, atria, and conduction system occur, with most pronounced changes in the posterobasal region and adjacent lateral wall of the left ventricle. The underlying cause of cardiac disease is not currently known, but it is speculated that the gene defect in DMD leads to instability of the translated cytoskeletal protein, leading to weakening of the myocyte membrane and subsequent myocyte death due to mechanical stress.

The dystrophin gene, on the short arm of the X chromosome,[168,169] is responsible for these disorders and when dystrophin abnormalities occur due to mutations, may cause either low level production of a nonfunctional protein or complete absence of dystrophin in the heart and skeletal muscle of affected patients. It is among the largest genes discovered thus far, comprising approximately 2.5 Mbp and transcribing a 14-kb mRNA molecule. This cytoskeletal protein-encoding gene is normally expressed in striated and smooth muscle as well as in brain. In muscle tissue, the dystrophin protein has been localized to the cytoplasmic surface of the sarcolemma and is associated with several integral membrane glycoproteins.[170] This glycoprotein/dystrophin complex-which involves the sarcoglycans, dystroglycans, syntrophins, and dystrobrevins-connects dystrophin to the sarcolemma and links to the extracellular matrix; it may be involved in the regulation of intracellular calcium, which is increased in dystrophin-deficient muscle, along with increased calcium channel transport.

The diagnostic approaches to DMD have changed dramatically over the past decade. Previously, serum CK-MM level and muscle biopsy were the standard approaches. Today DMD is diagnosed primarily by molecular analysis, which is rapid and accurate and may predict clinical course. Most commonly, dystrophin mutations that cause a frameshift[171] of the nucleotide sequence result in the severe form of muscular dystrophy, DMD.

Management of the congestive heart failure associated with the DCM seen in DMD is identical to that used for patients with other causes of heart failure and arrhythmias. Pacing is not usually necessary.

Becker's Muscular Dystrophy (BMD)

BMD is an X-linked disorder that differs in both severity and time of onset from DMD,[168] despite being due to allelic mutations in dystrophin, the gene responsible for DMD. BMD appears later and progresses more slowly than DMD, so that survival to middle age is seen. The pattern of muscle weakness, however, is identical to that in DMD, with early involvement of the pelvic girdle and proximal lower extremities.[168] The initial signs of weakness usually appear during the second decade but may be seen as late as the third decade. The weakness gradually progresses, with the upper extremities becoming involved after 5 to 10 years. Patients generally remain ambulatory until their mid-thirties. As in DMD, muscle hypertrophy is common; intellectual impairment, however, is less common and less severe. As in DMD, life expectancy is also reduced in BMD, with only 50 percent of patients surviving to 40 years of age.

Cardiac involvement may be seen in adolescence and ultimately affects 80 percent of patients.[172] As in DMD, dilated cardiomyopathy and cardiac failure are the usual abnormalities encountered ( Table 62-7) and are often the ultimate cause of death. Conduction abnormalities manifesting as fascicular block or complete heart block are also seen. As in DMD, muscle enzyme activity is markedly elevated in BMD, and preclinical cases may be detected by elevated CK-MM. Electromyographic examination shows a "myopathic" pattern with small, polyphasic motor units and early recruitment of motor units. The histology of BMD is similar to that of other forms of muscular dystrophy. In contrast to DMD, hyaline fibers are rarely seen. Electrocardiographic changes are similar to those seen in DMD. Other electrocardiographic abnormalities encountered include left axis deviation, right bundle-branch block, left bundle-branch block, and complete heart block. The echocardiogram may demonstrate the features of dilated cardiomyopathy.

BMD is also due to mutations within the dystrophin gene; i.e., it is allelic with DMD. As is the case with DMD, more than 30 percent of patients with BMD have no family history of the disease, an indication that they represent spontaneous mutations. The phenotypic difference

between DMD and BMD patients has been speculated to be due to frameshift mutations leading to more severe disease (DMD) while out-of-frame mutations cause less severe (BMD) disease.[171] The frameshift hypothesis explains more than 90 percent of the cases of DMD versus BMD. The cardiac abnormalities in BMD, like those described for DMD, require further study.[173] The treatment of CHF and arrhythmias is similar to that of other patients with these signs and symptoms.

Animal models have been created during the past several years that help to characterize the roles of dystrophin and the associated complexes.[174-180] Loss-of-function mutations of dystrophin lead to a DMD or BMD phenotype, while utrophin-deficient mice have defects in the postsynaptic membrane folds at the neuromuscular junction. Mice lacking both dystrophin and utrophin display a severe muscular dystrophy with premature death.[177-180] Sarcoglycan-deficient mice also demonstrate severe muscular dystrophy but, in addition, severe hypertrophic and/or dilated cardiomyopathy has been seen.[174,175]

Various methods evaluating the possibility of gene therapy for dystrophinopathies have been reported over the past several years in mice, with varying degrees of success. Minigene and stem-cell transplantation have both been considered promising using dystrophin and utrophin.[181,182]

Emery-Dreifuss Muscular Dystrophy (EDMD)

EDMD is a relatively rare disorder[168] characterized by weakness in the humeroperoneal distribution, early joint contractures, and dilated cardiomyopathy, with X-linked (occasionally, autosomal dominant) inheritance. The onset of disease in these patients occurs between 2 and 10 years of age, with weakness initially noted in the shoulder girdles and upper extremities. Contractures of the elbows and posterior cervical muscles appear early. The disease is slowly progressive, with involvement of the distal leg musculature following that of the upper extremities; contractures of the knees and ankles follow contractures of the elbows. Unlike the case in DMD and BMD, muscle pseudohypertrophy does not occur. The disease evolves slowly and usually stabilizes in the third decade, with most patients remaining ambulatory. Dilated cardiomyopathy is a common occurrence, but the severity of disease varies from family to family. Varying degrees of atrioventricular block are common (Table 62-7) and atrial standstill may occur. These electrical abnormalities may lead to episodes of syncope, transient ischemic attacks, stroke, and sudden death. A pacemaker is commonly required. Atrial fibrillation has also been observed. As in DMD and BMD, muscle enzyme activity is elevated, albeit to a lesser extent. Skeletal muscle biopsy histopathologic findings are similar to those associated with other forms of muscular dystrophy. Type I fiber atrophy has been described in some cases (Fig. 62-9). The gene responsible for X-linked EDMD was localized to Xq28[184] before being cloned. The gene called emerin (or STA) was shown to have an open reading frame of 762 nucleotides that encodes a serine-rich 254-amino acid protein with probable mechanical/structural function.[185] Emerin mRNA shows ubiquitous tissue distribution, with the highest expression in skeletal and cardiac muscles. The cDNA sequence of emerin predicts a tail-anchor membrane protein with an amino acid sequence similar to that of the thymopoietins, a group of nuclear lamina-associated proteins.[186] Nagano et al.[187] and Manilal et al.[188] both showed that emerin is a 34-kDa nuclear membrane protein in skeletal and cardiac muscle, which is absent in EDMD.

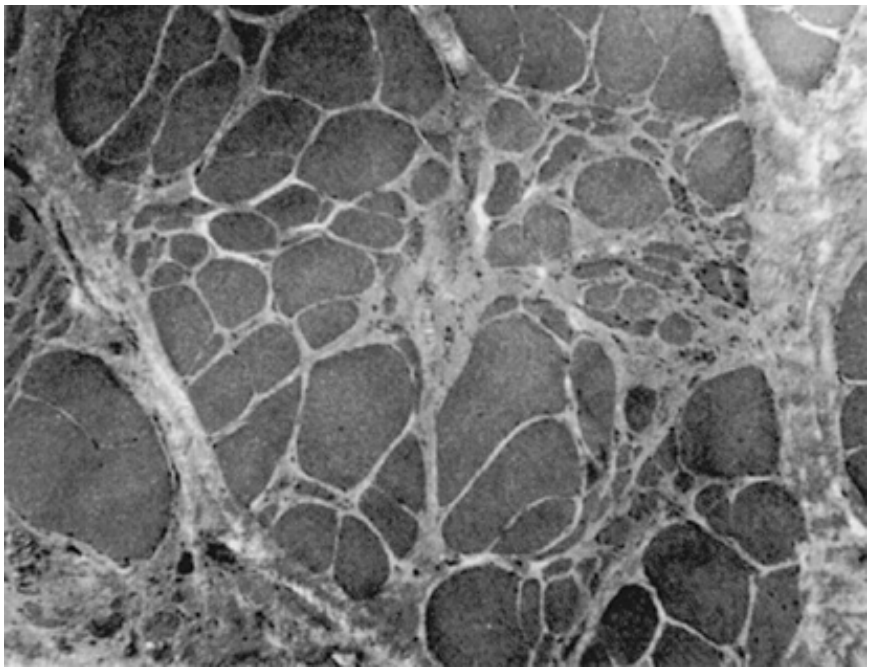

Figure 62-9: Skeletal muscle biopsy in Emery-Dreifuss muscular dystrophy. Increased endomysial and perimysial connective tissue, with marked variation in myofiber size, internal nuclei, and myofibers splitting (×153). (Reprinted with permission from Specht LA, McKee AC. MGH Case Records (case 34-1992): A 19-year-old man with progressive proximal muscle weakness, contractures, and cardiac abnormalities. *N Engl J Med* 1992; 327:558.)

The autosomal dominant form of EDMD was initially mapped to chromosome 1, and recently the gene was identified as lamin A/C.[189] The encoded protein is also thought to be a nuclear lamina-associated protein. The phenotypic spectrum of this gene appears to be broad when mutated. In some cases, only a DCM phenotype with conduction disease occurs in the absence of skeletal muscle disease clinically, similar to what is seen with dystrophin.

Myotonic Dystrophy (Steinert's Disease)

Myotonic dystrophy (DM) is the most common form of inherited muscular dystrophy in adults, with an incidence of 1 in 8000 to 10,000 persons.[168] This autosomal dominant disorder affects multiple organ systems and its name is derived from the combined myopathy, dystrophy, and myotonia of skeletal muscle. Myotonia, an abnormality in relaxation after muscle contraction, is the primary feature of this disease. DM is variably expressed, and individuals may present with signs and symptoms involving many different organ systems. Penetrance varies with age and the disease may affect different tissues at different periods of life; a severe form of DM exists with symptoms at birth.

Classically, DM presents in a young adult with new-onset weakness of the hands or mild foot drop. Asymptomatic myotonia-namely, sustained contraction and depolarization of skeletal muscle in response to a percussive or electrical impulse-may be elicited. Myotonia is usually in the hands and tongue, while weakness involves the distal extremities predominantly. A typical facies usually accompanies these findings, including loss of temporal muscle and slight weakness of the lips and mouth with a "hatchet-like" shape, frontal balding, and ptosis (Fig. 62-10). Other systems including heart, eyes, CNS, endocrine system, gastrointestinal system and respiratory system may be involved (Table 62-5). Electromyographic abnormalities are frequent and subcapsular; punctuate iridescent cataracts are common in middle-aged patients.

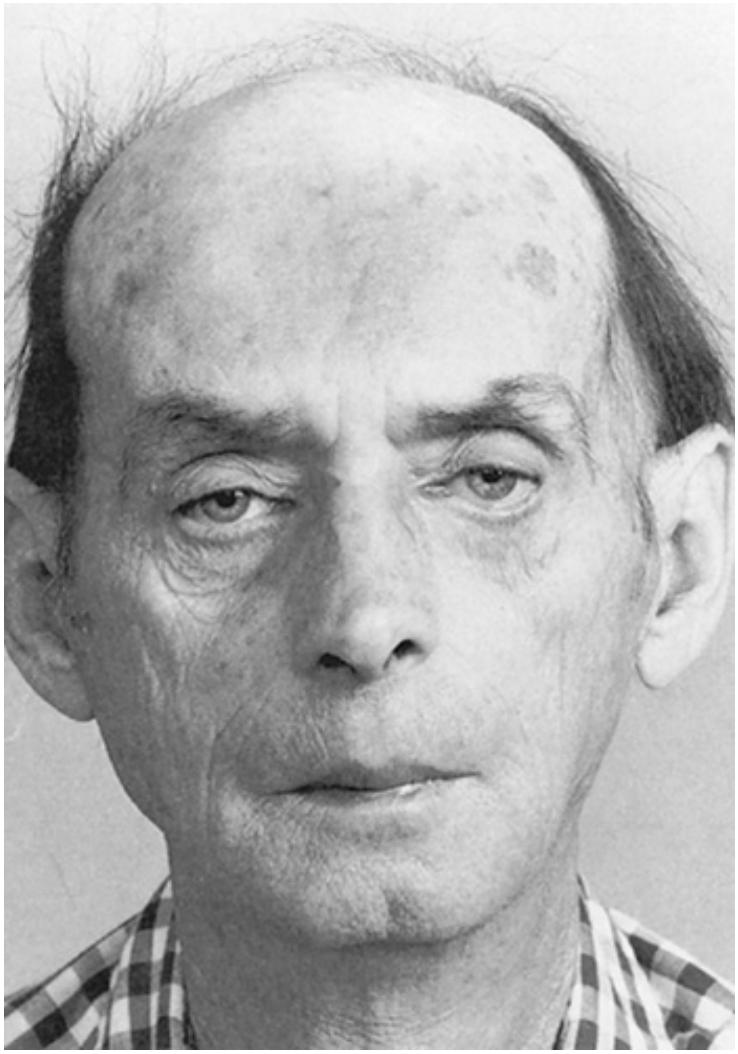

Figure 62-10: A 41-year-old man with myotonic dystrophy (DM). Muscle wasting of temporalis muscles with narrow small chin produces a "hatchet-like" facies. Baldness and ptosis (note droopy eyelids with pupils partially covered and sclerae visible) contribute to characteristic appearance. (Reprinted with permission from Roses AD, Pericak-Vance MA. In: *Molecular Basis of Neurology*. Cambridge, MA: Blackwell; 1993:147-159.)

Myotonia is best seen in the small muscles of the hand and in the tongue. There are repetitive discharges with gradual and uneven decay of amplitude on electromyography. Myotonic muscles undergo dystrophic changes, which may take years to several decades. In general, the younger the presentation, the more rapid the progression. Only a small percentage of affected individuals, probably less than 10 percent, progress to requiring a wheelchair for ambulation; many require a brace worn in the shoes to control foot drop.

Serious complications of DM involve the heart.[189] Cardiac conduction abnormalities are common (Tables 62-7 and 62-8) and may be progressive, particularly in younger patients. These are identified by periodic ECG monitoring and usually occur without obvious cardiac complaints. Sudden cardiac death in athletically inclined adolescents is relatively frequent. In studies of families with DM, cardiac findings may be the initial clinical manifestation of the disease, with bradycardia and first-degree heart block being common. Progression to complete heart block may occur over time and is not well tolerated, potentially ending in death and frequently requiring pacing. In some cases, ventricular tachycardia or dilated cardiomyopathy may also occur (Table 62-8). Typically, however, systolic function is preserved but diastolic dysfunction occurs.

Table 62-8: Systemic Involvement in Myotonic Dystrophy

Organ or System	Clinical	Diagnostic Signs
Muscle	Myotonia, weakness, dystrophy	*EMG:* decreased resting membrane potential, repetitive depolarization ('dive bomber' sound) *Pathology:* sarcoplasmic masses, ringed fibers, internal nuclei frequent; nuclei often in chains; large variation in fiber size
Cardiac	Bradycardia common, complete heart block frequent, prolonged PR interval, dilated cardiomyopathy	First-degree heart block, bradycardia on ECG; abnormal vectorcardiogram; SA node, right and left bundle branch dysfunction; increased His-Purkinje conduction (His bundle studies) with progressive conduction system abnormalities; dilated cardiomyopathy
Lens	Posterior subcapsular, iridescent, or scintillating cataracts	Dust-like cataracts may be visible only on slit lamp examination
Eye	Decreased vision (independent of cataracts and diabetic retinopathy); diplopia	Pigmentary disorders of macula keratosis sicca; decreased intraocular pressure; frequent ptosis and ultraocular muscle weakness
CNS	Mental retardation (especially congenital DM); hypersomnia	Possible neuronal heterotopias; suspicious, reticent personality characteristics
Gastrointestinal	Dysphagia, abdominal pain	Disordered esophageal and gastric peristalsis; dilation of bowel
Skeletal	Cranial and facial abnormalities, malocclusion of dentition	Cranial bony abnormalities, hyperostosis of skull (localized or diffuse), small sella turcica, large sinuses, micrognathia
Respiratory	Hypoventilation, postanesthesia respiratory failure	Diaphragmatic and intercostal muscle weakness
Smooth muscle	Dilation of hollow-viscus organs and ureters, abnormal bowel motility	Thinned or interrupted smooth muscle

DM patients may have a particular psychological profile that includes indifference, reticence, and hostility. Mild mental retardation may be seen, particularly in patients with congenital DM. Young and middle-aged patients may be hypersomnolent and indolent, sometimes sleeping up to 20 h daily. Testicular atrophy is common in males and amenorrhea and ovarian cysts may occur in females (Table 62-8). Increasing debilitation, handicap, and disability may occur in subsequent generations of a family; this increasing disease severity is known as *anticipation*.

The gene for myotonic dystrophy was localized to 19q13.3[190] and encodes for myotonin protein kinase (DMPK), a serine-threonine protein kinase.[191] The genetic basis for myotonic dystrophy

consists of long stretches of three bases repeated in tandem. The triplet repeat present in the DMPK gene is CTG, which in the mRNA is CUG and is located in the 3′ end of the gene beyond the protein coding region. The severity of disease (neuromuscular, cardiac, and CNS) relates to the length of the repeats. Less than 50 triplet repeats is usually associated with no disease. Usually 100 to 250 repeats are required to cause disease and, if more than 250 repeats are present, the disease is usually seen at birth and reflects genetic anticipation (increasingly severe expression and earlier onset of disease through generations as a result of the increase in the number of CTG repeats with subsequent generations). Clinical cardiac symptoms (i.e., syncope) and ECG abnormalities (i.e., left bundle-branch block) correlate directly with CTG expansion size.[189] In addition, the incidence of malignant ventricular arrhythmias also correlate directly with the size of CTG expansion.

Myotonic dystrophy is one of the many familial neuromuscular diseases due to the genetic defect of multiple triplet repeats.[189] However, the mechanisms whereby the triplet repeats induce the disease remains an enigma. Myotonic dystrophy is somewhat unique since the triplet repeats are in the 3′ end of the gene beyond the protein coding region. DMPK levels are reduced in patients with myotonic dystrophy; when the gene for DMPK is eliminated in knockout mice, muscle weakness results, but none of the other organs are involved, such as the eyes or testes, as observed in myotonic dystrophy. This has led to an extensive search for other explanations, including adjacent genes. One by-product of this research was identification of a novel group of proteins that bind specifically to triplet repeats in DNA and RNA[192]; binding is determined by the sequence of the triplet repeat. A specific protein was identified that binds only to the CUG sequence in the mRNA of DMPK. The CUG-BP protein has a molecular weight of 52 kDa and three binding sites for CUG repeats.[192] The protein has several serine and threonine phosphorylation sites, which appear to be regulated by DMPK. Further studies indicated that this protein is identical to another protein (NB50) that is known to be responsible for mRNA transport from the nucleus to the cytoplasm.[193] This has given rise to the hypothesis that the CUG-BP is sequestered by the multiple CUG repeats and not available to other mRNAs for processing or transport from the nucleus. The involvement of several mRNAs would explain the multiple organs involved. This would also explain why, in the mouse with the DMPK gene knocked out, one observes only muscle weakness because in the absence of the multiple triplet repeats, the other mRNAs are properly transported by the CUG-BP protein and function normally.[194,195] This hypothesis is now actively pursued by many investigators. Preliminary findings show an accumulation of the CUG-BP in the nuclei of cells from DM.[196,197] Another possible mechanism is variations in gene levels in the immediate vicinity, such as the homeobox gene DMPHP.

Relative to therapy, conduction disturbances typically require permanent pacemaker implantation and dilated cardiomyopathy requires treatment for heart failure.

Fascioscapulohumeral Dystrophy

Fascioscapulohumeral,[198] or Landouzy-Dejerine, muscular dystrophy exists as two clinical types. One type has autosomal dominant inheritance with onset at the end of the first or the beginning of the second decade. The weakness of the facial, shoulder, and upper arm muscles is slowly progressive, but wide variability is seen. The second clinical type of fascioscapulohumeral dystrophy is the infantile form. Onset is within the first 2 years of life, and many patients are wheelchair-bound by 1 year of age. Clinical manifestations of muscular dystrophy generally are absent in the parents.

The cardiac involvement involves progressive atrial dysfunction resulting in permanent paralysis of the atria, beginning with sinus bradycardia, junctional escape rhythm, and AV block (Table 62-7). Criteria for diagnosis of permanent paralysis of the atria include absence of P waves on surface ECG, esophageal electrogram, and intracardiac electrocardiogram, unresponsiveness of

the atrium to electrical stimulation, and immobility of the atria on fluoroscopy and echocardiography. Focal abnormalities of the atria precede these events. Nonparalytic regions of the atrium may demonstrate enhanced activity, apparent clinically as atrial tachycardia or flutter. Therapy depends on the clinical features. The chromosomal locus has been identified on chromosome 4q35,[199] but the responsible gene(s) are unknown.

Nemaline Myopathy

Nemaline myopathy is named for the small rod-like particles found in striated muscle. Inheritance is probably autosomal dominant, although autosomal recessive inheritance may occur.[200] Clinical features include hypotonia with truncal and extremity weakness from an early age and a narrow arched palate. Conduction abnormalities and cardiac dilatation have been described[200,201] but are unusual (Table 62-7). Nemaline rods are demonstrable in the myocardium and conduction tissues. The genetic cause of this disease was recently discovered by Nowak et al.,[202] who identified mutations in the human skeletal muscle α-actin gene (ACTA1), all missense mutations. Interestingly, the clinical phenotype varied significantly, from mild disease to severe, infantile-onset disease. In addition, a different clinical disorder, actin myopathy (i.e., congenital myopathy with excessive thin filaments), was also found to carry mutations in ACTA1.[202,203]

Two other forms of nemaline myopathy have also been identified. Mutations in TPM3, encoding α-tropomyosin slow, has been found mutated in both dominant and recessive nemaline myopathy.[204] In addition, mutations in NEB, encoding nebulin, has been seen in slowly progressive congenital nemaline myopathy.[205] Therefore, the underlying cause for this phenotype are mutations in skeletal muscle sarcomeric genes, similar to that seen in HCM and cardiac sarcomeric genes. Therapy is required when the conduction abnormalities or cardiac dilatation causes clinical symptoms.

Endocardial Fibroelastosis (EFE)

This disorder is characterized by endocardial thickening, which leads to decreased compliance and impaired diastolic function. Primary forms are typically unassociated with other cardiac anomalies. Most commonly, this disease presents in infancy and early childhood with signs and symptoms of congestive heart failure.[206] The diagnosis is usually made by biopsy. The incidence of primary EFE in the United States in the past was relatively high-approximately one case in 5000 live births.[207] During the past decade, however, this incidence has decreased markedly, for unknown reasons. Treatment of children with primary EFE with anticongestive and inotropic measures has been ineffective, and the clinical course usually results in either death or transplantation. Postmortem examination typically demonstrates enlargement of the left ventricle. Histopathology commonly reveals extensive deposition of extracellular matrix, primarily collagen and elastic fibers, in the endocardium. Three inherited forms of EFE have been described: autosomal recessive, autosomal dominant, and an X-linked recessive disorder. The majority of cases, however, occur sporadically. The X-linked form shows mitochondrial abnormalities similar to Barth syndrome[127,128] with the exception that EFE patients have endocardial scarring. It is likely, however, that this form is caused by mutations in the G4.5 gene found in Barth syndrome and LV noncompaction.[129] It was hypothesized in the 1950s and 1960s that EFE is secondary to intrauterine myocarditis in sporadic cases, particularly as a result of mumps or Coxsackievirus. Ni et al.[208] recently identified mumps viral genome in the majority of autopsy specimens retrieved from infants dying between the 1950s and 1980s. This disease essentially disappeared after the program of vaccination (mumps-measles-rubella or MMR) began in the United States.

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Chapter 62: CARDIOVASCULAR DISEASES DUE TO GENETIC ABNORMALITIES

DEFECTS OF METABOLISM CAUSING CARDIOMYOPATHY

Carnitine Deficiency

L-Carnitine is a small, water-soluble molecule containing seven carbon atoms and is important in the shuttling of long-chain fatty acids and activated acetate across the inner mitochondrial membrane. A specific translocase facilitates the exchange of long-chain acylcarnitine and acetylcarnitine. Carnitine also serves as the shuttle for the end products of peroxisomal fatty acid oxidation and for α-ketoacids derived from branched chain amino acids. These metabolites are transferred into the mitochondrial matrix for terminal oxidation.

Primary carnitine deficiency syndrome is characterized by a profound decrease in carnitine in affected tissues. The mechanism underlying the primary disorder is defective transport of carnitine from the serum into the affected cells.[209] End-stage disease of many different organs, including the heart, may induce depletion of carnitine stores and must be differentiated from the chronic inherited type. Based on carnitine levels, carnitine defiency is usually divided into two forms: a myopathic form and a systemic form. In the myopathic form, carnitine levels are decreased only in muscle tissue; in the systemic form, multiple tissues are affected, including muscle, liver, and plasma.[209] The systemic form presents in infancy or early childhood with episodes of hypoglycemia, ammonemia, acidemia, hepatomegaly, and EFE. A gene for primary systemic "carnitine" deficiency was recently mapped to chromosome 5q31.1-5q32,[210] the SCD locus. A murine model with juvenile visceral steatosis (*jvs*) has been identified[211] in which homozygotes have low serum total and free carnitine levels but no reduction in urinary excretion of carnitines.[212] This gene was mapped to the *jvs* locus on chromosome 11 of the mouse, which is syntenic to human 5q.[213] The human gene was recently found to be a novel sodium ion-dependent carnitine transporter, OCTN2.[214]

Therapy includes oral carnitine, occasionally reversing the cardiomyopathy. Additional therapy includes bicarbonate to reverse the acidemia, intravenous glucose, and anticongestive measures. Intercurrent illness commonly causes acute decompensation and death.

Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

This disorder appears to be the most common inborn error of fatty acid oxidation, estimated to occur in one per 6000 to 10,000 live Caucasian births. It is characterized by recurrent episodes of illness, provoked by fasting more than 12 h, with the first episode generally occurring between 6 and 24 months of life. The most common symptoms include vomiting and severe lethargy that can progress to coma, as well as the less striking symptoms of muscle weakness and exercise intolerance. Hypoglycemia is often present between episodes, when patients appear normal. Hepatomegaly and DCM (rarely) are also seen. Liver biopsy can show marked fatty infiltrate ranging from predominantly microvesicular to a macrovesicular pattern. This autosomal recessive disorder was localized to chromosome 1p31 and human and rat MCAD cDNAs were cloned and sequenced.[215] The coding region is 1263 bp and encodes a precursor protein containing 421 amino acids. A variety of mutations have been reported. An A-to-G nucleotide replacement at position 985 of MCAD cDNA appears to be the most prevalent mutation responsible for MCAD deficiency (greater than 90 percent).[216] This deletion is predicted to result in a truncated protein of

385 amino acids instead of the normal 421-amino acid product. The common A-to-G 985 mutation appears to be due to a founder effect. Poor genotype-phenotype correlation exists.[217]

The therapy for these patients includes treatment of the acidosis and, when present, treatment of heart failure. Glucose therapy is indicated for hypoglycemia while intravenous fluids are needed during episodes of vomiting.

Long-Chain Acyl-CoA Dehydrogenase (LCAD) Deficiency/Very Long Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency

First described in 1985, LCAD manifests itself as recurrent episodes of coma, vomiting, and hypoglycemia triggered by fasting. Some patients have much more severe illness with notable involvement of cardiac and skeletal muscle.[28] Both DCM and HCM have been seen. Like MCAD, LCAD patients have secondary carnitine deficiency, and their fasting urine organic acid profile is abnormal, with low ketones and increased levels of dicarboxylic acids. The LCAD gene was identified[218] in 1991. In addition to the well-known β-oxidation enzymes in the mitochondrial matrix, there are two additional membrane-bound enzymes of β-oxidation.[219,220] One of these has been called "very long chain acyl-CoA dehydrogenase" (VLCAD), while the other is known as the "trifunctional protein." VLCAD is a membrane-bound homodimer with monomers of larger size than the other enzymes of the complex. It catalyzes the initial rate limiting step in mitochondrial fatty acid β-oxidation. The human VLCAD cDNA[221222] and genomic sequence[210] were identified over the past several years, with multiple mutations subsequently identified.[224] Andresen et al.[225] recently showed that clear correlation of genotype with disease phenotype exists. Patients with severe childhood phenotype, which has a high incidence of cardiomyopathy and mortality, have mutations that result in no residual enzyme activity. Those with milder childhood and adult phenotypes have mutations that may result in residual enzyme activity. This clear genotype-phenotype correlation sharply contrasts that seen in MCAD deficiency, in which no correlation has been established. This new understanding of the mitochondrial β-oxidation pathway has led to new insights of the disorder once thought to be due to LCAD deficiency but now thought to be VLCAD deficiency.

Therapy for these patients includes aggressive treatment with glucose and hemodynamic support. When cardiac disease persists, chronic therapy for the dilated or hypertrophic heart disease should be instituted.

Fabry's Disease

An X-linked recessive disorder with complete penetrance and variable clinical expressivity, this entity is due to a deficiency of the enzyme α-galactosidase A, a lysosomal enzyme that participates in the catabolism of neutral glycosphingolipids, and is found in one in 40,000 live births. The disease frequently has its onset in adolescence and typically manifests with sensations of burning pain in the hands and feet. These sensations tend to be associated with fever, heat, cold, and exercise. Multiple angiokeratomas are noticeable with increasing age, with the umbilical area and genitalia the sites most commonly affected. Progressive renal failure develops with age, and CNS manifestations commonly include seizures, headaches, hemiplegia, and stroke. Corneal opacities are also frequently seen.

The cardiac manifestations of Fabry's disease generally appear in young adulthood. Aortic root dilation, dilated or hypertrophic cardiomyopathy,[226] valve dysfunction (especially mitral valve),[227] and myocardial infarction occur in these patients. Recently, association with tetralogy of Fallot was reported,[228] as was restrictive cardiomyopathy.[229] Electrocardiographic abnormalities commonly include atrial fibrillation, intraventricular conduction delay, right bundle-

branch block, ST-T wave changes, short PR interval, and left ventricular hypertrophy. The short PR interval can progressively shorten over time probably secondary to lipid deposition in the atrioventricular node. Chamber thickness and mitral valve prolapse are evident on echocardiographic examination. Light microscopy shows lipid accumulation in nearly all cardiac tissue. Concentric lamellae are seen within cells and contain the neutral glycophospholipid. Therapy for these cardiac abnormalities does not differ from that typically used for HCM, myocardial ischemia or infarction, or mitral insufficiency found in patients without Fabry's disease. Recently, cardiac transplantation has been reported.[230]

The disease-causing gene, lysosomal-galactosidase A (GLA), is localized to Xq12.1-Xq12.2. The full-length cDNA has 1393 bp with a 60-nucleotide 5′ untranslated region, encoding for a precursor peptide of 429 amino acids.[231] The gene was found to contain seven exons. Mutations have been described[232,233] and genotype-phenotypic correlation performed. Mouse models have been developed which closely mimic the human disorder.[234] Antenatal and postnatal diagnosis is available. Therapy is symptomatic at present, but enzyme replacement therapy is likely in the future. Recently, gene transfer studies have been reported that correct the enzymatic and lysosomal storage defects in Fabry-like mice.[235]

Homocystinuria

Homocystinuria, inherited as an autosomal recessive defect, occurs with a frequency of 1 in 75,000. There is a deficiency of cystathionine β-synthase (CBS), which leads to elevated methionine in the blood and homocystine and methionine in the urine[236] (see Chaps. 39 and 41). In the homozygous individuals, major clinical features include a marfanoid habitus with a thin, tall body build and arachnodactyly, pectus excavatum, kyphoscoliosis, and osteoporosis. Subluxation of the lens, usually in a downward position, is frequently seen by 10 years of age, and myopia is common. Approximately 60 percent of affected individuals are mentally retarded to some degree. Schizophrenic behavior has also been noted in some patients. Cardiovascular abnormalities consist primarily of arterial and venous thrombosis (Table 62-5), with medial degeneration of the aorta and large arteries and intimal hyperplasia and fibrosis. It is estimated that about one-third of patients with familial homocystinuria will experience arterial or venous thrombosis. It is interesting that even within the same family with the same mutation there is marked variability among affected siblings.[237] The thrombotic episodes usually occur before the age of 30 years and include deep vein thrombosis, pulmonary embolism, and arterial thrombosis in the cerebral, peripheral, and coronary arteries.[237] However, when this disease occurs in individuals with other thrombogenic risk factors such as factor V Leiden,[238] the incidence of thrombosis, both arterial and venous, is significantly increased. An increased risk of cardiovascular disease has also been observed in carriers of the gene for homocystinuria. The gene was initially assigned to the subtelomeric region of band 21q22.3 by in situ hybridization studies.[239] Three types of cDNAs differing in both their translated and untranslated regions were isolated, with the resultant differences due to alternative splicing. The human gene was cloned and complete-sequence, alternatively spliced forms, and mutations described.[240] Numerous mutations have now been identified and correlated with the phenotype. The gene is 28 kb in size, contains 23 exons, and contains many *alu* repeat sequences which predisposes the gene to rearrangements.[241] The defect can be treated in some cases by pyridoxine supplementation. The percentage of pyridoxine responders ranges between 13 and 47 percent. Betaine, lowmethionine diet, and aspirin treatments have also been tried with varying success. Prenatal diagnosis is available by an enzyme assay and gene analysis. Recently, tandem spectrometry has been used in the diagnosis.[241]

Homocystinuria, while a rare disease, has received increased attention recently because of several studies indicating that homocysteine is an important and independent risk factor for atherosclerosis and thrombosis.[242,243] In one such study performed recently, of 269 patients with the first episode of deep vein thrombosis, 10 percent had elevated plasma homocysteine levels,

compared with 4 percent in 269 matched controls.[243] Homocystinuria results from impaired enzyme activity in the metabolism of cobalamin, but may also occur from a deficiency of vitamin B_6, folate, or vitamin B_{12}. The mechanism whereby homocysteine induces atherosclerosis is postulated to be through induction of the cyclin A gene which induces vascular smooth muscle proliferation, a major component of atherosclerosis.[244] The mechanism whereby homocysteine induces thrombosis is probably through its known effect on activation of factor V in endothelial cells, inhibition of protein C, and decreased antithrombin III activity. It remains somewhat controversial as to how common hyperhomocysteinemia is as a risk factor for atherosclerosis and/or thrombosis. It is, however, very important to exclude hyperhomocysteinemia in patients with vascular disease such as myocardial infarction, strokes, or systemic thrombosis, particularly if these are occurring prematurely or there are no other risk factors, since, in the acquired form, the condition is relatively easy to treat by the administration of vitamins.

Mitochondrial Cardiomyopathies

The human mitochondrial genome[245] is a small, circular DNA molecule (Fig. 62-11) that is maternally inherited. Mitochondrial DNA (mtDNA) encodes 13 of the 69 proteins required for oxidative metabolism, 22 transfer RNAs (tRNAs), and 2 ribosomal RNAs (rRNAs) required for their translation. Since mtDNA has much less redundancy than the nuclear genome (in which essentially identical information is received from both parents), and tRNAs and rRNAs are present in multiple copies, the mitochondrial genome is an excellent target for mutations giving rise to human disease.[246,247] Mitochondria are dependent on nucleocytoplasmic mechanisms for most structural components, but do contribute vital peptides that are central to cellular respiration. The electron transport chain, which generates cellular ATP, is organized into complexes I to IV and the ATP synthase (complex V) (Fig. 62-12). The 13 mtDNA genes that encode enzymes in the respiratory chain include 7 complex I[246,248] subunits (ND1, 2, 3, 4L, 4, 5, and 6); 1 complex III subunit (cytochrome b); 3 complex IV subunits (COI, II, III); and 2 complex V subunits (ATPase 6 and 8). Each cell contains numerous mitochondria and each mitochondrion contains multiple copies of mtDNA. In most mitochondrial disorders, patients carry a mix of mutant and normal mitochondria-a condition known as *heteroplasmy*, with the proportions varying from tissue to tissue and individual to individual within a pedigree, in a manner correlating with severity of phenotype.

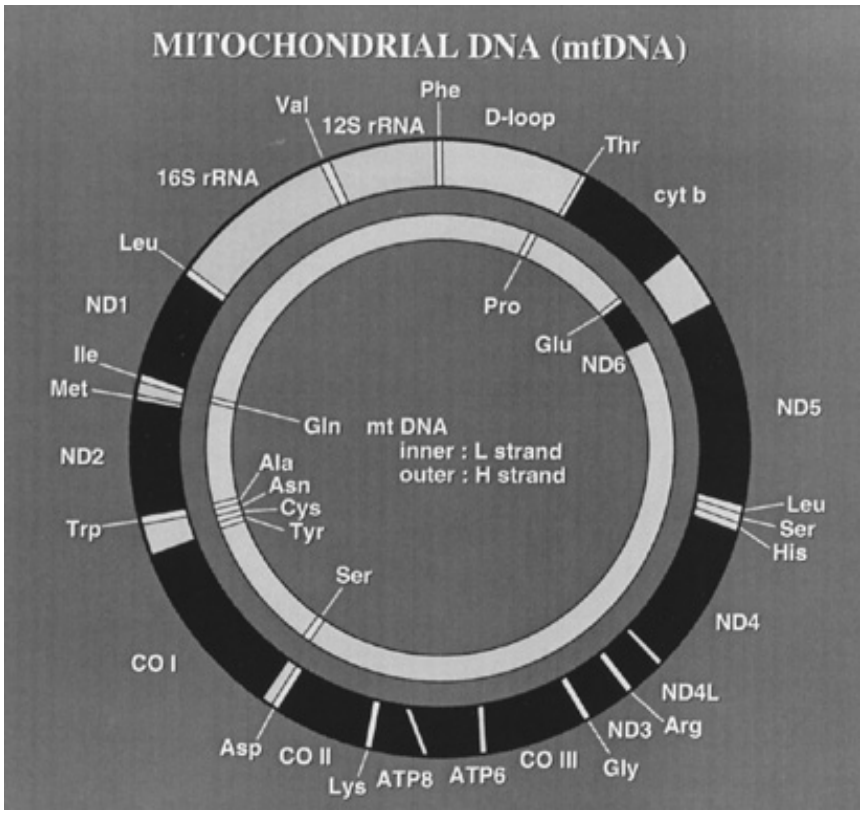

Figure 62-11: Mitochondrial genome. This small, circular DNA molecule encodes 13 enzymes of the respiratory chain, 22 tRNAs, and 2 rRNAs. When it is mutated, cardiac, neurologic, and myopathic disorders develop.

Mitochondrial diseases often produce disturbances of brain and muscle function and are usually evident during infancy or early childhood. Cardiac disease is most commonly seen with respiratory chain defects. Ragged-red fibers are present in muscle biopsy specimens almost invariably when the molecular defect involves mtDNA.[249] These defects represent the genetics of ATP production. The diverse clinical syndromes associated with various respiratory chain complexes are thought to result from involvement of tissue-specific isoforms in some cases, involvement of tissue-nonspecific (generalized) subunits in other cases, and the residual enzyme activity in affected tissues. The cardiac diseases seen associated with mitochondrial defects include both hypertrophic cardiomyopathy and dilated cardiomyopathy.[246]

Mitochondrial gene mapping, in contrast to the nuclear genome, does not require genetic linkage. One simply has to show that the disease exhibits transmission through all mothers and no fathers in a sufficiently large family. Once this is established, the mitochondrial genome can be sequenced to identify the mutation, which must be shown to segregate with the disease since there are many harmless polymorphisms.

Therapy for these disorders is generally symptom-based. Conduction disturbance generally requires placement of a permanent pacemaker, and heart failure is treated with the usual therapy. In some patients, beta-blockers may be useful. Hypertrophic heart disease is usually treated in a fashion similar to that of other forms of HCM. Mitochondrial-based therapy may include coenzyme Q10, carnitine, or vitamins, but these therapeutic approaches typically do not alter the clinical course.

COMPLEX I DEFICIENCY

Complex I, or nicotinamide adenine dinucleotide (NADH): ubiquinone oxidoreductase, is the

largest of the electron transport chain complexes[250,251] (Fig. 62-12) with at least 35 complex I nuclear gene products and 7 mitochondrially encoded proteins. It is embedded in the inner mitochondrial membrane and serves to dehydrogenate NADH and shuttle electrons to coenzyme Q. This electron transport generates a protein gradient across the inner mitochondrial membrane, helping to synthesize ATP. When complex I abnormalities occur, significant health problems arise.

Mitochondriocytopathies occur with an estimated incidence of 1 per 10,000 live births, and isolated complex I deficiency is one of those most frequently encountered.[248] The first clinical symptoms of complex I deficiency, presenting either at birth or in early childhood, result from brain dysfunction, sometimes combined with defects in other energy-consuming organs, such as skeletal muscle and the heart. For this reason, complex I deficiencies are grouped among the mitochondrial encephalomyopathies.

Robinson[248] categorized complex I-deficient patients into three major clinical groups. The most common presentation is Leigh syndrome, with cardiomyopathy occuring in about 40 percent of cases.[252] A second category often seen is fatal neonatal lactic acidosis (MELAS-see below). A third but uncommon group present with hepatopathy and tubulopathy with mild symptoms, such as exercise intolerance, or with cataracts and cardiomyopathy. The most frequently observed pathologic mtDNA mutations are found in genes for mitochondrial tRNAs for leucine (T3271C, A3243G) and lysine (A8344G, T8356C) and in the protein-encoding subunits ND1 (T4160A, G3460A), ND4 (G11778A), and ND6 (T14484C, G14459A).

Treatment of these disorders is limited. Riboflavin, succinate supplements (since the metabolite enters the respiratory chain at complex II), ubiquonone, and idebanone have been recommended for therapy in patients with MELAS. Carnitine and coenzyme Q10 have also been used.

COMPLEX III DEFECTS

This results in a myopathic or multisystem disorder. Cardiomyopathy has been found both alone or in conjunction with skeletal myopathy. Encephalomyopathy also presents with retinopathy, ataxia, spasticity, dementia, weakness, sensorineural hearing loss, and exercise intolerance.

COMPLEX IV DEFECTS

This abnormality is similar clinically to complex I defects. The mitochondrial genome encodes for three subunits of cytochrome C oxidase, which represents the terminal portion of the respiratory chain (Fig. 62-12) and catalyzes conversion of molecular oxygen to water. A benign reversible infantile myopathy which normalizes by early childhood may occur, as may a fatal infantile myopathy manifested by profound weakness, hypotonia, respiratory insufficiency, and death. This myopathy may occur alone, or in association with severe renal tubular dysfunction or cardiomyopathy with red ragged fibers.

HYPOXEMIA, mtDNA DAMAGE, AND CARDIAC DISEASE

Since cardiac tissue relies on mitochondrial oxidative phosphorylation (ox-phos) for energy production, deficiency of portions of this system or its end-product may cause cardiac abnormalities.[248] Hypoxemia can increase oxygen radical production, which results in elevated mtDNA damage and altered ox-phos gene expression. In addition, these enzymes decline with age while mtDNA deletions increase with age, especially deletion at nucleotide 4977 bp. Ischemic hearts may be more likely to have increased chances of mtDNA deletion due to the effect of hypoxemia[253] and, using PCR amplification across the deletion breakpoint of the common mtDNA4977 deletion, it was found that mtDNA damage was increased in chronically ischemic

hearts, as well as in some hearts with other forms of chronic cardiac disease (i.e., DCM, HCM), but this is probably an incidental finding and has no effect on cardiac function. Similarly, mitochondrial DNA damage increases with age independent of ischemia, but it is doubtful whether it in any way alters cardiac function.

KEARNS-SAYRE SYNDROME (KSS)

This mitochondrial myopathy is characterized by ptosis, chronic progressive external ophthalmoplegia, abnormal retinal pigmentation, and cardiac conduction defects as well as DCM.[255] Hearing loss and limb weakness are frequently associated, as are endocrinopathies such as diabetes mellitus, hypoparathyroidism, and growth hormone deficiency. Approximately 20 percent of KSS patients have cardiac involvement and of these, the majority usually have conduction defects causing progressive heart block (Table 62-7). These patients generally have large heterogeneous deletions in the mitochondrial genome, of which $tRNA^{leu(UUR)}$-3243 is most common.

Clinically, conduction abnormalities, bifascicular block, or progressive high-grade block may define the requirement for permanent pacemaker implantation. Symptomatic improvement using mitochondrial therapies may occasionally be seen with coenzyme Q10 therapy. The major function of coenzyme Q10 in mitochondria is to shuttle electrons from complexes I and II to complex III, while stabilizing the respiratory chain complexes. Vitamins such as phylloquinone (vitamin K_1), menadione (vitamin K_3), and ascorbic acid (vitamin C) have been used to donate electrons directly to cytochrome *c*. In addition, the endocrine abnormalities and heart failure should be treated in the usual way.

MERRF SYNDROME

This syndrome is characterized by *m*yoclonic *e*pilepsy with *r*agged-*r*ed muscle *f*ibers (MERRF) and is caused by a single nucleotide substitution in $tRNA^{Lys}$, which apparently interferes with mitochondrial translation.[256] The defining clinical features are myoclonus, generalized seizures, ataxia, and hypertrophic cardiomyopathy. Skeletal muscle biopsy demonstrates ragged-red fibers on microscopy. Symptoms usually begin in childhood, but adult onset has been described. Other common manifestations include impaired hearing, demential neuropathy, short stature, optic atrophy, lactic acidosis, and lipomas.

Shoffner et al.[256] showed an A-to-G transition mutation (position 8344) as the cause of the disease and associated with defects in complexes I and IV. This abnormality causes decline in ATP-generating capacity, with a resultant cardiomyopathy. Other reports have outlined various disease-causing mutations. Therapy is similar to other mitochondrial myopathies; anticonvulsant medications may also be indicated.

MELAS SYNDROME

*M*itochondrial *e*ncephalomypathy and *l*actic *a*cidosis with *s*troke-like episodes (MELAS) is clinically characterized by stroke before age 40 years; encephalopathy with seizures, dementia, or both; and lactic acidosis, ragged-red fibers, or both.[257] Recurrent headaches and recurrent vomiting are common. Other frequent manifestations include exercise intolerance, limb weakness, short stature, and elevated CSF protein. Hypertrophic cardiomyopathy or dilated cardiomyopathy may occur.

Variable respiratory chain defects have been described, but complex I abnormalities are most common. Between 80 and 90 percent of patients have an adenine-to-guanine point mutation in $tRNA^{Leu(UUR)}$ at position 3243. Therapy is similar to that described for MERRF.

THERAPY

Medical therapy for mitochondrial disorders has been disappointing and for that reason newer approaches have been sought. As most pathologic mtDNA mutations are heteroplasmic and there is a threshold whereby a certain level of mutated mtDNA is necessary before a disease becomes biochemically or clinically apparent, any approach that increases the proportion of wild-type to mutated mtDNA will reverse the phenotype and thus be a potentially useful treatment. When there is an extremely high level of the pathogenetic mutation in cells, as occurs with muscle necrosis, these necrotic cells form regenerated muscle. Clark et al.[258] took advantage of this phenomenon by inducing necrosis and regeneration in muscle by performing a muscle biopsy, which resulted in the absence of mutated mtDNA in the biopsied muscle. Due to the invasiveness of this approach, reduced utility of the therapy is anticipated unless other methods of inducing necrosis can be developed.

More recently, Taivassalo et al.[259] developed a novel therapy that they called *gene shifting*, which is similar to that described by Clark et al.[258] These authors enhanced the incorporation of new (satellite) cells through regeneration following injury or muscle hypertrophy induced by eccentric or concentric resistance exercise training. They were able to show a remarkable increase in the ratio of wild-type to mutant mtDNAs, and in the proportion of muscle fibers with normal respiratory chain activity. This work suggests that it might be possible to reverse the molecular events that led to the expression of metabolic myopathy and demonstrates that this form of "gene shifting" therapy could be effective.

Connective Tissue Disorders

The composition, structure, and function of normal and abnormal connective tissues are gradually being elucidated[260,261] (see Chap. 85). The annuli fibrosis that separate the atria and ventricles and support the two atrioventricular valves are largely type I collagen fiber bundles, while the blood vessel walls are elastin and collagen types I and III (50 percent), with lesser contributions from types IV, V, and VI collagen. Elastin in located at 7q11; collagen 1A1, at 17q21.13-17q22.05; collagen 1A2, at 7q21.3-7q22.1; collagen 2A1, at 12q13.1-12q13.3; collagen 3A1, at 2q31; and collagen 5A2, at 2q31.

MARFAN SYNDROME

Marfan syndrome is a heritable disorder of connective tissue caused by a defect in fibrillin protein encoded by the fibrillin-1 gene on chromosome 15 at 15q15-q20 (see Chap. 98). The Marfan syndrome occurs in approximately 1 in 10,000 individuals and is equally common in males and females. There is marked variation in clinical expression, and the diagnosis can be made at any age from the newborn period through adulthood.[263] Because of the variability in expression, overlap with nonpathologic features (such as tall stature) can be observed in the general population. Since fibrillin[264] is diffuse, Marfan syndrome affects skeletal, ocular, cardiovascular, skin, pulmonary, and central nervous system.[260,261] The skeletal manifestations of Marfan syndrome include tall stature, thin body build, long arms and legs (dolichostenomelia), long fingers and toes (arachnodactyly), hyperextensibility, pectus deformity, scoliosis, joint contractures, and narrow, high-arched palate. Cardiovascular abnormalities, particularly affecting the mitral apparatus and aorta, are also common. There may also be overlap with other disorders that share some of the same phenotypic features, such as the condition termed *congenital contractual arachnodactyly* (CCA).[265] Clinical manifestations of CCA include dolichostenomelia and arachnodactyly, contractures of large joints, and abnormal pinnae formation. In 1990, Marfan syndrome was mapped to the long arm of chromosome 15(15q15q-q20).[266] Subsequently, a defect in the gene for fibrillin-1 (FBN1)[267] was found to be the cause of Marfan syndrome. This large

glycoprotein has a molecular weight of 350 kDa[264] and is a component of microfibrils that are ubiquitous in the connective frequently occurs or increases during adolescence. The mRNA transcript of this gene is approximately 10 kb. Not only do defects in this gene cause Marfan syndrome, but Milewicz and Duvic[268] also showed that severe neonatal Marfan syndrome is due to a specific 3-bp insertion in the fibrillin-1 cDNA. Furthermore, fibrillin defects have been found in patients with atypical phenotypes including autosomal dominant ectopia lentis with skeletal features[269] and milder forms such as the MASS phenotype (mitral valve, aorta, skeleton, and skin)[269] or isolated ascending aortic aneurysm with dissection.[270,271] Unfortunately, each family appears to have an individual mutation in the gene, making screening difficult and requiring that each new mutation case be studied individually.[272] This high impact disorder is estimated to be responsible for 1 to 2 percent of the deaths in industrialized societies, with death usually caused by rupture of an asymptomatic, undiagnosed aneurysm. Mutations in FBN1 also have been associated with the marfanoid craniosynostosis (Shprintzen-Goldberg) syndrome.[273] Recent data suggest that CCA is a separate disorder due to a fibrillin-2 gene (FBN2) defect on chromosome 5 (5q23-q31).[274]

Another locus for Marfan syndrome has also been mapped to 3p24.2-p25.[275] Marfan syndrome has been observed in all racial and ethnic groups, and approximately 55 percent are sporadic cases with no family history. There appears to be an increased effect of paternal age, with the mean age of fathers of sporadic cases being increased.

Some of the skeletal features can be analyzed anthropometrically. For example, the increased limb length can be measured by the length of the upper and lower segments and by the upper-lower segment ratio (US/UL). The lower segment is measured from the top of the pubic ramus to the floor, and the upper segment is measured from the pubic ramus to the top of the head. US/UL is reduced for classic Marfan syndrome at all ages. The ratio of arm span to height is usually increased in Marfan syndrome, although scoliosis may complicate the calculation of both ratios. Arachnodactyly can be assessed by the ratio of the middle finger length to total hand length or by analysis of the metacarpal index on hand radiographs.

Hyperextensibility can be assessed by several simple maneuvers. The Steinberg (thumb) sign is positive when the thumb projects through the clenched hand on the ulnar side. The Walker-Murdock (wrist) sign is positive when the first and fifth digit of one hand wrap completely around the wrist of the other hand. Pectus excavatum of variable severity is fairly common. Scoliosis can occur at any age. The ocular findings of Marfan syndrome classically include subluxation of the lenses (ectopia lentis), usually but not always in an upward direction. This occurs in 50 to 60 percent of patients. Myopia is very common, and retinal detachments have also occurred, especially after surgical removal of the lenses. Corneal flattening is also described. Loss of vision occurs in a significant number of patients. Other manifestations include an increase in the occurrence of inguinal hernias, which may recur, and the development of spontaneous pneumothorax and lung abnormalities in some patients. Sacral meningoceles and dilated cisterna magna have also been reported. A severe neonatal form of the Marfan syndrome has cardiovascular, skeletal, and ocular complications present at birth,[261] and patients typically succumb within the first year of life, often from congestive heart failure.

The majority of cardiac abnormalities associated with Marfan syndrome affect the ascending aorta, the aortic valve, and the mitral valve (Table 62-6). Physical examination alone is insufficient to detect subtle changes in the heart and in the aorta. The dilation of the ascending aorta may occur gradually before physical findings occur. Echocardiograms are recommended annually and beta-blocker therapy should be considered.[276] If the diameter of the aorta corrected for body surface area exceeds the upper limits of normal by 50 percent, the frequency of evaluations should be increased to at least every 6 months. Prophylactic repair with composite graft including aortic valve should be performed when ascending aortic dilation reaches a

diameter of 6 cm[277] (see Chap. 98). Repair of a severe pectus excavatum may be indicated at an earlier stage, not only for cosmetic reasons, but to allow easier and safer aortic surgery, should it be indicated. After surgery, the use of beta blockers and anticoagulants should be maintained, and individuals should avoid contact sports and marked physical exertion. Surveillance of the aorta should continue after surgery. Some evidence suggests that beta blockers may reduce the rate of aortic dilation and the risk of serious complications.[276] Prophylactic antibiotics should be used on all patients to decrease the risk of bacterial endocarditis. In general, contact sports (e.g., football, basketball) should be avoided-along with isometric exercises, weight lifting, and extreme physical activity-and replaced with noncompetitive sports such as swimming and bicycling. Other abnormalities include mitral valve prolapse, mitral regurgitation, and aortic regurgitation. The cardiovascular abnormalities in neonatal Marfan syndrome differs somewhat from that seen in older patients, demonstrating significant mitral regurgitation as well as tricuspid and pulmonary valve regurgitation. In addition, these children have significant heart failure, as previously noted.

A special issue involves Marfan syndrome and pregnancy (see Chap. 92). In addition to the 50 percent recurrence risk in offspring, there is also a concern about the stress that pregnancy will put on the aorta. There are at least two dozen case reports of aortic dissection during pregnancy or shortly after delivery,[278] generally occurring with aortic regurgitation or other evidence of aortic dilatation. Pregnant women with Marfan syndrome should have echocardiograms every 6 to 8 weeks during pregnancy and should be followed as high-risk obstetrical patients.

The diagnosis of Marfan syndrome is currently made primarily on clinical grounds although molecular diagnosis is now feasible (although not useful).[279] Suspected patients with a positive family history should have positive clinical features in at least two organ systems. If the family history is negative for Marfan syndrome, positive findings should be present in the skeletal system and in at least two other organ systems. Suspected patients should also have a negative urine nitroprusside test to rule out homocystinuria, one of the disorders in the differential diagnosis. Management of patients with a negative family history and only suggestive skeletal features is unclear. In view of its implications, it may be unwise to inform such patients with minimal features that they have Marfan syndrome. Nonetheless, they should be followed clinically with perhaps periodic echocardiograms and ophthalmologic exams. In these individuals, strong consideration for molecular genetic evaluation is wise.

In terms of genetic counseling, families should be informed of the autosomal dominant inheritance pattern, with 50 percent recurrence in offspring. The rationale for patient follow-up and management should also be explained, along with psychosocial support and medical follow-up. Prenatal diagnosis may be possible.[263,268]

EHLERS-DANLOS SYNDROMES

There are at least 11 different forms of Ehlers-Danlos syndrome (EDS), which are generally given numerical designations.[279] The most common forms are types I through IV, as discussed here. Types II and III overlap with the features of type I, but both are progressively less severe; type III is sometimes known as *benign hypermobility syndrome*. The features of Ehlers-Danlos type I include hyperextensible and fragile skin with poor wound healing and "cigarette paper" scarring. Hyperextensibility of the joints increases susceptibility to dislocation of the hips, shoulders, elbows, knees, and clavicles. The ears tend to be hypermobile and are sometimes described as "lop ears." Scoliosis is a relatively common finding, as are clubfeet in infancy. There is an increased risk of premature birth resulting from premature rupture of membranes. Umbilical and diaphragmatic hemias tend to be relatively common.

The most common cardiac features include mitral valve prolapse, tricuspid valve prolapse, and dilation of the aortic root and/or sinus of Valsalva.[279] Atrial septal defects and other abnormalities of the aortic arch and mitral valve have also been seen. Probably the most significant

cardiovascular defect is the increased susceptibility to dissecting aortic aneurysm (Table 62-6), which can lead to death. Poor wound healing and decreased vascular integrity have been noted. Surgical procedures are freqeuntly not tolerated well, and patients should probably avoid unnecessary surgery. In addition, patients should be cautioned to avoid tauma as much as possible. Type I Ehlers-Danlos is inherited as an autosomal dominant disorder with variability in expression. The presumed defect in this disorder involves synthesis of normal collagen with mutations identified in the α2 (V) chain of type V collagen.[279,280]

Ehlers-Danlos type IV is sometimes referred to as the "malignant" form of Ehlers-Danlos syndrome,[281] since there is marked susceptibility to spontaneous rupture of large blood vessels or bowel. The hyperelasticity and hyperextensibility tend to be less obvious than in type I. Easy bruisability and susceptibility to bleeding, however, are very prominent. Spontaneous rupture of any of the major vessels has been reported. Pregnancy-related complications are particularly striking, the overall risk of death with pregnancy being 25 percent. The basic defect in this autosomal dominant disorder is in the type III collagen gene located on chromosome 2 (2q31),[282] and defects have been reported.[283] Other Ehlers-Danlos genes thus far identified include types VI (1p36.3-1p36.2; lysyl hydroxylase),[284,285] VII A1 (17q21.31-q22), and VII A2 (7q22.1),[286] with mutations of the COLIA2 gene,[281] and the progeroid variant,[287] which is caused by galactosyl-transferase mutations.

Patients with types I and IV EDS require yearly cardiac examinations. Initial evaluation with chest radiography and echocardiography will enable the cardiologist to decide the frequency of follow-up and repeat echocardiograms depending on the level of aortic dilatation and mitral valve prolapse (MVP). Annual chest x-rays are cost-effective as a minimal approach, with echocardiograms necessary every 1 to 2 years. Antibiotic prophylaxis for subacute bacterial endocarditis (SBE) is also needed in patients with MVP or aortic abnormalities.

FAMILIAL ANEURYSMS

It has been recognized for some time that certain aneurysms in peripheral and central arteries (see Marfan's syndrome above) have a familial tendency.[288] As data accumulates on genetic defects in fibrillin[261,279] (Marfan's syndrome) and in the collagen disorders,[289,290] there appears to be overlap in the genetic defects of fibrilin and procollagen, particularly type III, as causes for aneurysms. Some have a defect in type II procollagen (COL3A1) similar to defects that have been reported in Ehlers-Danlos syndrome (EDS) type IV.[283] Familial incidence of aneurysms is said to account for 7 percent of aneurysms.[291] Since EDS is relatively rare, many of the more common familial procollagen abnormalities may represent phenotypic overlap. These findings have resulted in a reassessment of the traditional teaching that most aortic aneurysms result from atherosclerosis. Family history should be carefully assessed in all patients with aortic or cerebral aneurysms, and, if it is positive, other family members should be assessed. Many should be followed with noninvasive evaluation in a fashion similar to that described for Marfan's syndrome.

PSEUDOXANTHOMA ELASTICUM (PXE)

This is a genetic disease of the elastic tissue which involves the skin, eyes, and cardiovascular system.[292] The characteristic lesion is that of the skin consisting of a highly raised, yellowish papule known as a *pseudoxanthoma,* overlying areas of flexural stress such as the neck, cubital and popliteal fossae, and groin. The eye changes are slate-gray linear bands representing tears in Bruch's membrane and subsequent fibrosis leading to loss of central vision in 70 to 80 percent of cases. Calcification of peripheral arteries occurs frequently, most commonly in the femoral artery, but also in the coronary arteries. The heart is affected by myocardial ischemia and infarction, secondary to the coronary disease, which is the major cause of morbidity and mortality (Table 62-

5). A restrictive cardiomyopathy is common due to endocardial fibrosis with mitral valve prolapse (MVP).[293294] Two genetic variants having autosomal dominant inheritance and two others with autosomal recessive inheritance occur. The only difference between the recessive and dominant forms is the presence of affected parents and offspring. Bale recently mapped a gene to 16p13.1, but the gene remains unknown.[281] Because the basic defect is unknown, no specific treatment is available.

The cardiac features should be followed closely once abnormalities are noted. In stable patients, yearly examinations are required at a minimum. Myocardial dysfunction with or without heart failure requires anticongestive and inotropic support, while SBE prophylaxis is needed for those patients with MVP. Symptoms should be used to direct therapy.

CUTIS LAXA

This designation refers not only to a specific dermatologic sign but also to a variety of mendelian and nonmendelian congenital and acquired syndromes sharing the characteristic feature of lax, nonresilient skin. Two varieties of autosomal recessive cutis laxa exist. Death from pulmonary complications may occur in the first months of life and most patients die by the third year. Signs of right-sided heart failure are often seen in infancy and are generally due to pulmonary disease, although pulmonary artery stenosis also occurs[295] (Table 62-5). Histopathologically, the pulmonary artery lesions are due to medioelastic fiber paucity. MVP has also been notable. A gene that causes this spectrum of disease has been identified as elastin (ELN), the same gene previously shown to cause supravalvular aortic stenosis (SVAS).[296-298] As increased fibroblast activity in acquired cutis laxa has also been noted,[299] there is molecular and biochemical correlation. In addition, ultrastructural alterations of skin elastic fibers has been reported.[300]

Primary Disorders of Rhythm and Conduction

Virtually all rhythm and conduction abnormalities have been reported to be familial. However, many families have been small so that the mode of inheritance (or even whether the inheritance is mendelian) is uncertain. In many cases, these conduction defects have been associated with other cardiac and systemic disorders. For a detailed clinical discussion of arrhythmia and conduction disorders, see Chap. 27.

ROMANO-WARD LONG-QT SYNDROME (LQTS)

The association of stress-induced syncope, sudden death, and ventricular arrhythmias in families has long been noted, including a distinct syndrome[301] having prolongation of the QT interval and abnormal T waves on ECG. Multiple families with this syndrome have demonstrated autosomal dominant inheritance, with torsade de pointes polymorphic ventricular tachycardia, bradycardia and T-wave alternans (see Chap. 36). The diagnosis is made when the QT interval corrected for heart rate (QTc) is greater than 480 ms using Bazzett's formula; T-wave abnormalities are usually seen. In symptomatic patients (i.e., patients with syncope or "seizures"), the diagnosis may be made with shorter QTc (i.e., 470 ms). A diagnostic algorithm has been useful.[302] Two likely hypothetical pathogenetic mechanisms for Romano-Ward LQTS was proposed by Schwartz.[303] They include (1) sympathetic nervous system abnormalities and (2) potassium channel (or other ion channel) abnormalities.

In 1991, Keating and coworkers[304] provided evidence for tight molecular genetic linkage to chromosome 11p (11p15.5). Shortly thereafter, Towbin and colleagues demonstrated genetic heterogeneity in families with Romano-Ward LQTS.[305] Linkage evidence was found for loci on chromosome 7 (LQT2)[301] and chromosome 3 (LQT3) and another gene was linked to

chromosome 4 (LQT4).[301] More recently, two other genes have been mapped for LQT5 and LQT6, both found on chromosome 21q22.[306]

The chromosome 11-linked (LQT1) gene was discovered to be KCNQ1, which encodes a potassium channel known as KVLQT1,[301] the slowly activated, delayed rectifier potassium channel I_{Ks}. Multiple mutations in KVLQT1 have been identified and this gene appears to be the most commonly mutated gene in LQTS. KVLQT1 was later shown to require a β-subunit to function normally. This β-subunit gene, KCNE1, encodes minK, which regulates the function of these combined channels, resulting in normal function of this slowly activated delayed rectifier potassium (I_{Ks}) channel. This gene, now also called LQT5, maps to chromosome 21q22. Mutations in either KVLQT1 or minK result in LQTS. The HERG gene, an I_{Kr} potassium channel, has been mapped to chromosome 7q35-q36 and mutations in a variety of domains of this channel were shown to be responsible for the disease in LQT2 families.[301] Another channel gene, the cardiac sodium channel called SCN5A, mapped to 3p21, was shown to be responsible for LQT3. Recently, LQT6 was discovered by Abbott and coworkers[306] to be the β-subunit, MiRP1 or KCNE2. This small channel protein regulates I_{Kr}, the rapidly activated delayed rectifier potassium channel, by interacting with HERG. Mutations in either MiRP1 or HERG result in the LQTS phenotype although the mutations in MiRP1 have been shown to also cause drug-induced (i.e., clarithromycin) VT or VF. The chromosome 4-linked (LQT4) gene remains undiscovered presently. The long-QT syndrome, therefore, appears to be an ion channelopathy, and multiple different ion-channel mutations could result in the long-QT syndrome (Fig. 62-13).

Phenotype-genotype studies have been reported in LQTS. Distinct ECG differences between patients have been demonstrated with mutations of different genes (LQT1-LQT3).[307] Important prognostic differences appear to occur with various mutations of the different genes.[301,308] Zareba et al.[308] recently provided genotype-phenotype correlation of mutations in LQT1, LQT2, and LQT3. In this study, mutations in LQT1 and LQT2 resulted in earlier onset of syncope than LQT3 (usually by age 15 years) and more frequent episodes of syncope. However, LQT3 patients appeared to be at higher risk of death than either LQT1 or LQT2. The mode of symptoms and death also appears to be gene-specific to some extent. LQT1 mutations have been associated with episodes of syncope, seizures, or sudden death during diving/swimming or emotional upset. LQT2 also appears to be triggered by emotions but auditory triggers (i.e., phone or alarm clock ringing) are also important. LQT3, on the other hand, has a high incidence of events during sleep. LQT3 patients appear to shorten their QT intervals with exercise, while exercise seems to trigger events in LQT1 and LQT2 patients.

Recently, Schwartz et al.[309] have provided evidence that sudden infant death syndrome (SIDS) could be due to QT prolongation. Using ECGs on the third or fourth day of life in over 34,000 infants over a >20 year period, they found 34 infants died prior to their first birthday. In 24 of these cases, SIDS was diagnosed. Retrospective ECG analysis demonstrated that one-half of these infants had QTc prolongation on the initial screening ECG. Although no molecular analysis exists, it is speculated that ion channel mutations could be at play for a group of children with SIDS.[309,310]

Gene based therapy has been reported to improve the ECG features of LQTS, including QTc shortening and T-wave normalization. Schwartz et al.[311] treated patients with LQT2 and LQT3 with the sodium channel blocker mexiletine and showed significant QTc shortenting. Compton et al.[312] used exogenous potassium to increase the serum potassium in LQT2 patients with QTc shortening noted, while Shimizu et al.[313] used potassium channel openers to achieve similar results. However, no long-term results or outcomes have been reported with any of these therapies.

JERVELL AND LANGE-NIELSEN LONG-QT SYNDROME

This syndrome, described in 1957, is characterized by congenital deafness, syncope, prolonged QT interval, sudden death, and autosomal recessive inheritance[301] (see Chap. 36). Affected individuals are usually diagnosed in childhood with congenital, severe high-tone perceptive bilateral deafness; fainting spells precipitated by exertion, rage or fright; and ECG evidence of QT interval prolongation and T-wave abnormalities. As would be expected for rare autosomal recessive traits, the parents of affected individuals are more likely than usual to be consanguineous. Homozygous mutations or compound heterozygous mutations in either KVLQT1 or *minK* (i.e., I_{Ks}) have been shown to result in Jervell and Lange-Nielsen syndrome.[314-317] In this circumstance, the deafness requires a homozygous mutation, which results in abnormal production of endolymph, a potassium-rich fluid, in the inner ear. Thus, deafness is autosomal recessive while LQTS is autosomal dominant (i.e., heterozygous mutation results in LQTS; homozygous mutation results in longer QTc and worse outcome).

BRUGADA SYNDROME (IDIOPATHIC VENTRICULAR FIBRILLATION)

First described in detail in 1992, the Brugada syndrome is characterized by ST-segment elevation in leads V_1-V_3, with or without right bundle-branch block[318,319] (Fig. 62-14). Clinical symptoms occur due to ventricular fibrillation. In many patients, spontaneous resuscitation occurs. In others, sudden death occurs, particularly during sleep. This disorder appears to be relatively common in Europe and Southeast Asia and commonly is familial, usually with autosomal dominant inheritance.[320] Some patients do not have overt ECG manifestations and provocation studies in the catheterization laboratory using procainamide, flecainide, or ajmaline may be necessary for diagnosis.

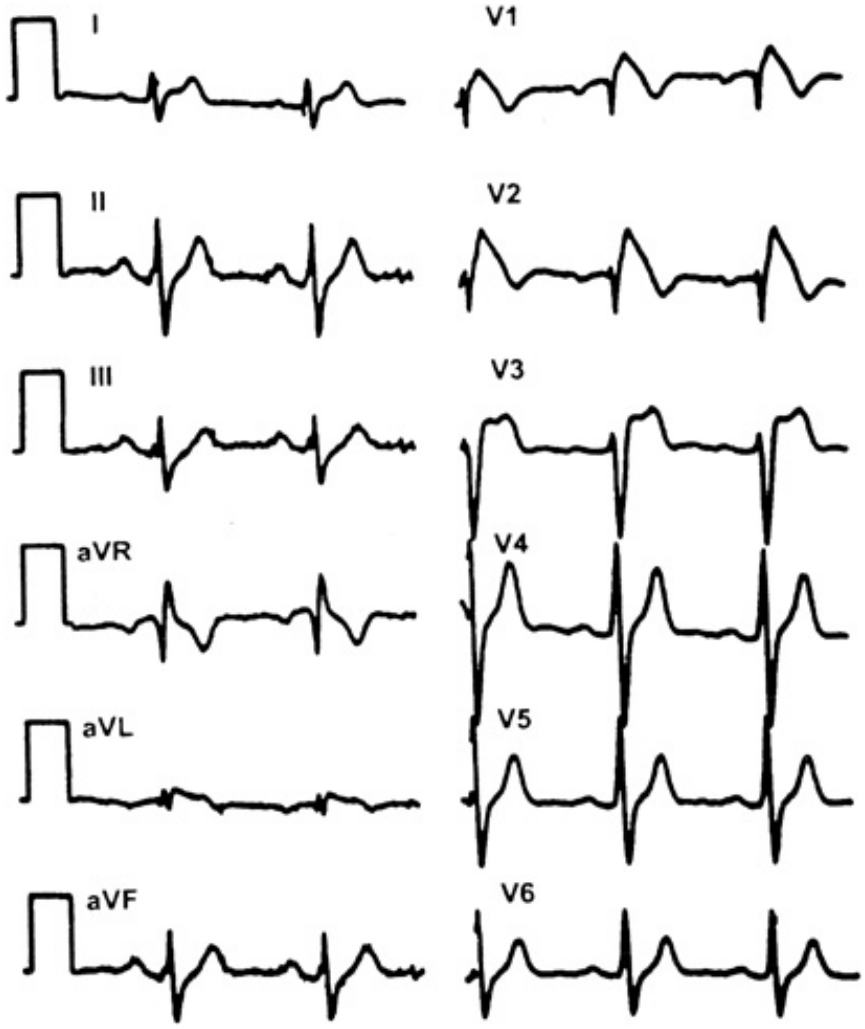

Figure 62-14: Electrocardiographic characteristics of Brugada syndrome. Note the ST-segment elevation in V_1 to V_3.

The genetics of Brugada syndrome appear to involve mutations in ion channels as well. Mutations in SCN5A, the cardiac sodium channel gene previously shown to cause LQT3, have been identified[320,321] (Fig. 62-15). Although the surface ECG and biophysical characteristics of these patients differ from LQT3, it is interesting that symptoms occur during sleep in both disorders. There also appears to be a temperature-dependent effect on the electrophysiologic properties of some of these mutations.[322] Genetic heterogeneity appears to occur, but no other genes have been reported to date.

FAMILIAL ATRIAL FIBRILLATION

Familial atrial fibrillation appears to be rare, but a moderately sized family was identified and the gene responsible for the disease mapped to 10q22.[323] This family inherited the disease as an autosomal dominant trait, with the average age of onset of atrial fibrillation being 17 years. This family has a highly penetrant form of the disease, with most affected developing atrial fibrillation very early in childhood. The signs and symptoms are those related to atrial fibrillation which include palpitations, syncope, and dyspnea. Several other families with familial atrial fibrillation have since been identified due to the same locus.

WOLFF-PARKINSON-WHITE SYNDROME (WPW)

The preexcitation syndromes, including WPW, have been considered to be congenital, but only a

small number of patients demonstrate familial occurrence; the majority of cases appear to be sporadic. ECG features of WPW include the presence of a short PR interval, and a prolonged QRS with slurred upstroke of the R wave, known as a delta wave[324] (see Chap. 26). Patients with WPW are prone to episodes of paroxysmal supraventricular tachycardia (see Chap. 27). An autosomal dominant pattern of inheritance of accessory pathways has been reported.[35] In a family with FHCM and WPW the locus was mapped to chromosome 7 (7q3) has been shown in patients with both FHCM and WPW.[35]

Autosomal Dominant Atrioventricular Block

This disorder, when familial, presents with adult onset (age 20 to 50 years) and has an autosomal dominant inheritance pattern.[301,325] Approximately 50 families have been identified with this disorder which, in each transmission, is consistent with autosomal dominant inheritance with full penetrance and variable expression. Whether all of these conditions represent a single disorder is not known. The common presentation of this disease includes one of the following: (1) right bundle-branch block (RBBB) alone; (2) left axis deviation (LAD) alone; (3) RBBB plus LAD; or (4) complete heart block. In addition, atrioventricular block has been associated with DCM and skeletal myopathy, and several genetic loci have been identified.[105,326,327] Another gene has been mapped to chromosome 19q13 in a family with AV block but without DCM.[326]

Congenital Heart Disease with or without Genetic Syndromes

FAMILIAL ATRIAL SEPTAL DEFECT (ASD)

Two mendelian forms of ASD exist as autosomal dominant traits. One form has no other associated abnormalities and was initially speculated to be on chromosome 6p, linked to the HLA complex, as yet unconfirmed by genetic linkage analysis. Further analysis identified mutations in the transcription factor Nkx2.5 in families and sporadic cases of ASD.[327] This is likely to be genetically heterogeneous and search for other disease-causing genes is being pursued. The more common form of familial secundum ASD is associated with atrioventricular conduction delay, which rarely progresses to heart block. In these patients, attention should be directed to the upper limbs, particularly the thumbs, to rule out the Holt-Oram syndrome, which will be described below. Another form of familial ASD has also been described which is thought to be mitochondrially inherited.

HOLT-ORAM SYNDROME (HOS)

The cardinal manifestations of this autosomal dominant condition include upper limb dysplasia, ASD, and marked variability within families. The abnormalities of the arm demonstrate a wide spectrum in heterozygous individuals, ranging from undetectable, to distally placed thumbs and hypoplastic thenar eminences, triphylangeal thumbs, anomalies of the carpus, and radial aplasia, to phocomelia and hypoplasia of the clavicles and shoulders. The upper extremity deformity is typically bilateral, but the left side commonly is more severe than the right. In addition to the ASD, other cardiac malformations are occasionally found, the most frequent of which is a ventricular septal defect (VSD). Cardiac conduction disturbances, usually involving the AV node in patients with septal defects and hypoplastic peripheral arteries, are also found (Table 62-6). Other noncardiac manifestations include dermatoglyphic abnormalities and pectus excavatum. Since the noncardiac abnormalities have a very wide spectrum, all patients with ASD should be evaluated closely for upper limb deformities.

A male with features consistent with Holt-Oram syndrome in addition to mental retardation and other anomalies was found to have a deletion of chromosome 14 in the q23-q24.2 region. Linkage

to chromosome 12 (12q213-q22) was later demonstrated in one family with Holt-Oram syndrome, while other families did not link to this region, indicative of heterogeneity.[328,329] The responsible gene for 12q21.3 was subsequently identified.[330-331] The chromosome 12-linked HOS was concomitantly reported by Basson et al.[330] and Li et al.[331] as TBX5, a member of the Brachyury (T) gene family, located at 12q24.1. This gene is a member of the T-box transcription factor family,[332-333] a group of genes that share a common DNA-binding motif (T box). Basson et al.[330] identified mutations in two families (nonsense, missense mutations) and suggested that haplo-insufficiency was the mechanism at play. Li et al.[331] identified mutations in three families and three sporadic cases, four of which encoded premature stop codons and two reading frame shift mutations. The authors pointed out that no obvious phenotype-genotype correlations existed. In fact, individuals with identical mutations had widely different skeletal and cardiac features. They also suggested that haplo-insufficiency was at play and occurred between days 26 and 52 of gestation.

SUPRAVALVULAR AORTIC STENOSIS (SVAS) AND WILLIAMS SYNDROME

SVAS occurs in three different situations, occurring with an estimated incidence of 1 in 20,000 births. The most common is associated with the Williams syndrome which is usually sporadic but may be a highly variable autosomal dominant condition. The full spectrum of Williams syndrome[334,335] includes dysmorphic facies, often called "elfin" facies, infantile hypercalcemia, mental retardation, short stature, SVAS, and multiple peripheral pulmonic stenoses.[279-334] Many of these individuals have robust (so-called cocktail party) personalities. Late-onset problems may include progressive joint contractures, gastrointestinal dysfunction, and genitourinary dysfunction.

Cardiovascular features of Williams syndrome are present in about 75 percent of patients,[279,335] the most characteristic of which is supravalvular aortic stenosis. Other findings include peripheral pulmonic arterial stenosis and pulmonic valvular stenosis. Occasionally, VSD or ASD may be present. Peripheral vascular anomalies, including renal arterial stenosis, diffuse narrowing of the aorta, and coarctation of the aorta, may be present and may be associated with systemic hypertension. Sudden death has occurred in children with Williams syndrome, especially after cardiac catheterization. Coronary arterial stenosis may occur and lead to myocardial infarction. Histopathology in these patients suggests the possibility of abnormal elastic fibers.[336]

A second setting for SVAS is the autosomal dominant entity which is distinct from that of Williams syndrome (WS). Mental retardation and abnormal facies are not found and these individuals present with SVAS and/or peripheral pulmonary artery stenoses.[279,334] In some cases, family members present with moderate pulmonic valve and branch pulmonary artery stenoses but without SVAS. Later, the valvular and branch pulmonary stenoses may disappear while SVAS becomes evident. The stenotic aortic lesion requires surgery in less than one-half of these patients. The diagnosis relies on echocardiography, but cardiac catheterization is sometimes required. Finally, SVAS may present as sporadic cases. Many investigators have long believed that the sporadic SVAS, WS, and autosomal dominant SVAS are all interrelated.

In 1993, WS was shown to result from a submicroscopic deletion involving chromosome 7q11.23 in the region of the elastin gene,[337] and subsequently confirmed.[338] Inherited or de novo deletion of one elastin allele was identified in each of the patients studied and suggested that hemizygosity at the elastin locus is responsible for the vascular pathology in WS. Concordance in monozygotic twins and occurrence in second cousins has been described and anecdotal reports of parent and child with WS have been reported. In addition, familial supravalvular aortic stenosis (SVAS) without WS, which appears to be inherited as an autosomal dominant trait, is well known. This autosomal dominant form of SVAS was found to be linked to the elastin gene at 7q11.23[334] as well, and deletions were identified. Baumer et al.[339] suggested that WS results from this deletion

at 7q11.23 that arises from recombination between misaligned repeat sequences flanking the WS region. It is currently believed that this syndrome is a contiguous gene syndrome. The first deleted gene identified in the critical region, elastin (ELN), has been shown to cause the SVAS phenotype but not any of the other features of Williams syndrome (Fig. 62-16, Plate 99). Elastin gene (ELN) deletion is seen in 90 to 95 percent of WS patients and translocations also occur. ELN rearrangements, point mutations, splice mutations, and nonsense mutations have been found in families and sporadic cases of SVAS or Williams syndrome. However, a few patients with classic features of WS, usually without cardiac defects, do not have a deletion involving elastin. This fact suggests that, while deletion of elastin is necessary for the SVAS phenotype, it may not be necessary for Williams syndrome. Elastin is an extracellular matrix protein that comprises 90 percent of the elastic matrix that restores a vessel's shape after it has been stretched. Intense efforts to identify other deleted genes that contribute to the phenotype subsequently identified deletions of LIMK1 (a protein tyrosine kinase expressed in developing brain), syntaxin IA (a component of the synaptic apparatus), WB-SCR1 (containing an RNA-binding motif), RFC2 (a subunit of the replication factor C complex involved in DNA replication), FKBP6 (a FK506-binding protein immunophilin which is thought to play a role in the calcium metabolism abnormalities and growth delay in these patients), WSTF (a putative transcription factor), WS-TRP (considered as playing a role in signal transduction), FZD3 (a gene homologous to *Drosophila* tissue polarity gene *frizzled*), and GTF21 (a multifunctional member of a widely expressed transcription factor complex that is phosphorylated by Bruton tyrosine kinase).[340-348] The roles of these genes in the Williams syndrome phenotype, however, is not known. In order to localize, isolate, and characterize the genes that contribute to the Williams syndrome phenotype, Hockenhull et al.[349] constructed a high-resolution integrated map of the critical region, established a panel of somatic cell hybrids from patients with classic clinical features, and defined deletion breakpoints and estimated the size of the deletions with classical Williams syndrome. They also identified two new genes, CPETR1 and CPETR2, which are deleted in these patients. A mouse knockout model has been created and is being studied.

NOONAN SYNDROME

In 1963, nine patients with valvular pulmonic stenosis, short stature, mild mental retardation, hypertelorism, and unusual facial features were described.[350] This disorder, sometimes confused with Turner syndrome, is distinct and females and males are equally affected. Noonan syndrome is relatively common, with an incidence of 1 in 1000 to 2500 live births. The diagnosis can sometimes be made prenatally. Postnatal growth, however, is generally delayed and tends to parallel the third percentile with normal growth velocity, although the adolescent growth spurt is usually blunted or absent. Facial features appear to change with age. The main features of the newborn period are hypertelorism with down-slanted palpebral fissures; low-set, posteriorly rotated ears with thickened helices; deeply grooved philtrum; micrognathia; and excess neck skin with low posterior hairline. As the infant ages, the head appears larger, with prominent eyes and thinning of the palpebral fissures and depression of the nasal root. The face appears more myopathic and becomes more triangular in shape. In some young adults, the eyes become less prominent. The neck length is relatively short, which exaggerates the webbing. Individuals tend to have prominent nasolabial folds, a high anterior hairline, and transparent, wrinkled skin. The hair is generally described as being curly or woolly in older children and adolescents. Approximately 60 percent of males have cryptorchidism. Sexual development is variable and may be delayed. Most females appear to be fertile. Pectus carinatum superiorly and pectus excavatum inferiorly appears to be present in about 70 percent of individuals. The chest appears to lengthen with age, giving the appearance of relatively low-set nipples. Other features include cubitus valgus, clinodactyly, vertebral anomalies, dental malocclusion, café-au-lait spots, pigmented nevi, bleeding disorders, lymphatic dysplasia, and pulmonary and intestinal lymphangiectasia. Mental retardation is present in 35 percent of cases.[351]

It appears that about two-thirds of patients with Noonan syndrome have some type of cardiac

defect. Approximately half of these patients have valvular pulmonic stenosis. Other relatively common cardiac anomalies include hypertrophic cardiomyopathy, ASDs, VSDs, and persistent patent ductus arteriosus. Pulmonic arterial branch stenosis, mitral valve prolapse, Ebstein's anomaly, and single ventricle have also been reported (Table 62-6).

The clinical features of Noonan syndrome can overlap with a number of other conditions. Chromosome studies should be done in females to rule out Turner syndrome. Phenotypic overlap with WS, primidone teratogenicity syndrome, fetal alcohol syndrome, Aarskog syndrome, Leopard syndrome, neurofibromatosis, and malignant hyperthermia (King syndrome) have been reported.

Most cases of Noonan syndrome appear to be sporadic. Thus, the percentage of inherited cases may actually be much higher than the 30 percent previously reported. The majority of inherited cases are apparently inherited from the mother, thought to be the result of decreased fertility in males. Therefore, although the recurrence risk for offspring is expected to be 50 percent, it might actually be somewhat lower. A gene causing Noonan syndrome has been mapped to chromosome 12(12q22-qter),[352] but the gene has remained elusive. Genetic heterogeneity has also been demonstrated.

TUBEROUS SCLEROSIS (TS)

Classically, tuberous sclerosis consists of the triad of mental retardation, seizures, and adenoma sebaceum. These features, however, may not be present in all patients. The term *tuberous sclerosis* primarily refers to hamartomatous lesions in the brain as well as intracranial calcifications primarily in the area of the basal ganglia. These lesions appear to be present in about 90 percent of patients. Seizures are a frequent finding, being seen in about 90 percent, and have some correlation with mental retardation. About 60 percent of tuberous sclerosis patients are mentally retarded, close to 100 percent of whom have seizures; of those without mental retardation, only 75 percent have seizures. Seizures tend to occur earlier in patients with mental retardation than those without mental retardation. Ocular lesions, particularly benign astrocytoma, occur in about 50 percent of patients. Cutaneous lesions are common; 80 percent of patients develop angiofibromas of the face, usually referred to by the misnomer adenoma sebaceum. Depigmented skin patches that are especially apparent by Wood's light examination are seen in about 80 percent of patients, frequently from birth. Pulmonary disease may occur primarily in adult females and is likely to be severe and life-threatening. The primary cardiac finding is the presence of rhabdomyomata.[353][354] Wolff-Parkinson-White (WPW) syndrome and supraventricular tachycardia have also been reported.[354-355]

Tuberous sclerosis is an autosomal dominant condition in which about 80 percent of cases are suspected as resulting from new mutations with unaffected parents. A child diagnosed with tuberous sclerosis should be evaluated by computed tomography (CT) of the brain and electroencephalography for the presence of CNS lesions and also have renal ultrasound. Parents should be examined for the presence of depigmented patches (by Wood's light), dental abnormalities, retinal findings, and abdominal ultrasound for renal cysts. It is now apparent that there are at least two genes causing tuberous sclerosis: TSC1 on chromosome 9 at 9q34 (hamartin)[356] and TSC2 (tuberin) on chromosome 16 at 16p13. These two protein products co-localize to cytoplasmic vesicles[357] and interact with each other. TSC2 spans 43 kb of genomic DNA and encodes a number of alternatively spliced transcripts of 16 kb. Constitutional inactivating mutations of the TSC2 gene, including complete deletion, have been detected in patients with TS and the associated hamartomas show loss of heterozygosity for markers in the TSC2 region, indicating that TSC2 functions as a tumor suppressor gene and that loss of function of both alleles is normally required before cellular growth becomes dysregulated. Various cancers[358] have been found to occur due to mutations in the TS complex. In addition, large deletions in TSC2 and its neighboring gene PKD1 have been seen in children with polycystic

kidney disease.[359] Genotype-phenotype correlations are not helpful.[360,361] Animal models have been developed with resultant tumors noted.[362-365]

FAMILIAL COARCTATION OF THE AORTA

Familial coarctation of the aorta (usually with autosomal dominant transmission) has been described but no locus or gene has been identified. This congenital lesion is the most common congenital anomaly of the aortic arch in humans, occurring in 5 to 8 percent of children with congenital heart defects. A recessive mutation, *gridlock*, in the zebrafish (*Danio rerio*) has been identified in which blood flow to the tail is impeded by a localized vascular defect.[366] There is some question as to whether this mutation is a model for human aortic coarctation,[367] but it may aid in learning about vascular obstruction. As coarctation of the aorta occurs in association with other left heart obstructive lesions in an individual or in members of a family with other left heart obstructive lesions, it is likely that the mechanism causing disease is complex. Other mutations, such as those of endothelin1, endothelin A receptor, Hand2, MFH-1, and retinoid receptor genes have been shown to lead to aortic arch malformations in mice (Fig. 62-16).

IVEMARK SYNDROME (ASPLENIA/POLYSPLENIA) OR HETEROTAXY SYNDROMES

Ivemark syndrome represents a group of defects that interferes with the normal establishment of laterality.[279,368] The more severe asplenia and polysplenia syndromes have an estimated incidence of 1 in 10,000 to 20,000 live births. The occurrence is usually sporadic, but familial cases have been described with autosomal recessive and X-linked transmission; chromosomal translocations (i.e., between chromosomes 12 and 13) and deletions (involving chromosomes 10 and 13) have been described, as has monozygotic twinning. Both forms tend to have similar cardiac defects, including ASDs, VSDs, endocardial cushion defects, and pulmonic stenosis as well as other defects.[369,370] Asplenia, however, tends to be more commonly associated with severe defects of the atrioventricular canal and VSDs, while polysplenia tends to be more associated with ASDs. In many cases, complex cardiac malformations occur, including single ventricle physiology. A total of 32 cases of asplenia were identified in 4059 autopsies, and all cases were sporadic with a male excess.

Rightward looping of the midline heart tube is the first overt manifestation of anatomic left-right differences, which eventually come to include the asymmetry of the lungs and most malformations associated with abnormal looping; therefore, they usually occur as one manifestation of a more global abnormality of left-right heart anomalies, abnormalities of spleen position and/or number, and some degree of malrotation of the gut. The overall left-right axis of the individual may be situs ambiguus (i.e., indeterminate sidedness) or situs inversus (complete left-right reversal), compared to normal sidedness (situs solitus).

Cardiac malformations attributable to abnormal laterality represent 3.4 percent of all heart defects.[371] Since there is familial clustering of situs, it appears that genetics contributes significantly to these abnormalities. This is supported by mutant mouse models with similar defects,[371] as well as gene defects in some humans.

The first gene locus for human situs defects was mapped to Xq26.2 in families with X-linked disease.[372] This gene was later shown to be a zinc-finger transcription factor Z1C3, and mutations were found in sporadic and familial cases.[371,372] Studies in other vertebrates yielded additional candidate genes as well. Several genes were found to be asymmetrically expressed along the left-right axis in chick prior to development of anatomic left-right asymmetry[274,368] and some of these same genes were also found to be asymmetrically expressed in the mouse (Fig. 62-16). These genes included nodal, pitx2, lefty-1 and lefty-2. Genetic studies in mice also implicated several additional genes that did not have asymmetric expression, such as HNF3, Actrllb, and

Smad.[373-375] Mutation analysis in patients have identified a small number of mutations in all of these genes.[376,377]

Other Genetic Syndromes

A variety of other genetic syndromes with associated cardiovascular disease occur primarily in childhood. These include Ellis-Van Crevald syndrome, Treacher Collins syndrome, Alagille syndrome, Smith-Lemli-Opitz syndrome, thrombocytopenia-absent radii (TAR) syndrome, Goldenhar syndrome, Cornelia de Lange syndrome, Rubinstein-Taybi syndrome, VACTERL association, and CHARGE association. Since these are primarily pediatric diseases, they are not included in this discussion. For detailed descriptions of these and other pediatric genetic syndromes with cardiovascular abnormalities, see current reviews of this topic.[378]

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Chapter 62: CARDIOVASCULAR DISEASES DUE TO GENETIC ABNORMALITIES

CARDIOVASCULAR DISORDERS ASSOCIATED WITH CHROMOSOME ABNORMALITIES

Chromosomal Nomenclature

Cytogenetics is the study of chromosomes and chromosomal abnormalities. Chromosomes are classified according to their size and shape. Chromosomes have two arms, one long and one short. The short arm is usually referred to as the "p" arm, and the long arm is usually referred to as the "q" arm. For instance, the long arm of chromosome 22 is designated 22q and the short arm 22p. The arms of the chromosomes meet at the centromere or primary constriction, which is responsible for division of chromosome pairs during meiosis and mitosis. There are three shapes of human chromosomes based on the position of the centromere. Metacentric chromosomes have the centromere in a central position and the long and short arms are approximately equal. Submetacentric chromosomes have an eccentric centromere, producing arms of unequal lengths. Acrocentric chromosomes have a centromere close to one end of the chromosome. Acrocentric chromosomes have small pieces of chromatin known as satellites attached to their short arms.

Since 1971, banding of chromosomes has become routine and the banding patterns of each chromosome can be distinguished separately. For this reason, chromosome abnormalities are designated by the actual chromosome number rather than the chromosome group (e.g., trisomy 18 rather than trisomy E).

Classification of Chromosomal Alterations

Chromosome alterations, especially those involving too many or too few chromosomes (called aneuploidy), are quite common in human development. Chromosome aberrations most commonly cause structural defects of the cardiovascular system, and typically these are evident at birth. Approximately 50 percent of all fetuses conceived are spontaneously aborted (usually in the first trimester), with one-half of these being aneuploid. Among live-born infants, about 1 in 200 (0.5 percent) have a chromosome abnormality. The frequency of chromosome abnormalities among live-born children with congenital heart defects is in the range of 5 to 13 percent.[378] Hence, the vast majority of chromosomal aberrations are lost in early fetal life and, in most instances, occur as new mutations. For this reason, with both parents being normal, the risk of recurrence to relatives is usually low.

1. Aneuploidy, defined as the gain or loss of chromosomes resulting in too many or too few chromosomes, occurs most commonly by nondysjunction (failure of a homologous pair of chromosomes to separate). Nondisjunction occurs during meiosis in one parent (i.e., in spermatogenesis or oogenesis) or in the first mitotic cleavage of the zygote. In meiotic nondysjunction, when a pair of chromosomes does not normally separate, both members of the pair (or neither member of the pair) pass into one gamete. When an additional copy of the chromosome is added during fertilization, three copies of the same chromosome (or only one copy) are found in the new zygote instead of the chromosome pair. Two of the most common chromosomal disorders causing heart disease, Down syndrome (trisomy 21) and Turner syndrome (XO), are due to nondisjunction. Absence of one chromosome is called *monosomy;* all autosomal monosomies, as well as those containing only a Y sex chromosome, are lethal for the embryo. The presence of three chromosomes is called *trisomy*, as seen in Down syndrome, while the presence of an entire extra set of

chromosomes is known as *triploidy*.

2. Chromosomal rearrangements occur when a chromosome breaks and rejoins within itself differently than normally occurs. This can potentially result in an inversion of genetic material. Typically there is no apparent phenotypic effect in persons carrying an inversion but their offspring may have severe abnormalities due to the disruption in chromosome pairing during melosis that can take place.
3. Chromosome deletions, or loss of chromosomal material, may be seen by light microscopy and consists of deletion of 10^6 bp or greater. If there is a large amount of DNA lost, more than one gene may be affected (disrupted or lost), a series of abnormalities in a single individual may result due to interruptions in a series of genes within the loci of a single chromosome. These contiguous gene deletion syndromes[379] may be heritable and the occurrence of the disorder in a family behaves as a dominant disorder (X-linked or autosomal dominant). Most deletions occur de novo. Two breaks in the same chromosome that reunite with the intermediate segment being inverted is referred to as an inversion. Isochromes are formed when two short or long arms join with loss of the other arm. Chromosomal translations occur when breaks occur in two chromosomes and reunite after exchange of segments. These deletions are best appreciated at the DNA level by Southern analysis or polymerase chain reaction (PCR) analysis.
4. Chromosome duplications or gains of chromosomal material may also be associated with phenotypic abnormality but most commonly cause no obvious aberration.

Cytogenetics and Techniques

High-resolution cytogenetic techniques allow unambiguous identification of each human chromosome and detection of most structural abnormalities of the chromosomes. These structural abnormalities include translocations, deletions, and duplications. High-resolution chromosome analysis involves synchronization of lymphocyte cultures in order to accumulate all cells at one point in the cell cycle. Other cells that may be used include skin, fibroblasts, and amniotic cells. Enrichment of this cell population in prophase and prometaphase rather than the middle to late stages of metaphase, which is characteristic of conventional harvesting techniques, allows improved visualization of the subbanding patterns of chromosomes. Each band seen at metaphase actually represents multiple subbands in earlier stages that have fused together as the chromosome contracts. Whereas a typical metaphase cell contains 300 to 400 bands per haploid genome, synchronized chromosome preparations make it possible to visualize 500 to 1000 bands per haploid set. With the development of banding methods, the human karyotype could be divided into 300 to 400 descrete bands or approximately 7 to 10×10^6 bp per band, and a much greater number of deletions, duplications, and translocations could be detected. High-resolution techniques allow visualization of from 500 to 2000 bands per haploid genome, and have enabled the delineation of a number of microdeletion or microduplication syndromes (also known as contiguous gene syndromes), including the DiGeorge syndrome and Beckwith-Wiedemann syndrome.

FLUORESCENCE IN SITU HYBRIDIZATION (FISH)

Fluorescence in situ hybridization or FISH provides for the detection of submicroscopic chromosomal deletions or duplications. This technique uses DNA probes conjugated with a fluorescent dye visible under a fluorescence microscope derived from chromosomal regions that hybridize to the specific chromosomes. This method makes possible direct visualization of single sequences not only on chromosomes but also within decondensed interphase nuclei, providing a high-resolution (<1 mb) approach to gene mapping and analysis of nuclear organization.

INDICATIONS FOR CHROMOSOMAL ANALYSIS

Chromosomal studies can provide valuable information to the family and the physician and should

be considered in any child who has a heart defect with (1) minor dysmorphic features, (2) growth retardation that cannot be explained by the heart defect, or (3) developmental delay. In addition, the practitioner might more strongly consider chromosome studies if there is a family history of multiple miscarriages or other infants with birth defects or mental retardation. A genetic consultant can help determine whether or not chromosome studies should be performed, and they can help to integrate the findings of the chromosome analysis with the clinical picture. The major disadvantage of doing chromosomal studies is the cost (generally between $300 to $500).

Chromosomal Disorders

Many chromosomal disorders have associated cardiovascular disease. The most common of these include Down's syndrome (trisomy 21), Patau syndrome (trisomy 13), Edwards syndrome (trisomy 18), and Turner syndrome. Since trisomy 13 and 18 usually result in death during infancy, these are not described. A significant number of other chromosomal abnormalities are also associated with cardiovascular disease and are seen primarily as pediatric disorders. These abnormalities include triploidy, aneuploidy (other than trisomy 21, trisomy 18, trisomy 13, and Turner syndrome), deletions, and duplications. The triploidy syndromes-which include 69,XXX, 69,XXY, or 69,XYY-have a greater than 50 percent incidence of congenital heart disease, the vast majority of which are atrial and ventricular septal defects (ASD, VSD). The aneuploidy syndromes, not discussed thus far, are varied and uncommon. These include mosaicism of chromosome 8 and chromosome 9, which clinically present with VSDs with or without other associated complex defects. Aortic root dilatation and MVP occur with partial monosomy of chromosome 22. Other cardiovascular abnormalities associated with partial trisomy of chromosome 7q includes VSD, pulmonic stenosis (PS), patent ductus arteriosus (PDA), coarctation of the aorta (CoA), and L-transposition of the great vessels. Partial trisomy of chromosome 7p also occurs and most commonly is associated with VSD, PS, or AV canal.

DOWN'S SYNDROME (TRISOMY 21)

Chromosome 21 is the smallest of all human chromosomes, containing less than 2 percent of the genomic DNA. Down's syndrome, however, is the most common phenotype caused by a human chromosome abnormality, occurring approximately once in every 500 to 600 births. This disorder is usually due to the presence of an extra chromosome 21 (i.e., trisomy 21), but in some cases it is caused by the presence of only the distal half of chromosome 21, band q22 (i.e., 21q22)-the "Down's syndrome critical region"-so-called due to the presence of a subset of major phenotypic features of Down's syndrome including mental retardation, congenital heart disease, characteristic facial appearance, hand and dermatoglyphic changes.[380-382] In order to produce this syndrome, the region of 21q22 must be triplicated. The gene or genes responsible for manifesting Down's syndrome are unknown, but the severity of the disease is believed to depend on the extent of the region q22 and beyond that is triplicated. Creation of a linkage map of chromosome 21 has allowed for consideration of potential candidate genes. Recently, several genes have been implicated in some of the phenotypic features, but the cardiac features currently have no known cause.

The typical trisomy 21 occurs in 95 percent of cases of Down's syndrome and results from chromosomal nondisjunction. Some 2 to 3 percent of Down's syndrome cases are mosaics, having one trisomy cell line and one normal cell line, and the remainder (1 to 4 percent) are due to an extra copy of all or part of the long arm of chromosome 21 being translocated to another chromosome. The risk of trisomy 21 is exponentially related to maternal age, with the lowest risk for young women, rising steeply after age 35 years, and reaching 4 percent for women older than 45 years.

The recurrence risk is generally quoted at 1 to 2 percent. When a child with a translocation type of Down's syndrome is discovered, parental chromosomal analysis should always be performed to

determine whether the translocation was inherited. If the translocation was not inherited and both parents have normal chromosomes, the recurrence risk is probably low, although prenatal chromosome diagnosis may be considered for future pregnancies. If the mother carries translocation of chromosome 21, the recurrence risk is approximately 10 percent. If the father is determined to be the carrier of a D;21 translocation, the recurrence risk is about 2 percent.[378] If one of the parents is determined to specifically be a 21;21 translocation carrier, the parents have a 100 percent chance of recurrence of Down's syndrome and no possibility of having normal offspring.[378] Luckily, the latter occurs in only about 1 in every 2000 cases of Down's syndrome but clearly has a significant impact on family planning.

Some 40 to 50 percent of patients with Down's syndrome have congenital heart disease (40 to 60 percent of these are atrioventricular septal defects, AVSDs) and this, along with hematologic malignant disease and duodenal atresia, are among the most common causes of morbidity and mortality.[378] Patients who escape these problems generally survive into the fifth decade and beyond. The most characteristic cardiac defect in Down's syndrome is the AVSD (also called *endocardial cushion defect* or *atrioventricular canal defect*) (Table 62-9).[378] In addition to problems of volume overload secondary to left-to-right shunting, these patients are predisposed to early pulmonary hypertension. Elevated pulmonary vascular resistance becomes a significant risk beyond 1 year of age. Once this occurs, these patients become unsuitable for surgical repair. Approximately one-third of patients with Down's syndrome and congenital heart defects have complex heart disease, increasing the morbidity and mortality further. Other clinical features of Down's syndrome include hypotonia and decreased Moro reflex with joint hyperextensibility in the newborn period, a flat facial profile with excessive, redundant skin in the posterior neck, antimongoloid slant (upward) of palpebral fissures, and small white Brushfield spots around the circumference of the irides in children with blue irides. The hands and feet may reveal a simian crease (50 percent), clinodyactyly, or incurving of the fifth finger, brachydactyly with short metacarpals and phalanges, and a wide gap between the first two toes. Individuals are mentally retarded to varying degrees, with IQs ranging from 25 to 70. Generally, males are infertile.

Table 62-9: Chromosomal Abnormalities Associated with Specific Types of Congenital Heart Defects

Endocardial cushion defect	Trisomy 21
Coarctation of the aorta	Turner syndrome
Total anomalous pulmonary venous return	Partial trisomy 22q 9,XXXXX; 49,XXXXX
Patent ductus arteriosus	Partial trisomy 8q
Tetralogy of Fallot	Monosomy 22q11
Conotruncal abnormalities	Partial trisomy 5q
Conduction defect	Turner syndrome
Hypoplastic left heart	

TURNER SYNDROME

This disorder, which is due to a single X chromosome in females (i.e., XO genotype), occurs in approximately 1 female in 2500.[378] The frequency of nonmosaic XO karotypes is significantly higher in spontaneous abortuses than in liveborns, with less than 2 percent of such conceptuses reaching term. Clinically, there is a variable and often mild phenotype, and the diagnosis may go

unsuspected until a child's short stature is evaluated or a women complains of amenorrhea. The clinical findings[378] of patients with Turner syndrome includes lymphedema of hands and feet, inguinal hernias, short stature, primary amenorrhea, facial features including a slightly traingular face with downslated palpebral fissures, epicanthal folds, and ptosis. Ears are frequently low-set and posteriorly rotated, and the mandible is commonly micrognathic. The neck is typically short with marked webbing and the posterior hairline may be low, extending to the upper shoulders. A broad thorax with widely spaced nipples is common, as is cubitus valgus and shortening of fourth and fifth metacarpals. Abnormalities of sexual development are usually associated, including hypogonadotropic hypogonadism with ovarian dysgenesis. Intelligence is normal. Many cases are mosaic for cell lines with the normal 46XX or 46XY makeup. The frequency of congenital cardiac disease varies from 20 to 50 percent, with at least one-half of these having CoA. A variety of other cardiac defects may also occur either singly or in combination with CoA. The majority of these include other left heart abnormalities including bicuspid aortic valve, aortic stenosis, dilated ascending aorta,[378] and hypoplastic left heart syndrome (HLHS). ASD and VSD as well as partial anomalous pulmonary venous return have also been reported (Table 62-9).

Coarctation of the aorta can usually be diagnosed clinically due to poor femoral pulses and differential blood pressure, with the arm blood pressure being consistently hypertensive, while the leg pressures are typically very low. Echocardiography or magnetic resonance imaging will confirm the diagnosis. Therapy may include surgical repair or, in some cases, balloon angioplasty. Infants may require prostaglandin E therapy to keep the ductus arteriosis patent; these young patients may present in heart failure or cardiac collapse if duct-dependent. Those patients with HLHS are duct-dependent and will die unless a Norwood operation or cardiac transplant is performed. Bicuspid aortic valves do not usually require therapy unless stenosis occurs. All cardiac defects require prophylaxis for subacute bacterial endocarditis (SBE). Chromosomal studies are recommended in all cases of Turner syndrome, since only about 60 percent of cases will have monosomy X. The remaining cases have mosaicism or various abnormalities of the X chromosome. Most cases of Turner syndrome are sporadic and the recurrence risk appears to be relatively low. However, parents may choose to have prenatal chromosomal diagnosis in subsequent pregnancies.

CATCH-22 Syndromes

DIGEORGE ANOMALY

First described in 1965,[383] the combination of thymic hypoplasia, parathyroid hypoplasia, and cardiac defects has been termed DiGeorge syndrome or DiGeorge anomaly. Because the disorder is of heterogeneous etiology, the term *DiGeorge anomaly* is currently preferred to *DiGeorge syndrome*. These thymic, parathyroid, and cardiac defects all result from developmental abnormalities of the third and fourth branchial arches.

Eighty percent of affected infants present with congenital heart defects within the first 48 h of life. According to the classification system of Clark,[384] the two types of defects associated with DiGeorge anomaly are conotruncal defects and branchial arch mesenchymal tissue defects. Among conotruncal defects, truncus arteriosus is the most common type. Among the branchial arch mesenchymal tissue defects, interrupted aortic arch type b and right aortic arch are the most common.[378]

The second key feature is persistent hypocalcemia, occurring either as the initial presenting feature or in combination with the cardiac defect. Parathyroid glands may be absent or reduced in size and number, and serum parathyroid hormone levels are decreased. Hypocalcemia may require continuous calcium infusions and/or frequent calcium supplementation. In cases of partial defect, the hypocalcemia may improve over time.

There are multiple etiologies for DiGeorge which include chromosome abnormalities, single-gene defects, teratogenic exposures, and association with other defects.[384] Approximately 5 to 10 percent of infants with features of DiGeorge anomaly will have an obvious abnormality of chromosome 22 with monosomy of the proximal portion of the long arm. However, approximately 70 percent of patients will have submicroscopic deletions of 22q11 detectable only by FISH.[384,385] In addition, many of these patients have features of the Sprintzen velocardiofacial (VCF) syndrome and the Takao conotruncal face syndrome.[386,387] These syndromes are currently referred to as a group by the mnemonic of CATCH-22 syndrome for the associated defects: *c*ardiac, *a*bnormal facies, *t*hymic hypoplasia, *c*left platate, *h*ypocalcemia, *22*q11 deletions). Approximately 15 percent of infants with DiGeorge anomaly can be found to have obvious chromosome abnormalities of which about two-thirds involve a monosomy 22q11.[388] This usually results from an unbalanced translocation involving chromosome 22 and another chromosome. More recent studies using fluorescence in situ hybridization (FISH) with probes from the critical region have shown that a total of about 85 percent of DiGeorge anomaly patients are deleted, with about 70 percent of patients having submicroscopic, molecular deletions, del22 (q11.21 q11.23). Although patients have different deletion endpoints, a 1.5-Mb region is deleted in most. Rarely, a syndrome of "partial" DiGeorge syndrome due to balanced translocation has been described. This translocation was cloned and a disrupted gene DNA-binding protein.[389] More recently, a variety of candidate genes have been identified, including the human homolog of the *Drosophila disheveled* segment-polarity gene,[390] the *clathrin heavy chain-like* gene (CLTCL),[391] *UFD1L* (a developmentally expressed ubiquitination gene),[392] *HIRA*,[393] *DGSI*,[394] and the *goosecoid-like* (GSCL) homeobox gene[395] (Fig. 62-16). The best of these candidate genes, fulfilling most of the criteria necessary to cause this complex, are *HIRA* and *UFD1L*. *HIRA* is a mammalian homolog of yeast proteins, which are corepressors of cell cycle-dependent histone gene transcription, expressed in neural crest and neural crest-derived tissues.[396] This gene has been shown to be required for outflow tract septation. However, mice with haploinsufficiency are normal. *UFD1L*, the homolog of a highly conserved yeast gene involved in degradation of ubiquinated proteins, results in the same craniofacial and cardiac defects seen in CATCH-22 when mutated.[397] Recently, Lindsay et al.[398] engineered a chromosomal deletion (Dfl) in mice that spanned the critical region. The heterozygous deleted animals developed heart disease identical to that seen in humans. They suggested that the cardiovascular lesions occurred due to inadequate formation, early regression, or growth failure of the fourth aortic arch arteries. It should be noted that Yamagishi et al.[397] reported a DGS and/or VCFS patient who is heterozygous for a de novo deletion spanning 20 kb of DNA, disrupting *CDC45L* and *UFD2L*, both candidate genes. The authors suggested these genes to be involved in the development of these syndromes and argued that these genes were regulated by dHAND, a basic helix-loop-helix transcription factor. They proposed a model whereby downregulation of UFD1L activity results in accumulation of certain proteins and excessive apoptosis or maldevelopment of neural crest cells. Based on their view, they suggested disruption of UFD1L function alone, or in combination with CDC45L and/or HIRA is the most likely etiology for most defects seen in DGS. This is currently being carefully studied.

Several therapies have been used to treat the profound T-cell immunodeficiency associated with the DiGeorge syndrome. These therapies have included bone-marrow transplantation. Recently, Market et al.[399] described use of cultured postnatal thymus tissue transplantation in five infants, with good results.

SHPRINTZEN VELOCARDIOFACIAL (VCF) SYNDROME

This condition was first recognized in 1978 with ascertainment primarily in children with palatal defects[386]; this is the most common syndrome associated with cleft palate and appears to be the same disorder as the Takao conotruncal anomaly face syndrome.[387] The clinical features include mild short stature, cleft palate especially of the secondary palate with submucous clefts, pharyngeal incompetence leading to speech disorders, and speech delay. Most cases are sporadic

but some autosomal cases have been reported.

Cardiac defects are prominent in this disorder, the majority being conotruncal-type defects.[400-403] Ventricular septal defect occurs in 70 to 75 percent, while right-sided aortic arch occurs in about 50 percent and tetralogy of Fallot is found in 15 to 20 percent of children. Partial DiGeorge anomaly seems to be present in some cases. About 85 percent of VCF syndrome patients have deletions of chromosome 22q11, usually submicroscopic and visible only by FISH techniques.

Takao syndrome (conotruncal face anomaly syndrome) first described in 1976, has similarities to both DiGeorge and Shprintzen syndromes clinically,[387,402] hence its incorporation in the CATCH-22 association. These Japanese children were noted to have a specific dysmorphic facial appearance in association with conotruncal malformations. Deletions within the 22q11 region in these patients have been found,[402] confirming its similarity to the DiGeorge syndrome and VCF syndrome.

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Figure 62-8: The "final common pathway hypothesis" described by Towbin, showing the pathways involved in development of hypertrophic (HCM) and dilated cardiomyopathy (DCM). In HCM, mutations in the sarcomeric protein-encoding genes result in the phenotype. In addition, the phenotype may be altered or modified by metabolic or mitochondrial derangements as well as by activation of a molecular pathway such as calcineurin. These cascade effects lead to the wide variety of clinical presentations in HCM. In DCM, direct mutations in cytoskeletal protein-encoding genes or effects on these proteins (i.e., coxsackie B3 virus cleavage of dystrophin by enteroviral protease 2A) also modify the clinical phenotype. Cascade effects via metabolism, mitochondrial abnormalities, or drug interactions are also influential in the severity of disease. HCM/DCM abbreviations: β-MHC = β-myosin heavy chain; αTM = α tropomyosin; cTnT = cardiac troponin T; MBP-c = myosin binding protein C; ELC = essential light chain; RLC = regulatory light chain; TNI = troponin I; CVB = coxsackie virus B; MLP = muscle LIM protein; DAG = dystrophin-associated glycoprotein complex; Ox-phos = oxidative phosphorylation pathway; SR = sarcoplasmic reticulum.

Figure 62-9: Skeletal muscle biopsy in Emery-Dreifuss muscular dystrophy. Increased endomysial and perimysial connective tissue, with marked variation in myofiber size, internal nuclei, and myofibers splitting (×153). (Reprinted with permission from Specht LA, McKee AC. MGH Case Records (case 34-1992): A 19-year-old man with progressive proximal muscle weakness, contractures, and cardiac abnormalities. *N Engl J Med* 1992; 327:558.)

Figure 62-10: A 41-year-old man with myotonic dystrophy (DM). Muscle wasting of temporalis muscles with narrow small chin produces a "hatchet-like" facies. Baldness and ptosis (note droopy eyelids with pupils partially covered and sclerae visible) contribute to characteristic appearance. (Reprinted with permission from Roses AD, Pericak-Vance MA. In: *Molecular Basis of Neurology*. Cambridge, MA: Blackwell; 1993:147-159.)

Figure 62-11: Mitochondrial genome. This small, circular DNA molecule encodes 13 enzymes of the respiratory chain, 22 tRNAs, and 2 rRNAs. When it is mutated, cardiac, neurologic, and myopathic disorders develop.

Figure 62-12: The electron transport chain enzyme complex (complexes I to V).

Figure 62-13: Genetic loci and ion channels encoded by the genes responsible for long-QT syndrome.

Figure 62-14: Electrocardiographic characteristics of Brugada syndrome. Note the ST-segment elevation in V_1 to V_3.

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Figure 62-16: (Plate 99) Genetic defects causing congenital heart disease with or without genetic syndromes. Mutants from zebrafish, mouse, and human relating to primary developmental processes or maintenance of the vascular system are illustrated, including those of vasculogenesis and angiogenesis (*A*), embryonic development of the vascular system (*B*), and LV outflow tract obstruction (*C*).

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Part 10: CONGENITAL HEART DISEASE
Chapter 63:

THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

Author: Michael D. Freed

INCIDENCE AND ETIOLOGY

The incidence of congenital heart disease in the United States is approximately 8 per 1000 live births.[1,2] Many infants who are born alive with cardiac defects have anomalies that do not represent a threat to life, at least during infancy. Almost one-third of those infants, or 2.6 per 1000 live births, however, have critical disease, which is defined as a malformation severe enough to result in cardiac catheterization, cardiac surgery, or death within the first year of life.[3] Today, with early detection and proper management, the majority of infants with critical disease can be expected to survive the first year of life.[3] Most who now survive infancy will join the increasingly large cohort of adults with congenital heart disease.

Estimates of the incidence of specific lesions vary, depending on whether the data are drawn from infants or older children and whether the diagnosis is based on clinical, echocardiographic, catheterization, surgical, or postmortem studies.[1-4] The incidence in other countries is remarkably similar to that reported for the United States.[5,6]

Despite these differences in case material, except for bicuspid aortic valve and mitral valve prolapse, it is apparent that ventricular septal defect (VSD) is the most common malformation, occurring in 28 percent of all patients with congenital heart disease (Table 63-1).

Among 2251 infants with critical congenital heart disease in the New England Regional Infant Cardiac Program,[3] 53.7 percent were male. Certain defects, however, are considerably more common in one sex than in the other. Aortic stenosis occurs more commonly in boys (4:1), and atrial septal defects occur more frequently in girls (2.5:1).

Although earlier theories concerning the etiology of congenital heart diseases suggested that most defects were multifactorial-that is, the malformations are caused by a combination of a hereditary predisposition (presumably caused by abnormalities in the genetic code) and an environmental trigger[7]-more recent advances in molecular biology suggest that a much higher percentage are caused by point mutations.[8]

Some abnormalities are caused by chromosomal aberrations (see Chap. 62). Trisomy 21 (Down's syndrome) is highly associated with complete atrioventricular (AV) canal, VSDs, and tetralogy of Fallot, and children with Turner's syndrome (XO) frequently have coarctation of the aorta. Other anomalies are caused by teratogens: VSD in fetal alcohol syndrome, Ebstein's anomaly in a fetus with prenatal exposure to lithium, and patent ductus arteriosus (PDA) in mothers who contracted rubella during the first trimester are examples.

Some syndromes are inherited as single-gene defects and have congenital heart disease as one of their manifestations. Holt-Oram syndrome, an association of radial limb abnormalities and atrial septal defects (ASDs), is caused by an abnormality of a T-box transcription factor Tbx5, and the

cardio-velo-facial syndrome, associated with abnormalities of the conotruncus, resulting in a high proportion of infants born with truncus arteriosus or interrupted aortic arch, is a result of a deletion on chromosome 22 (22 q 11)[9] (see Chap. 62).

It is clear now that a higher proportion of congenital heart disease than previously thought is due to single-gene defects and that the same malformation may be caused by mutant genes at different loci.[8] With increasing knowledge of molecular mechanisms, it seems inevitable that the etiology and pathogenesis of congenital heart disease will be clarified increasingly in the years ahead.

NEXT

Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

FETAL CIRCULATION AND THE TRANSITION TO NEONATAL AND ADULT CIRCULATION

The fetus obtains all metabolic necessities, including oxygen, from the placenta. The fetal circulation is an adaptation to allow most of the right ventricular output to bypass the lungs and go instead to the placenta to pick up oxygen. Most of the understanding of this adaptation comes from more than 40 years of research,[10-18] primarily on fetal lambs. The fetal circulation is arranged in parallel rather than in series, with mixing at the atrial (foramen ovale) and great vessel (ductus arteriosus) level (Fig. 63-1). Normally, blood returning from the body goes into the right atrium via the superior vena cava or inferior vena cava. Inferior vena cava blood is diverted by the crista dividens so that approximately 27 percent of combined ventricular output passes through the foramen ovale into the left atrium, with the remainder passing through the tricuspid valve to the right ventricle. Left atrial return is mixed with blood returning from the lungs into the left ventricle and then to the ascending aorta, where it goes to the coronary arteries, head, and upper body vessels, with a small proportion going across the arch into the descending aorta. Right ventricular blood passes out of the pulmonary artery, where approximately 90 percent (59 percent of combined ventricular output) is diverted through the ductus arteriosus into the descending aorta by the elevated pulmonary vascular resistance. Thus, approximately two-thirds of the blood passes through the right side of the heart and one-third passes through the left side of the heart.

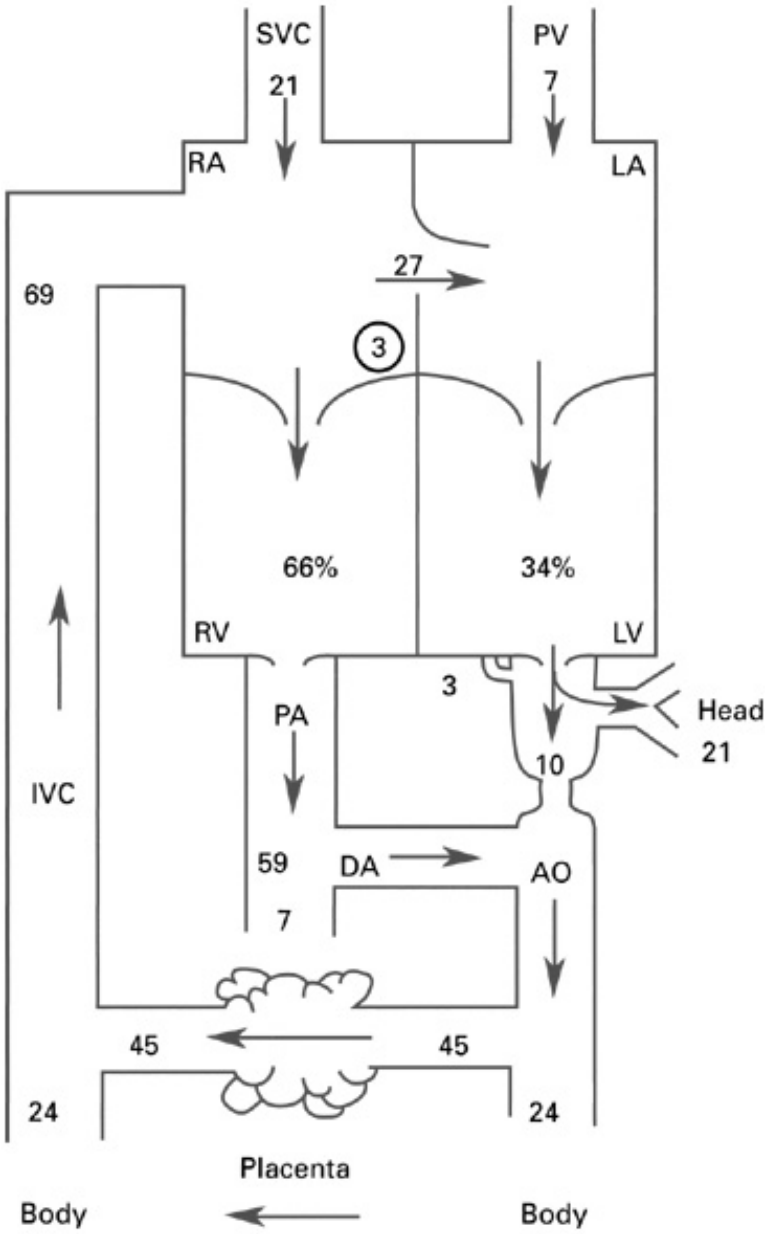

Figure 63-1: The course of the circulation in a late-gestation fetal lamb. *The numbers represent the percentage of combined ventricular output*. Some of the return from the inferior vena cava (IVC) is diverted by the crista dividens in the right atrium (RA) through the foramen ovale into the left atrium (LA), where it meets the pulmonary venous return (PV), passes into the left ventricle (LV), and is pumped into the ascending aorta. Most of the ascending aortic flow goes to the coronary, subclavian, and carotid arteries, with only 10 percent of combined ventricular output passing through the aortic arch (indicated by the narrowed point in the aorta) into the descending aorta (AO). The remainder of the inferior vena cava flow mixes with the return from the superior vena cava (SVC) and coronary veins, passes into the right atrium and right ventricle (RV), and is pumped into the pulmonary artery (PA). Because of the high pulmonary resistance, only 7 percent passes through the lungs (PV), with the rest going into the ductus arteriosus (DA) and then to the descending aorta (AO), the placenta, and the lower half of the body. (From Freed MD. Fetal and transitional circulation. In: Fyler DC, ed. *Nadas' Pediatric Cardiology*. Philadelphia: Hanley & Belfus; 1992. Reproduced with permission from the publisher and author.)

The oxygen saturation of fetal blood is considerably lower than that in a newborn or infant because of the lower efficiency of the placenta compared with the lungs for oxygen exchange (Fig. 63-2). The blood with the highest saturation (approximately 70 percent) is that returning from the placenta. Some of this higher-saturation blood is diverted across the foramen ovale so

that saturation on the left side of the heart (65 percent) is somewhat higher than it is on the right side (55 percent). This allows diversion of the lowest-saturation blood (~55 percent) through the ductus arteriosus to the placenta, increasing the efficiency of oxygen pickup. An additional fetal adaptation to oxygen transport at low oxygen saturation is the presence of high levels of fetal hemoglobin with a higher affinity for oxygen than normal hemoglobin. This leftward shift of the oxygen dissociation curve facilitates oxygen uptake at the relatively low P_{O_2} of the placenta vasculature.

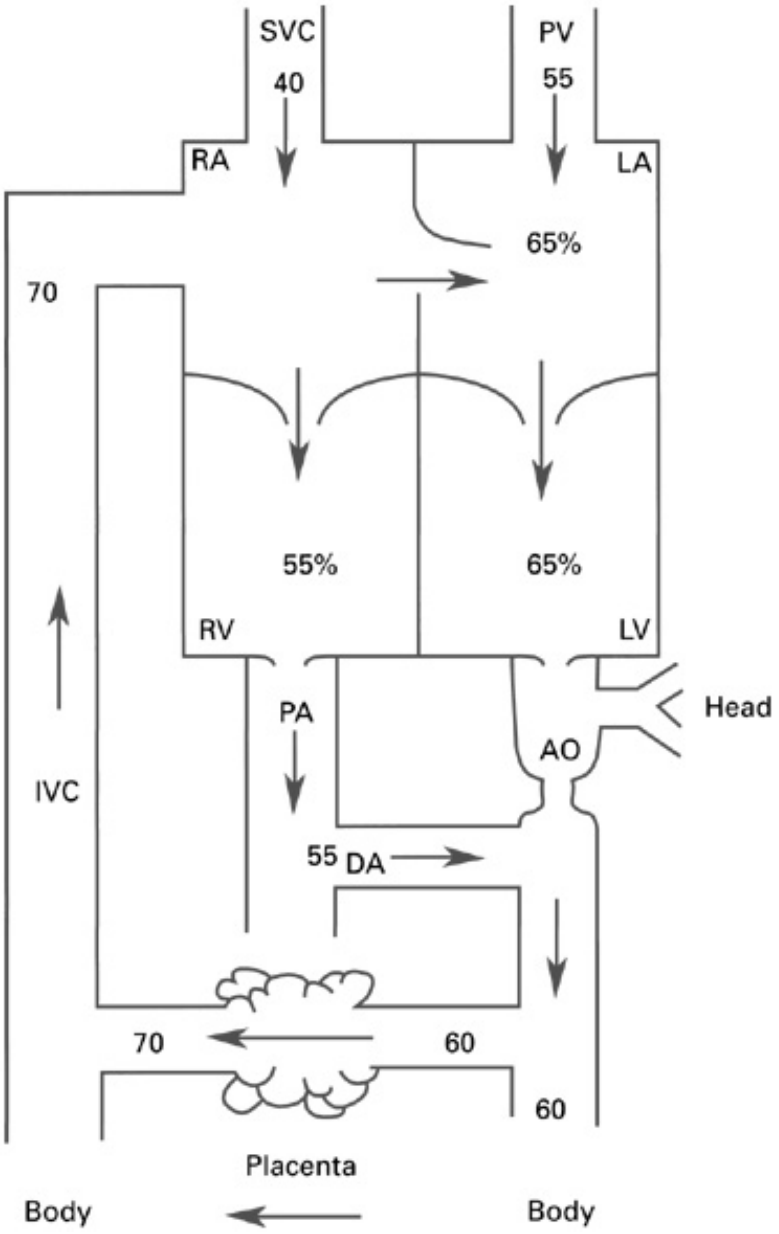

Figure 63-2: *The numbers indicate the percent of oxygen saturation in a late-gestation lamb*. The oxygen saturation is highest in the inferior vena cava, representing that primarily from the placenta. The saturation of blood in the heart is slightly higher on the left side than on the right side. The abbreviations in this diagram are the same as those in Fig. 63-1. (From Freed MD. Fetal and transitional circulation. In: Fyler DC, ed. *Nadas' Pediatric Cardiology*. Philadelphia: Hanley & Belfus; 1992. Reproduced with permission from the publisher and author.)

The wide communication at the atrial level (foramen ovale) allows for near equalization of atrial and ventricular end-diastolic pressures. The wide communication at the great vessel level (ductus

arteriosus) allows equalization of systolic pressures in the aorta and the pulmonary artery and, in the absence of aortic or pulmonic stenosis, at the ventricular level (Fig. 63-3).

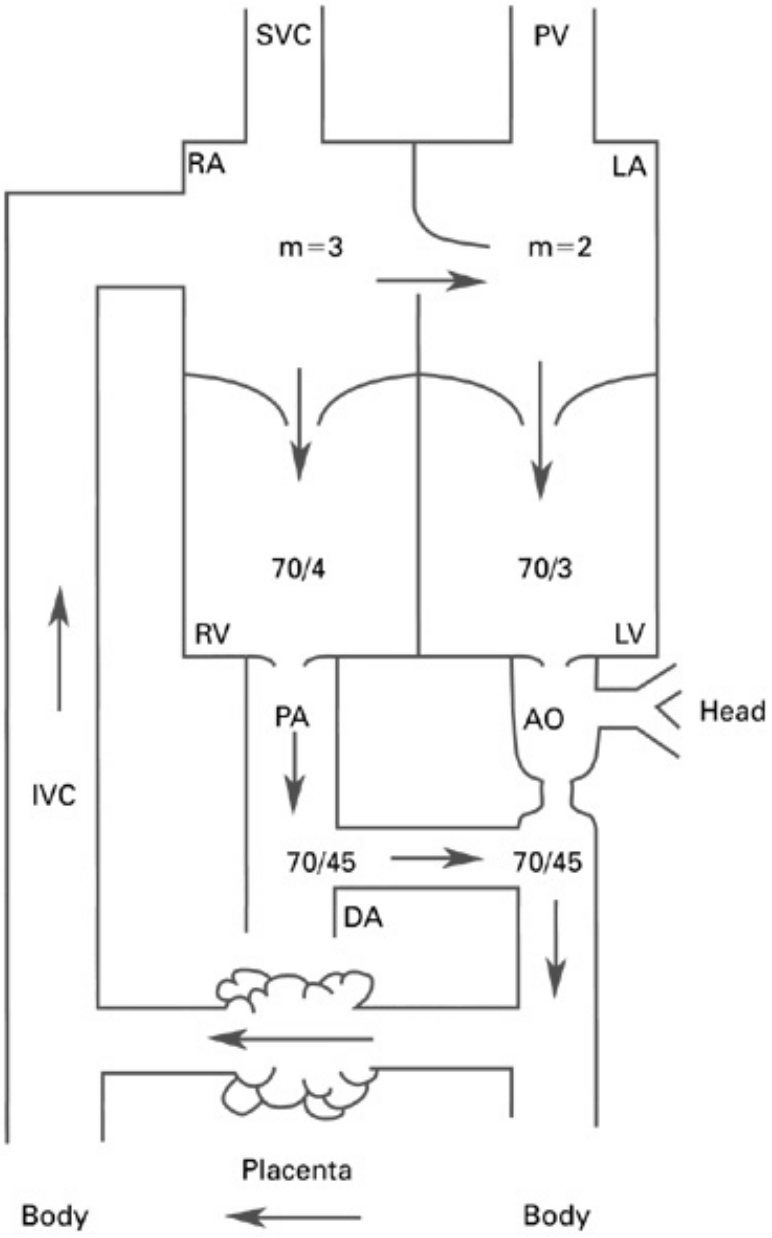

Figure 63-3: The numbers indicate the pressures observed in late-gestation lambs. Because large communications between the atrium and the great vessels are present, the pressures on both sides of the heart are virtually identical. The abbreviations are the same as those in Fig. 63-1. (From Freed MD. Fetal and transitional circulation. In: Fyler DC, ed. *Nadas' Pediatric Cardiology*. Philadelphia: Hanley & Belfus; 1992. Reproduced with permission from the publisher and author.)

Within a few moments after birth, the circulatory physiology must switch rapidly from the placenta to the lung as the organ of oxygen exchange. Failure of any one of a number of a complex series of pulmonary and cardiac events may result in cerebral and then generalized hypoxemia, with lasting damage or death. With the onset of spontaneous respiration, the lungs are expanded and the pulmonary arterioles, which probably have been actively vasoconstricted, dilate. The reduction in pulmonary vascular resistance results from both simple physical expansion of the

lung with the onset of respiration and the vasodilation of the pulmonary resistance vessels, probably partly as a result of the high level of oxygen in alveolar gas. Simultaneously, the placenta is removed from the circulation either by clamping the umbilical cord or by constriction of the umbilical arteries. This sudden increase in systemic vascular resistance and drop in pulmonary vascular resistance cause blood leaving the right ventricle to go out into the lung rather than through the ductus arteriosus. The sudden increase in left atrial return of blood now going through the lung increases left ventricular end-diastolic and left atrial pressure, shutting the flap valve of the foramen ovale against the edge of the cristae dividens, eliminating the atrial-level shunt.

With pulmonary vascular resistance lower than systemic vascular resistance, there may be some left-to-right (aorta to pulmonary artery) shunting through the ductus arteriosus. The mechanism for closure of the ductus arteriosus is not completely understood. The increased level of oxygen probably causes vasoconstriction of the ductus musculature, but there are strong suggestions that a reduction in circulating prostaglandins (PGs) of the E series plays a role. Within 3 or 4 days, the biochemical closure becomes irreversible when cellular necrosis of the endothelium leads to obliteration of the lumen. The pulmonary artery pressure drops to approximately half systemic levels within a day or so but takes another 2 to 6 weeks to drop down to adult levels.

The structure and hemodynamics of the field circulation have significant consequences in a neonate with congenital heart disease.[19] The parallel circulation with connections at the atrial and great vessel level allows a wide variety of congenital cardiac malformations to exist while still picking up oxygen at the placenta and delivering it to the tissues. For example, atresia of the tricuspid or mitral valve, while devastating after birth, does not have a significant effect in utero. Furthermore, since the right ventricle performs two-thirds of the cardiac work before birth, the left ventricle is underloaded; this may explain why congestive heart failure is seen not uncommonly with congenital defects. Because the normal flow across the aortic isthmus is relatively low (only about 10 percent of combined ventricular output), this area is especially vulnerable to small changes in flow across the foramen ovale. A somewhat small foramen may result in left-sided hypoplasia, which almost always is associated with narrowing (coarctation) or atresia (interrupted) at the distal transverse aorta just proximal to ductal insertion.

Since the pulmonary blood flow in utero is less than 10 percent of combined ventricular output and increases four to five times at birth, anomalies that obstruct pulmonary venous return may be masked in utero when the pulmonary venous return is low. Finally, the low circulating levels of oxygen before birth (P_{O_2} 26 to 38 mmHg) with the saturation at 50 to 60 percent may account for the relative level of comfort in infants with cyanotic heart disease, who may do well, at least in the short run, with a P_{O_2} of 30 mmHg and an aortic saturation of 50 percent, a level that would lead to cerebral and cardiac anoxia, acidosis, and death within a few minutes in an older child or adult.

Persistence of Fetal Circulation

Persistence of fetal circulation[20,21] or persistent pulmonary hypertension in a newborn results in right-to-left shunting through the patent foramen ovale and/or PDA. It most commonly occurs in full-term infants. Severe hypoxia usually is manifested in the first few hours of life with tachypnea and acidosis, and a chest roentgenogram shows diminished vascular flow but no evidence of pulmonary parenchymal disease. Physical examination may reveal a parasternal heave, a loud second heart sound, and a systolic murmur.

Polycythemia, transient myocardial ischemia from hypoglycemia, and cyanotic congenital cardiac defects must be excluded. A higher oxygen level in the right radial artery than in the umbilical artery confirms right-to-left shunting through the ductus arteriosus. Echocardiography and Doppler evaluation are of the utmost importance to rule out structural heart disease, especially total anomalous pulmonary venous connection.

The initial treatment[21] includes an increase in the inspired oxygen level and correction of acidosis with sodium bicarbonate. Frequently, artificial ventilation is required. Hyperventilation to diminish the partial pressure of carbon dioxide often is successful in lowering the pulmonary pressure and diminishing the right-to-left shunt. Recently, inhaled nitric oxide to reduce pulmonary vascular resistance has been found to be a useful adjunct to other therapies.[22] Treatment of severe disease with an extracorporeal membrane oxygenator is successful in a significant number of patients.[23] Similar hemodynamic alterations also may be seen in newborns with parenchymal lung disease.

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Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

COMPLICATIONS OF CONGENITAL HEART DISEASE

Complications associated with congenital heart disease are listed in Table 63-2.

Table 63-2: Complications of Congenital Heart Disease in Children

Congestive heart failure	Growth retardation
Hypoxemia	Pulmonary vascular disease

Congestive Heart Failure

Congestive heart failure is a potentially lethal complication of congenital heart disease and occurs in over 80 percent of infants who have malformations severe enough to require cardiac catheterization or surgery within the first year of life.[24] Its onset is usually a phenomenon of the first 6 months of life. Onset after 1 year of age is rare without a serious intercurrent problem such as infective endocarditis, pneumonia, or anemia.

Heart failure within the first 12 to 18 h of life usually is due to malformations that involve pressure or volume overload independent of pulmonary flow, as occurs with severe valvular regurgitation or a systemic arteriovenous fistula. Rarely, myocarditis may produce failure from the time of birth, as may congenital complete heart block or supraventricular tachycardia. Other causes in this age group include primary cardiomyopathy, severe polycythemia or anemia, and depressed myocardial contractility from neonatal asphyxia, hypocalcemia, hypoglycemia, or sepsis.

A majority of full-term infants presenting with severe heart failure during the remainder of the first week have critical obstruction to systemic arterial flow, which in virtually all cases has been unmasked by narrowing or closure of the ductus arteriosus. Examples are aortic atresia, coarctation of the aorta, interruption of the aortic arch, and critical aortic stenosis. *During the second week of life, aortic atresia and coarctation remain the most common causes of heart failure, but left ventricular volume overload from VSD, transposition of the great arteries with a VSD, and truncus arteriosus make their appearance*. These malformations present as the pulmonary vascular resistance falls, increasing the left-to-right shunt. *Statistically, VSD is the primary cause of congestive failure, followed by transposition, coarctation, complete AV canal, and PDA*.

The most common symptom of congestive heart failure is difficulty in breathing, with rapid, grunting, or gasping breathing or breathlessness with feeding. Observation of an undisturbed infant reveals dyspnea, the signs of which are nasal flaring and subcostal or intercostal retractions. A respiratory rate consistently above 60 is to be expected, and rates in the range of 90 to 100 are not uncommon. Poor weight gain is the rule. Cool moist skin, a subdued and rapid arterial pulse, and hepatic enlargement are common accompanying signs. A gallop rhythm, pulmonary rales, and expiratory wheezes may be present. It may be difficult to distinguish the pulmonary findings of

heart failure from those of pneumonia or bronchiolitis; indeed, many infants develop heart failure during an intercurrent pulmonary infection. Edema, if present, usually is found in the periorbital area and on the dorsa of the feet and hands. Cardiac enlargement is confirmed by chest roentgenography. Infants with malformations such as coarctation of the aorta and total anomalous pulmonary venous connection, abnormalities that usually are not characterized by an impressive murmur, sometimes are referred only after weeks of tachypnea and failure to thrive, when a chest roentgenogram taken to explore the possibility of lung disease has revealed cardiac enlargement.

When a sizable systemic-to-pulmonary communication exists in a premature infant, usually as a result of a PDA, signs of heart failure usually are associated with signs of ventilatory failure.

Hospitalization is recommended for all infants with heart failure. Elevation of the head and chest to an angle of approximately 30° and administration of humidified oxygen by techniques that do not disturb the infant help relieve dyspnea and systemic arterial hypoxia as determined by pulse oximetry. Arterial oxygen saturation levels should be monitored in newborns, particularly the premature, to avoid the risk of retrolental fibroplasia. Rest, aided by sedation, is beneficial. With severe failure, oral feedings should be suspended temporarily to prevent aspiration and fluid intake should be restricted to 65 mL/kg per day intravenously for at least the first 24 h. Anemia, acidosis, hypoxia, hypercarbia, hypoglycemia, or hypocalcemia should be corrected; serum sodium, potassium, blood urea nitrogen, and creatinine concentrations should be monitored. A low threshold for the administration of antibiotics is appropriate.

Digoxin is recommended for the management of congestive failure in infants and children, especially those with decreased ventricular systolic function, because of its excellent absorption when given orally, rapid onset of action, relatively rapid excretion, and convenience of administration. The recommended oral maintenance doses of digoxin for the different age ranges of children, expressed in μg/kg per day, are as follows: for the premature, 5; for neonates, 10; for infants between 4 and 24 months of age, 15; for older children, 10; and for adolescents, 5. The daily maintenance dose usually is given in two divided doses approximately 12 h apart. The total digitalizing dose is three times the daily maintenance dose. Parenteral doses of digoxin are approximately 75 percent of oral doses for digitalization and maintenance. Half the digitalizing dose may be given initially, followed by the remaining two quarter doses at 4-, 8-, or 12-h intervals, depending on the desired speed of total digitalization. Maintenance therapy should be started 8 to 12 h after the last digitalizing dose. In a severely ill infant with decreased perfusion and unpredictable absorption, digitalization by the intravenous route is recommended. Impaired renal function leads to digoxin accumulation and toxicity, and so the initial and maintenance doses should be adjusted accordingly. Toxicity, if it is to occur, usually appears within the first week of therapy. If anorexia, nausea or vomiting, or electrocardiographic evidence of either atrial or ventricular ectopy or AV block appears, digoxin should be stopped and the serum digoxin level should be determined. Toxicity is probable if the level exceeds 3.0 ng/mL in an infant less than 6 months of age or 2.0 ng/mL in an older infant or child. If the need for digoxin continues, the dose is adjusted as the patient grows and gains weight.

The diuretic furosemide used intravenously in doses of 1.0 to 2.0 mg/kg or orally in doses of 1.5 to 2.0 mg/kg is very effective in the acute management of congestive heart failure. With severe failure, the dose may be increased by increments of 1.0 mg/kg intravenously if no urinary response has been achieved after 45 min. For long-term oral diuretic therapy, 1.5 to 2.0 mg/kg once daily or, if necessary, twice daily is recommended. Chlorothiazide, a slightly less potent diuretic but one with a longer duration of action, may be given orally in a dose of 20 to 50 mg/kg per day. Hypokalemia and hypochloremia can be induced with these potent diuretics, and a daily oral supplement of potassium chloride in the range of 1.0 to 1.5 meq/kg, with adjustment depending on the serum level, is recommended. Spironolactone, an aldosterone antagonist, has proved useful in supplementing the diuresis and preventing the hypokalemia induced by the diuretics described above. It may be given orally in a single daily dose of 2 to 3 mg/kg. A regimen of spironolactone 2 mg/kg given every day and furosemide 1 mg/kg is usually adequate for long-

term diuretic therapy for mild to moderate heart failure and usually does not require potassium supplementation.

In emergency situations, it may be necessary to provide an immediate inotropic stimulus in the form of intravenous sympathomimetic amines administered by constant infusion pump. Isoproterenol in a dose of 0.1 μg/kg per minute exerts a powerful inotropic effect, but its usefulness may be limited by induced tachycardia and peripheral vasodilation, sometimes to the detriment of renal perfusion. Epinephrine in a dose of 0.1 to 1.0 μg/kg per minute or dobutamine or dopamine in a dose of 5 to 15 μg/kg per minute generally has been more helpful, with dopamine providing more adequate renal flow. The systemic arterial blood pressure, urinary output, and electrocardiogram (ECG) should be monitored continuously. Vasodilator therapy in the form of intravenous sodium nitroprusside may be of considerable help in patients with severe congestive failure that is not associated with large left-to-right shunts. The infusion rate at the start should be no higher than 0.5 μg/kg per minute, but it may be increased gradually to 4.0 μg/kg per minute to achieve the desired effect. Systemic arterial pressure should be monitored continuously to detect serious hypotension. The angiotensin-converting enzyme inhibitors captopril, enalapril, and lisinopril given orally have proved effective in selected patients: captopril starting at 0.1 to 0.4 mg/kg per dose in a neonate and 0.3 to 0.6 mg/kg per dose in an older child given one to four times per day, enalapril 0.16 to 0.25 mg/kg per day in two divided doses, or lisinopril 0.16 to 0.25 mg/kg per day in a single daily dose. Hypotension and/or hyperkalemia are the primary adverse effects of these agents.[25]

Infants with potentially exhausting respiratory effort or with hypoxia or hypercapnia secondary to pulmonary edema or respiratory failure benefit from endotracheal intubation and ventilation on a volume-controlled, positive-pressure respirator, usually with the addition of positive end-expiratory pressure. These measures may permit additional therapy, cardiac catheterization, and surgical intervention with a much greater margin of safety.

In newborns who have failure as a result of narrowing or closure of the ductus arteriosus in the presence of critical obstruction to flow from the left side of the heart, dramatic and lifesaving relief can be expected with reopening of the ductus by the infusion of PGE_1 at a dose of 0.1 μg/kg per minute.

Finally, infants or children in whom medical therapy is clearly inadequate or only temporarily successful may require prompt surgical intervention for control of heart failure. *As a rule, the earlier the onset of congestive failure, the more likely the need for surgery*.

Hypoxemia

The sequelae of hypoxemia are listed in Table 63-3. *Cyanosis*, a bluish tinge to the color of the skin caused by the presence of at least 3 to 5 g/dL of reduced hemoglobin, is frequently the initial sign of congenital heart disease in an infant. It also may be an early sign of pulmonary, central nervous system, or metabolic disease or methemoglobinemia. Nonsurgical palliation with PGE_1 and the rapid development of surgical techniques for infants make a prompt distinction between cardiac and noncardiac cyanosis, usually by echocardiography, extremely important.

Table 63-3: Sequelae of Hypoxemia

Cyanosis	Exercise intolerance
Clubbing	Hypoxic spells
Polycythemia	Brain abscess
Squatting	Cerebrovascular accidents

Hypoxia leading to cyanosis in congenital heart disease may be due to heart failure with pulmonary edema and pulmonary venous desaturation or to intracardiac right-to-left shunting. The hypoxia that is due either to heart failure or to lung disease with intrapulmonary shunting usually responds dramatically to oxygen administration, whereas hypoxia that is due to cyanotic defects does not. Since many infants are relatively anemic during the first few months of life (hemoglobin concentration, 10.4 to 12 g/dL), cyanosis may be subtle.

When cyanosis has been present in older children for several months, the distal tips of the fingers and toes become hyperemic. Eventually, the capillary end loop dilation causes *clubbing* of the fingers and toes with a loss of the normal angle of the base of the nail and fingers. Also, with long-standing hypoxemia, the hematocrit increases to maintain the oxygen-carrying capacity of the blood (*polycythemia*). The increased hemoglobin concentration at any given oxygen saturation will result in more reduced hemoglobin, exaggerating the cyanosis.

The central nervous system may be the target organ of cerebrovascular accidents or brain abcess. *Brain abcess* probably is due to bacteremia primarily with mouth organisms that cross from the venous system to the arterial system right-toleft from shunting. The incidence seems to be directly related to arterial saturation and occurs mostly in older children and adolescents.[26]

Cerebrovascular accidents are due directly to hypoxemia or indirectly in children who are polycythemic presumably secondary to sludging.[27] The former group usually consists of infants less than 2 years old who are anemic and thus may have markedly reduced oxygen levels. The latter group consists of children or young adults who are polycythemic and have sludging or in situ microthrombosis. Interestingly, iron deficiency leads to stiff red cells, and so sludging may occur with modest levels of polycythemia (hematocrit 55 to 60 percent) in the presence of iron deficiency. With hematocrits in the range of 65 percent or higher, increased viscocity may lead to a cerebrovascular accident. Maintaining a proper level of hemoglobin has a salutory effect on hemodynamics and oxygen delivery in the presence of significant hypoxemia.[28,29]

Other systems also may be affected by hypoxemia or polycythemia. In older adolescents, the increase in hemoglobin breakdown may result in hyperuricemia and can precipitate a secondary form of gout.[30]

Disturbances in hemostasis also occur with polycythemia. Coagulation factors are commonly abnormal in patients with hematocrits in excess of 60 percent.[31] Actual platelet counts may be normal but can be increased initially in some patients, with subsequent decreases related to persistent and worsening desaturation. There is evidence of shortened platelet survival time in patients with cyanotic heart disease.[32] Laboratory evaluation of coagulation status requires that correction be made for the diminished volume of plasma and for the volume of anticoagulant used in blood samples to avoid false results. Hematologic management of adults with cyanotic congenital heart disease requires special experience and knowledge.[33]

The major consequences of cyanosis can be avoided in many instances, although differences in intelligence have been demonstrated between cyanotic and acyanotic children.[34]

Retardation of Growth and Development

Children with severe cardiac malformations frequently exhibit retardation of growth and development, with height and weight near or below the third percentile or weight 20 percentile points below the mean percentile for height.[35]

Growth retardation is most severe among children with overt cyanosis and those with large left-to-right shunts that cause heart failure. Heart failure tends to cause a greater retardation of weight than of height. Skeletal retardation, reflected by bone age, usually occurs with height and weight retardation and, among children with cyanotic heart disease, correlates with the severity of hypoxemia.

Other factors contribute to growth retardation, including insufficient caloric intake, dyspnea, frequent infections, psychological disturbances, malabsorption, and hypermetabolism. Among infants with severe congenital heart disease recognized within the first year of life, there is a significantly increased incidence of subnormal birth weight, intrauterine growth retardation, and major extracardiac anomalies.[3] Finally, a relatively small number of children have associated syndromes known to be characterized by growth retardation, such as rubella and Noonan's, Turner's, and Down's syndromes.

Growth retardation related primarily to congenital heart disease usually responds to surgical correction or palliation, with an impressive acceleration of growth and a return to or toward normal.

Although cardiac surgery seldom is recommended on the basis of growth failure alone, decelerated growth should be recognized early and, until proved otherwise, considered an index of the severity of heart disease. In general, the more successful the surgery is, the less will be the retardation of growth and development, with its sequelae of physical, psychological, and intellectual problems.[36]

Pulmonary Arterial Hypertension and Pulmonary Vascular Obstructive Disease

Pulmonary arterial hypertension (PAH) and pulmonary vascular obstructive disease (PVOD) are serious complications of congenital heart disease. PAH usually results from direct transmission of systemic arterial pressure to the right ventricle or pulmonary arteries via a large communication. Less frequently, it is due to severe obstruction to blood flow through the left side of the heart at the pulmonary venous level or beyond. PVOD refers to a process involving structural and developmental changes in the smaller muscular arteries and arterioles of the lung that gradually diminishes and eventually destroys the ability of the pulmonary vascular bed to transport blood from the larger pulmonary arteries to the pulmonary veins without an abnormal elevation of proximal pulmonary arterial pressure.

Pulmonary resistance (R_p) may be as high as 8 to 10 Wood units immediately after birth but falls rapidly throughout the first week of life. Indexed Wood units, as a measure of resistance to flow across either the pulmonary or the systemic vascular bed, are obtained by dividing the mean pressure difference (in millimeters of mercury) across the pulmonary or systemic vascular beds by the blood flow index (expressed in liters per minute per square meter) across those respective beds. By 6 to 8 weeks, it usually has reached the normal adult level (1 to 3 Wood units). These changes are accompanied by a gradual dilatation of first the smaller and then the larger muscular pulmonary arteries and then, in the weeks and months that follow, a thinning of their muscular walls, the growth of existing arteries, and the development of new arteries and arterioles. The latter process contributes over 90 percent of the smaller or intraacinar pulmonary arterial vessels present in older children and adults.[37]

Increased pulmonary arterial pressure has an adverse effect on the normal maturation of the pulmonary vascular bed. Such pressure encourages a persistence of the thick muscular medial layer present in the smaller pulmonary arteries of term newborns, stimulates an extension of smooth muscle into smaller and more peripheral arteries than normal for age, and retards the growth of existing acinar arteries and the development of new ones.

In the presence of a large systemic-to-pulmonary communication, pulmonary arterial pressures remain at or near systemic levels, with the result that the diminution in pulmonary muscle mass and pulmonary resistance is less rapid and of a lesser magnitude than it is in a normal infant. Nevertheless, the diminution is usually sufficient to permit a large pulmonary blood flow and, as a result, congestive failure by the end of the first month. Exceptions are found among infants with a large systemic-to-pulmonary communication but with alveolar hypoxia, a stimulus for pulmonary vasoconstriction, in whom there is less than normal involution of the medial musculature and a diminution in pulmonary vascular resistance. Clinically, this is expressed by the lower incidence of congestive failure observed among infants with large VSDs born and living at high altitude and in some children with Down's syndrome and a large VSD or atrioventricular canal who may hypoventilate or have upper airway obstruction. Rarely, an infant will maintain a very high pulmonary vascular resistance in the face of an anatomically large systemic-to-pulmonary communication without evidence of significant hypoxemia or acidemia and remain free of the signs and symptoms of congestive failure. Conversely, in a premature infant in whom the medial muscle mass is less at birth than it is in a full-term infant, the fall in pulmonary vascular resistance is usually much more rapid than normal.

Chronic PAH, increased flow, or both produce a characteristic series of histologic changes in the smaller pulmonary arteries and arterioles originally described and graded by Heath and Edwards (grades I through VI below)[38] (Fig. 63-4, Plate 100) and, more recently, by Rabinovitch[37] (grades A through C below):

- Grade I-medial hypertrophy
- Grade II-concentric or eccentric cellular intimal proliferation
- Grade III-relatively acellular intimal fibrosis with occlusion of the smaller pulmonary arteries and arterioles
- Grade IV-progressive, generalized dilatation of the distal muscular arteries and the appearance of plexiform lesions, complex vascular structures composed of a network or plexus of proliferating endothelial tissue, frequently accompanied by thrombus, within a dilated thin-walled sac
- Grade V-thinning and fibrosis of the media superimposed on the plexiform lesions
- Grade VI-necrotizing arteritis within the media
- Grade A-extension of muscle into normally nonmuscular peripheral arteries with or without a mild increase in medial wall thickness of normally muscular arteries (less than 1.5 times normal)
- Grade B-extension of muscle as described above with an even greater increase in medial wall thickness of normally muscular arteries (mild, 1.5-2 × normal; severe, >2 × normal)
- Grade C-changes seen in grade B (severe) but with a decreased arterial concentration relative to alveoli (mild, ≥1/2 normal; severe, <1/2 normal)

Grades A and B are partitions of Heath-Edwards grade I and may be seen with large left-to-right shunts with (B) or without increased pressure (A). Grade C criteria may be found with grades I and II, are invariable with grade III, and usually preclude a complete return to normal of pulmonary arterial pressures and resistance despite successful surgical correction of the systemic-to-pulmonary communication.

Estimation of pulmonary vascular resistance from data obtained at cardiac catheterization remains the most widely used means of assessing the state of the pulmonary vascular bed.

Hypoxemia from oversedation, atelectasis, or pneumonitis at the time of study should be avoided scrupulously. If pulmonary vascular resistance is elevated, its responsiveness to vasodilation induced by the inhalation of 100% oxygen, the pulmonary arterial administration of prostacyclin, or the inhalation of nitric oxide should be tested.[39]

Values of $R_p \leq 3$ Wood units are considered normal. The status of the pulmonary vasculature also can be expressed as a ratio of pulmonary vascular resistance to systemic vascular resistance (R_p/R_s). *Pulmonary/systemic resistance ratios less than 0.2:1 are considered normal.*

As pulmonary vascular resistance increases, pulmonary blood flow generally decreases. Eventually, a point is reached where surgical closure of the defect will produce only a small diminution of blood flow, a proportionately small decrease in pulmonary arterial pressure, and no significant change in the factors contributing to the progression of vascular disease. At this point surgery usually is not recommended, since the benefits are minimal and closure of the defect may eliminate a useful "blow-off" for increasing resistance. *An R_p/R_s ratio of 0.7:1 or an R_p of 11 Wood units with a pulmonary/systemic blood flow ratio of 1.5:1 is the criterion generally used to define this situation.* Without surgery, these patients survive as examples of the Eisenmenger syndrome, in which $R_p \geq R_s$ and at least some right-to-left shunting occurs at rest or with exercise. Some of these patients can survive for several decades and lead productive lives, with relatively mild symptoms and few limitations.[40]

The decision regarding surgery for patients with less severe PVOD is a clinical one. The higher the calculated resistance is and the greater the structural changes in the pulmonary vasculature are, as judged by lung biopsy or quantitative pulmonary arterial wedge angiography, and the older the patient is with any given level of elevated resistance or grade of structural change, the less likely it is that the outcome will be satisfactory.[37]

The prevention of PVOD requires the identification of the patients at risk, i.e., all patients with a systemic-to-pulmonary communication and a pulmonary arterial systolic pressure higher than half the systemic arterial systolic pressure. Also included are all patients with transposition, regardless of pressure or flow, with the possible exception of those with severe pulmonary stenosis. Ideally, all patients at risk should undergo correction or pulmonary arterial banding unless there is proof that the pulmonary arterial systolic pressure has fallen to or is less than half the systemic systolic pressure before the end of the first year of life among those with normally related great arteries. Among patients with transposition with a large VSD or patent ductus arteriosis, action must be taken within the first 3 months of life.

Long-Term Problems with Surgically Corrected Defects

With the advances that have occurred in the surgical treatment of congenital heart defects, more of these patients are living to adulthood. This discussion of potential long-term problems is intended for those who follow these children after surgery and through adult life[41] (see Chap. 64).

There are residua, sequelae, and complications that result from most surgical procedures for congenital heart defects. A residual part of the original defect, such as mitral prolapse in repaired ASD, may purposefully not have been approached surgically. Some sequelae are unavoidable consequences of the surgery, such as pulmonary regurgitation after pulmonary valvotomy. There are also complications that occur as unexpected but related events after successful surgery, such as late complete heart block. When viewed with these possibilities in mind, only surgical correction of a PDA is likely to result in no long-term problems.

Most patients have residual murmurs after surgery for congenital heart defects. Determination of the origin of these murmurs and evaluation of the severity of the hemodynamic abnormalities they

represent are important. Noninvasive diagnostic tools, especially Doppler and two-dimensional echocardiography, are often useful.

The risk of infective endocarditis to patients persists after surgery, with the exception of those who have undergone patent ductus ligation or division or repair of an ASD or VSD in whom there is no residual shunt. Patients in whom it has been necessary to place an artificial valve are at increased risk of endocarditis.[42,43]

There are specific problems related to some of the more common defects. For those with repaired ASDs, VSDs, and AV (canal) septal defects, a residual shunt may be present, but ordinarily it is small and not of hemodynamic significance. Those with repaired AV canal defects may have important AV valvular regurgitation. Repaired coarctation of the aorta can gradually become narrowed again, or patients may develop idiopathic hypertension. Surgery for valvular pulmonary stenosis usually results in mild residual stenosis and regurgitation, which are well tolerated and have little tendency to progress with time. The natural history of valvular aortic stenosis after surgery is not as benign.[44] Because significant regurgitation must be avoided, the initial results may not be as good in terms of the severity of residual stenosis. In addition, aortic stenosis tends to worsen with time; thus, proper follow-up is mandatory for these patients.

Few patients enter adulthood with the continued problem of cyanosis. Since those with residual defects amenable to surgical correction should have had surgery well before this time, only patients with complex and uncorrectable defects and those with pulmonary vascular disease should have problems of cyanosis during the adult years. Particularly important among these patients is management of any attendant psychosocial problems (employment, insurability,[45] and learning disabilities) and difficulties related to pregnancy.[46]

Those who have had surgery for cyanotic defects are more likely to have sequelae and complications. Some degree of exercise intolerance is not unusual in this group of patients, and exercise stress testing aids in their management.[47]

Dysrhythmias are particularly common among these patients. *In those who have had intraventricular repairs, most commonly for tetralogy of Fallot, late complete heart block and serious ventricular arrhythmias can occur and may result in sudden death.*[48] This risk appears to be highest in those who had transient complete heart block at the time of surgery and who develop right bundle branch block with left anterior hemiblock after surgery. Extensive interatrial surgical procedures for transposition of the great arteries also frequently lead to dysrhythmias, most commonly sick sinus syndrome with bradytachyarrhythmias and atrial flutter, with a high incidence of sudden death.[49] Ambulatory 24-h electrocardiographic monitoring (see Chap. 25) and stress testing (see Chap. 14) and intracardiac electrophysiologic studies are important in following patients who have had complex repairs. Atrial dilation after the Fontan operation has resulted in atrial flutter and/or fibrillation, which are frequently problematic therapeutically.[50]

Serious ventricular dysfunction[51] and venous obstructions also may occur, usually in those who had severe defects. Interatrial repairs for transposition of the great arteries leave the anatomic right ventricle to do the work of the systemic ventricle.[52] In addition, these repairs may lead to pulmonary and/or systemic venous obstruction. Atriopulmonary connections for the repair of tricuspid atresia and many types of univentricular hearts frequently leave an anatomically abnormal ventricle as the systemic ventricle. In this group of patients, the right atrium has become the "pulmonary ventricle," with an elevated right atrial pressure that may lead to problems of systemic venous hypertension such as protein-losing enteropathy.[53]

Finally, some children have had repairs in which synthetic prostheses were utilized. Artificial valves do not grow as the child does, and they must be much more durable in view of the child's

life expectancy. There are also some surgical procedures that require the placement of conduits, with or without valves, that can degenerate and become obstructive with time. *Bioprosthetic valves undergo accelerated fibrosis and calcification in patients less than about 30 to 35 years of age*.

It should be kept in mind that in spite of these problems, the majority of patients who reach adulthood after surgical repair of congenital defects are relatively asymptomatic; they can and do lead productive lives.

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Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

INTRACARDIAC COMMUNICATIONS BETWEEN THE SYSTEMIC AND PULMONARY CIRCULATIONS, USUALLY WITHOUT CYANOSIS

Ventricular Septal Defect

PATHOLOGY AND INCIDENCE

A ventricular septal defect is the most common congenital cardiac anomaly (Table 63-4). It may be an isolated defect or part of a complex malformation. Approximately 80 percent of these defects are paramembranous but may extend into the inlet, trabecular, or outlet sections of the muscular septum. Less common are conal septal or subarterial doubly committed defects (5 to 7 percent), inlet defects lying beneath the septal leaflet of the tricuspid valve in the region of the atrioventricular canal (5 to 8 percent), and defects in the muscular septum that may be in the inlet, trabecular, or outlet area[54] (Fig. 63-5). Multiple muscular defects are not infrequently seen.

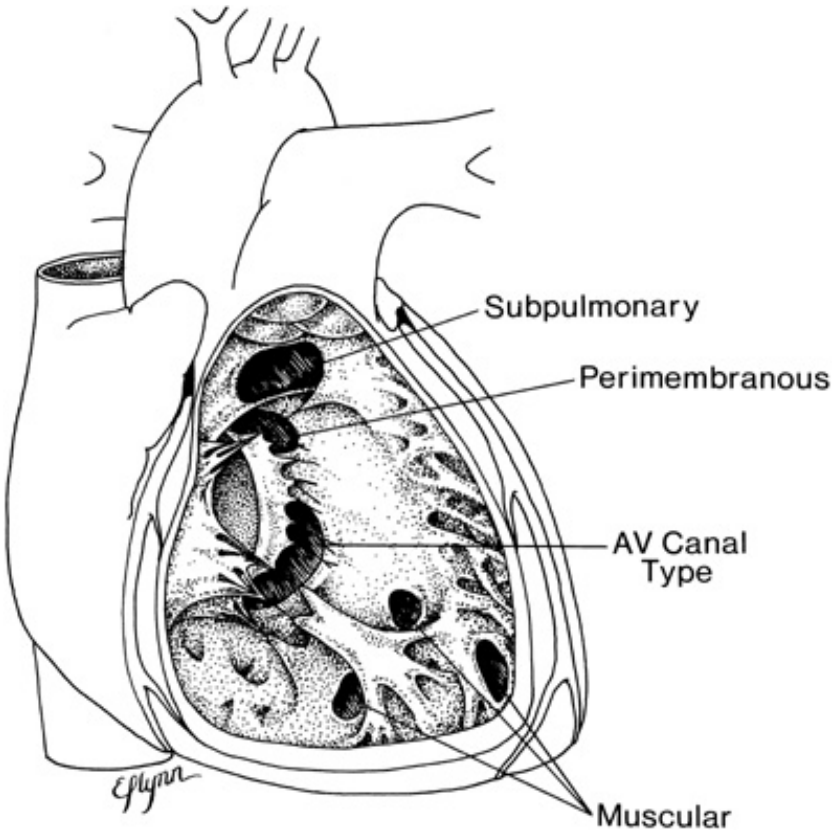

Figure 63-5: Different types of ventricular septal defects when viewed from the right ventricle. (From Fyler DC, ed. *Nadas' Pediatric Cardiology*. Philadelphia: Hanley & Belfus; 1992. Reproduced with permission from the publisher and author.)

Table 63-4: Communications with Predominant Left-to-Right Shunting

Ventricular septal defect	Atrioventricular canal
Atrial septal defect	Patent ductus arteriosus
Partial anomalous pulmonaryvenous connection	Sinus of Valsalva fistula

The incidence of VSDs is about 2 per 1000 live births, and its prevalence among school-age children has been estimated as 1 per 1000, constituting about one-quarter of the congenital cardiac malformations in combined series (Table 63-1). Males and females are affected equally.

VSDs may be isolated or associated with other congenital cardiac abnormalities. Malformations associated with VSD are, in order of decreasing frequency: (1) coarctation of the aorta, (2) additional shunts, most commonly ASD and PDA, (3) intracardiac obstructions such as subpulmonary or subaortic stenosis, mitral stenosis, and anomalous muscle bundle of the right ventricle, and (4) incompetent atrioventricular valves.

ABNORMAL PHYSIOLOGY

The consequences of a VSD depend on the size of the defect and the pulmonary vascular resistance. A small defect offers a large resistance to flow. There is no elevation of right ventricular or pulmonary arterial pressure, and the left-to-right shunt may be so small that it can be detected only by selective left ventricular angiography or two-dimensional imaging with Doppler color flow mapping. This type of defect imposes little physiologic burden on the heart, although there is always the danger of infective endocarditis.

A defect of moderate size still permits a difference between the right and left ventricular systolic pressures but may allow a large left-to-right shunt with resulting left atrial hypertension and dilatation and left ventricular volume overload. The development of pulmonary vascular disease among these patients is unusual but possible.

When the effective area of the defect is large, approximately equal to or greater than the aortic valve orifice, the defect offers virtually no resistance to flow and the systolic pressures in both ventricles, the aorta, and the pulmonary artery are essentially the same. The relative proportion of blood going to the two circulations is directly governed by the relative resistance of the two vascular beds.

At birth, pulmonary vascular resistance is high and there is little, if any, left-to-right shunt despite the presence of a large defect. This resistance to flow gradually falls over the first few weeks of life, permitting a progressively greater amount of blood to flow through the defect, through the lungs, and back to the left atrium and left ventricle. In most infants, the left ventricular volume overload eventually leads to left ventricular "failure" with elevated left ventricular end-diastolic and left atrial pressures and pulmonary congestion.

In term infants born at sea level with a large VSD, clinical deterioration may occur at any time from about 3 to 12 weeks after birth. In premature infants, in whom the less well developed pulmonary vascular hypertrophy regresses more rapidly, failure frequently is noted at 1 to 4 weeks.

History

Infants or children with a small isolated defect are asymptomatic. The murmur of a small defect

may be detected within the first 24 to 36 h of life, since the very restrictive opening permits the normal rapid fall in pulmonary arterial resistance and pressures. Infants with larger defects usually present between 3 and 12 weeks of age with congestive failure, frequently with associated lower respiratory tract infections. Parents describe tachypnea, grunting respirations, and fatigue, particularly with feedings. Weight gain is slow, and excessive sweating is common.

Physical Examination

A child with a small defect is comfortable. With moderate holes, a systolic thrill at the lower left sternal border is common. If the defect is small, the pulmonary artery pressure is normal and so the second heart sound is not accentuated. The systolic murmur along the lower left sternal border is characteristically holosystolic but may be limited to early or midsystole. This latter feature suggests a defect in the muscular septum rather than the membranous septum.

Infants with large defects, large left-to-right shunt, and PAH tend to be restless, irritable, and underweight. Moderate respiratory distress may be present. Both the right and the left ventricular systolic impulses are impressively hyperdynamic to palpation. A thrill at the lower left sternal border is common. The second heart sound is narrowly split, with a loud, frequently palpable pulmonary component. Third heart sound gallops at the apex are common. Characteristically, the systolic murmur is holosystolic at the lower left sternal border and is accompanied by a middiastolic rumble of grade 2 to 3 intensity at the apex, with the latter indicating a pulmonary/systemic blood flow ratio (Q_p/Q_s) of 2:1 or greater. Hepatic enlargement can be identified below the right costal margin. Pulmonary rales may be seen with severe failure.

With the passage of time, one may observe signs of a diminishing left-to-right shunt with an improved rate of weight gain, less dyspnea, a diminution of the precordial hyperactivity, and disappearance of the apical diastolic flow rumble. This clinical improvement may be a result of the defect becoming smaller, the development of subvalvular pulmonary stenosis with little or no appreciable change in the size of the defect, or, most worrisome, the development of PVOD with continued severe PAH. With developing subpulmonary stenosis, the systolic murmur radiates more and more impressively to the upper left sternal border and the second heart sound becomes more widely split, with a progressive diminution in the intensity of the pulmonary component. Decreased flow resulting from pulmonary vascular disease is characterized by a gradual reduction in the intensity and duration of the systolic murmur, more narrow splitting of the second heart sound, and marked accentuation of the pulmonary component.

The clinical picture of advanced pulmonary vascular disease secondary to a congenital left-to-right shunt, or Eisenmenger's syndrome, is that of a relatively comfortable older child, adolescent, or young adult with mild cyanosis and clubbing in whom one finds a prominent a wave in the jugular venous pulse, a mild right ventricular lift, and a second heart sound that is narrowly split or virtually single with a very loud, usually palpable pulmonary component. An early pulmonary systolic ejection sound, reflecting dilatation of the main pulmonary artery, may be heard, and there may be no systolic murmur at all. In older adolescents and adults, an early diastolic murmur of pulmonary regurgitation or a holosystolic murmur of tricuspid regurgitation may appear.

Chest Roentgenogram

In the presence of a small defect, the heart size and shape and the pulmonary blood flow are barely altered. With large defects, there is moderate to marked enlargement of the heart, with prominence of the main pulmonary arterial segment and impressive overcirculation in the peripheral lung fields. The left atrium is dilated unless an associated ASD is present, allowing decompression of the left atrium. With increasing pulmonary vascular disease, there is diminution in heart size toward normal while the central pulmonary arteries remain dilated. The peripheral pulmonary arterial markings become attenuated, and a "pruned" effect is produced in the outer

third of the lung fields.

Electrocardiogram

With a small defect, one can expect the normal progression of the mean QRS axis from right to left and the normal gradual diminution of the prominent right ventricular voltages characteristic of newborns. The left ventricular forces remain within normal limits or become slightly augmented as a reflection of the mild left ventricular volume overload. With large defects, the mean QRS axis tends to remain oriented to the right and there is little or no regression in right ventricular voltage. The left ventricular forces gradually increase, resulting in a pattern of biventricular hypertrophy within the first few weeks of life. Left atrial hypertrophy is usually present, and frequently right atrial hypertrophy as well. With the development of pulmonary vascular disease or significant pulmonary stenosis, the mean QRS axis tends to remain oriented to the right; there is no regression in right ventricular voltage, but the evidence of left ventricular and left atrial hypertrophy lessens or disappears.

Echocardiogram

Two-dimensional imaging can distinguish an uncomplicated VSD from more complex malformations and is capable of imaging most defects directly when multiple transducer positions are used. The addition of pulsed-wave Doppler with color flow mapping permits the identification of small, multiple, muscular, and other less easily visualized defects. The position and size of the opening can be determined as well as its relationships to the aorta, pulmonary artery, and AV valves. Continuous-wave Doppler echocardiography can predict the systolic right ventricular pressure from the difference between the systolic pressure measured by a blood pressure cuff if there is no aortic stenosis and the Doppler gradient (Fig. 63-6). In the absence of associated pulmonic stenosis, the right ventricular systolic pressure provides an estimate of the pulmonary artery pressure. An accurate approximation of right ventricular systolic pressure also can be made by estimating the right ventricular to right atrial systolic pressure gradient across the tricuspid valve if tricuspid regurgitation is present.

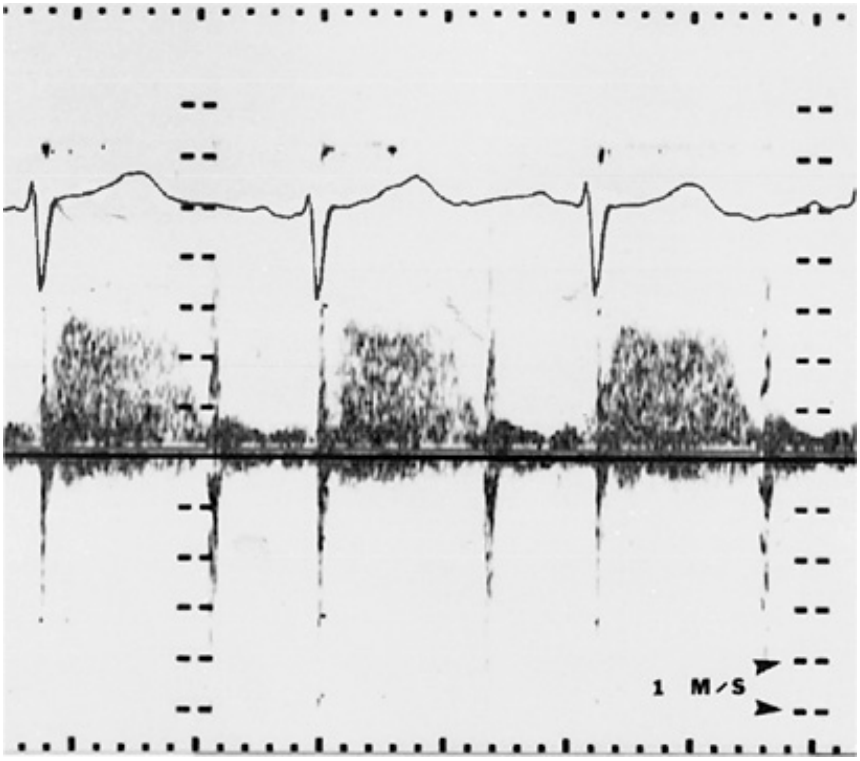

Figure 63-6: Continuous-wave Doppler with spectral display from the left lower sternal border of a child with a ventricular septal defect that demonstrates holosystolic turbulence with peak velocity = 2.8 m/s across the defect, compatible with an instantaneous systolic pressure difference of 31 mmHg between the right and left ventricles.

Cardiac Catheterization

Cardiac catheterization is being done less commonly in VSDs not associated with other cardiac malformations. When it is performed, an increase in oxygen saturation at the right ventricular level reflects the left-to-right shunt via the VSD. With small defects, the right ventricular and pulmonary arterial systolic pressures are normal. With large defects, these pressures are at or near systemic levels, and the mean left atrial pressure may be elevated to the range of 10 to 15 mmHg.

Selective left ventricular angiography in the anteroposterior, lateral, and oblique views with craniocaudal angulation can be done to establish the spatial relations of the great arteries to each other and to the ventricles and also to determine the exact site, size, and number of septal defects (Fig. 63-7). Aortography is helpful in eliminating the possibility of an associated ductus arteriosus or unsuspected coarctation of the aorta if the arch cannot be well imaged by echocardiography.

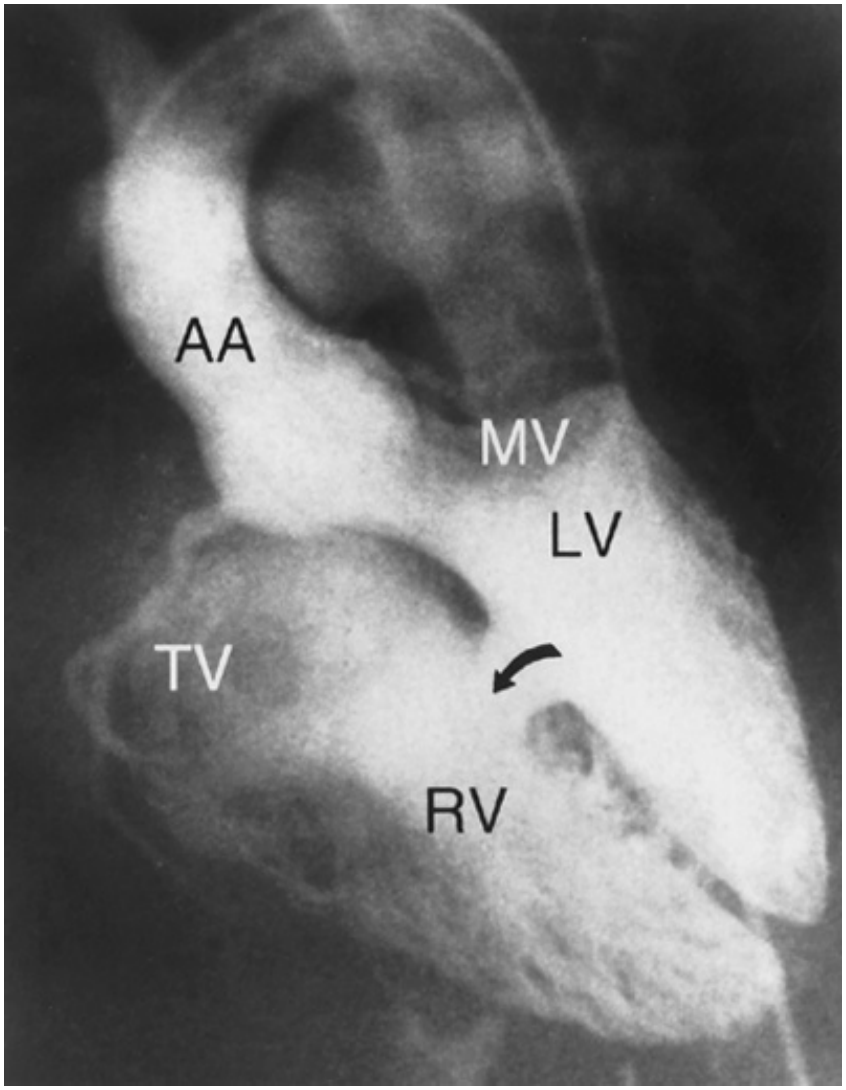

Figure 63-7: Multiple trabecular ventricular septal defects. Retrograde left ventriculogram, four-

chamber projection, profiles the mitral and tricuspid valves and the midtrabecular VSD (*arrow*). Additional VSDs closer to the apex are more anterior in location and are not profiled in this projection. AA = ascending aorta; LV = left ventricle; MV = mitral valve; RV = right ventricle; TV = tricuspid valve. (From Lock JE, Keane JF, Perry SB. *Diagnostic and Interventional Catheterization in Congenital Heart Disease*, 2d. ed. Boston: Kluwer; 2000.)

NATURAL HISTORY AND PROGNOSIS

Fortunately, the majority of VSDs are small and do not present a serious clinical problem. Approximately 24 percent of these small defects close spontaneously by 18 months, 50 percent by 4 years, and 75 percent by 10 years.[55] A spontaneous closure rate approaching 45 percent within the first 12 to 14 months has been observed among infants with an uncomplicated paramembranous or muscular VSD in the neonatal period.[56] Even large defects tend to become smaller, but the likelihood of eventual spontaneous closure is much lower (probably in the range of 60 percent if judged large at 3 months of age and only 50 percent if it is still large at 6 months).[55]

Congestive failure is a threatening and almost inevitable complication of a large VSD. Almost 80 percent of infants with large defects require hospitalization by age 4 months.[3] The risk of death with congestive failure is in the range of 11 percent. Significant subvalvular pulmonary stenosis develops in approximately 3 percent of these individuals and may progress to the point of severe tetralogy of Fallot. PVOD is seldom severe and rarely is irreversible in the first 12 months of life, but thereafter it becomes progressively more common and less likely to regress. At risk of this complication are infants and children with a pulmonary systolic pressure in excess of 50 percent of the systemic arterial systolic pressure beyond the first year of life.[57] A very small number of infants with large VSDs maintain a high level of pulmonary vascular resistance throughout the first year of life and remain almost entirely free of symptoms and congestive heart failure. In these patients, irreversible pulmonary vascular disease may develop without the usual and expected clinical signs and symptoms described above.

A small number of children, 0.6 percent in a large group of carefully followed patients, will develop aortic regurgitation as a result of prolapse of the right, the posterior, or both aortic valve leaflets into the defect.[58] This complication is more prevalent among males, in a ratio of 2:1, and seems particularly likely to occur with defects of the subpulmonary type. Shunt size appears not to be related to the development of this complication. The characteristic aortic diastolic murmur may appear at any time between ages 6 months and 20 years. Regurgitation is usually progressive, sometimes rapidly so, and predisposes these individuals to infective endocarditis.

The risk of infective endocarditis in patients with an uncomplicated VSD that is managed medically lies somewhere between 4 and 10 percent for the first 30 years of life.[59] The development of aortic regurgitation more than doubles this risk. Attempts at surgical closure of the defect with or without aortic regurgitation reduce the risk to less than half that of unoperated patients.[60]

MEDICAL MANAGEMENT

The basis of the medical management of children with ventricular septal defects is an understanding that defects frequently get smaller and may close spontaneously. Approximately 70 percent of small ventricular septal defects probably close.[55] Even large muscular defects may get significantly smaller, and up to 25 percent of them will become hemodynamically insignificant if one can wait long enough. Nevertheless, significant complications can occur, and the decision whether to proceed with medical or surgical management must be reevaluated constantly.

For children with a large ventricular septal defect, the first decision point usually occurs before 8 to 12 weeks of age. Infants with large septal defects usually develop significant left-to-right shunts as the pulmonary resistance drops. Congestive heart failure ensues with tachypnea, tachycardia, and difficulty feeding. Digoxin and diuretics are occasionally useful, but if the left-to-right shunt is very large, feeding may be problematic. For children who cannot gain at least 15 g per day (30 g per day is normal) in whom no other cause is found for failure to thrive, surgical repair is indicated. Occasionally, in marginal cases, increasing the caloric density of the formula from 20 calories per ounce up to 30 to 32 calories per ounce may be useful. In children whom the increased work prevents from taking more than 10 to 12 ounces per day, however, caloric supplementation is unlikely to be sufficient and surgical repair is necessary.

The second decision point in children who do not fail to thrive occurs between 9 and 12 months of age. Children with unrestrictive or mildly restrictive ventricular septal defects have pulmonary artery hypertension that may lead to irreversible pulmonary vascular obstructive disease. If the pulmonary artery pressure is elevated at 9 to 12 months of age, surgery is indicated to prevent this serious life-shortening complication. In some children, the high-pitched nature of the murmur, the normal pulmonary component of the second heart sound, the absence of right ventricular hypertension on ECG, and the large intraventricular pressure gradient on echocardiography make the estimation of normal pulmonary artery pressure firm. Occasionally in children in whom the signs, symptoms, and laboratory findings are ambiguous or conflicting, cardiac catheterization may be necessary to assure that the pulmonary artery pressure is normal and that pulmonary vascular obstructive disease is not a risk.

The third decision point occurs somewhere in midchildhood (5 to 10 years of age). If the defect has not caused failure to thrive and is not associated with pulmonary hypertension, it still may be associated with a significant left-to-right shunt, causing a volume overload to the left ventricle. Eventually, congestive heart failure is possible, and some recommend surgical closure during childhood if there is a significant volume overload. There is no firm number that suggests a dangerous level of left ventricular volume overload. Some centers close the ventricular septal defect when the pulmonary-to-systemic flow ratio (measured by cardiac catheterization, radionuclide angiography, echocardiography or magnetic resonance imaging) is more than 2 to 1. Others use significant left atrial and left ventricular dilation by echo. A minority of centers do not recommend surgical closure as long as the pulmonary artery pressure is normal since there are few adults with a ventricular septal defect who develop problems with late congestive heart failure.

Unfortunately, not all patients with a large defect are encountered during the first or second year of life, when it is possible to prevent injury to the pulmonary vascular bed. If significant PAH is allowed to persist, one can expect progression to irreversible pulmonary obstructive disease. For this reason, *prompt surgical closure of defects is recommended in all individuals beyond the age of 2 years if the pulmonary arterial systolic pressure is greater than half the systemic arterial systolic pressure, the mean pulmonary pressure exceeds 25 mmHg, or the R_p/R_s ratio is higher than 0.3:1*. With severe pulmonary vascular disease, a point eventually is reached where the risk of death at operation or in the months or years immediately after the operation as a result of progressive vascular disease more than offsets the possible benefits from surgical closure. At present, surgery is recommended if the calculated R_p is less than 10 Wood units/m^2 or the R_p/R_s ratio is 0.7:1, provided that the Q_p/Q_s ratio is still 1.5:1. In adults, the upper limit of pulmonary vascular resistance for surgery is approximately 800 dynes, or 10 Wood units.

Patients in whom the defect is judged clinically to be small at 6 months of age may be reexamined at 1- or 2-year intervals to reassure the patient and family, reemphasize the importance of antibiotic protection against infective endocarditis, document further narrowing or closure of the defect, and (in a very small number of patients) detect the first signs of aortic valve prolapse.

In patients with Eisenmenger's complex,[40] stamina is limited by systemic arterial hypoxemia and,

in some, right-sided heart failure. Complications to be anticipated include syncope, hemoptysis, brain abscess, hyperuricemia, and congestive failure. Pregnancy, with a maternal mortality of 30 to 60 percent, and oral contraceptives are contraindicated. Transient symptomatic relief from extreme polycythemia (usually >68 percent) may be achieved with careful erythropheresis. Travel to or living at high altitudes is poorly tolerated, and supplemental oxygen should be provided and used during air travel. The average age of death for individuals with Eisenmenger's complex is 33 years, with sudden death the mode of exit in the majority.

The risk of congenital heart disease for a subsequent sibling of a single affected child is on the order of 1 to 2 percent. The risk to a newborn who has one parent with VSD is approximately 3 percent.[61] Pregnancy in the presence of a small defect and normal pulmonary vascular resistance does not appear to carry an increased risk to the patient or infant, although precautions against infective endocarditis should be taken.

SURGICAL MANAGEMENT

Banding of the pulmonary artery to reduce pulmonary blood flow and pressures played an important role in the management of congestive heart failure and the prevention of PVOD before the era of predictably successful closure of VSDs in infants but now is used rarely. Complications of pulmonary arterial banding include deformity of the pulmonary arteries and/or pulmonary valve, progressive right ventricular hypertrophy with loss of ventricular compliance, and the development of subaortic left ventricular outflow tract obstruction.

VSDs are closed during a total cardiopulmonary bypass with cardioplegic arrest and moderate systemic hypothermia. Total circulatory arrest or minimal perfusion with profound hypothermia (18°C) is sometimes necessary in infants who weigh less than 5 kg.[62]

Paramembranous VSDs may be exposed through the right atrium and the tricuspid valve orifice. A transverse or longitudinal right ventriculotomy may be necessary for closure of high conal septal defects associated with aortic valve leaflet prolapse.

Care is required to prevent injury to the AV node near the ostium of the coronary sinus and to the bundle of His as it courses inferiorly, passing on the left side of the ventricular septum near the posterocaudal margin of the septal defect. Interoperative transesophageal echocardiography with Doppler color flow assessment can be used for the detection of significant residual or previously unsuspected problems that may be corrected in the operating room.

Results from primary surgical closure of VSDs are generally excellent, with surgical mortality less than 1 percent in centers with extensive experience, when surgery is performed during the early months of life before the evolution of PVOD. Operative risk should be even lower in older children if the pulmonary vascular resistance remains low. The pulmonary vascular bed responds favorably when the systemic-to-pulmonary shunt is eliminated before age 2 years. Normal life expectancy and functional capabilities should be anticipated postoperatively. Survival 25 years after the closure of a VSD is approximately 95 percent.[63] The mortality rate is unquestionably higher among patients who are operated on with R_p > 7 Wood units.

The surgical repair of a multiple muscular VSD has been problematic. The highly trabecular right ventricular septal surface can make the localization of all the defects difficult. Recently, techniques have become available to close these defects in the catheterization laboratory.[64] A device that can be anchored on the left ventricular and right ventricular septal surface was approved by the U.S. Food and Drug Administration in 1999 for this indication. Other devices are now in phase 2 testing.

Between February 1989 and July 1998, 148 transcatheter closures were preformed at Children's Hospital in Boston with no deaths or late morbidity resulting from catheter-related events. By echocardiography, 83 percent of the defects were closed or had trivial residual leaks.[64] The relative role of surgery versus interventional catheterization closure remains to be determined in this subset with multiple trabeculated septal defects.

Atrial Septal Defect

DEFINITION

An ASD is a through-and-through communication between the atria at the septal level. It is to be distinguished from a valvular-competent foramen ovale, which may persist into adulthood.

PATHOLOGY

ASDs are usually sufficiently large to allow free communication between the atria. They may be subdivided according to anatomic location[65] (Fig. 63-8).

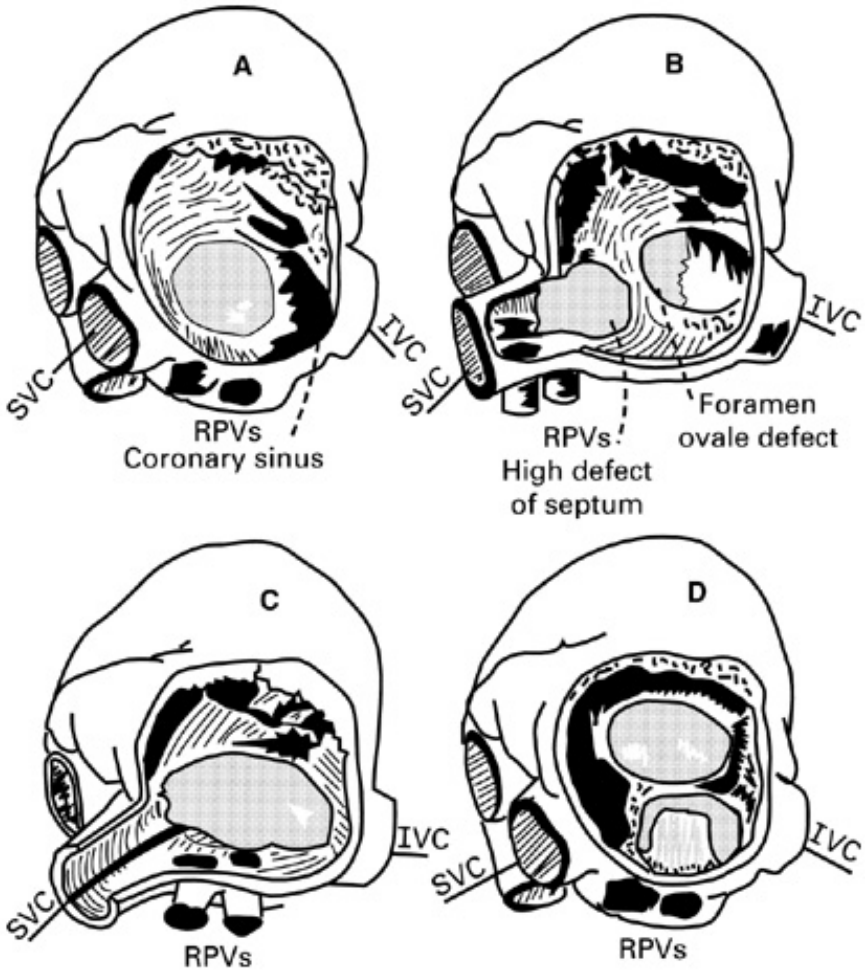

Figure 63-8: Types of interatrial communications. *A*. Large ostium secundum type of atrial septal defect. *B*. So-called sinus venosus type of defect-one high in the atrial septum associated with anomalous connection of the right superior pulmonary vein to the junctional area of the superior vena cava and right atrium. *C*. Very large ostium secundum type of atrial septal defect with absence of the posterior rim. *D*. Partial form of common atrioventricular canal with cleft mitral

valve. SVC = superior vena cava; RPVs = right pulmonary veins; IVC = inferior vena cava. (From Lewis FJ et al.[65] Copyright 1957, American Medical Association. Reproduced with permission from the publisher and authors.)

ANATOMIC TYPES

Defect at the Fossa Ovalis (Ostium Secundum)

This defect classically involves the region of the fossa ovalis and is the most common type (70 percent)[65,66] (Fig. 63-8*A* and *C*). Atrial septal tissue separates the inferior edge of the defect from the AV valves. Associated partial anomalous pulmonary venous connections are not uncommon, with one or more of the right pulmonary veins draining into the right atrium or one of its tributaries. Mitral valve prolapse is present in some cases.

Partial Atrioventricular Canal Defects

Defects of the AV septum, which lies inferior to the fossa ovalis, constitute approximately 20 percent of ASDs and are part of a complex malformation known as *common atrioventricular canal defects*, which are considered below (Fig. 63-8*D*).

Sinus Venosus Defects

These defects, accounting for approximately 6 percent of the total, appear to represent a biatrial connection of the superior vena cava (or, in rare instances, the inferior vena cava), which straddles the otherwise normal intact atrial septum. Also involved is an anomalous termination of one or more of the right-sided pulmonary veins either into the vena cava or into the right atrium near its junction with the vena cava (Fig. 63-8*B*).

Coronary Sinus Defects

A coronary sinus defect is an uncommon type of ASD located in the position normally occupied by the ostium of the coronary sinus. This defect is part of a developmental complex consisting of the absence of the coronary sinus and entry of the left superior vena cava directly into the left atrium.

Conditions Common to All Anatomic Types

The right atrial and ventricular chambers as well as the central pulmonary arteries become enlarged. When pulmonary hypertension intervenes, it usually does not do so before the third decade. The earliest lesion is cellular fibrous intimal thickening in the proximal segments of arterioles. The pulmonary arterial pressure then rises, followed by the development of medial hypertrophy of muscular arteries and the appearance of plexiform lesions. The right ventricular wall hypertrophies, and atherosclerosis may occur in the major pulmonary arteries. Saccular aneurysm and thrombosis with dissecting aneurysm or rupture may occur (see above, "Pulmonary Arterial Hypertension and Pulmonary Vascular Obstructive Disease"). In the final state, the pulmonary vascular bed may be difficult to distinguish from that in VSD with PVOD.

ABNORMAL PHYSIOLOGY

Usually there is no resistance to blood flow across the defect and no significant pressure difference between the two atria. A left-to-right shunt of blood occurs (Fig. 63-9) because (1) the right atrial system is more distensible than the left, (2) the tricuspid valve is normally more capacious than the mitral valve, and (3) the thinner-walled right ventricular chamber more readily

accommodates a larger volume of blood at the same filling pressure than does the left ventricle. A large left-to-right shunt may be found in a neonate or young infant before the right ventricular compliance has had time to change appreciably from that of the left ventricle. Presumably, this occurs because a rapid fall in pulmonary vascular resistance encourages a larger right ventricular stroke volume, a smaller end-systolic volume, and hence an increased ability of the right ventricle to accept a larger volume of blood during the diastolic filling phase of the cardiac cycle.[67]

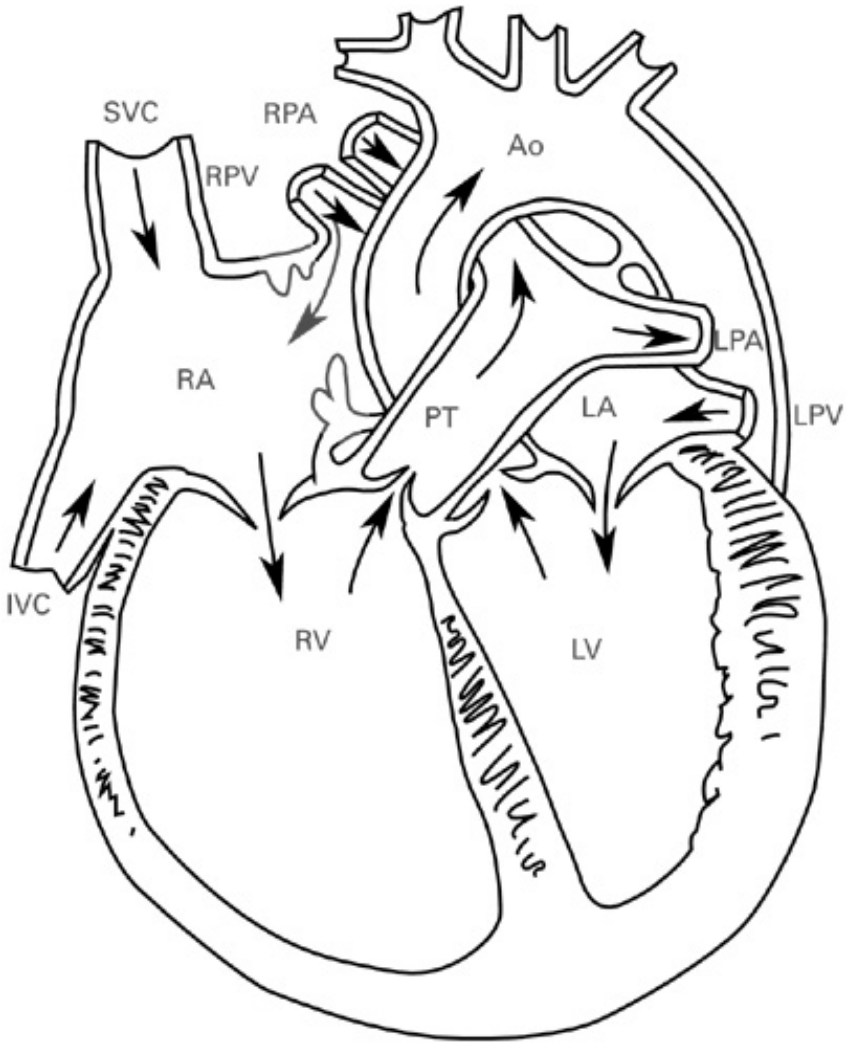

Figure 63-9: Atrial septal defect at fossa ovalis with left-to-right shunt. SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; PT = main pulmonary arterial trunk; RPA = right pulmonary artery; LPA = left pulmonary artery; RPV = right pulmonary vein; LPV = left pulmonary vein; LA = left atrium; LV = left ventricle; AO = aorta. (From Edwards JE.[66] Reproduced with permission from the publisher and author.)

The pulmonary arterial system undergoes normal maturation after birth, with most patients tolerating the large volume load on the right ventricle and pulmonary circuit quite well for many years. With the development of pulmonary vascular disease and PAH, the left-to-right shunt decreases, largely because of the increased thickness and decreased compliance of the right ventricle. In some patients, this process continues until there is eventually shunt reversal, with arterial desaturation and cyanosis.

CLINICAL MANIFESTATIONS

ASD is found in approximately 6 percent of children who survive beyond the first year of life with congenital heart disease.[5] *If one excludes mitral valve prolapse and a congenitally bicuspid aortic valve, it is the most common form of congenital heart disease among adults.*

ASDs are more common among females, with a female/male ratio of approximately 2:1. The mode of transmission is best explained in most instances on a multifactorial basis, in which the risk would be approximately 2.5 percent for first-degree relatives of a single affected family member. However, examples of autosomal dominant transmission are recognized[68] either as an isolated entity associated with severe AV conduction disturbances or with upper extremity malformations as in the Holt-Oram syndrome. Examples of mendelian autosomal recessive transmission are found in the Ellis-van Creveld syndrome (see Chap. 62).

History

The majority of these children are considered asymptomatic but probably most have some mild diminution of stamina, since it is not unusual for the patient or the parents to comment on the increased endurance that follows surgical correction. Symptoms of mild fatigue and dyspnea tend to be recognized in the late teens and early twenties, and at least three-quarters of these individuals will be definitely symptomatic as adults. Congestive heart failure is rare in childhood, but a few infants, perhaps 5 percent, have heart failure in the first year of life. Failure becomes more common again in the fourth and fifth decades, usually associated with the onset of arrhythmias.[69]

Physical Examination

Many of these children have a slender habitus, but normal growth and development are the rule. Prominence of the left anterior chest is common, and a hyperdynamic right ventricular systolic lift usually can be felt. Looking at the jugular venous pulse demonstrates that the *v* wave is equal to the *a* wave instead of revealing the normal a wave predominance. The first heart sound may be slightly accentuated at the lower left sternal border. The two components of the second heart sound are characteristically widely split, with the interval of splitting fixed despite expiration or the Valsalva maneuver. The pulmonary component of the second heart sound may be accentuated even in the absence of PAH. With increasing pulmonary arterial pressure and resistance, the interval between the aortic and pulmonary components of the second heart sound narrows and the pulmonary component becomes louder, but the lack of respiratory influence on the interval between the two components persists. A midsystolic spindle-shaped murmur of grade 2 to 3 intensity at the left upper sternal border, reflecting increased right ventricular stroke volume and relative pulmonary stenosis, is to be expected. A low- to medium-pitched early diastolic murmur over the lower left sternal border, denoting increased diastolic flow across the tricuspid valve, is present in most individuals with large shunts (see Chap. 10). Cyanosis and clubbing reflect right-to-left shunting. In this setting, the murmurs of tricuspid and pulmonary regurgitation are not uncommon.

Chest Roentgenogram

Mild to moderate cardiac enlargement and prominence of the main and branch pulmonary arteries are characteristic. The absence of left atrial displacement of the barium-filled esophagus in the lateral view helps distinguish ASD from large left-to-right shunts at other levels (Fig. 63-10).

Electrocardiogram

An rsR′ pattern over the right precordium indicating mild right ventricular conduction delay or

mild right ventricular hypertrophy is characteristic in secundum-type ASD. The mean QRS axis in the frontal plane is 90° or greater in 60 percent of patients. Left-axis deviation is common in primum-type ASD. Abnormal leftward p axis is common in sinus venosus-type ASD. Serious arrhythmias are usually, though not invariably, limited to adults; atrial fibrillation and atrial flutter are the most common arrhythmias.

Echocardiogram

M-mode studies reflect volume overload of the right side of the heart with increased right atrial and right ventricular dimensions and paradoxical ventricular septal motion. Two-dimensional and Doppler echocardiography with color flow mapping (see Chap. 13) permit identification and visualization of secundum, AV canal, and sinus venosus defects. Visualization of anomalous draining pulmonary veins is slightly more difficult. The transesophageal approach offers excellent images for those patients in whom the transthoracic approach is inadequate.[70] Recently three-dimensional (3-D) echocardiograms have been used to get excellent images of the atrial defects[71] (Fig. 63-11).

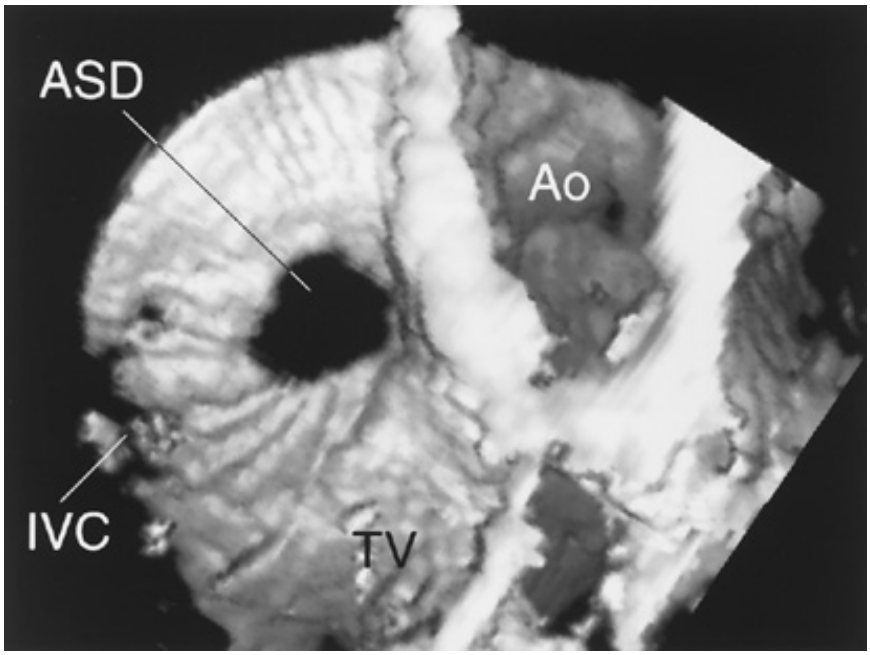

Figure 63-11: Three-dimensional echocardiogram of a secundum atrial septal defect (ASD). This is a right atrial en-face view that shows the size, shape, and position of the defect in relation to the right atrial septal surface. Ao = aortic valve; TV = tricuspid valve; IVC = inferior vena cava. Courtesy of Dr. Gerry Marx.

Cardiac Catheterization

There is a significant increase in oxygen saturation in the blood samples drawn from the right atrium, right ventricle, and pulmonary artery compared with those drawn from the superior or inferior venae cavae. Pulmonary arterial and right ventricular systolic pressures are normal or only slightly elevated. A systolic pressure gradient of up to 20 mmHg across the right ventricular outflow tract is accepted as being secondary to flow rather than to organic obstruction. The right and left atrial mean and phasic pressures are virtually identical, with little, if any, elevation above normal (mean pressure gradient <3 mmHg) unless there are associated abnormalities.

NATURAL HISTORY AND PROGNOSIS

Defects of the secundum type usually go undetected in the first year or two of life because of the lack of symptoms and the unimpressive auscultatory findings. A soft systolic murmur is the usual reason for referral. Symptoms become more common in persons in their late teens and twenties, and by age 40 the majority of these individuals are symptomatic, some severely so.[72] Pulmonary vascular disease with serious pulmonary hypertension begins to make its appearance in the early twenties. *It affects approximately 15 percent of young adults, particularly women, and may be rapidly progressive, especially with pregnancy*. The incidence of atrial fibrillation or flutter also increases with each decade and is closely linked to the onset of congestive failure. Spontaneous closure of secundum defects is rare beyond the first 2 years of life.[69] Congestive heart failure is the most common cause of death among unoperated patients. Other causes of death include pulmonary embolism or thrombosis, paradoxical emboli, brain abscess, and infection.

MEDICAL MANAGEMENT

The few infants who present with symptoms of congestive failure are treated with digoxin and, if necessary, diuretics and are studied by cardiac catheterization. If the defect is uncomplicated and the symptoms persist despite a trial of therapy, surgical closure is advised without further delay. For asymptomatic infants and children, closure is recommended just before entry into school. Restrictions of activity or exercise are unnecessary. If the physical, laboratory, and echocardiographic findings are completely characteristic, preoperative catheterization is not necessary. Closure is recommended if the defect is large and if there is right ventricular volume overload on echocardiography. In those with pulmonary hypertension closure is recommended for patients with Q_p/Q_s ratios >1.5:1 by catheterization provided that the systemic arterial saturation is >92 percent and total R_p < 15 Wood units.[73] Closure would seem prudent before pregnancy or the use of contraceptives in view of the tendency to develop rapidly progressive PVOD in this setting. Transcatheter closure of centrally located secundum in selected older infants, children, and adults using a double-umbrella ("clamshell") or a buttoned device appears to be an acceptable alternative to surgical closure.[74-76] *Infective endocarditis is rare, and antibiotic coverage at times of possible bacteremia is recommended only if associated mitral valve disease is suspected*.

SURGICAL MANAGEMENT

Defects of the interatrial septum are exposed through the lateral wall of the right atrium.

Ostium secundum (fossa ovalis) defects frequently are closed by direct suturing; a very large defect or one with tenuous margins is closed with a patch, usually glutaraldehyde-treated autologous pericardium. Anomalous pulmonary veins are sought along the posterolateral aspect of the superior or inferior vena cava and from within the right atrium before closure of the defect. Sutures are placed with care along the posterior rim of the inferior vena caval orifice to prevent the creation of a tunnel from the inferior vena cava into the left atrium, which would cause postoperative hypoxemia.

High ASDs of the sinus venosus type, which often are associated with anomalous drainage of one or more right pulmonary veins into the superior vena cava, are corrected by means of the placement of a pericardial or tubular Dacron patch from above the abnormally draining vein or veins down to and around the ASD (Fig. 63-12). Pulmonary venous blood thus is diverted through the ASD into the left atrium. Pericardial gusset enlargement of the superior vena cava at the cavoatrial junction may be required. Anomalous right pulmonary veins draining to the right atrium are diverted into the left atrium by placement of a patch baffle well anterior and to the right of the pulmonary vein orifices. The risks of surgery are minimal (less than 0.5 percent), with virtually all these children home by the fourth postoperative day.

In adults, clinical benefit after closure of ASDs can be anticipated even in those with significant physiologic compromise, but mortality is higher than it is in the young and the magnitude of improvement is less certain. Nonetheless, surgical closure of ASDs is advised even when R_p approaches 15 Wood units because of the excessive morbidity and mortality associated with a persistent interatrial communication.[77] *Morbidity in adults and the low risk of surgical closure in young children mandate surgery in the preschool or preadolescent years.*

Although life-threatening complications after closure of ASDs in children are rare, transient postoperative atrial arrhythmias and postpericardiotomy syndrome with pericardial effusions occasionally are seen. The long-term prognosis for a normal life expectancy and functional capability is excellent for patients who have closure of an uncomplicated ASD during the first two decades of life.

Partial Anomalous Pulmonary Venous Connection

PATHOLOGY

In partial anomalous pulmonary venous connection, one or more, but not all, of the pulmonary veins enter the right atrium or its venous tributaries. The atrial septum may rarely be intact, but an ASD is usually present. There are many patterns of anomalous pulmonary venous connection, but the four most common, in order of decreasing frequency, are (1) pulmonary veins from the right upper and/or middle lobe to the superior vena cava, usually with a sinus venosus ASD, (2) all the right pulmonary veins to the right atrium, usually in the polysplenia syndrome, (3) all the right pulmonary veins to the inferior vena cava, entering this systemic vein just above or below the diaphragm, and (4) the left upper or both left pulmonary veins to an anomalous vertical vein draining to the left brachiocephalic vein.

When the right pulmonary veins are connected to the inferior vena cava, the atrial septum may be intact. This venous anomaly may be isolated or may be part of the *scimitar syndrome*. That syndrome includes hypoplasia of the right lung, bronchial abnormalities, anomalous systemic pulmonary arterial supply to the right lung from branches of the descending thoracic and/or abdominal aorta, and dextroposition of the heart.

CLINICAL MANIFESTATIONS

In an old autopsy series, partial anomalous pulmonary venous connection occurred in 0.6 percent of 801 anatomic dissections,[78] a much higher incidence than was suspected clinically, suggesting that many cases may not be recognized during life. There is no sex predilection. Approximately 15 percent of all ASDs have this coexisting anomaly; however, in the case of the sinus venosus type, the association is in the range of 85 percent.

History

When partial anomalous pulmonary venous connection coexists with an ASD, the symptoms, as well as the other clinical manifestations, are indistinguishable from those of an isolated ASD. Isolated, uncomplicated anomalous connection of a single pulmonary vein usually goes undetected clinically, since in this circumstance only about 20 percent of the pulmonary venous flow returns to the right atrium or its tributaries. When the entire venous return from one lung or two pulmonary veins is connected anomalously, approximately 65 percent of the pulmonary venous flow returns to the right side of the heart and the symptoms are similar to those of an ASD with a comparable increase in pulmonary blood flow.

Physical Examination

The findings are the same as those in patients with an ASD with the exception that *the two components of the second heart sound, though usually widely split, move normally with respiration if the atrial septum is intact*.

Chest Roentgenogram

Right ventricular enlargement, pulmonary arterial dilatation, and increased pulmonary blood flow are characteristic when more than one pulmonary vein connects anomalously. With anomalous connection of the right pulmonary veins to the inferior vena cava, the pulmonary venous pattern may assume a crescent-shaped or scimitar curve in the right lower lung field along the right lower heart border (scimitar).

Electrocardiogram

The ECG is normal (in the case of anomalous connection of a single pulmonary vein) or reflects volume overload of the right side of the heart, as was described above in "Atrial Septal Defect."

Echocardiogram

If more than one pulmonary vein drains anomalously, the volume usually is sufficient to produce the characteristic pattern of right ventricular diastolic overload. Failure to visualize an atrial septal opening with two-dimensional imaging and color flow mapping from a subcostal coronal or high right-sided parasternal longitudinal view should arouse suspicion of an intact atrial septum. A variety of views supplemented by color flow mapping may be necessary to identify the anomalous connection.[79]

Cardiac Catheterization

Anomalously connected pulmonary veins may be entered directly with the venous catheter. Selective biplane angiograms in these vessels will document their site of connection. Left-to-right shunting with partial anomalous pulmonary venous connection and an intact atrial septum is usually small or moderate and may go undetected by oximetry techniques. Selective indicator dilution curves in the right and left pulmonary arteries with systemic arterial sampling can detect the lung with the anomalous pulmonary venous connection, and selective biplane angiograms in the pulmonary arterial branches will visualize these connections.

NATURAL HISTORY AND PROGNOSIS

Patients with partial anomalous pulmonary venous connection with ASD appear to follow a course similar, if not identical, to that of patients with an isolated ASD. When the atrial septum is intact, the course depends primarily on the volume of pulmonary venous blood returning to the right side of the heart. Rarely, PVOD may be found even in the presence of a single anomalously connected pulmonary vein and an intact atrial septum.[80] Finally, increasing left atrial pressure caused by mitral valve disease or diminishing left ventricular compliance will, in the course of time, encourage a greater redistribution of pulmonary arterial blood flow to the portion of the lung drained by the more compliant right atrium. Thus, patients who were initially asymptomatic and had a very modest volume of anomalous pulmonary venous return in youth may become symptomatic and even develop congestive failure in adult life.

MEDICAL MANAGEMENT

Asymptomatic patients with small shunts require no treatment. Those with symptoms, larger pulmonary blood flows, congestive failure, or PAH require surgical correction. With an intact

atrial septum, precise preoperative identification of the site of the anomalous venous connection is essential. Long-term follow-up in patients who have not had surgery is indicated to detect increasing flow or the appearance of PAH.

SURGICAL MANAGEMENT

Anomalous connection of a right pulmonary vein or veins to the superior vena cava usually is associated with a sinus venosus ASD (Fig. 63-12). (see "Atrial Septal Defect, Surgical Management," above.) Partial anomalous pulmonary veins draining to the superior vena cava, inferior vena cava, or right atrium are repaired by being diverted through the ASD into the left atrium, using an appropriately placed patch baffle. Isolated left-sided anomalous pulmonary veins draining to the left ascending vertical vein or the left superior vena cava are detached and anastomosed directly to the left atrial appendage. Long-term morbidity and mortality are minimal among patients with uncomplicated partial pulmonary venous connections, equivalent to those observed after closure of an ASD.

Common Atrioventricular Canal Defects

DEFINITION

Atrioventricular canal defects are characterized by an ASD in the lowermost part of the atrial septum (ostium primum), a cleft of the mitral valve (either alone or in combination with a cleft of the tricuspid valve), or deficiency of ventricular septal tissue or some combination. In the most severe form (complete AV canal defect), there is a large deficiency of the lower part of the atrial septum and the upper muscular portion of the ventricular septum and a common AV valve that straddles the ventricular septum. The condition appears to result from incomplete growth of the AV endocardial cushions and the AV septum.

PATHOLOGY

The ostium primum type of ASD is characterized by a crescent-shaped upper border and no septal tissue forming the lower border. The lower aspect of the defect is bounded by the atrial surfaces of the AV valves and, in the complete type (see below), in part by the upper edge of the ventricular septum. A small amount of septal tissue separates the defect from the posterior atrial wall.

ANATOMIC TYPES

Variations occur with respect to the nature of the AV valves. The terms *partial* and *complete* were first introduced to describe these types by Rogers and Edwards.[81]

Partial Type

The ostium primum ASD is associated with a "cleft" in the anterior mitral leaflet or, probably more accurately, a septal commissure between the superior and inferior leaflets of the left AV valve (Figs. 63-8*D* and 63-13).[66] The tricuspid valve is not cleft or shows a minor central deficiency. The ventricular aspects of the anterior mitral valve elements are fused to the upper edge of the deficient ventricular septum, precluding an interventricular communication. If there is no atrial septal tissue or if the atrial septum is so rudimentary that it produces a common chamber involving both atria, the term *common atrium* or *single atrium* is applied.

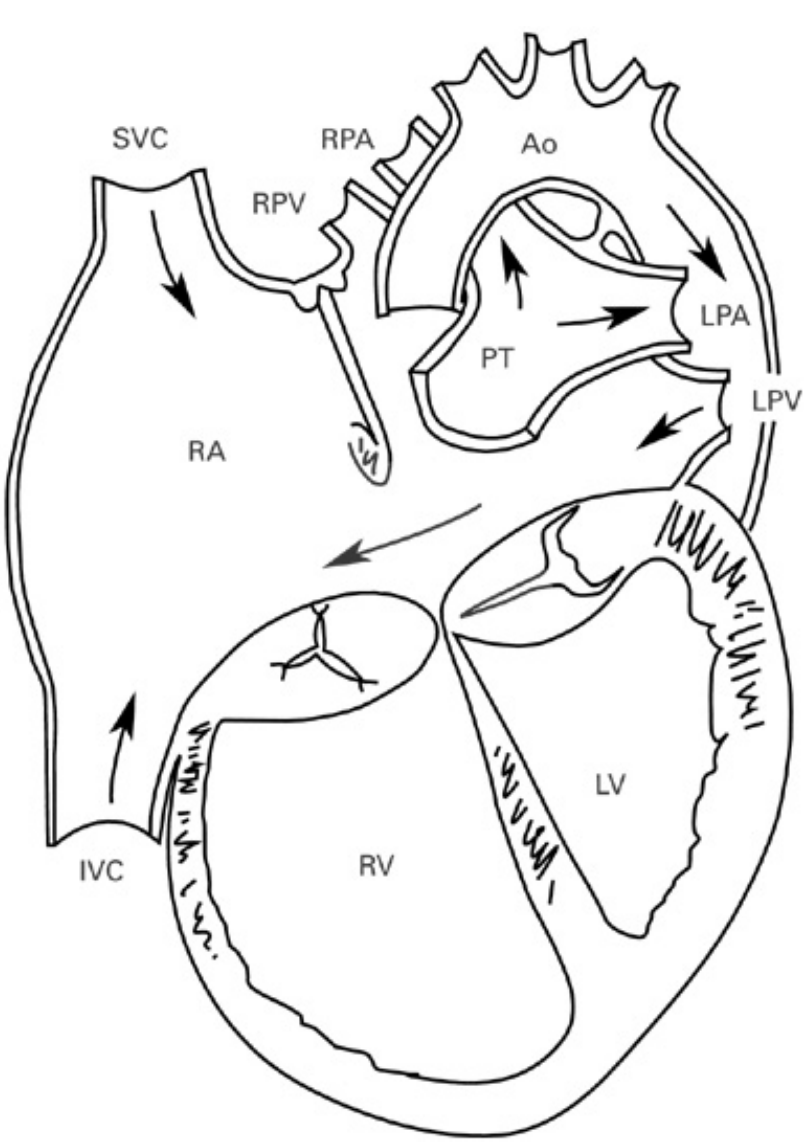

Figure 63-13: Common AV canal of the partial type. The mitral valve shows a cleft in its anterior leaflet, while the tricuspid valve is undisturbed. SVC = superior vena cava; IVC = inferior vena cava; RA = right pulmonary artery; LPA = left pulmonary artery; RPV = right pulmonary vein; LPV = left pulmonary vein; LV = left ventricle; Ao = aorta. (From Edwards JE.[66] Reproduced with permission from the publisher and author.)

Complete Type

The complete type of common AV canal is characterized by failure of partitioning of the primitive canal into separate AV orifices. The orifice between the atria and the ventricles is guarded by a common valve, of which the anterior leaflet is derived from the ventral AV endocardial cushion and represents the anterior halves of the anterior mitral and septal tricuspid leaflets. The posterior leaflet is derived from the dorsal AV endocardial cushion and represents the posterior halves of the anterior mitral and septal tricuspid leaflets.

Usually, considerable space exists between the anterior and posterior leaflets above and the ventricular septum below; thus, in most cases of the complete type, there is free communication between the ventricles.

Rastelli and associates[82] subdivided the complete variety into three subgroups-types A, B, and C-on the basis of the structure of the common anterior leaflet and its chordal attachments to the

ventricular septum and/or papillary muscles (Fig. 63-14). With regard to the posterior common leaflet, there is variation among the three types in regard to the presence or absence of subdivision and whether the posterior leaflet is attached to the ventricular septum by chordae or by an imperforate membrane.

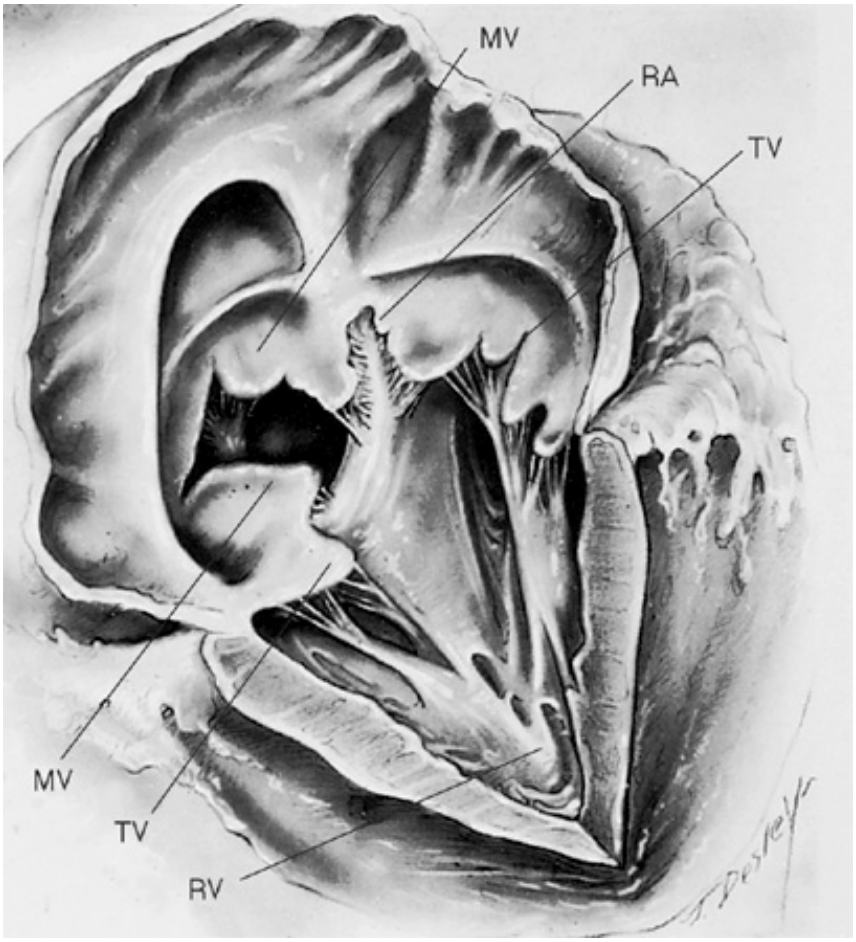

Figure 63-14: Complete form of common AV canal, type A. The common anterior leaflet has a recognizable mitral component (MV) and tricuspid component (TV). In type B, not illustrated, those components are attached by chordae to a papillary muscle in the right ventricle. In type C, not illustrated, the common anterior leaflet is a single unit without any attachment to the underlying ventricular septum. Type A is most amenable to repair. RV = right ventricle; RA = right atrium. (From Rastelli GC et al.[82] Reproduced with permission from the publisher and authors.)

Variations from the classic types of AV canal defects are recognized, the most common being the AV canal type of isolated VSD, isolated ostium primum ASD without malformed AV valves, and isolated cleft of the anterior mitral or septal tricuspid valve leaflets.

ASSOCIATED CONDITIONS

In the asplenia syndrome, the complete variety is almost universal; with polysplenia, it occurs in about one-quarter of cases.[83] An ASD of the secundum type is present in about half the cases. Double orifice of the mitral valve may be associated with the incomplete type, and tetralogy of Fallot may be associated with the complete type.

ABNORMAL PHYSIOLOGY

If the communication at the ventricular level is large, the right ventricular and pulmonary artery pressures will be elevated. These patients are similar to those with large VSDs. Patients with a communication at the atrial level usually have only normal or slightly elevated systolic pressures in the right side of the heart and a large pulmonary blood flow, as in the secundum type of ASD. Defects in the tricuspid valve, mitral valve, or both may result in severe regurgitation or direct shunting of blood from the left ventricle to the right atrium.

CLINICAL MANIFESTATIONS

Approximately 3 percent of infants and children with congenital heart disease have AV canal defects. The majority, some 60 to 70 percent, have the complete form. The female/male ratio is approximately 1.3:1. Well over half the patients with the complete form have associated Down's syndrome. Among children with Down's syndrome, 45 percent have some form of congenital heart disease. Malformations of the AV canal type, usually of the complete variety, account for approximately 50 percent of these abnormalities.[84]

History

Only if the mitral valve is incompetent do the symptoms of patients with partial AV canal differ from those associated with a secundum type of ASD. The complete form of AV canal or the partial form connected with significant mitral regurgitation may be associated with poor weight gain, easy fatigue, dyspnea, repeated respiratory infections, and congestive heart failure. Patients with complete AV canal are almost invariably very sick.

Physical Examination

The findings with a partial defect are those of an ASD. If the cleft anterior mitral leaflet is incompetent, the findings of mitral regurgitation also will be present.

The physical findings with the complete AV canal defect are those of a very large VSD, usually with full-blown congestive failure, but the second heart sound is split and fixed. The murmur of mitral regurgitation may not be heard or recognized as such.

Chest Roentgenogram

Overall cardiac enlargement that is out of proportion to the degree of pulmonary plethora or a cardiac silhouette suggesting combined ventricular dilatation may serve to distinguish an uncomplicated secundum ASD from a primum defect with significant mitral regurgitation. Marked cardiac enlargement and severe pulmonary overcirculation are features of the complete AV canal defect.

Electrocardiogram

One of the most helpful diagnostic features in distinguishing individuals with AV canal defects from those with isolated ASDs or VSDs is the characteristic superior orientation of the mean QRS axis in the frontal plane, with a right bundle branch delay in the precordial leads. Between 92 and 95 percent of both types of canal have a QRS axis lying between 0 and -150°. The patterns of atrial and ventricular hypertrophy reflect the underlying hemodynamic abnormalities.

Echocardiogram

Two-dimensional echo is capable of visualizing the extent of septal defects and, with Doppler study and color flow mapping, left-to-right shunting at the atrial and/or ventricular level and associated mitral and/or tricuspid valvular regurgitation (Fig. 63-15). The anatomic features of the anterior AV leaflet and its connections may be visualized with sufficient clarity to permit subdivision of complete AV canal defects into types A, B, and C (Fig. 63-14). Straddling AV valves, a double-orifice mitral valve, single papillary muscles, and hypoplasia or outflow obstruction of the right or left ventricle also can be determined with this technique.[85]

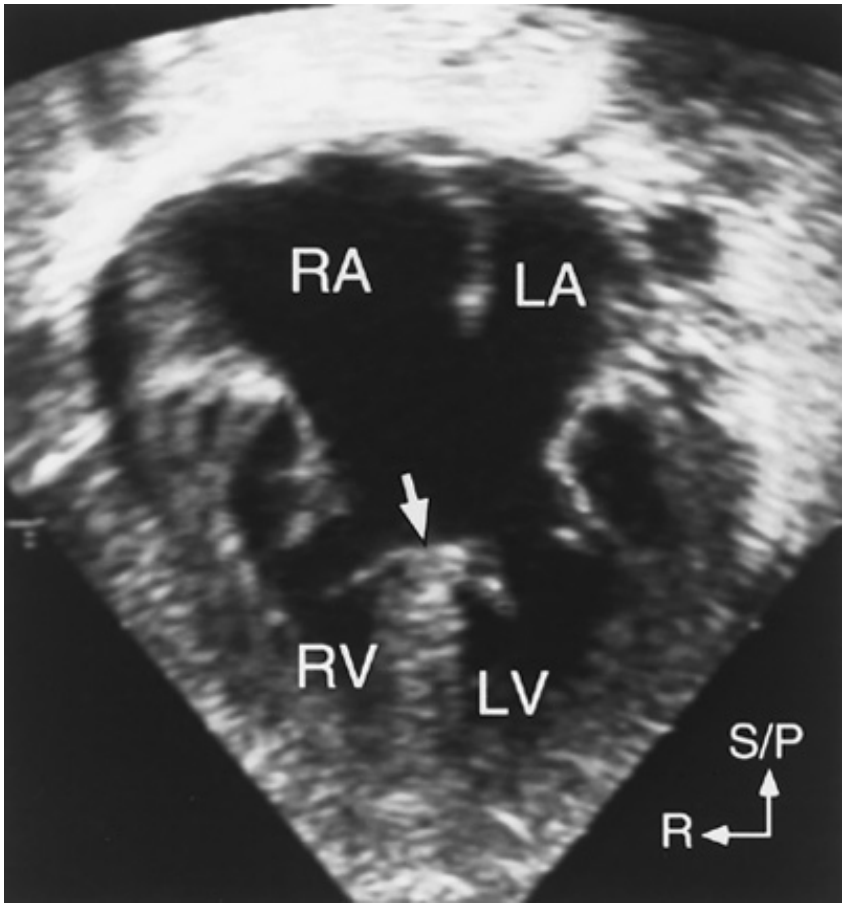

Figure 63-15: Apical four-chamber view of complete common AV canal. Note the large deficiency of both atrial and ventricular septa as well as apical displacement of the AV valves. The arrow points to the attachment of the inferior bridging leaflet to the ventricular septal crest. (From Levine J and Geva T.[85] Reproduced with permission.)

Cardiac Catheterization

Cardiac catheterization rarely is performed if the echocardiogram is characteristic and if the history, clinical examination, and echo suggest a large left-to-right shunt and low pulmonary resistance. When it is performed, a significant increase in oxygen saturation between the superior vena cava and the right atrium is present. A right ventricular or pulmonary arterial systolic pressure in excess of 60 percent of the systemic systolic pressure favors the presence of a complete canal. With a large communication between the two ventricles below the AV valves, the right ventricular, pulmonary arterial, and systemic arterial systolic pressures are virtually identical. Left ventricular angiography in the frontal view demonstrates the "gooseneck deformity" of the left ventricular outflow tract that is characteristic of AV canal malformations and allows a semiquantitative assessment of the degree of mitral regurgitation and shunting from the left

ventricle to the right atrium. The left anterior oblique view with craniocaudal angulation is recommended for visualizing the interventricular defect and judging the extent of ventricular septal deficiency. Aortography is essential to eliminate the possibility of a PDA if the echocardiogram was not diagnostic.

NATURAL HISTORY AND PROGNOSIS

Partial defects without significant mitral regurgitation follow a course similar to that described for the secundum type of septal defects. An exception would be the greater likelihood of infective endocarditis because of the mitral valve deformity. Moderate or severe mitral regurgitation produces heart failure with resulting symptoms and growth retardation. Infants with a complete AV canal without protective pulmonary stenosis quickly develop and continue to have congestive failure until the course is altered by death, the development of PVOD, or surgical intervention.

MEDICAL MANAGEMENT

Children with an uncomplicated partial defect are managed in the same manner as children with an uncomplicated ASD. Those who are symptomatic should undergo early surgical closure of the primum ASD and, if possible, plication of the cleft in the septal commissure of the left AV ("mitral") valve. The few patients with significant residual mitral regurgitation after surgery are managed medically until mitral valve replacement is appropriate. Those without symptoms are repaired before they start school.

The approach to an infant with complete AV canal is the same as that for an infant with a large VSD but is tempered by the knowledge that spontaneous improvement is very unlikely except at the expense of the pulmonary vascular bed. Repair is recommended early if there is significant congestive heart failure or between 4 and 6 months of age if the pulmonary arterial systolic pressure is greater than half the systemic arterial systolic pressure. Elevation of pulmonary vascular resistance in the first year of life warrants surgical intervention without delay.

With regard to genetic counseling, the risk of a subsequent sibling having heart disease in the presence of a single affected family member is in the range of 2 percent; it is probably higher for the offspring of an affected parent, particularly if that parent is the mother.[86] Concordance for AV canal defects among affected siblings or offspring is much higher than it is with other forms of congenital heart disease and approaches 90 percent.

SURGICAL MANAGEMENT

The remarkable clinical improvement that follows anatomic repair of complete common AV septal defects in infancy encourages early correction within the first year of life. Banding of the pulmonary artery in a critically ill infant with a large interventricular defect was used in the past but has been replaced by a more reparative operation in most centers. The specifics of repair are dictated by anatomic detail: Individual variation is considerable (Fig. 63-16), but the creation of a competent, nonstenotic left-sided AV ("mitral") valve is essential for an acceptable early and long-term prognosis.

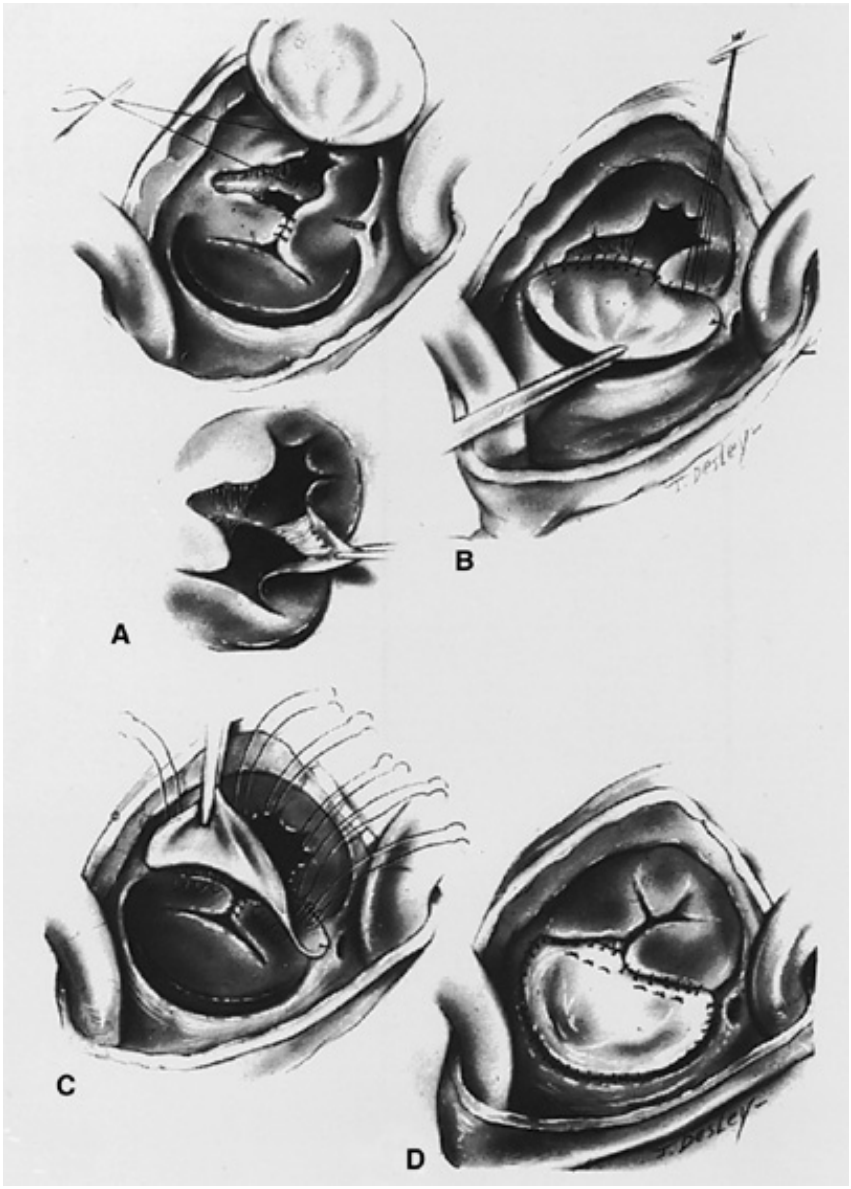

Figure 63-16: Steps in the repair of the complete form of common AV canal, type A. *A* and *B.* A pericardial patch is sutured to the ventricular septum. *C* and *D*. The anterior leaflet of the mitral valve is reconstructed and attached to the patch. A portion of the tricuspid leaflet is attached to the patch. (From Rastelli GC et al.[82] Reproduced with permission from the publisher and authors.)

A patch usually is sutured to the right side of the ventricular septum to obliterate the interventricular communication. The anterior and posterior components of the common valve are divided, and the mitral valve is sutured to the patch at an appropriate level. The "cleft" between the left anterior and left posterior leaflets should be closed by suturing if approximation of these edges appears to increase competence without the creation of stenosis. Prosthetic valve implantation rarely is required during primary anatomic repair.[87] The right-sided AV ("tricuspid") apparatus, although less critical to survival, is repaired using the same principles. The interatrial communication usually is closed with a separate piece of pericardium to minimize hemolysis in the presence of residual mitral regurgitation.[87] Mitral valve competence is assessed by gentle distention of the left ventricle with cold saline.

A partial AV canal is repaired through a right atriotomy. The cleft may be closed with a few simple interrupted sutures to encourage inversion and coaptation of the leaflet margins. The ASD usually is closed with a pericardial patch.

Permanent complete heart block once contributed substantially to early mortality and morbidity but is now rare. Patients undergoing repair of a partial AV canal should be observed for the possible development of subaortic left ventricular outflow tract obstruction caused by redundant or residual endocardial cushion tissue.

In-hospital mortality after correction of a complete AV canal in infancy ranges from 3 to 10 percent;[88,89] the highest mortality is encountered during the first few months of life and in infants with severe AV valve regurgitation, elevated pulmonary vascular resistance, hypoplasia of the left or right ventricle, or other cardiac malformations. At Children's Hospital in Boston, 191 children with a median age of 4.6 months were repaired between January 1990 and December 1998 with an operative mortality of 1.5 percent. Reoperation was necessary in 22 patients (11.7 percent), a mean of 20 months later: 18 for residual mitral regurgitation and 4 for left ventricular outflow tract obstruction.[90] Successful correction of a complete AV canal can be accomplished despite associated tetralogy of Fallot, double-outlet ventricle, and other complex anomalies.[87]

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Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

EXTRACARDIAC COMMUNICATIONS BETWEEN THE SYSTEMIC AND PULMONARY CIRCULATIONS, USUALLY WITHOUT CYANOSIS

Patent Ductus Arteriosus

DEFINITION

Patent ductus arteriosus, the most common type of extracardiac shunt, represents persistent patency of the vessel that normally connects the pulmonary arterial system and the aorta in a fetus (Fig. 63-17).

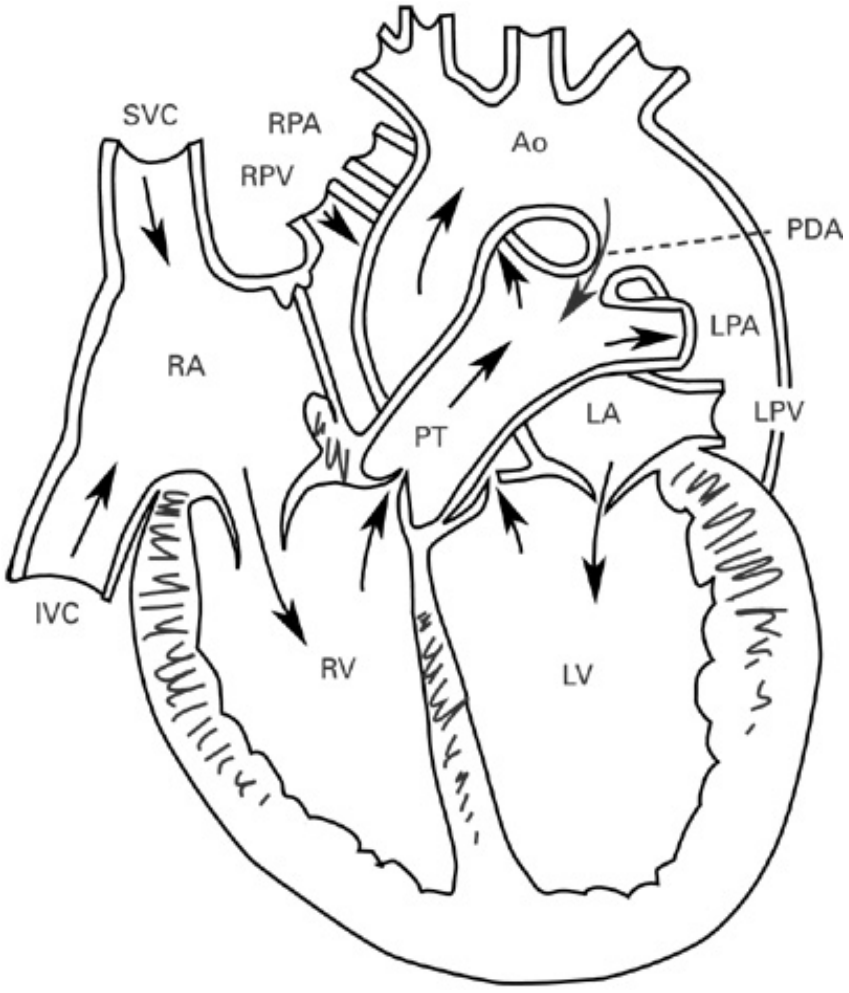

Figure 63-17: Patent ductus arteriosus (PDA). SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; PT = main pulmonary arterial trunk; RPA = right pulmonary artery; LPA = left pulmonary artery; RPV = right pulmonary vein; LPV = left pulmonary vein; LA = left atrium; LV = left ventricle; Ao = aorta. (From Edwards JE.[66]

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PATHOLOGY

The ductus arteriosus usually closes within 2 or 3 days after birth and becomes the *ligamentum arteriosum*, but it may remain patent as long as 8 weeks postnatally. It runs from the origin of the left pulmonary artery below to the lower aspect of the aortic arch just beyond the level of origin of the left subclavian artery above. The recurrent branch of the left vagus nerve hooks around its lateral and inferior aspects. Closure postnatally involves a complex interaction of increased oxygen tension in the blood and circulating prostaglandins. Exogenous PGE_1 has been used extensively to keep the ductus open postnatally,[91] and indomethacin, a prostaglandin inhibitor, can close the ductus in many premature infants in whom persistent patency is disadvantageous.[92]

ABNORMAL PHYSIOLOGY

Patients with PDA may be divided into groups according to whether the vascular resistance through the ductus is low, moderate, or high. The resistance of the ductus is related not only to its cross-sectional area but also to its length. In patients with a very small ductus that offers high resistance, the flow across the ductus is relatively small. The extra volume of work on the left ventricle is small, and the pulmonary pressure and resistance are not elevated. Patients with only moderate resistance in the ductus have some increase in pulmonary artery pressure, with a moderately greater volume of shunting across the ductus.

In patients with a large patent ductus, the aorta and pulmonary artery are essentially in free communication; the systolic pressure in the pulmonary artery is equal to that in the aorta. The volume load of blood recirculating through the lungs is on the left ventricle, with pulmonary congestion resulting from increased pulmonary flow and/or left ventricular failure. With time, the left ventricle compensates with dilation and hypertrophy to carry the volume load, and the pulmonary vasculature may respond to the high pressure (see the section on PAH, above). The right ventricle is burdened mainly by a pressure load.

If the pulmonary resistance equals or exceeds the resistance of the systemic circulation, there is shunting of unsaturated blood from the pulmonary artery to the aorta, resulting in hypoxemia, especially in the lower body and legs.

CLINICAL MANIFESTATIONS

History

The history of the mother's pregnancy and of perinatal events may provide clues that are associated with a high incidence of PDA, such as exposure to rubella in the first trimester in a nonimmunized mother. PDA is also more common in premature infants, especially those with birth asphyxia or respiratory distress.[93]

Symptoms usually are restricted to patients with large shunts that produce heart failure or with other complicating problems, such as respiratory distress in a premature infant. The symptoms related to heart failure were discussed above. Heart failure is most likely to develop in the first few weeks or months of life. If it does not appear during infancy, it is unlikely to occur before the third decade. Growth may be affected in those with large shunts and failure. The clinical presentation in a premature infant is usually very different from that in a full-term infant, particularly in those with a birth weight under 1.5 kg, who are more likely to have moderate to severe respiratory distress. In these infants, the clinical features of respiratory distress often blend over the course of several days into those of heart failure. Increasing ventilatory or oxygen

requirements with carbon dioxide retention or episodic apnea and bradycardia are often the first signs that a PDA may be complicating the picture.

Physical Examination

In a full-term infant or child with PDA, there is frequently a systolic thrill over the pulmonary artery and in the suprasternal notch. The peripheral pulses are generally brisk and bounding, especially with the larger shunts secondary to runoff from the aorta to the pulmonary artery in diastole. A patient with elevated pulmonary vascular resistance and a right-to-left shunt will have "differential cyanosis," with cyanosis and clubbing of the toes but not the fingers, from shunting of hypoxemic blood from the pulmonary artery into the descending aorta. The apex impulse may be increased or displaced in those with large shunts. The right ventricular impulse is increased in a premature infant with respiratory distress and in infants and children with significant pulmonary hypertension. The typical murmur is a continuous, or "machinery," murmur that is best heard at the left upper sternal border and below the left clavicle. It is usually a rough murmur with eddy sounds, which are helpful in making the diagnosis, and it peaks at or near the second heart sound. In patients with at least a moderate shunt, there is a middiastolic rumble at the apex as a result of relative mitral stenosis from increased flow across the mitral valve. The second heart sound may be difficult to hear because of the continuous murmur, but it is usually normal. The pulmonary component is accentuated in those with pulmonary hypertension.

Chest Roentgenogram

Findings on chest roentgenography also are dependent on the magnitude of the shunt. In patients with a small shunt, the chest roentgenogram is normal. With larger shunts, the left atrium and left ventricle are enlarged. Increases in pulmonary arterial flow on x-ray parallel the magnitude of the shunt. In the presence of heart failure, there are signs of pulmonary edema. In older patients who have developed Eisenmenger physiology, the only abnormality may be marked prominence of the central pulmonary arteries, with rapid tapering to the periphery of the lung fields.

Electrocardiogram

With a small shunt, the ECG is normal. Left atrial hypertrophy is probably the most common abnormality found, but left ventricular hypertrophy of the volume overload type, with deep Q waves and increased R-wave voltage in the left precordial leads, is also common as the shunt size increases and left ventricular dilation occurs. Right ventricular hypertrophy is seen with pulmonary hypertension.

Echocardiogram

There is left atrial enlargement, and the left ventricular end-diastolic dimension and mean velocity of circumferential fiber shortening are increased significantly. Small shunts can be detected with color Doppler imaging with a typical spectral flow pattern into the pulmonary artery, while a larger ductus can be visualized with two-dimensional echocardiography. Occasionally, a trivial amount of flow is seen through the ductus as an incidental finding in those with or without associated heart disease.

Cardiac Catheterization

In those with typical, uncomplicated PDA, cardiac catheterization is not necessary. When catheterization is performed, the catheter usually passes preferentially from the left pulmonary artery into the descending aorta, except when the ductus is too small. The saturation is increased in the pulmonary artery compared with the right atrium and ventricle to a degree relative to the size of the shunt. The pulmonary arterial and right ventricular pressures are elevated in those with

a large ductus. The pulmonary vascular resistance is elevated in older patients who have developed changes in the pulmonary vascular bed. These patients also have diminished saturation in the descending aorta once the pulmonary resistance reaches a level that will reverse the shunt. Aortography will opacify the ductus and pulmonary arteries.

NATURAL HISTORY AND PROGNOSIS

The complications related to PDA include infective endarteritis, heart failure, and pulmonary hypertension with vascular damage. Infection of the ductus is a risk regardless of its size. This risk increases with the length of survival. This can lead to the development of a mycotic aneurysm with the potential to compress the recurrent laryngeal nerve, embolize septic material to the lungs, or rupture. Calcification of the ductal wall is common in adults.

In patients with large shunts, heart failure can cause significant morbidity and mortality, particularly in a premature and young infant, and sudden death can occur. Progressive damage to the pulmonary vascular bed can occur in some, but it rarely occurs to an irreversible degree in the first year of life. Once irreversible damage occurs, premature death in late adolescence or early adulthood can be anticipated.

With improved technology, children without associated heart disease are noted to have a trivial amount of flow through a very small (<1 mm) patent ductus. Frequently, the shunt is too small to produce an audible murmur. The natural history of this echo-Doppler-discovered ductus arteriosus without clinical findings is unknown, but most think it is benign since cardiologists have not noted patients with endarteritis in a "silent" ductus.

MEDICAL MANAGEMENT

Interruption of flow through the PDA is the ultimate goal of management. For those in congestive heart failure, usually premature infants, medical management with digoxin and diuretics with fluid restriction may play a minor role, but the ultimate aim is closure to prevent heart failure and promote growth in infants and prevent infective endarteritis and pulmonary vascular disease in older children.

For premature infants, treatment with indomethacin is usually the first-line therapy.[94] Successful closure depends on both the dosage and the timing of treatment, although the major determinants seem to be gestational and postnatal age rather than the concentration of the drug. Because of ductal reopening, serial treatment regimens may be necessary, especially in those weighing less than 1000 g at birth. There is increasing evidence that the administration of "prophylactic" indomethacin in infants weighing less than 1000 g at birth may be associated with a higher closure rate and a better outcome.[92] Indomethacin therapy has been associated with an increased bleeding tendency resulting from platelet dysfunction, decreased urine output secondary to renal dysfunction, and necrotizing enterocolitis.[92] For the very premature with a PDA, however, a trial of indomethacin is preferable to the other options.

For premature infants who failed to close their PDA with a course of indomethacin or for term infants with a persistent PDA, closure has been recommended. If the PDA is large, there is usually a large left-to-right shunt with congestive heart failure. In these infants, the indication for closure is heart failure and usually failure to thrive. Even in the absence of these indications, when a large PDA is associated with PAH, closure is recommended to prevent PVOD. In children with a smaller PDA with an audible murmur but no evidence of significant hemodynamic embarrassment, closure usually is recommended because of the incidence of bacterial endarteritis, which over a lifetime is in the range of 30 percent. For children with a PDA without a heart murmur, which usually is discovered incidentally when an echocardiogram is performed for other

reasons, the author does not currently recommend closure.

SURGICAL AND INTERVENTIONAL CATHETER CLOSURE

Surgery for a persistent PDA was first reported more than 60 years ago and is now done routinely in most centers. The safety and efficacy of this procedure even in very young children are well established, with risks that are very low (well under 1 percent), and success at interrupting flow is almost universal.

The PDA is exposed and mobilized through a small left thoracotomy in the fourth intercostal space.[95] Ductus obliteration is accomplished by division or ligation. A short, broad, or thin-walled ductus is divided between vascular clamps. The ends are closed with a continuous suture. A long, narrow, thick-walled ductus can be divided or ligated with two or three sutures spaced a few millimeters apart. The suture ligatures at each end are anchored superficially in the ductus wall to prevent migration and assure thrombosis and obliteration.

The fragile and thin-walled PDA of a premature infant is obliterated by gentle ligation with a thick suture to minimize disruption or, if small, by occlusion using metallic surgical clips. Extrapleural exposure is preferred by some surgeons. Ligation in the neonatal intensive care unit, avoiding transport to the operating room, is common. Transport from a remote intensive care unit to a cardiac surgical unit for ductus ligation on a "day-stay" basis is also efficacious.[96] Ductus obliteration offers clinical improvement in infants weighing as little as 500 g, with minimal operative risk, a reduced incidence of necrotizing enterocolitis, a reduced duration of intubation, and improvement in late survival.

Closure of a PDA in an adult requires particular caution; calcification and rigidity of the ductus wall complicate clamping. Placement of a Dacron patch over the aortic orifice of the ductus from within the aorta may be advisable.[97]

Recently, advances in less invasive surgery have been applied to the closure of a PDA using video-assisted thoracoscopic surgery. A miniaturized camera is inserted into the thorax, and through a separate tiny incision, a surgical stapler is inserted and a clip is placed across the PDA, interrupting flow. Among 230 patients, there was only 1 with minimal residual flow, 1 with persistent recurrent laryngeal nerve dysfunction, and no deaths, transfusions, or chylothoraces. The mean operating time was 20 min, and the hospital stay lasted only a couple of days.[98] At Children's Hospital in Boston, this procedure has been applied to premature infants as small as 575 g, with discharge from the hospital the day after the procedure in full-term infants and children.[99]

The PDA sometimes can be closed by interventional catheterization techniques. In 1971, Portsmann and Wierny introduced a rather complex methodology to plug a PDA by using a transarterial and transvenous approach employing very large catheters.[100] More recently, Rashkind and Cuaso introduced and others have since popularized the use of a double-umbrella device to plug a PDA,[101] but the large size of the delivery sheath of the Rashkind device makes it inapplicable to young and very small children. Gianturco coils-thin metallic wires glossed with Dacron that assume a coil configuration when released from a catheter-have become an attractive alternative (Fig. 63-18). They can be delivered through relatively small catheters and have been found to be quite effective, although their utility is limited in those <8 months of age with PDAs that are more than 3.5 or 4.0 mm at the narrowest point.[102] In the others using these coils, the results have been very promising, with a 90 percent success rate.

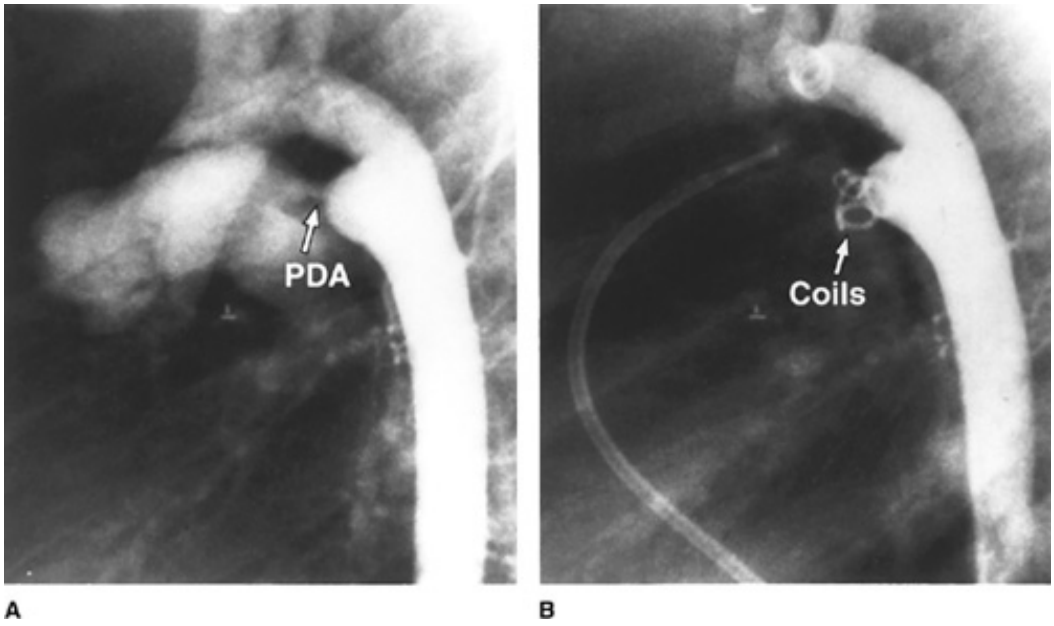


Figure 63-18: Lateral angiogram showing coil occlusion of a patent ductus arteriosus. *A.* Small PDA allows shunting from descending aorta to pulmonary artery. *B.* Shunting is eliminated by a coil placed in the ductus arteriosus. (Courtesy of John F. Keane, MD.)

With several highly successful, low-risk, inexpensive, and minimally traumatic procedures available to close a persistent PDA in a neonate, child, adolescent, or adult without pulmonary vascular disease, local experience is likely to be the best guide to which option is preferable in an individual child.

Sinus of Valsalva Fistula

PATHOLOGY

Sinus of Valsalva fistula is uncommon; it also is referred to as *aortic sinus aneurysm* (see also Chap. 88). Because of an assumed intrinsic weakness at the union of the aorta with the heart, the aortic media may separate from the aortic annulus and retract upward. The structure that lies between becomes aneurysmal and may rupture to form a fistula. The usual sites of the defects are the posterior (noncoronary) sinus aneurysms that rupture through the atrial septal wall into the right atrium (Fig. 63-19*A*) and those of the right sinus that rupture into the right ventricular infundibulum (Fig. 63-19*B*).[103] The aneurysm is represented by a colored pouch with multiple perforations in the wall. The principal associated condition is a supracristal VSD in cases with aneurysms of the right sinus (about 50 percent).

CLINICAL MANIFESTATIONS

Sinus of Valsalva fistulas are most common in adults.[104] When the rupture is secondary to bacterial endocarditis, evidence of a preceding infection is found. If the rupture occurs slowly, a small fistulous tract into the right atrium or ventricle develops and presents recent-onset findings of a small left-to-right shunt. With sudden rupture, there is usually a tearing pain in the midchest associated with the dramatically rapid development of pulmonary congestion caused by the sudden onset of a large shunt. Characteristically, the murmur is loud and continuous but is heard lower on the chest than is the murmur of PDA. A to-and-fro murmur rather than a continuous one may be heard at times. The apex impulse is hyperdynamic, and the pulse pressure is widened. VSD may complicate the clinical picture. Cardiac catheterization will confirm the level of the shunt. A pressure difference across the right ventricular outflow tract may be present if the right

sinus is involved. Aortography or Doppler echocardiography[105] will confirm the diagnosis.

NATURAL HISTORY AND PROGNOSIS

With slow rupture and a small shunt, the major risk is infective endocarditis or extension of the rupture with an increasing shunt. With a large shunt, the heart failure is usually rapidly progressive and may result in death very quickly. A few patients seem to stabilize in this situation.

MEDICAL MANAGEMENT

Appropriate cultures should be drawn and antibiotics should be begun if endocarditis is suspected. Treatment of heart failure should be instituted rapidly. *Because of the natural history, all patients should have this condition corrected surgically*.

SURGICAL MANAGEMENT

Aneurysms or fistulas from the noncoronary or right coronary sinuses are repaired through the aortic root while the patient is supported on total cardiopulmonary bypass with moderate hypothermia, using techniques similar to those employed for aortic valve replacement. The aortic valve leaflets, the margins of the aneurysm, and the coronary arterial orifices must be visualized precisely. Aneurysms of the noncoronary sinus can be repaired through the right atrium; those arising from the right coronary sinus are accessible through the right ventricle. In most cases, the orifice of the aneurysmal fistula is surgically obliterated, using a Dacron patch. In a recent series of 129 patients, reparative methods included plication (47 percent), patch repair (40 percent), and aortic root replacement (12 percent). Sixty percent of those patients needed aortic valve replacement at the same time.[104]

A conal, or supracristal (type I), VSD must be sought and closed through either the aortic valve or the right ventricular outflow tract when an aneurysm of the right coronary sinus extends into the right ventricle.

Surgical results are usually quite good. In the large series cited above, the operative survival was 96 percent with no late deaths in an average of 5.9 years of follow-up.[104]

PREVIOUS | NEXT

Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

VALVULAR AND VASCULAR MALFORMATIONS OF THE LEFT SIDE OF THE HEART WITH RIGHT-TO-LEFT, BIDIRECTIONAL, OR NO SHUNT

Coarctation of the Aorta

PATHOLOGY

Coarctation of the aorta is a discrete narrowing of the distal segment of the aortic arch. The characteristic lesion is a deformity of the media of the aorta that involves the anterior, superior, and posterior walls and is represented by a curtain-like infolding of the wall that causes the lumen to be narrowed and eccentric[106] (see Chap. 88).

In infants, the lesion lies either opposite the ductus or in a preductal location. In adolescents and adults, it is usually at the ligamentum arteriosum. An aberrant right subclavian artery may be associated. In rare cases, the narrowing lies proximal to the origin of the left common carotid artery or involves a segment of the abdominal aorta.

The principal cardiac abnormality is left ventricular hypertrophy. In some infants, left ventricular endocardial fibroelastosis may be associated. Tubular hypoplasia of the distal aortic arch and isthmus is very common, especially with associated cardiac abnormalities involving left heart obstruction.[107] The proximal aorta may show a moderate degree of cystic medial necrosis. Beyond the coarctation, the lining may show a localized jet lesion.

Prominent collaterals are characteristic in older infants, children, and adolescents. They may be divided into anterior and posterior systems, with the anterior system originating with the internal mammary arteries and making use of the epigastric arteries in the abdominal wall to supply the lower extremities. The posterior system involves parascapular arteries connected with the posterior intercostal arteries and carries blood to the distal aortic compartment principally for supply of the abdominal viscera. The anterior spinal artery, receiving branches from the proximal and distal compartments of the aorta, is also dilated and tortuous.

ASSOCIATED CONDITIONS

The most commonly associated defects are tubular hypoplasia of the aortic arch, PDA, VSD, and aortic stenosis (valvular and/or subvalvular). A bicuspid aortic valve is present in 46 percent of autopsy cases.[106]

ABNORMAL PHYSIOLOGY

In most instances, both the systolic and diastolic arterial pressures above the coarctation are elevated above normal levels. Below the coarctation, the systolic pressure is lower than that in the upper extremities, and the diastolic pressure is usually near or only slightly below the normal range. The mechanism of upper extremity hypertension appears to involve the increased resistance to aortic flow produced by the coarctation itself, the decreased capacity and distensibility of the vessels into which the left ventricle ejects, and humoral factors.[108]

CLINICAL MANIFESTATIONS

Coarctation of the aorta occurs in approximately 4 percent of all infants and children with congenital heart disease and is the predominant lesion in approximately 8 percent of infants presenting with critical heart disease in the first year of life. It ranks behind only VSD, dextrotransposition of the great arteries, and tetralogy of Fallot.[3] Among all individuals born with coarctation, approximately half present within the first month or two of life with heart failure. About 50 percent of infants so admitted have uncomplicated coarctation; the remaining half can be expected to have at least one complicating cardiac abnormality. VSD is the most common (64 percent), followed by left ventricular outflow tract obstruction (31 percent).[109] The timing of ductal tissue constriction in terms of both ductal closure and perhaps aortic constriction appears to play a decisive role in the onset or worsening of symptoms in most of these patients. The male/female ratio is approximately 3:1 for isolated coarctation but is only 1.1:1 for complicated coarctation. Approximately 45 percent of children with Turner's syndrome have coarctation.

History

The clinical picture in a symptomatic infant is one of dyspnea, difficulty in feeding, and poor weight gain. Older children are for the most part asymptomatic, although a few complain of mild fatigue, dyspnea, or symptoms of claudication in the legs when running.

Physical Examination

In a symptomatic infant, signs of congestive heart failure are characteristic. A gallop rhythm is common, and a murmur from associated defects or from the coarctation itself (posteriorly in the interscapular area) may be heard. Frequently, these murmurs are either inaudible or nondescript on admission and become characteristic only when congestive failure is brought under control. Prominent arterial pulsations may be visible in the suprasternal notch and carotid arteries, and the left ventricular impulse is forceful. An early systolic ejection click at the apex suggests the presence of a bicuspid aortic valve. The murmur from the coarctation is medium-pitched, systolic, and blowing in quality. It is best heard posteriorly in the interscapular area, usually with some degree of radiation to the left axilla, apex, and anterior precordium. Low-pitched, continuous murmurs of collateral circulation may be heard over the chest wall, particularly posteriorly, but seldom before adolescence. A short middiastolic rumble at the apex without clinical evidence of mitral disease is relatively common.

The characteristic systolic blood pressure difference between the upper and lower extremities may be difficult to appreciate or measure in infants with severe congestive failure or with a large VSD or PDA. With improved compensation, pulses in the upper extremities become readily palpable. The femoral pulses remain weak, delayed, or absent. In these very young infants, it is important that the pulses in both brachial and carotid arteries be assessed. Weak or absent pulses in all sites are more characteristic of critical aortic stenosis or aortic atresia.

In older children and adults, the radial arterial pulses typically are strong; those in the femoral arteries are diminished, delayed, or absent. A repeatedly measured systolic or mean pressure difference between the upper and lower extremities greater than 10 mmHg is diagnostic. The pulse pressure in the leg is reduced, and in some patients no pressure can be measured by auscultation or Doppler. Approximately one-third of older children have mild to severe hypertension, with severe hypertension defined as a systolic pressure above 150 mmHg, a diastolic pressure above 100 mmHg, or both. Some patients have only a mild pressure difference between the arms and the legs at rest but a much larger difference during treadmill exercise. A systolic pressure difference between the two arms suggests that the origin of one subclavian artery is at or below the obstruction, e.g., aberrent right subclavian from the descending aorta.

In light of the simplicity of measuring blood pressure in the upper and lower extremities of children and the importance of early detection, it is surprising and disappointing that approximately 95 percent of children and adolescents with coarctation are referred by pediatricians and other health care providers to a pediatric cardiologist for evaluation of a heart murmur and/or hypertension without this serious underlying malformation being recognized.[110]

Chest Roentgenogram

For a symptomatic infant, the pattern is one of impressive cardiac enlargement and venous congestion. In an older and asymptomatic child, the heart size is generally at the upper limits of normal with a left ventricular prominence. A figure-three configuration of the left margin of the aorta at the level of the coarctation may be seen in overpenetrated films, with the upper curve formed by the slightly dilated aorta just above the coarctation, the central indentation by the coarctation itself, and the lower curve by the poststenotic dilatation below the coarctation. Notching of the inferior margin of the ribs by tortuous intercostal arteries acting as collaterals is seldom present before 7 or 8 years of age.

Electrocardiogram

The ECG of a symptomatic infant reflects right or biventricular hypertrophy during the first 3 months of life. T-wave inversion in the left precordial leads is common. In older children, the ECG is usually normal or may indicate mild left ventricular and left atrial hypertrophy.

Echocardiogram

Two-dimensional echocardiographic imaging of the aortic arch from the suprasternal notch permits visualization of the coarctation and detection of anatomic variations such as isthmic or transverse arch hypoplasia. The precordial and subxiphoid views are of great value in assessing the presence and severity of associated defects. Doppler flow studies are helpful for diagnostic confirmation. In infants with heart failure, left ventricular dilation and decreased contractility are common. The severity of the coarctation can be evaluated by Doppler gradients and the diminished pulsatile flow in the abdominal aorta.

Cardiac Catheterization

Study of symptomatic infants characteristically reveals left atrial and left ventricular hypertension and a significant systolic pressure difference between the left ventricle and the femoral artery, particularly if the coarctation is isolated. In the presence of a large VSD and PDA, the left ventricular hypertension and the systolic pressure difference between the left ventricle and the femoral artery are less impressive and may not exist at all. Every attempt should be made to define the nature and severity of associated defects. Imaging is recommended in older children to demonstrate the exact site and length of the coarctation as well as to show unusual features of the collateral circulation that may be of importance to the surgeon. Magnetic resonance imaging is an excellent and in most instances preferable alternative to angiography today for demonstrating the site and length of the coarctation (Fig. 63-20).

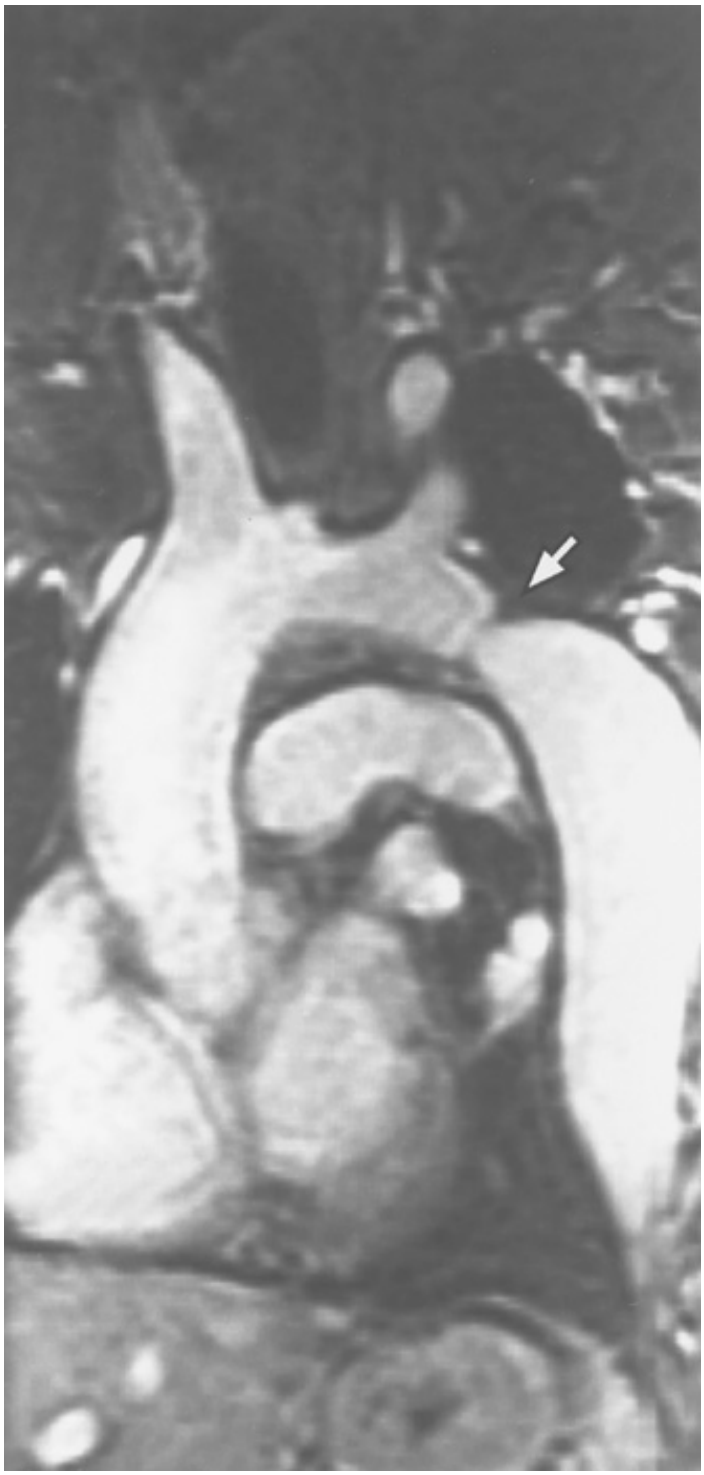


Figure 63-20: Selected frame from magnetic resonance angiogram in a child with discrete coarctation (*arrow*) distal to an enlarged left subclavian artery. (Courtesy of Andrew Powell, MD.)

NATURAL HISTORY AND PROGNOSIS

Approximately one-half of infants admitted with heart failure within the first weeks of life have coarctation without significant associated defects.[109] The majority of these infants respond well to medical management and, if no repair is performed, reach a stage at 2 or 3 years of age where they are indistinguishable from asymptomatic children of the same age whose coarctation is first detected during a routine physical examination. Upper extremity hypertension usually increases during the first several months of life and then tends to diminish again as collateral circulation

improves, while signs of failure diminish at the same time. For infants with severe failure and any serious associated defects, balloon dilation or surgery provides virtually the only chance of survival.

The consequences of persistent hypertension in an individual who has not undergone surgery appear in the second and third decades in the form of severe hypertension, aortic rupture, or intracranial hemorrhage from an aneurysm of the circle of Willis. Congestive heart failure that often is complicated by mitral or aortic valve disease, a dissecting aneurysm of the aorta, or atherosclerosis is seen in the fourth decade. The risk of endocarditis on the aortic or mitral valves or endarteritis at the site of coarctation appears to be spread relatively evenly over the years. The average age of death of patients who survive childhood with coarctation without surgery is 34 years.[111]

MEDICAL MANAGEMENT

Vigorous medical treatment is indicated for infants with severe heart failure. A newborn with severe failure may experience dramatic relief from the intravenous infusion of PGE_1 to reopen the closing ductus.[91] Prompt correction of the coarctation is recommended for all infants in whom there are one or more associated defects and for all infants with isolated coarctation unless the response to medical management has been dramatic and sustained.

The timing and type of correction of isolated discrete coarction of the aorta remain a topic of some dispute. There is general agreement that all children with congestive heart failure should be repaired after a brief period of stabilization and treatment of the failure. Since heart failure usually is limited to infants in the first few months of life and since balloon dilation of native coarctation in children under 6 months of age has had an unacceptable restenosis rate of up to 75 percent,[112] virtually all physicians would consider surgical repair the favored approach. For infants and children without congestive heart failure, the timing has been somewhat more problematic. Historically, the preferred approach was waiting until age 1 to 4 to avoid the problem of recoarctation that was found occasionally among patients corrected before 1 year of age[113] and residual or recurrent hypertension among patients without demonstrable recurrent coarctation, renal disease, or significant aortic regurgitation, which appears to be related to the duration of hypertension before surgery. More recently, the ability to reduce the restenosis rate has led some centers to reduce the age of elective surgical repair of coarctation to 3 to 6 months. For those in whom balloon dilation is contemplated, waiting until age 1 to 4 still seems appropriate.

Although there is general agreement that symptomatic children under 6 months of age with coarctation ought to be repaired surgically and that the first approach to those who develop restenosis at virtually any age should be balloon dilation or stent placement, the proper therapy for the treatment of native coarctation in children older than 1 year of age remains somewhat controversial. For balloon dilation, immediate success (defined as an increase in the coarctation diameter with a residual gradient of less than 20 mmHg) occurs in 80 to 95 percent of patients who are dilated, with the gradient reduction averaging 75 percent. However, long-term gradient relief after angioplasty has been somewhat less than that with surgery. Restenosis rates in the intermediate term seem to be directly related to the age at dilation, with 85 percent of neonates, 35 percent of infants, and 10 percent of children over 2 years of age developing restenosis.[112] Repeat dilation is almost invariably successful, and many advocate this approach even if it requires two dilations rather than a one-step surgical approach. Occasionally in older children a stent can be placed if the balloon dilation fails to persistently increase the luminal diameter (Fig. 63-21). In selected older children and adults, this has been very successful, with an average reduction in the gradient from 25 to 5 mm in 32 patients at Children's Hospital in Boston.[114] Complications usually have been related to associated diseases, although aneurysms, usually small, at the site of dilation have been reported in about 5 percent of cases. Large catheters are necessary, and trauma to the femoral artery is not uncommon.

Patients who have repaired coarctation need to be followed indefinitely. For those with significant recoarctation, expressed as a systolic pressure gradient between the upper and lower extremities of 20 mm or more at rest, balloon angioplasty and/or stent placement are recommended. Repeat surgery for recurrent coarctation is rarely necessary. Occasionally, patients are seen who have insignificant or small resting gradients but manifest abnormal upper extremity hypertension and significant gradients with exercise.[109] These patients probably should undergo balloon angioplasty and stent replacement with pharmacologic control of their hypertension if it is present at rest and beta blockade if the hypertension becomes significant with exercise.

SURGICAL MANAGEMENT

The coarctation is exposed and mobilized through a left posterolateral thoracotomy. It is usually possible to resect the narrow segment and restore continuity with a direct end-to-end anastomosis (Fig. 63-22). When the narrowed segment is longer, repair by subclavian flap aortoplasty or rarely a tubular vascular prosthesis to bridge the gap between the two ends of the aorta may be necessary. In adults with a relatively nonelastic or calcified aorta, a tubular vascular prosthesis can be used to bypass the unresected coarctation or the previous repair. Dacron patch repair of coarctation has an unacceptably high incidence of late aneurysm formation and is no longer advised.[115] Tension-free suture lines are essential. Postoperative bleeding, chylothorax, paraplegia, and injury to the phrenic and recurrent laryngeal nerves remain potential complications.[116]

If a significant VSD is also present, a pulmonary arterial band is placed at the time of coarctation repair during infancy. The VSD then may be repaired electively during the next several months, when the child's congestive heart failure is well controlled. Primary repair of the VSD shortly after or simultaneously with coarctation repair is a viable alternative that has been gaining favor recently.[117]

Adequacy of collateral circulation to the spinal cord is crucial for the safe repair of coarctation. A rise in proximal systemic arterial pressure of more than 20 mmHg when the aorta is clamped above the coarctation suggests a marginal collateral circulation. Mild systemic hypothermia is a simple and useful adjunct, and monitoring of somatosensory cortical evoked potentials may warn of an impending ischemic insult to the spinal cord.[118]

Postoperative paradoxical hypertension is common between the second and fifth postoperative days and may contribute to the *postcoarctation syndrome*, in which ileus, abdominal pain, mesenteric vasculitis, and even visceral infarction can occur. This syndrome rarely is encountered if the postoperative blood pressure is maintained within the normal range for age with sodium nitroprusside, a beta blocker such as propranolol, or captopril.

Operative mortality for infants with isolated coarctation is in the range of 0 to 3 percent [113,116,117] but is 10 percent or higher when other cardiovascular defects are present. Subsequent deaths are uncommon in surviving infants with isolated coarctation but are more likely in those with complicated associated defects.

Valvular Aortic Stenosis

DEFINITION

Aortic stenosis is defined as subtotal obstruction of varying severity in the channel of left ventricular outflow. In order of decreasing frequency, the sites of obstruction by congenital lesions are (1) valvular, (2) subvalvular, and (3) supravalvular (see Chap. 56).

PATHOLOGY

Most commonly, the aortic valve is bicuspid with two commissures, one or both of which are fused to varying degrees. A third rudimentary commissure, or raphe, is frequently present in the larger of the leaflets. The valve opening is eccentric. Less frequently encountered is a unicuspid, unicommissural, or noncommissural valve in which the orifice is often slitlike, at first glance suggesting a bicuspid valve. Uncommonly, a true dome is present, resembling the valve of congenital isolated pulmonary stenosis. Rarely, the valve is tricuspid with fusion of one or more of the three commissures. When survival to adult life occurs, calcification may appear in the valvular tissue, leading to rigidity of the valve. Poststenotic dilation of the ascending aorta occurs in all cases to some degree. Coarctation of the aorta is the most common associated anomaly.

ABNORMAL PHYSIOLOGY

The hemodynamics of congenital valvular aortic stenosis are similar to those of acquired aortic stenosis (see Chap. 56) except that a persistent PDA or stretched foramen ovale in the immediate postnatal period may lessen the severity of pulmonary edema by diverting blood away from the left ventricle.

Severity usually is judged by the peak systolic pressure gradient (PSPG) across the aortic valve, which is determined at cardiac catheterization, and the calculated aortic valve area. In the presence of a normal cardiac output, a PSPG ≥75 mmHg or an aortic valve area <0.5 cm^2/m^2 is considered severe, a PSPG between 50 and 75 mmHg or a valve area between 0.5 and 0.8 cm^2/m^2 is considered moderate, and a PSPG <50 mmHg or a valve area >0.9 cm^2/m^2 is considered mild (see Chaps. 15 and 56).

CLINICAL MANIFESTATIONS

About 7 percent of infants and children with congenital heart disease have aortic stenosis in one of its several forms, and approximately 80 percent of these patients have valvular aortic stenosis. Valvular stenosis is much more common among males than females, with a ratio of 4:1.

History

The detection of a systolic murmur leads to the discovery of this malformation in most patients, the vast majority of whom are asymptomatic. Easy fatigue, dyspnea, syncope, and angina suggest severe obstruction, but severe obstruction may exist in the absence of any symptoms. Sudden death may occur from this malformation, but in most such cases death is preceded by either symptoms or ECG changes. Infants with critical stenosis from birth present with congestive failure within the first week or two of life and represent true emergencies. A similar small number of patients with less critical but still very severe obstruction are detected over the course of the next 4 to 6 months.

Physical Examination

The arterial blood pressure and the quality of the peripheral arterial pulses of older infants and children are usually normal. A measured pulse pressure <20 mmHg suggests severe stenosis. The cardiac apex impulse may be forceful and sustained, and a systolic thrill along the right upper sternal border and over the carotid arteries is present in most of these patients. The absence of such a thrill at the right upper sternal border or suprasternal notch suggests a PSPG less than 30 mmHg. Paradoxical splitting of the second heart sound is rare and is associated with very severe obstruction or coexisting myocardial disease. An early systolic ejection click at the apex is characteristic and serves to distinguish valvular aortic stenosis from other forms of left ventricular

outflow tract obstruction. The classic auscultatory finding is a harsh systolic spindle-shaped murmur that is loudest at the right upper sternal border with radiation into the carotid arteries and down the left sternal border to the apex (see Chap. 56). Among infants with critical obstruction, there may be no palpable peripheral pulses and no distinctive murmur, with a return of weak pulses and a typical murmur only after decongestive therapy.

Chest Roentgenogram

The overall heart size is normal, but infants with failure will have generalized cardiac enlargement and varying degrees of pulmonary edema. Poststenotic dilatation of the ascending aorta is characteristic.

Electrocardiogram

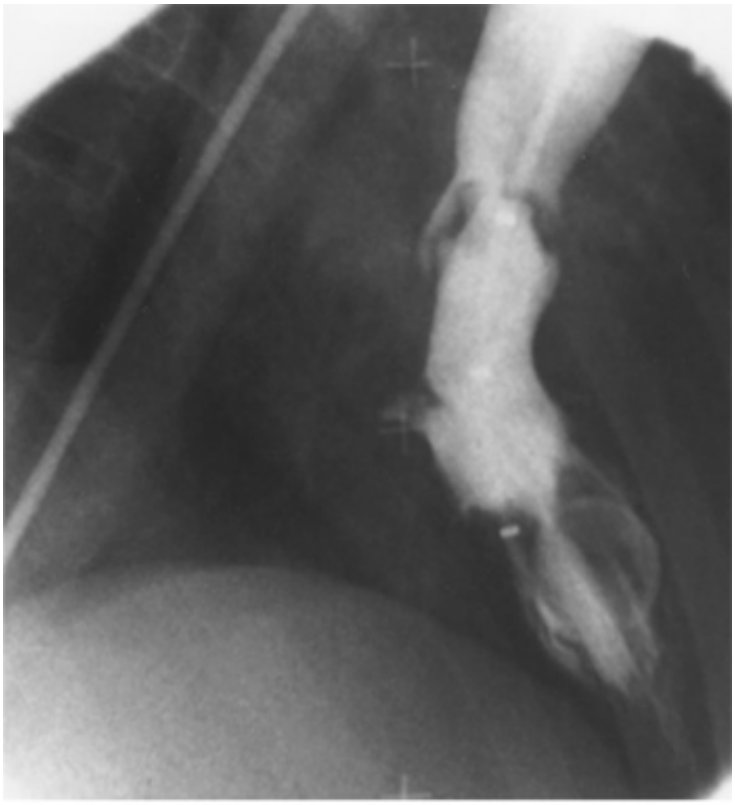
Left ventricular hypertrophy, as indicated by voltage criteria in the left precordial leads, is seldom helpful in distinguishing patients with severe obstruction from those with mild to moderate obstruction. However, diminished anterior forces in the right precordial leads and a deep $SV_1 \geq 30$ mm suggest severe stenosis, as does absence of the Q wave in V_6. Fifty percent of patients with severe obstruction have a flat, biphasic, or inverted T wave in V_6 (Fig. 63-23). Severe and even critical obstruction may be present with none of the ECG abnormalities mentioned above. Monitoring of the ST segment in leads V_5 through V_7 during cautious exercise testing appears to be a reliable method of detecting children in whom a significant PSPG (>50 mmHg) has developed and in whom that gradient may represent a threat of sudden death.[119] Symptomatic infants may show right, left, or biventricular hypertrophy, frequently with T-wave inversion over the left precordium.

Echocardiogram

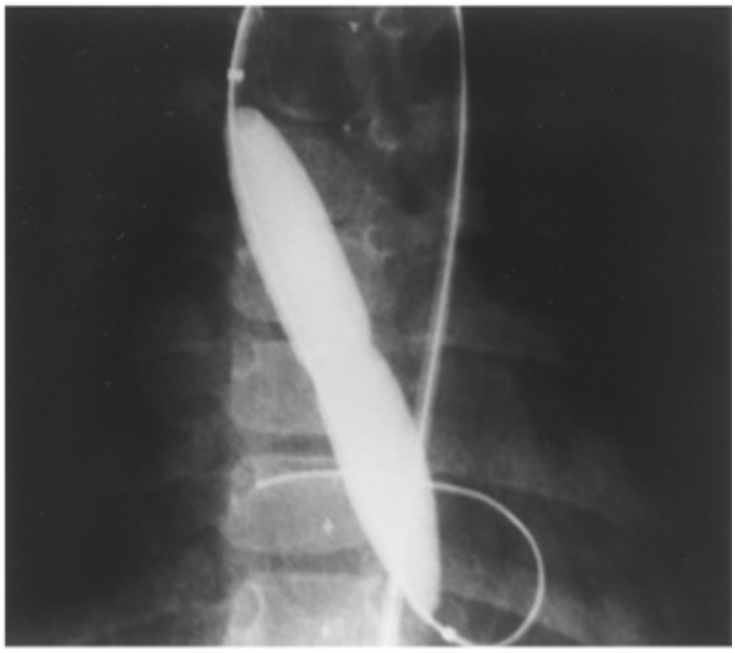
Continuous-wave Doppler echocardiography guided by two-dimensional echocardiographic imaging predicts very accurately the peak and mean instantaneous systolic pressure gradient across discrete forms of left ventricular outflow tract obstruction (see Chap. 13) (Fig. 63-24). Two-dimensional echocardiography can distinguish valvular from supravalvular or subvalvular obstruction and identify critically ill infants in whom the size of the left ventricle, mitral valve annulus, or aortic root is hypoplastic to a degree that would preclude survival.[120,121]

Cardiac Catheterization

Infants symptomatic with severe aortic obstruction often have a left-to-right shunt through a stretched foramen ovale, PAH, and a right-to-left shunt through a PDA. A marked increase in left ventricular end-diastolic pressure is usually present. The PSPG between the left ventricle and the central aorta should be documented whenever possible. If left ventricular output is markedly diminished, this gradient may be relatively small even in the presence of severe obstruction. Left ventricular angiography will confirm the site of obstruction and outline the size of the left ventricular cavity (Fig. 63-25*A*).



A



B

Figure 63-25: Balloon aortic valvuloplasty. *A.* Left ventricular angiogram showing a domed, thickened aortic valve with fusion of the right and left commissures. *B.* Balloon dilation using a retrograde technique. A waist is demonstrated in the midportion of the balloon before full inflation. (From Lock JE, Keane JF, Perry SB. *Diagnostic and Interventional Catheterization in Congenital Heart Disease.* Boston: Kluwer; 2000: 151.)

In older infants and children, pressures on the right side of the heart are usually normal. Simultaneous recording of central aortic and left ventricular pressures or a pressure tracing upon catheter withdrawal from the left ventricle to the aorta, coupled with an accurate estimate of

cardiac output, is necessary for reliable assessment of severity. Left ventricular angiography will document the site of obstruction. The aortic leaflets typically are thickened and domed, with a central or eccentric jet of contrast material entering the ascending aorta. Poststenotic dilatation is characteristic. Supravalvular aortography is recommended to assess the presence and severity of aortic regurgitation.

NATURAL HISTORY AND PROGNOSIS

About half the infants born with severe valvular aortic stenosis are symptomatic enough to require hospitalization within the first week of life. Not uncommonly, the murmur is mistaken for that of a VSD. Congestive heart failure beyond infancy and before adolescence usually is not seen without the presence of complicating factors. Symptomatic infants require prompt relief of obstruction by balloon or surgical valvotomy, but the mortality rate remains significant. Endocardial fibroelastosis, papillary muscle necrosis, associated intra- and extracardiac deformities, and a small left ventricular cavity contribute to this mortality rate. Survivors may have significant aortic regurgitation, but the majority can be managed medically until valve replacement is feasible.

Most infants beyond the newborn period and children with mild aortic valvular stenosis (PSPG at catheterization <25 mmHg or a Doppler mean pressure gradient <25 mmHg) remain stable, with only a 21 percent likelihood of progression in severity and the need for intervention within the subsequent 25 years. For patients with a PSPG between 25 and 49 mmHg, the likelihood of significant progression rises to 41 percent, and with a PSPG >50 mmHg, it rises to 71 percent.[122] Patients with a PSPG >50 mmHg are judged to be at risk of serious ventricular arrhythmias and sudden death. Infective endocarditis on the aortic valve (see Chap. 73) poses an extremely serious complication in the form of systemic arterial emboli and the production of serious and sometimes catastrophic aortic regurgitation with congestive failure, shock, and death.[60]

MEDICAL AND SURGICAL MANAGEMENT

Infants with the characteristic murmur detected in the first weeks of life should be evaluated very carefully to be certain the obstruction is not severe and does not become severe in the next few weeks or months.[123] Those who develop heart failure should be operated on or undergo balloon valvuloplasty without delay. In a critically ill neonate, intravenous PGE_1 infusion to open the ductus may provide temporary relief of pulmonary edema en route to the operating room or catheterization laboratory. Beyond infancy, a plan of reexamination with careful questioning regarding symptoms and an ECG each year, an echocardiogram with Doppler assessment of the mean and maximum pressure gradient every year or two, exercise testing, and 24-h ECG monitoring about every 3 years should suffice to prevent progression from going unrecognized. Indications for cardiac catheterization for gradient assessment and possible balloon dilation include the appearance of symptoms or syncope, decreased anterior forces with an $SV_1 \geq 30$ mm or flattening or inversion of the T wave in V_6 in the resting ECG, abnormal ST-T segments on exercise testing, or an estimated maximum instantaneous gradient of 65 mmHg or a mean pressure gradient >60 mmHg by echocardiographic Doppler techniques.

Transluminal catheter balloon valvuloplasty has become the acceptable alternative to surgery. In skilled hands, it can provide effective reduction of the transvalvular gradient while producing only a mild increment in aortic regurgitation in most instances.[124,125] Elective balloon dilation is recommended if the PSPG is >50 mmHg at catheterization and aortic regurgitation is mild or nonexistent. For a neonate with critical valvular obstruction, some centers continue to rely on surgical intervention, but catheter balloon valvuloplasty has become a very competitive alternative and in the author's institution is the procedure of choice for these very sick infants.

Balloon dilation has been performed since the mid-1980s, and long-term follow-up studies are not

yet available. Early studies and more recent experience suggest that the balloon diameter should not exceed that of the valve ring, and most centers now use balloons that are 85 to 90 percent of the diameter of the aortic annulus. The balloon usually is inflated to a pressure of 4 to 6 atmospheres until the "waist" produced by the stenotic valve has been abolished (Fig. 63-25*B*). Transient arrythmias are seen occasionally, but other than creating aortic regurgitation, other complications are uncommon.

In older children, the results are usually quite good, with a reduction of the peak gradient of approximately 60 percent, a mortality rate under 2 percent, and a complication rate of about 3 percent.[124,125] In neonates, the results are more problematic, probably because of severity of disease, unstable conditions, and the size of the patient, with 12 percent early and late mortality in one series. In this center, reintervention (usually repeat balloon dilation) was necessary in 40 percent with a mean follow-up of 4.3 years.[126]

When surgical intervention is required for critical aortic stenosis during infancy, the heart is exposed through a median sternotomy and the aortic valve is visualized through the ascending aorta during a brief period of low-flow perfusion with mild hypothermia. Standard cardiopulmonary bypass, mild hypothermia, and cardioplegia are used in older children.[127] The surgeon must discriminate between true commissures and abnormal raphes because incision of the latter produces intolerable aortic valvular regurgitation. Relief of valvular stenosis is accomplished with a carefully placed incision in the middle of each fused but well-supported true commissure.

A conservative attitude is essential during operation for aortic stenosis in an infant or small child. Mild valvular regurgitation almost always occurs consequent to commissurotomy but is usually well tolerated. Moderate residual stenosis is preferred to intolerable aortic valvular regurgitation, especially in infants in whom valve implantation is technically difficult. If valve replacement is necessary in an infant or small child, use of the autograft pulmonary valve in the aortic position offers the attractive possibility of continuing growth of this neoaortic valve that may parallel that of the patient.[128]

The risk of operation is high in critically ill infants, in the range of 10 to 15 percent, particularly in those with a low ejection fraction, high left ventricular end-diastolic pressure, endocardial fibroelastosis, marked congestive failure, or features of left ventricular hypoplasia.[129] Morbidity after aortic valvotomy in an older child is rare, and the likelihood of relief of left ventricular outflow tract obstruction and survival is good. The Natural History Study of Congenital Heart Defects, reporting on 133 children undergoing aortic commissurotomy after age 2 years, found that only 27 percent required a second operation in the subsequent 20 years, with 78 percent of those operations consisting of valve replacement. Aortic regurgitation was the indication for operation in 14 percent of those with valve replacements.[122]

Relief of aortic valve obstruction, whether by balloon valvuloplasty or surgical valvotomy, is palliative rather than curative. Gradual restenosis is the rule, with almost one-third of infants who undergo valvotomy requiring a second operation, usually valve replacement, within the next two decades. Aortic regurgitation, a well-recognized complication of valvuloplasty, valvulotomy, and/or infective endocarditis, may require surgical intervention as well. Endocarditis is a serious and lifelong hazard, with an incidence among patients followed for 20 years of approximately 5 percent, a mortality rate of just over 25 percent, and a predilection for patients in the second, rather than first, decade of life and with PSPGs >50 mmHg.[60,122]

Secondary valvulotomy by balloon or surgery for recurrent or residual stenosis can be attempted, but calcification and restenosis eventually force aortic valve replacement in almost all those requiring surgery on the aortic valve in infancy or childhood. A small aortic annulus severely limits the relief of left ventricular hypertension unless one resorts to Konno's operation, in which

the annulus is divided, the upper ventricular septum resected creating a VSD, patching the VSD with prosthetic material, and replacing the valve (a homograft or pulmonary autograft) into the enlarged annulus. The ascending aorta and anterior right ventricular wall are reconstructed using a prosthetic graft, and in the case of an autograft, the main pulmonary artery and pulmonary valve are replaced with a cryopreserved pulmonary homograft.[130]

Children with more than mild aortic stenosis are restricted from strenuous organized athletics, isometric exercises, and activities that require a good deal of stamina and produce shortness of breath.[131]

Supravalvular Aortic Stenosis

PATHOLOGY

The obstruction in the ascending aorta includes the following three types: (1) hourglass (discrete), (2) hypoplastic (diffuse), and (3) membranous. Associated obstructions in the pulmonary trunk, peripheral pulmonary arteries, and branches of the aortic arch are common.[132] Hypertrophy of the coronary arterial walls and premature coronary atherosclerosis have been described.[133]

CLINICAL MANIFESTATIONS

Supravalvular stenosis may be familial, associated with characteristic facies and mental retardation, sporadic, or (rarely) the result of congenital rubella. All forms may be and usually are associated with varying degrees of peripheral or branch pulmonary arterial stenosis. The familial form is transmitted as an autosomal dominant trait with variable expression (see Chap. 62). Mental retardation is not present, and there are no characteristic facial features.[134] Supravalvular aortic stenosis associated with mental retardation, frequently called *Williams' syndrome*, is associated with a high and prominent forehead, epicanthal folds, underdevelopment of the bridge of the nose and mandible, and a broad, overhanging upper lip. It is due to a deletion of the elastin gene on chromosome 7 and can now be identified by florescent in situ hybridization studies. It has been linked with idiopathic hypercalcemia of infancy, but in the majority of patients recognized beyond infancy, hypercalcemia is not present.[135]

The symptoms of supravalvular aortic stenosis are similar to those of subvalvular aortic stenosis (see below). Patients with the familial form usually have a distinctive family history but one that seldom emerges in its entirety on initial questioning. The physical findings are also similar to those of subvalvular aortic stenosis, although a systolic blood pressure difference may be recorded between the two arms on occasion, with the right arm pressure being greater than the left (Coanda effect).[136] Chest roentgenography and ECG are not distinctive unless associated pulmonary arterial stenosis leads to right ventricular hypertrophy. Echocardiography can identify the narrowed aortic lumen just above the aortic valve and provide an estimate of the severity of the obstruction by the Doppler-derived instantaneous pressure gradient.

At cardiac catheterization, a systolic pressure gradient can be demonstrated just above the aortic valve by careful pullback. Supravalvular aortography or left ventricular angiography will visualize the supravalvular narrowing (Fig. 63-26). Pressure recordings in the branch pulmonary arteries should be obtained, and pulmonary arterial angiography should be performed in the presence of any significant stenoses. Narrowing at the branch points of major arteries (coronary, carotid, mesenteric, renal, etc.) is seen occasionally.

NATURAL HISTORY AND PROGNOSIS

The sequence of progressive obstruction, the appearance of symptoms and ECG changes, and the

possibility of sudden death appear to apply for supravalvular aortic stenosis as well as for valvular aortic stenosis. Infective endocarditis represents a threat to these patients throughout life.

MANAGEMENT

The indications for cardiac catheterization and follow-up are the same as those with valvular aortic stenosis. Noninvasive imaging frequently suffices, but angiography may be necessary to evaluate the gradient and rule out arterial narrowing. Surgery usually is recommended if the gradient across the narrowing exceeds 40 mmHg.

Discrete supravalvular aortic stenosis is relieved by one or more incisions through the narrow segment of the ascending aorta, usually at the level of the sinotubular ridge at the top of the commissures. Incisions are extended well down into the aortic sinuses. Ridges of obstructing fibrous tissue are excised. The aorta is enlarged by the insertion of a gusset of prosthetic vascular graft material or pericardium to increase the circumference.[127] A favorable outcome can be anticipated postoperatively in most patients with supravalvular aortic stenosis if the arterial wall abnormality is localized.[137] Intimal obstruction of the coronary arterial ostia may require debridement, dilation, or even saphenous vein or internal mammary bypass grafting.

Diffuse tubular hypoplasia of the ascending aorta is a technically challenging problem that is associated with a higher mortality rate and usually poor postoperative hemodynamic results.

Subvalvular Aortic Stenosis

PATHOLOGY

Three classic varieties of subvalvular aortic stenosis involve the left ventricular outflow tract: the discrete, tunnel, and muscular types. The discrete type is characterized by a localized fibrous encirclement of the left ventricular outflow tract a short distance below the aortic valve (Fig. 63-27) or fibromuscular tissue that extends onto the mitral leaflet and also may attach to the aortic cusps. The tunnel type involves hypoplasia of the aortic annulus and a channel with a fibrous lining in the subjacent left ventricular outflow tract.[138,139] The muscular type also is known as *hypertrophic cardiomyopathy* (or idiopathic hypertrophic subaortic stenosis) and is discussed in Chap. 67.

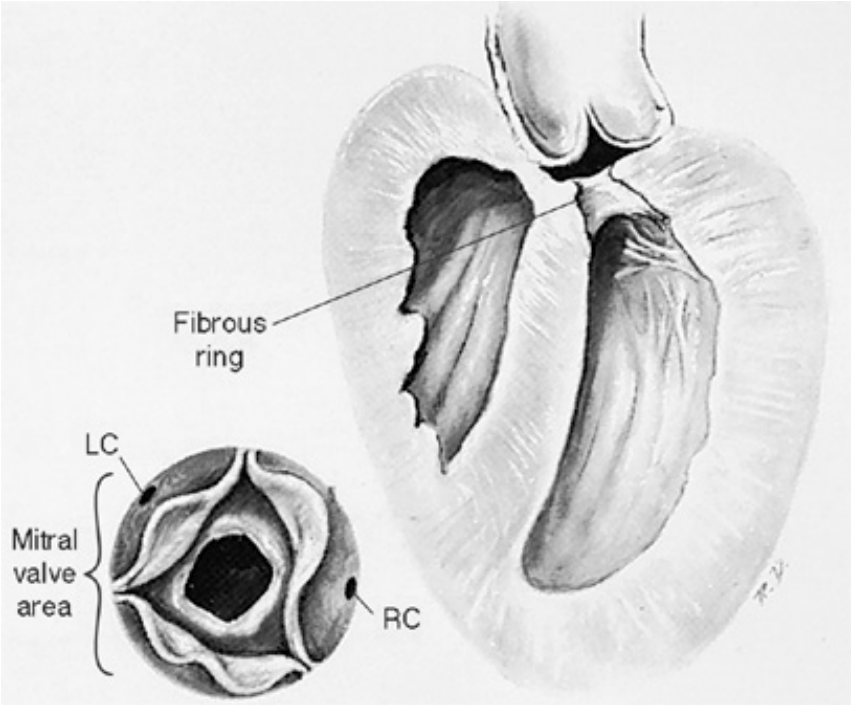


Figure 63-27: Localized subvalvular aortic stenosis. Obstruction is immediately upstream from the aortic valve. LC and RC = left and right coronary arteries. (From Kirklin JW and Ellis FH Jr.[144] Reproduced with permission from the publisher and authors.)

More than half these patients have associated malformations, of which PDA, VSD, or coarctation are the most common.

CLINICAL MANIFESTATIONS

Discrete stenosis is more common among males, with a male/female ratio of approximately 2.5:1. In the isolated forms, the majority of patients are referred because of the detection of a murmur that not uncommonly is mistaken initially for that of a VSD. The symptoms have the same implications as they do for valvular aortic stenosis.

The physical examination is similar to that of valvular aortic stenosis, with two exceptions: An early systolic ejection click is not heard, and an early diastolic murmur of aortic regurgitation is present in approximately one-half of these patients.

The roentgenographic features and ECG are also similar to those of valvular aortic stenosis except for the absence of poststenotic dilatation of the ascending aorta. Two-dimensional echocardiography permits excellent visualization of the anatomy of the obstruction. Estimation of the systolic pressure gradient can be obtained from Doppler echocardiographic studies.

When catheterization is performed, a careful pullback pressure tracing across the left ventricular outflow tract will document the severity of the gradient and establish the site of the obstruction. Left ventricular biplane angiography will outline the nature of the obstruction. Aortography is recommended to evaluate the degree of aortic regurgitation.

NATURAL HISTORY AND PROGNOSIS

Severe congestive failure in infancy is unusual and, if present, is almost invariably associated with complicating defects.[138] The obstruction is progressive in most instances, sometimes rapidly so. In one study, 75 percent of patients showed an increase of 25 mmHg or more in a 5-year

period.[140] The cause of the progression is not known, but an intriguing theory suggests that distorted anatomy increases shear stress, leading to a stimulation of growth factors and cellular proliferation.[141] Associated aortic regurgitation also tends to be progressive and appears to result from damage from the jet of blood through the obstruction, with secondary thickening and deformity of the valve leaflets. The results of surgery depend on the extent of involvement of the left ventricular outflow tract, with the best results being obtained in patients with a thin, discrete subvalvular membrane. The least satisfactory results occur in patients with tunnel obstruction.

MANAGEMENT

Medical management is similar to that of patients with valvular aortic stenosis, but surgery for the discrete type usually is recommended for pressure gradients ≥30 mmHg because of the possibility of progression of obstruction, and the likelihood of progressive aortic valvular deformity and regurgitation.[142]

Continued follow-up for assessment of reobstruction and progression of aortic regurgitation and for reemphasis of the precautions against infective endocarditis is essential in all patients.[143]

Subvalvular fibromuscular (membranous) left ventricular outflow tract obstruction is exposed through the aortic root as was described for aortic valvular stenosis (Fig. 63-27). Small half-circle needles and sutures or hooks are placed into the abnormal fibromuscular tissue, pulling it into view for precise excision from the underlying ventricular septum and the anterior mitral valve leaflet. The area of the bundle of His, which usually is just beneath the anterior commissure between the right and noncoronary leaflets, is avoided. An additional septal myectomy or myotomy beneath and to the left of the commissure between the right and left leaflets may be required if secondary hypertrophy is significant. Immediate and early operative outcome is generally good, but *residual, recurrent, and progressive subaortic obstruction occurs in up to 25 percent of these patients, requiring long-term follow-up*.[144,145]

Diffuse tunnel obstruction in the left ventricular outflow tract poses a difficult technical problem that requires aortoseptoplasty, reconstruction of the left ventricular outflow (Konno's operation or a modification of it).[130,142]

Bicuspid Aortic Valve

PATHOLOGY

Classically, the two cusps are oriented anteriorly and posteriorly, with the anterior or conjoined cusp being the larger. A raphe, or ridge, is present along the aortic aspect of the larger cusp, running from the aortic wall to the free edge of the cusp. The most common associated condition of significance is coarctation of the aorta. The most common complication is calcification of the valve. *In about 85 percent of cases of calcific aortic stenosis in patients below age 70, the valve is congenitally bicuspid*. Aortic regurgitation from prolapse of the larger cusp is a less common complication and is usually not evident until adolescence or adult life.

CLINICAL MANIFESTATIONS

The incidence in the general population approaches 2 percent; therefore, it is the most common congenital abnormality of the heart or great vessels except possibly for mitral valve prolapse (see Chap. 58). Its importance lies in its frequent association with other forms of congenital heart disease: the predisposition of the valve to become stenotic as a result of fibrosis and deposition of calcium over the course of years, the tendency of the valve to become regurgitant, its association with aortic root dilatation and dissection,[146] and finally, the susceptibility of the valve to infective

endocarditis. It is also common among patients with isolated or dominant aortic regurgitation, patients with infective endocarditis with or without a history of predisposing heart disease, and, probably most frequently, otherwise normal individuals who come to the physician's attention because of unrelated illnesses. Patients with uncomplicated bicuspid aortic valve are asymptomatic. The incidence among males is approximately 2.5 times that among females (see Chap. 56).

The characteristic feature is auscultatory and consists of an early systolic ejection click, which is best heard at the apex and does not vary with respiration. A soft, early, or midsystolic murmur is frequently present at the right upper sternal border. Less commonly, a soft murmur of aortic regurgitation may be heard. Two-dimensional echocardiography with adequate images can identify the bicuspid valve with a high degree of sensitivity and diagnostic accuracy.

NATURAL HISTORY AND PROGNOSIS

The majority of congenitally bicuspid aortic valves are nonobstructive at birth, but with the passage of time, a few of these valves become fibrotic, stiffer, and more obstructive and eventually become the site of calcium deposition, primarily among individuals between ages 15 and 65. Important calcium deposition is unusual before age 30, whereas grossly visible deposits of calcium are present in the valves of virtually all patients with severe stenosis beyond that age. A much smaller number of individuals born with a bicuspid aortic valve develop isolated aortic regurgitation. In approximately one-third, this is the result of fibrosis, prolapse, or retraction of one or both of the leaflets; in the remainder, regurgitation results from infective endocarditis on an apparently functionally normal bicuspid valve (see Chaps. 56 and 73).

Congenital Mitral Regurgitation

PATHOLOGY

Mitral regurgitation may be due to a primary valve abnormality or secondary to a more complex defect (see "Common Atrioventricular Canal Defects," above). There are a variety of rare primary malformations, including isolated cleft, fenestration, and double orifice. Mitral regurgitation also occurs frequently with conditions that cause left ventricular dilatation and failure.

CLINICAL MANIFESTATIONS

Poor growth, frequent respiratory infections, and failure occur with significant mitral regurgitation. The physical findings are generally similar to those with mitral regurgitation of other causes (see Chap. 10). There may be a prominent left precordial bulge if cardiomegaly has been present from infancy. The systolic murmur may radiate to the base of the heart. Left atrial and left ventricular enlargement correlate with the degree of volume overload. Echocardiography with Doppler color flow mapping will demonstrate these as well as left ventricular function and the severity of regurgitation. The specific defect may be outlined, such as an isolated cleft or a double-orifice valve. Findings at cardiac catheterization substantiate the hemodynamic alterations (see Chap. 15).

NATURAL HISTORY AND PROGNOSIS

Mild and even moderate mitral regurgitation may be well tolerated, but severe regurgitation leads to progressive deterioration. Endocarditis is a risk.

MANAGEMENT

Vigorous medical treatment of heart failure and infections is warranted. Every attempt should be made to control symptoms to a degree that will allow growth in infants. In infants and young children, only those with very severe and uncontrollable failure are subjected to surgery. In adolescents, continued symptoms justify surgery. Afterload reduction with an angiotensin-converting enzyme blocker may be tried. Surgery is indicated for congestive heart failure or deteriorating left ventricular function.

At surgery, the valve and its apparatus are inspected carefully. In many cases a valvuloplasty is possible, but occasionally replacement may be necessary. Currently, the St. Jude medical prosthesis often is utilized. Lifelong anticoagulation with warfarin (see Chap. 44) is required. With body growth, replacement with a larger prosthesis may be difficult, and no good annular enlarging operation exists.

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Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

VALVULAR AND VASCULAR MALFORMATIONS OF THE RIGHT SIDE OF THE HEART WITH RIGHT-TO-LEFT, BIDIRECTIONAL, OR NO SHUNT

Pulmonary Stenosis with Intact Ventricular Septum

PATHOLOGY

Valvular pulmonary stenosis with an intact ventricular septum usually is characterized by a dome-shaped stenosis of the pulmonary valve and less commonly by dysplasia of the valve. The valve may be unicuspid, bicuspid, or tricuspid. The annulus also may be narrow. The pulmonary trunk exhibits poststenotic dilatation. In adult patients, calcification of the valve may appear.

In pulmonary valvular dysplasia, the annulus of the valve may be abnormally narrow, but the most dramatic changes are related to the cusps, of which three are identifiable. The cusps are exceedingly thickened by mucoid and dense connective tissue.[147]

Concentric hypertrophy of the right ventricle is present, with its degree reflecting the degree of obstruction at the valve level. *The hypertrophy of the infundibular musculature may cause secondary infundibular stenosis*.

Less commonly, there may be isolated subvalvular pulmonary stenosis caused by infundibular narrowing or an anomalous muscle bundle across the middle of the right ventricle.[148] Both types may be associated with a VSD.

Isolated supravalvular pulmonary stenosis, or pulmonary arterial coarctations, also may occur. From angiographic studies, these are classified into four types: (1) *localized stenosis with poststenotic dilatation*, (2) *segmental stenosis*, (3) *diffuse hypoplasia*, and (4) *multiple peripheral stenoses*. The stenosis may be localized to any segment of the pulmonary arterial system. The process is unilateral in about one-third of cases and bilateral in two-thirds. Pulmonary arterial stenosis is commonly (about 75 percent), though not universally, associated with other cardiovascular abnormalities, such as tetralogy of Fallot. It also may be seen as a sequela of congenital rubella, Williams', Noonan's,[149] or Alagille's syndrome.

ABNORMAL PHYSIOLOGY

There is a pressure difference during systole between the main right ventricular cavity and the pulmonary artery. The area of the pulmonary valve orifice is normally 2 cm^2/m^2; it is about 0.5 cm^2 at birth and increases in size with body growth. In general, the effective valve area must be decreased about 60 percent before there is a hemodynamically significant obstruction to flow. PSPG may reach 150 to 240 mmHg in severe cases. The degree of obstruction is assessed by the peak and mean systolic pressure gradients and the amount of flow across the valve. In neonates, severe stenosis can be associated with a relatively small pressure difference if the flow is very low as a result of right ventricular failure. If pulmonary flow is normal, patients with PSPG at rest <40 mmHg have mild stenosis and patients with PSPG >75 mmHg have severe stenosis.

When the pulmonary stenosis is severe, the right ventricle may fail and the cardiac output may be decreased at rest; this is associated with elevation of both the right ventricular end-diastolic pressure and the right atrial mean pressure. This may cause the foramen ovale to open and allow shunting of blood from the right atrium to the left atrium, resulting in arterial oxygen desaturation and cyanosis. In most adolescent or adult patients with significant pulmonary stenosis, the resting cardiac output is within normal limits but usually does not increase normally during exercise. In contrast, younger children may be able to increase cardiac output during exercise, even with significant obstruction.[119,150]

CLINICAL MANIFESTATIONS

Pulmonary stenosis is one of the most common congenital heart defects and accounts for about 10 percent of patients in most large study populations (Table 63-1). The stenosis is at the level of the pulmonary valve in most instances, but it can occur within the right ventricle, in the pulmonary arteries, or in a combination of the two. Infants with severe stenosis with patency of the foramen ovale may have right-to-left shunting.

History

Most infants and children are asymptomatic, but a small percentage with very severe obstruction manifest symptoms, usually mild fatigue or shortness of breath with exertion. Young infants with critical obstruction present with cyanosis if there is a patent foramen ovale or ASD. Squatting and syncope are rare in childhood.[151]

Physical Examination

Patients with a dysplastic valve and occasional supravalvular stenosis have consistent noncardiac abnormalities in a familial syndrome described by Noonan,[149] with short stature, hypertelorism, ptosis, low-set ears, and mental retardation.

In older patients with valvular pulmonary stenosis, cyanosis is uncommon, except with severe obstruction and an atrial communication. Hepatomegaly and the murmur of tricuspid regurgitation may be present with severe obstruction. With at least moderate obstruction, a prominent a wave is seen on examination of the jugular venous pulse. A systolic thrill in the suprasternal notch and at the left upper sternal border is present with significant obstruction unless there is isolated subvalvular stenosis. The right ventricular parasternal impulse becomes increasingly forceful with more severe obstruction. *An early systolic click with expiration that disappears with inspiration heard at the left upper sternal border is the hallmark of valvular stenosis unless the obstruction is severe or the valve is dysplastic*. A click is not present with isolated stenosis at other levels. As the obstruction increases in severity, the pulmonary component of the second heart sound becomes progressively softer and more delayed, becoming inaudible when the right ventricular pressure reaches systemic levels or greater. The second heart sound is normal or accentuated with supravalvular stenosis. A fourth heart sound is heard if the obstruction is severe. The characteristic systolic murmur is harsh, crescendo-decrescendo in shape, and best heard at the left upper sternal border with radiation toward the left clavicle. The murmur radiates more to the axilla and back with supravalvular stenosis. The duration of the murmur and the timing of peak intensity correlate well with the severity of obstruction. With mild to moderate stenosis, the murmur peaks in midsystole and ends at or before the aortic component of the second heart sound. In patients with severe stenosis, the murmur peaks late in systole and extends beyond the aortic component of the second heart sound (see Chaps. 10 and 59).[151]

Chest Roentgenogram

Most patients have a normal or only slightly increased heart size, primarily of the right ventricle.

Significant enlargement is seen with critical obstruction and is an ominous sign. Characteristically, the main and proximal left pulmonary arteries are prominent as a result of poststenotic dilatation when the stenosis is valvular. This finding may be absent with very severe obstructions, with a dysplastic valve, in very young infants, or with stenosis above or below the valve. The pulmonary vascular pattern is normal in most of these patients, but the vascularity is diminished in those with a right-to-left shunt at the atrial level.

Electrocardiogram

Right ventricular forces in the anterior precordial leads correlate reasonably well with the degree of obstruction.[151] They are normal or demonstrate mild hypertrophy with an rsR′ pattern if there is mild obstruction. With severe stenosis, there is right axis deviation, right atrial hypertrophy, and very tall pure R waves in the anterior precordial leads. The presence of a qR pattern in these leads is almost always a sign of very severe obstruction. Those with a dysplastic valve frequently have a superior QRS axis.

Echocardiogram

Two-dimensional imaging allows identification of the level of obstruction, and Doppler studies provide an excellent measure of severity. Shunting at the atrial level also can be evaluated.[152]

Cardiac Catheterization

Diagnostic catheterizations are rarely necessary, but data obtained before balloon dilation demonstrate an elevated right ventricular systolic pressure with a distinct systolic pressure difference across the narrowed segment, as demonstrated by slow withdrawal of the catheter from the distal pulmonary arterial branches to the proximal right ventricle. Simultaneous measurement of systemic arterial and right ventricular pressures with measurement of flow is necessary to assess severity accurately. The right ventricular end-diastolic pressure and right atrial *a* wave may be elevated. Systemic oxygen saturation is diminished only in those with more severe obstruction and a patent foramen ovale or, less commonly, a true ASD. A left-to-right shunt at the atrial level is detected in some patients with mild to moderate obstruction. With valvular stenosis, right ventricular angiography demonstrates thickened and doming valve leaflets and a jet of contrast material entering the dilated pulmonary artery (Fig. 63-28*A*). Doming is not characteristic of the dysplastic valve. Infundibular subvalvular narrowing caused by muscular hypertrophy may occur secondary to the valvular stenosis or rarely as an isolated anomaly. Isolated anomalous muscle bundles in the right ventricle also may be seen. Pulmonary arterial angiography best demonstrates the sites of obstruction with supravalvular stenoses. Ventricular volume studies have demonstrated depressed ventricular function in patients with rightto-left shunts. Balloon dilation is discussed below under "Management."

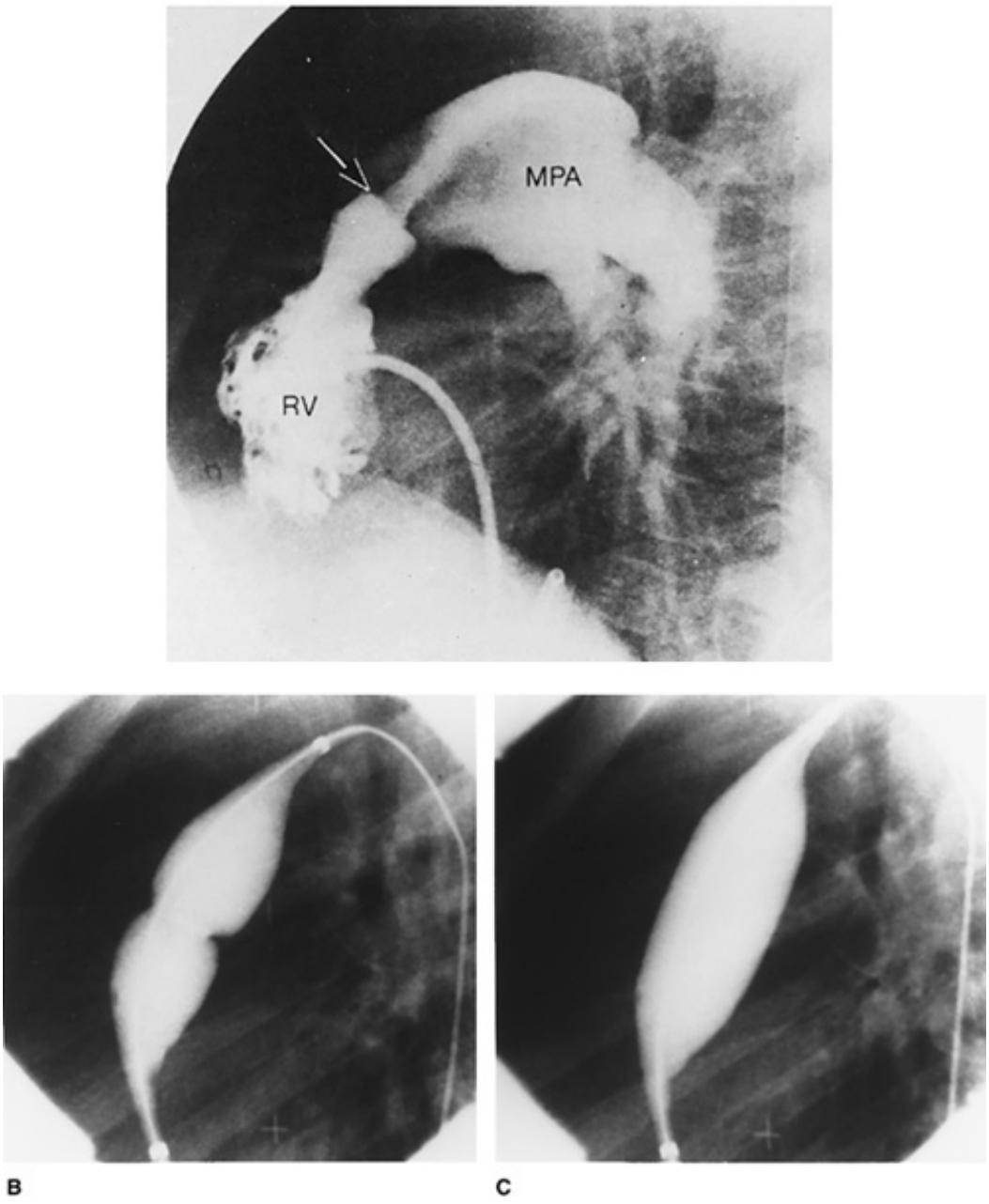

Figure 63-28: *A.* Lateral view of a right ventricular (RV) angiogram demonstrating the typical features of valvular pulmonary stenosis with doming of the pulmonary valve (*arrow*) and a narrow jet of contrast entering the dilated main pulmonary artery (MPA). *B.* An 18-mm balloon is inflated across the 14-mm annulus. A moderate waist is seen at 1 atmosphere of pressure. *C.* The waist is eliminated at 4 atmospheres of pressure. (From Lock JE, Keane JF, Perry SB. *Diagnostic and Interventional Catheterization in Congenital Heart Disease.* 2d ed. Boston: Kluwer; 2000.)

NATURAL HISTORY AND PROGNOSIS

The clinical course of valvular stenosis is favorable in most patients with mild to moderate obstruction. In a national cooperative study,[153] 86 percent of patients had no significant increase in their pressure gradients over a 4- to 8-year interval. Those with a significant increase were less than 4 years of age and had at least moderate stenosis initially. Progression during the period of growth seems to be the likely explanation for most of the increases, but a few patients developed subvalvular muscular hypertrophy, which increased the obstruction. Even mild obstruction may progress significantly in some infants during the first year of life. The prognosis of those with severe obstruction without intervention is poor, especially in infants with critical obstruction. With severe obstruction, right ventricular damage and dysfunction can ensue over the years, and heart

failure or arrhythmias can cause premature death in adults.[154] Tricuspid regurgitation also may result. Obstruction of the subvalvular type frequently increases with time, while supravalvular stenosis usually does not progress. Brain abscess can occur if a right-to-left shunt is present. Infective endocarditis with vegetations on the valve, pulmonary arterial wall, or infundibular region is also a risk. The children originally followed and treated as part of the national cooperative study cited above[151,153] were reevaluated 15 to 25 years later.[155] Among the 580 patients alive at the completion of the previous study, new data were available on 464 (78.4 percent). The probability of 25-year survival was 95.7 percent compared with an expected age- and sex-matched control group survival of 96.6 percent. Ninety-seven percent were asymptomatic. Although cardiac catheterization studies were not repeated, clinical examination and echocardiography at follow-up suggested no pulmonary stenosis in 2 percent, mild stenosis in 93 percent, moderate stenosis in 3 percent, and severe stenosis in only 1 percent. Pulmonary regurgitation was present in 40 percent, usually secondary to surgical valvotomy. Endocarditis was uncommon, as were ventricular arrhythmias.

MANAGEMENT

Management obviously depends on the severity of obstruction. For those with mild to moderate valvular pulmonary stenosis, periodic reexamination is indicated to detect any evidence of progression, with more frequent evaluation for those under 1 year of age. Measures to treat heart failure should be instituted in an infant with critical stenosis, but prompt intervention is mandatory. Cyanosis or a right ventricular systolic pressure well above systemic levels also is an indication for prompt intervention. Intervention is warranted in older children when the gradient exceeds 75 mmHg and is clearly not indicated when the gradient is less than 25 mmHg. *In the intermediate group, there is still some controversy, but general practice suggests valvuloplasty when the gradient exceeds 40 mmHg, although objective data to support therapy at this level are lacking*.

Balloon valvuloplasty has replaced surgical therapy as a first approach. Through the femoral vein, a balloon catheter is advanced across the valve and inflated to about 120 percent of the size of the pulmonary annulus, ripping the domed valve and thus relieving the obstruction (Fig. 63-28*B*).

The Valvuloplasty and Angioplasty of Congenital Anomalies Registry has published the combined results on 822 children.[156] Valvuloplasty resulted in improvement in most children with valvular obstruction, reducing the gradient from 71 ± 33 mmHg to 28 ± 24 mmHg. Valvuloplasty is, not surprisingly, less effective in children with a dysplastic pulmonary valve.[156,157] Complications were uncommon (5 in 822, or 0.6 percent), including two deaths. Valvuloplasty also has been performed in critical neonatal pulmonary stenosis with cyanosis caused by right-to-left shunting at the atrial level with a high success rate.[158,159] Subvalvular obstruction is less amenable to dilatation.

Peripheral pulmonary stenosis also has been occasionally amenable to dilatation, although the results are frequently less dramatic because of the multiple areas of stenosis and the fact that the complications, including pulmonary artery rupture, are more common.[160,161] Recently, stents have been used, with promising results,[161] in those with peripheral pulmonary artery stenosis in an attempt to keep open vessels that recoil back to normal size after the balloon is deflated. For those in whom there is isolated subvalvular stenosis or associated defects or in whom balloon dilatation has failed, surgical intervention is recommended.

The risk of death after pulmonary artery dilation is higher than that after dilation of the valve.[160] In the large collaborative study cited above, the death rate was 3 percent, although a more recent study from the author's institution found a mortality rate less than 1 percent among 400 cases.[162]

SURGICAL MANAGEMENT

Operation rarely is indicated for isolated pulmonary valvular stenosis; balloon valvuloplasty is virtually always successful in eliminating a clinically significant obstruction. A thickened, immobile, dysplastic pulmonary valve, however, is best treated by complete surgical excision (valvectomy). A small annulus is augmented with a pericardial or Dacron gusset.[163]

Subvalvular pulmonary stenosis is relieved through a right ventriculotomy, a main pulmonary arteriotomy, or a right atriotomy. Hypertrophic parietal and septal muscle bands constituting the fibrous orifice of the os infundibulum and obstructing moderator bands or muscle bundles within the body of the right ventricle are excised. Care is exercised to avoid injury to major coronary arterial branches. The right ventriculotomy usually can be closed by direct suturing, but a small oval patch of pericardium or Dacron can be used to prevent constriction of the outflow tract. Right ventricular function is compromised minimally by a small patch that does not extend across the annulus; larger patches to the pulmonary arterial bifurcation probably impair ventricular performance but may be necessary when there is associated annular or main pulmonary arterial hypoplasia. When possible, excision from the pulmonary artery or the right atrium is preferred to avoid ventricular injury. Excellent relief of right ventricular outflow tract obstruction can be expected after resection. Mortality and significant morbidity are rare.

Stenoses of main or extraparenchymal branch pulmonary arteries can be relieved by pericardial, synthetic, or homograft aortic or pulmonary arterial patches if the obstruction is proximal. Proximal coarctations in the larger portion of the arterial tree are more readily corrected than are those in small distal branches beyond the bifurcation of either the right or the left pulmonary artery, where results are poor.[164] In these instances, catheter balloon angioplasty, although certainly not without risk, offers nonsurgical relief of obstruction even in the small pulmonary arterial branches and should be considered the procedure of choice for distal pulmonary arterial stenoses.[160,161]

Prophylaxis against infective endocarditis is recommended for all patients whether or not surgery is performed, although the risks seem to be lower than they are with many other congenital anomalies.

Tetralogy of Fallot

PATHOLOGY

Tetralogy of Fallot is characterized by biventricular origin of the aorta above a large VSD (Fig. 63-29), obstruction to pulmonary blood flow, and right ventricular hypertrophy. Fibrous continuity of the aortic origin and the anterior mitral valve is maintained.[66]

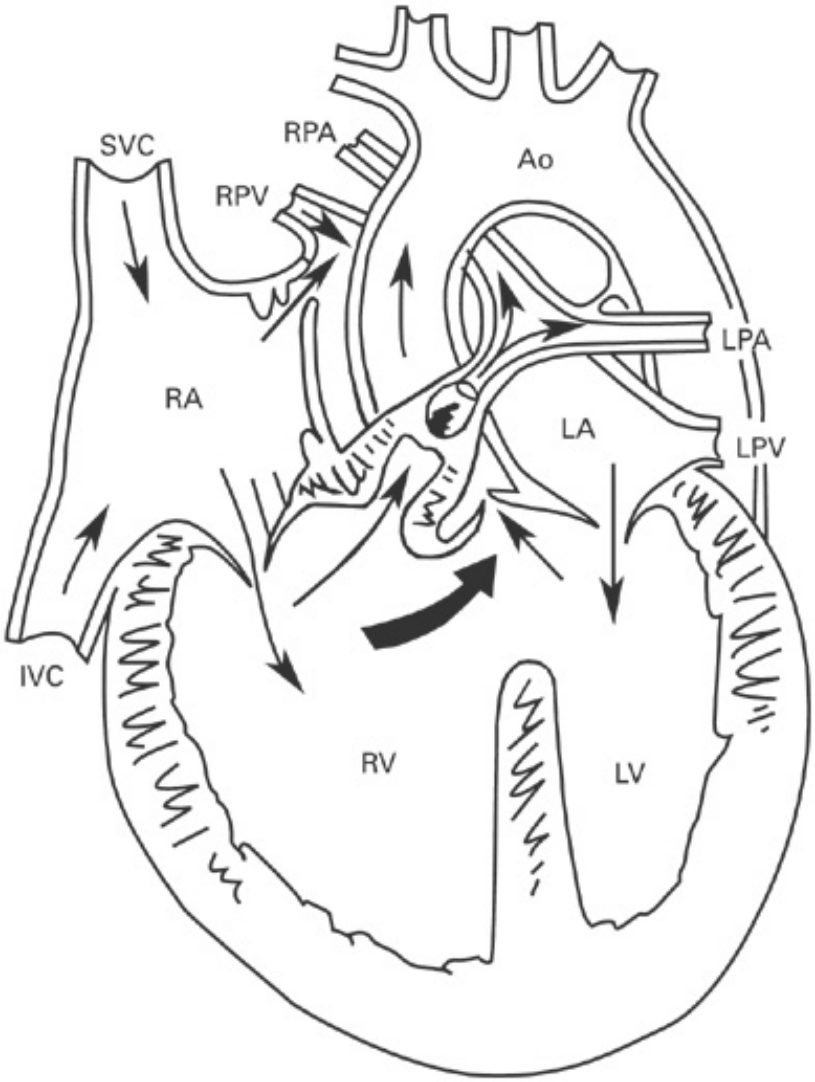

Figure 63-29: Classic tetralogy of Fallot. There are infundibular and pulmonary valvular stenoses. There is also right-to-left shunting at the atrial level. SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; RPA = right pulmonary artery; LPA = left pulmonary artery; RPV = right pulmonary vein; LPV = left pulmonary vein; LA = left atrium; LV = left ventricle; Ao = aorta. (From Edwards.[66] Reproduced with permission from the publisher and author.)

The right ventricular infundibulum lies anterior to the position of the VSD and is bounded by the anterior and septal walls anteriorly and medially; the posterior wall is said to be a vertical crista supraventricularis or displaced conus septum.[165] The right ventricular infundibulum is a distinctive channel, but the caliber varies widely from only mild obstruction to atresia. Usually, it exhibits a significant degree of stenosis and is the dominant site of the obstruction to pulmonary flow that is characteristic of tetralogy.

The pulmonary valve is often malformed, usually being either bicuspid or unicuspid. That valve may contribute to pulmonary stenosis, but only uncommonly is it the only site of significant obstruction to pulmonary flow. Characteristically, the pulmonary trunk is thin-walled and its lumen is more narrow than normal, but usually it is wider than either the right ventricular infundibulum or the orifice of the pulmonary valve. The aorta is wider than normal, its change in caliber being roughly opposite to that of the pulmonary trunk. The foramen ovale is frequently patent in patients of all ages. In all cases of tetralogy with significant pulmonary obstruction, collateral branches to the lungs arise from the aorta.

There is invariably a large malalignment VSD. Anterior, middle, or apical muscular defects are also present in up to 5 percent of children seen as infants. Many close spontaneously, but if corrective surgery is to be performed successfully, they must be evaluated.

Coronary artery abnormalities are not uncommon. The anterior descending coronary artery in the interventricular septum may arise from the right instead of the left coronary artery. Although physiologically unimportant preoperatively, the course across the right ventricular outflow tract makes the usual site of right ventriculotomy and outflow patch unavailable during reparative surgery, frequently necessitating a conduit to "jump over" the vessel. The anatomy of the coronary circulation used to require angiography to establish, but more recently echocardiography with Doppler color flow has been sufficient to detail the distribution of the proximal coronary circulation in most cases.

ASSOCIATED CONDITIONS

The condition most commonly associated with tetralogy of Fallot is right aortic arch (about 30 percent).[166] A persistent left superior vena cava has been described in 10.6 percent of cases. When an associated ASD exists, this anomaly is referred to as *pentalogy of Fallot.* The ductus arteriosus may be absent, present unilaterally on either the right or the left side, or bilateral.

ABNORMAL PHYSIOLOGY

Since the VSD is usually large, with an area about as great as that of the aortic valve, both ventricles and the aorta have essentially the same systolic pressures. The most important hemodynamic factor is the ratio between the resistance to flow into the aorta and the resistance to flow across the stenotic right ventricular infundibulum. If the stenosis is not severe, the resistance to right ventricular outflow is not large, the pulmonary flow may be twice the systemic flow, and the arterial oxygen saturation may be normal (acyanotic tetralogy of Fallot). However, the resistance to the pulmonary flow may be increased markedly, causing right-to-left shunting, arterial desaturation, and subsequent polycythemia. When the pulmonary stenosis is very severe, the pulmonary blood flow may be by way of collateral vessels from the systemic arteries to the distal pulmonary arteries beyond the stenosis. The infundibular obstruction, which may be in part dynamic, is increased by drugs, heart rate maneuvers, and activities that increase myocardial contractility or decrease right ventricular volume. In addition, the infundibular hypertrophy may increase gradually over time. Since the systolic pressure in the right ventricle cannot exceed that in the left ventricle because of the large VSD, the right ventricle is "protected" from excessive pressure and work, and so congestive heart failure is uncommon.

Hypercyanotic episodes (spells) in patients with tetralogy are of uncertain origin. It is likely that some episodes are caused by unusual hyperactivity of muscular fibers in the right ventricular outflow tract that produce or exaggerate the infundibular stenosis, increasing pulmonary resistance and thus increasing the right-to-left shunting. Some spells may be caused by a decrease in peripheral resistance and systemic arterial pressure, which also may cause the right-to-left shunt to increase and pulmonary blood flow to decrease.

CLINICAL MANIFESTATIONS

Tetralogy of Fallot is the most common congenital cardiac defect that causes cyanosis. Tetralogy with an associated ASD, or pentalogy of Fallot, is not distinguishable clinically. For a discussion on the hypoxemia and the consequences in tetralogy, see the section on cyanosis and its complications earlier in this chapter.

History

Most of these patients now are diagnosed prenatally by ultrasound or present in the first days or weeks of life with a heart murmur. If the right ventricular obstruction is severe, cyanosis is present at birth and is exacerbated when the ductus closes. If the obstruction is milder, the infant may be acyanotic with left-to-right flow through the VSD and occasionally may develop congestive heart failure. In this group, gradually increasing right ventricular obstruction may reduce the left-to-right shunt, and eventually, when infundibular resistance and pulmonary resistance exceed systemic resistance, right-to-left shunting develops, resulting in cyanosis.

Dyspnea with exertion occurs commonly in toddlers and older children with unrepaired defects. Attacks of suddenly increasing cyanosis associated with hyperpnea, or hypoxic spells,[167] are common between ages 2 months and 2 years. There are many precipitating events, including infection, exertion, and summer heat. They occur most often in the morning, with increasing irritability. The frequency and duration vary widely, but prolonged episodes can lead to syncope, seizures, and death. Squatting with exercise is common from 1.5 to 10 years of age in those not previously repaired. These problems are becoming uncommon as more and more children undergo early repair.

Physical Examination

Growth is usually normal unless cyanosis is extreme. Clubbing of the fingers and toes occurs after 3 months of age and is proportional to the level of cyanosis. Signs of congestive heart failure do not appear in tetralogy of Fallot during childhood unless there is a superimposed illness such as anemia or infective endocarditis.

Increased right ventricular activity is observed. A systolic thrill may be palpable at the left midsternal border, with a harsh midsystolic murmur in that location. Softer murmurs signal more severe obstruction and are common when presentation is in the newborn period or during hypoxic spells. The murmur ends before the second heart sound, which is characteristically single. A continuous murmur is heard if a PDA or large collateral vessels are present. An early systolic ejection sound at the left sternal border and apex is uncommon; its presence suggests primarily valvular pulmonary stenosis.

Chest Roentgenogram

The total heart size is usually normal on chest roentgenography, but right ventricular enlargement is present in the lateral view. The aorta arches to the right in many cases. Pulmonary flow is diminished. The pulmonary segment is concave and the apex is elevated, giving the *coeur en sabot* (boot-shaped) contour. A very young infant may have only diminished pulmonary flow.

Electrocardiogram

In tetralogy of Fallot, the mean QRS axis of the ECG is usually to the right, between +90° and +210°. There is right ventricular hypertrophy, with a tall R wave in the right precordial leads and a deep S wave in the left leads. Some of these patients have right atrial hypertrophy.

Echocardiogram

Two-dimensional echocardiography can delineate the anatomic components of tetralogy.[168] Anomalies of the coronary arteries can be demonstrated, and associated defects can be excluded.

Hematologic and Other Laboratory Studies

Before surgical repair, the hemoglobin and hematocrit should be measured and pulse oximetry

should be performed in all patients at initial evaluation and periodically thereafter for determination of the degree of polycythemia and the early detection of anemia relative to the degree of cyanosis. The latter is common, especially in those under 2 years of age, and may predispose a patient to cerebrovascular accidents. Platelet counts and clotting studies may be advisable in older unrepaired patients with marked polycythemia, particularly if a surgical procedure is planned. Serum uric acid levels should be measured if polycythemia is severe and long-standing.

Cardiac Catheterization

In an increasing number of centers, the quality of echocardiography (especially when done in neonates or infants) is sufficiently diagnostic to outline the right ventricular and proximal pulmonary artery anatomy, rule out additional muscular VSDs, and establish the proximal coronary circulation. As a consequence, diagnostic cardiac catheterization and angiography are less commonly performed preoperatively than they were in the past in children with tetralogy of Fallot.

In those in whom the study is performed, the right ventricular systolic pressure is equal to the pressure in the left ventricle and aorta. If the pulmonary artery can be entered, the pressure will be normal or low. The level or levels of obstruction can be evaluated by careful pullback to the right ventricle. Caution should be observed if the pulmonary artery is entered, as the catheter may critically reduce the pulmonary flow and cause a hypoxic episode. Systemic arterial oxygen saturation is reduced because of right-to-left shunting from the right ventricle to the left ventricle. If a patent foramen ovale or ASD is present, there may be an additional right-to-left or bidirectional shunt at the atrial level. Selective biplane right ventricular angiography will demonstrate levels of obstruction, continuity and size of the pulmonary arteries, and size and position of the ventricular defect. If this is not demonstrated by echocardiography or aortography, selective coronary arteriography should be performed on all patients preoperatively to demonstrate the coronary arterial pattern.[169]

MEDICAL MANAGEMENT

Although the definitive treatment of tetralogy of Fallot is surgical, medical management plays a role before surgery and in the postoperative period. For a severely cyanotic newborn, prostaglandin administration is of benefit[91] to keep the ductus open until surgery can be done. Before surgery, the hematocrit and hemoglobin should be monitored and iron-deficiency anemia should be treated promptly to prevent strokes. Fever or other illness that would lead to dehydration and possible thrombotic complications should be treated promptly.

Hypoxic spells in an infant should be treated initially by placing the infant in the knee-chest position and administering a high concentration of oxygen and morphine sulfate. If acidosis is present and does not correct spontaneously and promptly, intravenous sodium bicarbonate and an alpha-adrenergic agonist should be given. Propranalol may be useful in preventing hypoxic spells.[170]

Bacterial endocarditis is a serious complication, especially in those who have had a systemic-to-pulmonary artery shunt. Meticulous care should be taken to maintain good dental hygiene, and prophylactic antibiotics at times of predictable risk are mandatory (see Chap. 73).

SURGICAL MANAGEMENT

Historically, the approach to tetralogy of Fallot has been either palliation or corrective surgery. The introduction of an aorta-to-pulmonary-artery shunt for the treatment of tetralogy of Fallot[171] truly can be called the beginning of effective treatment for pediatric cardiovascular disease. When

open heart surgery was initiated in the 1950s, tetralogy of Fallot was among the first lesions to be corrected.[172] Over the years, the age at which corrective surgery can be performed has dropped so that in many centers primary repair is the procedure of choice at any age. Palliation, when it is now performed, almost inevitably involves a modified Blalock-Taussig shunt that interposes a graft between the subclavian artery and the ipsolateral pulmonary artery, usually on the side opposite the aortic arch.[173] Even in the perinatal period, the placement of a 4-mm tube will result in satisfactory palliation for a year in more than 90 percent of infants.

Surgical correction for those with pulmonary stenosis involves closing the VSD, usually through a right ventriculotomy, resecting infundibular muscle, and, if the infundibulum, pulmonary valve, and main pulmonary artery are hypoplastic, using a pericardial patch to open the narrowed area. Care must be taken to avoid heart block while closing the VSD and avoid cutting a major branch of the coronary artery. If a patent foramen ovale is present, it usually is left open to allow decompression in the perioperative period. If a true ASD is present (pentology of Fallot), it should be closed to avoid left-to-right shunting once the right ventricle has recovered from the perioperative insult.[174]

Children with tetralogy of Fallot and pulmonary atresia with good-sized pulmonary arteries usually are repaired by closing the VSD and interposing a conduit, frequently an aortic homograft, between the right ventricle and the pulmonary artery.[175] If this is done in children under 7 or 8 years of age, replacement of the conduit is to be expected secondary to somatic growth. Children with tetralogy of Fallot and hypoplastic and/or discontinuous pulmonary arteries require an individualized approach that frequently involves balloon dilation of hypoplastic vessels, unifocalization of discontinuous vessels, and, it is hoped, eventual repair with a conduit closing the VSD.[176] Operative and early mortality rates for repair of tetralogy of Fallot are now quite low in most centers. Kirklin and coworkers[173] in the early 1980s reported mortality rates of 1.6 percent with operations at 5 years of age to 4.1 percent at 1 year of age. At Children's Hospital in Boston, there was a 4.2 percent mortality rate among 330 children under 1 year of age operated on between 1973 and 1990, with a mortality rate of only 2.5 percent in the past 6 years of the study (1984-1990).[174] Late complications have included residual peripheral pulmonary stenosis, a small incidence of residual VSDs, and, rarely, aortic regurgitation. The long-term survivors have had atrial or, more commonly, ventricular arrhythmias and continue to be at risk for infective endocarditis.

Physicians at the Mayo Clinic, the first center to use the pump oxygenator to repair tetralogy of Fallot in the 1950s, have reported a minimum 30-year follow-up of the 162 30-day survivors of surgery.[177] The 32-year actuarial survival rate was 86 percent, with subgroup survival rates of those less then 5 years old, 5 to 7 years old, and 8 to 11 years old at the time of surgical repair being 90, 93, and 91 percent, respectively. Late sudden death from cardiac causes occurred in 10 patients during the 32-year period. The performance of some previous palliative operation (Waterston or Pott's shunts) but not a palliative Blalock-Taussig shunt was associated with higher mortality. With earlier surgery and less utilization of palliative procedures, it is hoped that the surgical results will be even better for children born in the 1980s and 1990s and beyond.

Ebstein's Anomaly

PATHOLOGY

In Ebstein's anomaly, the anterior leaflet of the tricuspid valve is attached normally to the annulus, but varying portions of the posterior and septal leaflets are displaced downward, being attached to the ventricular wall below the annulus. The proximal part of the right ventricle is thin-walled and continuous with the right atrium. The functional right ventricle is small and is made up of the apical and infundibular portions of the right ventricle. An additional common finding is that the papillary muscles and chordae are highly malformed, with great variation in the manner of

attachment of the two involved leaflets to the right ventricular wall. Commonly, multiple direct attachments of valvular tissue to the right ventricular mural endocardium occur.[178,179]

An interatrial communication is present in most cases, usually taking the form of a patent foramen ovale. Continuity of right atrial and right ventricular myocardial tissues, in addition to the usual connections by way of the main conduction pathways, has been observed. *The presence of Ebstein's anomaly has been associated with maternal lithium use during pregnancy, although the risk ratio remains unclear*.[180]

ABNORMAL PHYSIOLOGY

Ebstein's anomaly results in obstruction to right ventricular filling because of a decrease in the size of the right ventricle, part of which is incorporated into the huge right atrium. The deformed tricuspid valve also frequently is associated with tricuspid regurgitation with a right-to-left shunt through the foramen ovale. In the perinatal period, when the pulmonary vascular resistance is high, the tricuspid regurgitation may be severe. This results in increased right atrial pressure and, when the patent foramen ovale is open, severe cyanosis. As the pulmonary vascular resistance falls, the right-to-left shunting is decreased and hypoxemia improves. In older children, right-sided congestive heart failure with edema and/or ascites may develop.

CLINICAL MANIFESTATIONS

History

Approximately one-half of reported patients develop symptoms of cyanosis and right-sided heart failure in early infancy. The remainder present with a murmur or abnormal chest roentgenogram, but with no symptoms, in early childhood or because of gradual progression of symptoms through late childhood or adult life.[181] The most common symptom is dyspnea on exertion. The spectrum of exercise intolerance has been described.[182] Palpitations resulting from supraventricular tachyarrhythmias occur in 20 to 30 percent of these children. Occasionally, syncope occurs as a result of arrhythmia or low cardiac output if the atrial septum is intact.

Physical Examination

A newborn with elevated pulmonary vascular resistance has severe cyanosis. In older infants and children, cyanosis and clubbing are mild. Only a small percentage do not have an ASD or patent foramen ovale and thus are not cyanotic. The precordium is generally quiet even in those with striking cardiomegaly. The liver is enlarged, and the jugular venous pulse may be elevated. The holosystolic murmur of tricuspid regurgitation is heard at the lower left sternal border and may be accompanied by a "scratchy" diastolic murmur of tricuspid stenosis. The first heart sound is split and loud, and the second heart sound is widely and persistently split. Loud third and fourth heart sounds are usual, especially in older patients.

Chest Roentgenogram

Heart size, as shown by chest roentgenography, varies, but the heart is ordinarily very large because of the very dilated right atrium. In those with cyanosis, pulmonary blood flow is diminished correspondingly.

Electrocardiogram

Giant, peaked P waves are common, along with a prolonged PQ interval and right ventricular conduction delay or complete right bundle branch block. In approximately 10 percent of these

patients, the pattern of Wolff-Parkinson-White syndrome (with a short PQ interval and slurring of the initial QRS forces or a delta wave) is seen.[181]

Echocardiogram

Two-dimensional echocardiography is very helpful in the diagnosis (Fig. 63-30), identifying the lesion, depicting the degree of displacement of the tricuspid valve into the right ventricle, and assessing the severity of the tricuspid regurgitation. In neonates, evaluation of the pulmonary valve usually allows a distinction between anatomic pulmonary atresia from absence of opening of the valve caused by severe tricuspid regurgitation and high pulmonary vascular resistance.[183]

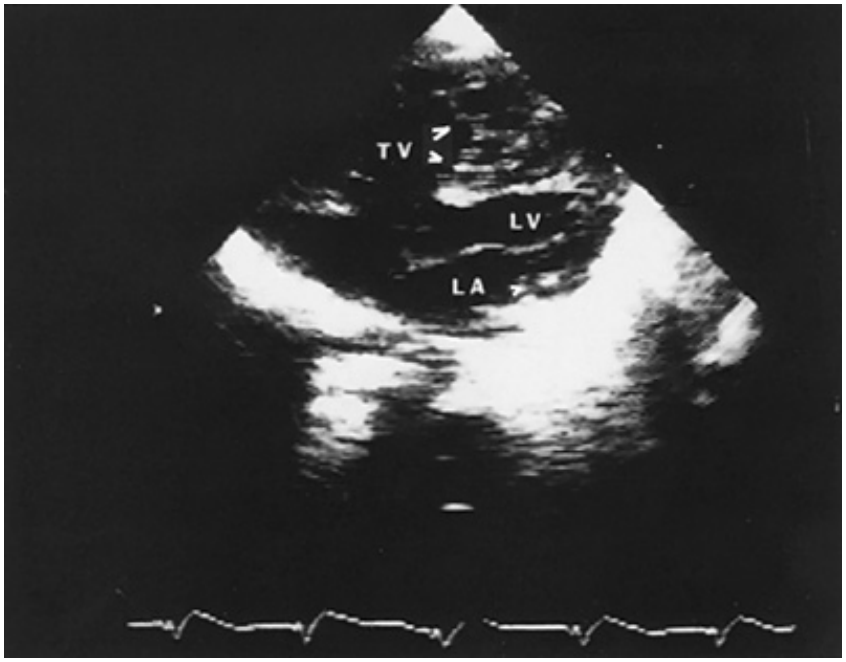

Figure 63-30: Two-dimensional echocardiogram in parasternal view in a patient with Ebstein's anomaly of the tricuspid valve (TV). Numerous attachments of the tricuspid valve (*arrowheads*) to the interventricular septum and right ventricular apex are seen. LV = left ventricle; LA = left atrium.

Cardiac Catheterization

There is a higher than usual risk associated with cardiac catheterization because of the frequency of rhythm disturbances. Proper precautions and prompt use of cardioversion when necessary minimize this risk. In most cases, echocardiography and color Doppler evaluation are sufficient, and catheterization is performed less commonly than it was previously.

There is usually right-to-left shunting at the atrial level. Right atrial hypertension is present. The characteristic right ventricular pressure recording is not obtained until the catheter is advanced to the apex or outflow tract. An intracardiac ECG demonstrates, on pullback from the right ventricle, an area where the ECG is ventricular but the pressure is atrial in contour.[184] This method is not infallible, but it provides good evidence of tricuspid displacement with an "atrialized" portion of the right ventricle.

NATURAL HISTORY AND PROGNOSIS

The natural history varies greatly with the severity of the abnormality. In a study of 50 patients who presented in the neonatal period, 9 (18 percent) died in the perinatal period, with late deaths in another 15 (9 from hemodynamic deterioration, 5 sudden, and 1 noncardiac), for a 10-year actuarial survival of 61 percent.[185] In a study that included more children who presented after the perinatal period, the probability of survival was 50 percent at 47 years of age.[186] Predictors of poor outcome were New York Heart Association class III or IV, cardiothoracic ratio >65 percent, and atrial fibrillation.

For women who survive into adulthood without significant arrhythmias or cyanosis, successful pregnancy with good fetal outcome is possible.[187]

MEDICAL MANAGEMENT

Medical therapy varies depending on the severity of disease and the age at presentation. For those presenting with cyanosis in the perinatal period, procrastination until the pulmonary vascular resistance has decreased may be the best strategy. For those who are severely hypoxemic, maintaining the patency of the ductus with PGE_1 may be lifesaving. Reducing the pulmonary vascular resistance with nitric oxide may reduce right-to-left shunting and improve oxygenation.[188] Persistence of severe cyanosis beyond 1 week of age suggests pulmonary stenosis or pulmonary atresia in addition to Ebstein's deformity of the tricuspid valve.

For children with arrhythmias, an electrophysiologic study may be indicated. For those with disabling or life-threatening arrhythmias, radiofrequency ablation may be performed with initial success rates of about 80 percent but recurrences in 30 percent of patients.[189]

In older children who develop right-sided congestive heart failure, anticongestive measures with digoxin and diuretics may be tried, although this level of deterioration is usually an indication for surgical intervention.

SURGICAL MANAGEMENT

The surgical management of Ebstein's disease remains problematic. In the perinatal period, when the pulmonary vascular resistance is high, watchful waiting is probably the best approach. If the child remains severely hypoxemic (saturations <75 percent) after the pulmonary vascular resistance falls, palliation with a Blalock-Taussig shunt to improve pulmonary blood flow may be sufficient to relieve hypoxemia, and this should allow growth to an age at which other procedures can be considered.[190] For children in whom hypoxemia remains a significant problem, three approaches have been used. The first is a Glenn anastomosis connecting the superior vena cava to the right pulmonary artery, allowing inferior vena cava blood to go through the right atrium and ventricle to the pulmonary artery.[191] A more definitive procedure that eliminates hypoxemia that is used primarily for children with single ventricle but now is applied in this situation as well is the modified Fontan. In this approach, the tricuspid valve is oversewn and the patent foramen ovale is closed, diverting all systemic venous return to the pulmonary arteries by passing the right heart.[192] In a small group of patients, this has been done with success.

The more common approach has been tricuspid valve reconstruction or replacement, usually with a bioprosthesis. Among 189 patients operated on at the Mayo Clinic over a period of almost 20 years, there were 12 hospital deaths (6.3 percent) and an additional 10 late deaths. Among those followed more than 1 year after operation, more than 90 percent were in New York Heart Association class I or II.[193] More recently, other approaches have been suggested, including reconstruction of the normally shaped right ventricle with repositioning of the displaced leaflet of the tricuspid valve at the normal level[194] and reimplantation of the tricuspid valve leaflets with a vertical plication of the atrialized portion of the right ventricle to reduce its size ( Fig. 63-

31).[195] *Although the newer approaches seem promising in small numbers of patients in the short run, many patients with the milder form of the disease can live well into adulthood,*[196] *and so indications for the newer operations in patients who are asymptomatic or only mildly limited remain problematic.*

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Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

ABNORMALITIES OF THE PULMONARY VENOUS CONNECTIONS

Total Anomalous Pulmonary Venous Connection

PATHOLOGY

When all pulmonary veins terminate in a systemic vein or the right atrium, the term *total anomalous pulmonary venous connection* or *return* is applied (Fig. 63-32). Usually the pulmonary veins leave the lung and then join a chamber-like confluence posterior to the left atrium. From the confluence of veins, one primitive embryologic vessel persists and leads to the anomalous termination. Less commonly, two or more vessels lead to multiple sites of termination.

If the left cardinal vein persists, drainage flows superiorly into the innominate vein and then to the superior vena cava and right atrium or inferiorly into a persistent left superior vena cava and coronary sinus to the right atrium. If the right cardinal vein persists, drainage is to the superior vena cava, the azygous vein, or the right atrium directly. These types are sometimes referred to collectively as supracardiac or supradiaphragmatic drainage and almost never are associated with pulmonary venous obstruction.[197]

If the site of termination is infradiaphragmatic, with connection to the portal venous system or the inferior vena cava, the anomalous vein leaves the confluence of pulmonary veins and descends into the abdomen along the esophagus to join the ductus venosus, the portal vein, or the left gastric vein. *Pulmonary venous obstruction is present in virtually all cases of infradiaphragmatic connection.*[197]

In all cases of total anomalous pulmonary venous connection, there is a patent foramen ovale. The atrium and ventricle of the left side are small in comparison with the right-sided chambers but are within normal limits in regard to absolute size. In the absence of asplenia or polysplenia syndromes, associated anomalies are not common.

ABNORMAL PHYSIOLOGY

In this anomaly, all the blood from both the pulmonary and systemic circulations eventually returns to the right atrium. In neonates with the connection below the diaphragm, the increase in pulmonary flow as the pulmonary resistance decreases after birth cannot be accommodated and the obstruction to flow causes a marked increase in pulmonary venous pressure, resulting in a very high pulmonary vascular resistance. If the ductus arteriosus is still open, the pulmonary vascular resistance exceeds systemic vascular resistance with a right-to-left shunt at the ductal level. When the ductus closes, the increased pulmonary resistance results in increased right ventricular pressure. If the right ventricle fails, the right atrial pressure will increase, and right-to-left shunting at the atrial level may be present, often with profound hypoxemia.

In older children with unobstructed damage above the diaphragm (supracardiac), the pulmonary resistance is usually low. This low resistance facilitates a high pulmonary flow. With mixing of all pulmonary and systemic flow in the right atrium, the oxygen saturation is usually relatively high, resulting in physiology similar to that of an ASD and mild cyanosis.[198]

CLINICAL MANIFESTATIONS

Total Anomalous Pulmonary Venous Connection with Pulmonary Venous Obstruction

Neonates with total anomalous pulmonary venous connection below the diaphragm who have pulmonary venous obstruction present with cyanosis, which may be severe, and dyspnea. Symptoms frequently develop beyond 12 h of age, allowing differentiation from respiratory distress syndrome. In addition to dyspnea, feeding difficulties and cardiac failure are seen.

The physical findings are usually unimpressive. The heart is not hyperactive, and thrills are absent. The second heart sound may be split, with an increased pulmonary component. Significant murmurs are uncommon.

Total Anomalous Pulmonary Venous Connection without Pulmonary Venous Obstruction

These patients are usually asymptomatic at birth, although some may develop transient tachypnea. Presentation typically occurs during the first year of life. Some of these children have tachypnea and feeding difficulties, with frequent respiratory infections. Cyanosis often is mild and may not be clinically apparent. Other children may be asymptomatic and present with a heart murmur.

The cardiac examination is similar to that of an ASD with increased right-sided flow. The right ventricular impulse is usually hyperactive. The jugular venous pulse is elevated, and hepatomegaly appears early. There is a diffuse and hyperdynamic right ventricular impulse. The second heart sound is split and relatively fixed; the loudness of the pulmonary component may be increased. There is usually a grade 2 or 3 midsystolic flow murmur at the left sternal border. At the lower sternal border, there are a middiastolic rumble and prominent third and fourth heart sounds. Rales may be heard over the lung fields, and periorbital edema is common. A continuous murmur rarely may be heard over the common venous channel.

Chest Roentgenogram

With the unobstructed types, the heart is enlarged with increased pulmonary flow. Pulmonary edema is uncommon. In patients with return to the left innominate vein, there may be a characteristic bulging of the superior mediastinum bilaterally, producing a "snowman," or figure-of-eight, contour. With obstructed types, the heart size is nearly normal; there is very marked pulmonary edema, which may give a granular appearance to the lungs, making differentiation from respiratory distress syndrome difficult in a newborn.

Electrocardiogram

There is right axis deviation and right atrial and right ventricular hypertrophy. Commonly, there is a qR pattern in the right precordial leads.

Echocardiogram

Echocardiography with color Doppler is specific in defining the anomaly and the site of drainage.[199] The right side of the heart is enlarged when the venous return is unobstructed with increased flow. Although the right-sided chambers may dwarf the left heart, the left heart is usually of normal size. With obstructed return, there is evidence of severe pulmonary hypertension.

Cardiac Catheterization

If echocardiography is inconclusive in delineating the site or sites of the pulmonary venous connection, catheterization may be necessary. There is an increase in oxygen saturation at the level of the abnormal connection, with similar saturations in the remainder of the chambers on both sides of the heart. Pulmonary arterial pressure is elevated to a variable degree, but it may be above systemic pressure if there is marked pulmonary venous or pulmonary vascular obstruction. Pulmonary capillary wedge pressures are elevated in proportion to the degree of venous obstruction. The atrial communication may rarely be obstructive,[198] and if it is, balloon atrial septostomy may be helpful. Pulmonary arteriography usually will show the anomalous venous connection. Angiography directly in the common venous channel, if it is entered, will outline its course and any sites of obstruction optimally.

NATURAL HISTORY AND PROGNOSIS

The natural history varies depending on the degree of obstruction of egress of blood from the pulmonary veins.[198] Those who present in the perinatal period with severe cyanosis and respiratory distress, usually with pulmonary venous drainage below the diaghram, represent a medical emergency and will die without early surgery.

Those with supracardiac drainage and some degree of obstruction and therefore pulmonary hypertension are frequently sufficiently tachypneic that feeding is problematic, and they fail to gain weight at a normal rate. They tolerate respiratory infections poorly and occasionally need emergency surgery for respiratory failure.

Those with no pulmonary venous obstruction have large left-to-right shunts and mild cyanosis but may have no or minimal symptoms at rest or exercise. If corrective surgery is not performed, they are at risk for pulmonary vascular disease.[200]

MEDICAL MANAGEMENT

For neonates with severe cyanosis and respiratory disease, oxygen, a respirator, and PGE_1 can be used to temporize but survival is dependent on early surgery. For those with mild pulmonary hypertension and failure to thrive, surgery usually is performed semielectively. For those with no pulmonary hypertension, who usually present with murmurs and findings similar to those of an atrial septal defect, surgery is more elective but little is gained by waiting, and more centers are advocating early repair in this group as well.[201]

SURGICAL MANAGEMENT

Correction of total anomalous pulmonary venous connection requires (1) creation of a large communication between the left atrium and the pulmonary venous system, (2) obliteration of the anomalous pulmonary venous connection to the systemic circulation, and (3) closure of the associated interatrial communications.[201]

Supracardiac anomalous connection to the left brachiocephalic (vertical) vein and infracardiac connections to the portal venous system or the inferior vena cava are corrected by the creation of a wide anastomosis between the posterior aspect of the left atrium and the common transverse pulmonary vein. The stretched foramen ovale is closed. The ascending or descending anomalous pulmonary venous connection to the systemic circulation is ligated, as is the PDA.

Anomalous pulmonary venous connection to the coronary sinus is repaired by creating of a large fenestration in the common wall between the coronary sinus and the left atrium. The coronary sinus is diverted into the left atrium by the placement of an intracardiac patch, which also closes the interatrial communication.

Total anomalous pulmonary venous connection to the right atrium is repaired by excision of the atrial septum and the placement of a patch that diverts the opening of the anomalous pulmonary venous connection into the left atrium.

Mixed forms of total anomalous pulmonary venous connection pose particular technical difficulties that require individualized operations. Mortality rates are slightly higher after early repair of symptomatic neonates with mixed types of total anomalous pulmonary venous connections.

Although the results of repair of total anomalous pulmonary venous connection without obstruction in an older child have always been quite good, until recently neonates with obstructed total venous return have been problematic. In the 1960s and early 1970s, the surgical mortality rate exceeded 50 percent.[202] Between 1970 and 1980, surgical techniques improved and the mortality rate was reduced to 10 to 20 percent.[203] More recently, surgical results have continued to improve, with no mortality among 27 infants who underwent reparative surgery at Children's Hospital in Boston in the late 1980s.[204] Late survival has been quite good, with 98 percent surviving a median of 87 months in one study.[205]

After a satisfactory operative course, the prognosis has been excellent in those in whom a large common pulmonary vein can be attached to the back wall of the left atrium with a relatively large anastomosis. For those initially with obstructed total anomalous pulmonary venous return, the left atrium may be small and the anastomosis may be more difficult. Late obstruction of one or more pulmonary veins has been seen. When present, the obstruction can be approached by balloon dilation, stent placement, or repeat surgery.[206]

PREVIOUS | NEXT

Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

MALPOSITION OF THE CARDIAC STRUCTURES

Definition and Terminology

The *segmental approach* to the diagnosis of complex congenital heart disease[207] provides an orderly, effective method for determining the anatomic and hemodynamic interrelationships of the cardiac chambers, valves, and great vessels. For this approach to be better understood, certain definitions are helpful. Positioning of viscera is described as situs solitus, inversus, or ambiguous. In *situs solitus* (S), the distribution of all the organs is recognized as normal, for example, a left-sided stomach and spleen, a predominantly right-sided liver, a trilobed right lung, and a bilobed left lung. In *situs inversus (totalis)* (I), the organs show a perfect mirror image in regard to left and right to that of situs solitus. Anteroposterior relations are not disturbed. When neither situs solitus nor situs inversus can be identified, *situs ambiguous* (A) is said to be present. This usually applies in cases of asplenia or polysplenia.

With the rarest of exceptions, the *atria follow the body situs* and are so designated (morphologic right atrium to the right of the left atrium in atrial situs solitus and to the left of the left atrium in atrial situs inversus). The AV canal consists of the tricuspid valve, the mitral valve, and the septum of the AV canal and connects the atrial portion with the ventricular portion of the heart. As a rule, *each AV valve is part of the specific ventricle into which it leads*. The valve situs may be solitus, inversus, or ambiguous.

The alignment or type of AV or ventriculoarterial (VA) connection addresses the issue of what flows into what. The connection may be described at the AV or VA level as concordant (e.g., right atrium to right ventricle, left ventricle to aorta) or discordant (e.g., right atrium to left ventricle, left ventricle to pulmonary artery) or may be considered an arrangement that requires a special description. In the case of AV alignment in which the atria are not lateralized, the alignment would be ambiguous. In the univentricular heart, the designation would be double-inlet, absent right, or absent left AV connection. Special descriptions in the case of VA alignment or type of VA connection include double-outlet and single-outlet VA connection. The mode of connections, either AV or VA, addresses the structural makeup of the connecting segments: the AV canal and the infundibulum or conus. The mode of AV connection may be normal, common, stenotic, imperforate, atretic, double-orifice, overriding, straddling, or unguarded. The mode of VA connection may be expressed in terms of the position and development of the conus or infundibulum, which, although normally incorporated into the right ventricle, is not an intrinsic part of the true right ventricle. It may be described as subpulmonary, subaortic, very deficient, or bilaterally present or absent.[208]

The position of the ventricles may be described by the terms *d loop* and *l loop*. When the morphologic right ventricle lies to the right of the morphologic left ventricle, the ventricular portion of the heart is said to exhibit a d loop (D). The ventricles are said to be noninverted or in the solitus position. When the ventricular relations are reversed, l loop (L) is said to be present. The ventricles are inverted or in the inversus position. *These relationships are independent of the visceral or atrial situs as well as the position of the heart or its chambers within the chest.*

The great arteries may deviate from the usual with respect to both their anteroposterior and lateral (left-to-right) relationships. In solitus (S) or *normally related great arteries* (NRGA), the aortic origin lies to the right of and posterior to the position of the pulmonary valve. In the inversus (I) relationship, the anteroposterior relationships are not disturbed but the aortic origin lies to the left of the pulmonary arterial origin. In *transposition of the great arteries* (TGA), the aorta arises from the anatomic right ventricle, the pulmonary artery arises from the anatomic left ventricle, and usually the aortic origin is more anterior than that of the pulmonary artery.

When the aortic origin lies to the right of the pulmonary origin, the transposition is called *dextro* or *d transposition* (D-TGA) (see the discussion of complete transposition of the great arteries, below). When the aortic origin lies to the left of the pulmonary origin, *levo transposition* (L-TGA) is said to be present (see the section on congenitally corrected transposition, below).

When the abnormal relationship of the great arteries is neither complete nor corrected transposition, the term *malposition of the great arteries* (MGA) may be used. Malpositions are designated as D-MGA or L-MGA, depending on the laterality in the relation between the origins of the two great arteries.[208] Within this group are found examples of the abnormal VA alignment, where one great artery arises from the appropriate ventricle and the other great artery also arises from the same (or inappropriate) ventricle. These are examples of *double-outlet right ventricle* (DORV) or *double-outlet left ventricle* (DOLV). Also included is the arterial malposition termed *anatomically corrected malposition* (ACM). This is characterized by the great arteries having a normal VA alignment (concordant), but with the aorta anterior to the pulmonary artery by virtue of an abnormal mode of VA connection: the presence of a well-developed conus lying beneath both the aorta and the pulmonary artery or only beneath the aorta. The route for the flow of blood in ACMs may be normal or abnormal, depending on the AV alignment.[208]

The Segmental Approach to Diagnosis

The segmental, or step-by-step, approach is a valuable tool for arriving at the correct diagnosis in patients with complex congenital heart disease and is independent of cardiac position. In order, one determines (1) the locations of the right and left atria and their venous connections, (2) the location of the right and left ventricles and their alignment with the atria, (3) the mode of connection of the AV valves to the ventricles, (4) the position of the great arteries and their alignment with the ventricles, and (5) the location and status of the infundibulum. In addition, one must search for associated malformations between and within each of these segments.

Determining atrial situs can be accomplished in most instances by taking advantage of the high degree of abdominal visceroatrial concordance. With abdominal situs solitus (S), the liver is on the right and the right atrium almost invariably is on the right as well; with abdominal situs inversus (I), the liver is on the left and the right atrium almost invariably is on the left. With abdominal situs ambiguous (A), the liver may be placed almost symmetrically across the midline and the atria may be located normally or inverted or both atria may have morphologic characteristics of either the right atrium or the left atrium (Fig. 12-4). A symmetric liver is found in approximately 60 percent of patients with situs ambiguous. Lateralization of the liver, which is evident in the remainder, may simulate either situs solitus or situs inversus.

When both atria have characteristics of a right atrium,[209] *dextroisomerism*, or "bilateral right-sidedness," is said to be present. This situation is usually, though not invariably, accompanied by asplenia. When both atria have characteristics of a left atrium, *levoisomerism*, or "bilateral left-sidedness," is said to exist. This usually, but again not invariably, is accompanied by polysplenia.

Bronchial situs, as determined by overpenetrated chest roentgenogram or bronchial tomography, is an excellent predictor of atrial situs, but the most accurate technique appears to be two-dimensional echocardiography with Doppler color flow mapping. The hepatic portion of the

inferior vena cava, which almost always enters the morphologic right atrium, usually can be identified easily, as can the connections and structural details of the superior vena cava, coronary sinus, pulmonary veins, atrial septum, and atrial appendages.

Additional clinical clues to atrial situs may be obtained from the ECG, where a superior and leftward orientation of the P-wave vector suggests levoisomerism and polysplenia. Howell-Heinz and Howell-Jolly bodies in the peripheral blood smear are characteristic of dextroisomerism or asplenia.

For determination of the AV, ventricular, and VA relationships, high-quality selective biplane angiography, supplemented by equally high-quality two-dimensional echocardiography with Doppler color flow mapping, is essential.[209] Symbols used to designate the combination or sequence of segments are arranged in order as follows: (1) the visceroatrial or bronchoatrial situs, (2) the ventricular loop, and (3) the relations of the great arteries. These may be included within parentheses and preceded by abbreviations that indicate the VA alignment, for example, TGA, DORV, or single ventricle (SV). Associated malformations such as VSD, pulmonary stenosis, and straddling tricuspid valve may be listed after the parentheses. Thus, the typical or usual transposition of the great arteries with situs solitus, d-ventricular loop, and aorta arising from the right ventricle and to the right of the pulmonary artery, with an intact ventricular septum (IVS), would be designated TGA (SDD) IVS. The designation for typical corrected transposition (TGA) with situs solitus (S), l-ventricular loop (L), aorta arising from the morphologic right ventricle and lying to the left of the pulmonary artery (L), with VSD and pulmonary stenosis (PS), would be TGA (SLL), VSD, PS. This designation would apply to transposition with situs solitus, whether the heart lay in the right or left chest (dextrocardia or levocardia, respectively). It should be noted that the description of the position of the heart within the chest would offer no additional information referable to the intracardiac anatomy or great vessel alignment.[207]

Levocardia, Dextrocardia, and Mesocardia

The position of the cardiac apex indicates a condition of levocardia, dextrocardia, or mesocardia.

The trend today is to discard the terms *dextroposition, dextroversion, mirror-image dextrocardia*, and *isolated dextrocardia* because they do not provide any significant information beyond what is already known-that the cardiac apex is in the right chest-and to use the broad term *dextrocardia* for all right-sided hearts, followed by a description of the visceroatrial situs. In the case of patients in whom the heart appears to have been pulled or pushed into the right chest by massive atelectasis or hypoplasia of the right lung, diaphragmatic hernia, eventration of the diaphragm, pleural effusion, obstructive emphysema, or pneumothorax, an appropriate descriptive phrase should be added. The term *isolated levocardia* is applied to all left-sided hearts with situs inversus or situs ambiguous, and a description of the visceroatrial situs should follow.

Dextrocardia with complete situs inversus occurs in approximately 2 per 10,000 live births. *The incidence of congenital heart disease is relatively low among these individuals and is estimated to be about 3 percent*. Dextrocardia with situs solitus or situs ambiguous is considerably less common and occurs in perhaps 1 in 20,000 live births. The incidence of congenital heart disease is extremely high in this situation, however, probably in the range of 90 percent or greater. From these figures, one could project that approximately 12 percent of individuals found to have dextrocardia and congenital heart disease would have complete situs inversus. This estimate compares favorably with the figure of 18 percent observed in large autopsy series. About 50 percent of patients with dextrocardia and heart disease have situs solitus, and the remainder, perhaps 30 percent, have situs ambiguous.[207] An l-ventricular loop is found in the majority of patients with dextrocardia regardless of situs but is most common, as one might expect, among patients with situs inversus, in whom it approaches 80 percent. Cardiac malformations usually, although not invariably, are severe and complex. The most common lesions and their approximate

frequency are as follows: transposition of the great arteries, 50 to 75 percent; double-outlet right ventricle, 10 to 18 percent; VSD, 60 to 80 percent; single ventricle, 15 to 40 percent; and pulmonary stenosis or atresia, 70 to 80 percent.[207] Approximately three-quarters of transposed great arteries have the segmental arrangement of corrected transposition. Tetralogy of Fallot is distinctly uncommon. Polysplenia or asplenia is found in about one-third of patients with dextrocardia and almost invariably with situs ambiguous. Kartagener's syndrome, the triad of situs inversus, sinusitis, and bronchiectasis, results from impaired ciliary movement. It is present in approximately 20 percent of patients with dextrocardia and situs inversus totalis.[210] The incidence of isolated levocardia has been estimated at approximately 0.6 per 10,000 live births. It is estimated that over 90 percent of affected individuals have associated heart disease. Situs inversus is present in approximately 15 percent, and the remainder have situs ambiguous, with the ratio of asplenia to polysplenia or accessory spleens being from 2.5:1 to 1.5:1. The associated defects are comparable in complexity and severity to those associated with dextrocardia. *Mesocardia* may exist as a variant position of the normal heart or a variant position of dextrocardia or isolated levocardia.

MEDICAL AND SURGICAL MANAGEMENT

Medical management of patients with cardiac malposition is similar to that of patients with normally located hearts, with the exceptions of continuous daily antibiotic coverage and pneumococcal vaccine for patients with asplenia and the particular attention to detail that is necessary to establish the correct diagnosis in individuals with unusual and complex malformations. Surgical management differs in the technical considerations imposed by the malposition of the heart itself, the frequency of occurrence of the l-ventricular loop, and the variability of the intracardiac conduction system.

Dextro Transposition of the Great Arteries

DEFINITION

In this condition, the aorta and the pulmonary artery are misplaced in relation to the ventricular septum, with the aorta arising from the right ventricle and the pulmonary artery arising from the left ventricle (discordant VA connection).

PATHOLOGY

In the majority of cases, there are situs solitus of the atria and viscera (S) and concordance of the AV connection and the right ventricle lies to the right of the left ventricle (d loop, D) (Fig. 63-33). The aorta lies to the right of the pulmonary arterial origin (d transposition, D) and is anterior. Of the communications between the two sides of the circulation, a narrow patent foramen and PDA are common in very young infants. The ventricular septum is intact in approximately half these patients, and another 10 percent have only a very small VSD. The remainder have a large VSD or multiple VSDs.[211]

Pulmonary stenosis of significance is very uncommon among neonates with an intact ventricular septum but develops with the passage of time in approximately one-third of patients in whom the right ventricle continues to be the systemic ventricle. In most cases it is mild and usually, though not invariably, is the result of a bulging of the ventricular septum into the left ventricular outflow area. Approximately one-third of patients with a large VSD have significant left ventricular outflow tract obstruction (pulmonary stenosis). Causes of this obstruction include leftward malalignment of the infundibular septum, the presence of a membranous collar or ridge encircling the left ventricular outflow tract, anomalous adhesion of the anterior mitral leaflet to the ventricular septum, stenotic deformity of the pulmonary valve, and, rarely, an aneurysm of

endocardial tissue related to the VSD.[212]

The coronary arteries usually arise from the two aortic sinuses adjacent to the pulmonary trunk-the "facing sinuses"-with the most common arrangement being the right coronary artery arising from the rightward sinus and the left coronary artery, with its anterior descending and circumflex branches, arising from the leftward sinus.

Hypertensive pulmonary vascular disease may occur at an inordinately early age and may occur even in patients with an intact ventricular septum and initially low left ventricular pressures. Three-quarters or more of patients with d transposition, situs solitus, and d loop [TGA (SDD)] either have no significant associated cardiac defects or have relatively simple malformations in the form of VSD, ASD, PDA, or pulmonary stenosis. The remainder have more complicated lesions and will not be discussed in this section.

ABNORMAL PHYSIOLOGY

The systemic and pulmonary circulations are arranged so that the systemic venous return is conducted back to the systemic arterial system and the pulmonary venous return is conducted back to the pulmonary arterial system, with no obligatory mixing or interchange. For survival, there must be communication between the two circulations in the form of a patent foramen ovale, a PDA, or a VSD. The hemodynamics are dependent on the combination of defects present and particularly on the amount of mixing between the systemic and pulmonary circulations. The right ventricle is the systemic ventricle, and its systolic pressure is the same as systemic arterial pressure.

CLINICAL MANIFESTATIONS

Approximately 3 to 4 percent of children with recognized congenital heart disease have transposition of the great arteries (Table 63-1). Males are more commonly afflicted than are females in a ratio between 2:1 and 3:1.

History

Among infants with an intact ventricular septum, very early, severe, and progressive cyanosis is the presenting sign, making its clinical appearance within the first hour in over half and by the end of the first 24 h in over 60 percent of neonates so afflicted.[3] In a very few, a persistent PDA in combination with an incompetent foramen ovale or a small VSD permits survival for several weeks, but narrowing or closure of any of the three communications produces critical hypoxemia. Infants with a sizable VSD present with severe congestive failure and only mild or barely detectable cyanosis toward the middle or later part of the first month of life. Infants with a large VSD and significant pulmonary stenosis may present within the first days of life with cyanosis if stenosis is severe; with more moderate stenosis, they may present with cyanosis and little if any congestive failure somewhat later within the first year.

Physical Examination

Among infants with an intact ventricular septum, the most prominent feature is intense cyanosis. Tachypnea and mild dyspnea are present. The right ventricular lift is forceful, and the first sound is usually loud at the lower left sternal border. In most patients, the second heart sound may be heard to be split narrowly, confirming the presence of two semilunar valves. Murmurs are seldom impressive or distinctive. Signs of congestive failure are uncommon unless the infant is beyond the first week of life and a large ductus is present. Among infants with a large VSD, slenderness and mild cyanosis or a grayish pallor are apparent. Breathing is labored, and both the right and left

ventricular impulses are hyperactive. A thrill is uncommon. A systolic murmur at the lower left sternal border is usually present but is seldom loud or completely holosystolic. A gallop rhythm and a diastolic flow rumble at the apex are typical. Infants and children with VSD and significant pulmonary stenosis generally are severely cyanotic.

Chest Roentgenogram

With an intact ventricular septum, the heart size and pulmonary vascularity appear normal or at the upper limits of normal during the first week. Later, a narrow base caused by the displaced pulmonary artery may give rise to the characteristic "egg-on-side" contour. Impressive cardiomegaly, pulmonary plethora, and this characteristic contour are more common during the second week and beyond. With a large VSD, marked cardiac enlargement involving all chambers, impressive pulmonary plethora, and the egg-on-side contour are present. With significant pulmonary stenosis, the heart resembles that of a patient with tetralogy of Fallot, but it is usually slightly larger and the pulmonary vascularity is less diminished than one would expect for a comparable degree of clinical cyanosis. A right aortic arch is present in 4 to 16 percent of those patients.

Electrocardiogram

If the ventricular septum is intact, the ECG may reveal tall or peaked P waves by the second or third day of life; however, clearly abnormal right ventricular forces usually are not apparent until the latter part of the first week. The persistence of an upright T wave in leads V_1 and V_{3R} beyond 4 days of age provides an early clue that the right ventricular systolic pressure is at systemic levels. An older infant will have abnormal right axis deviation and marked right ventricular hypertrophy. A large VSD with a large pulmonary blood flow usually will produce biatrial and biventricular hypertrophy. If pulmonary blood flow is reduced toward normal, whether by significant pulmonary stenosis, pulmonary arterial banding, or severe PVOD, the pattern becomes one of right ventricular and right atrial hypertrophy.

Echocardiogram

Two-dimensional study with Doppler color flow mapping is the diagnostic procedure of choice. The pulmonary artery can be seen arising from the left ventricle, and the aorta from the right ventricle (Fig. 63-34*A*). The presence or absence of VSDs, anomalies of the AV connections, the status of the left ventricular outflow tract, and the coronary arterial pattern can be identified.

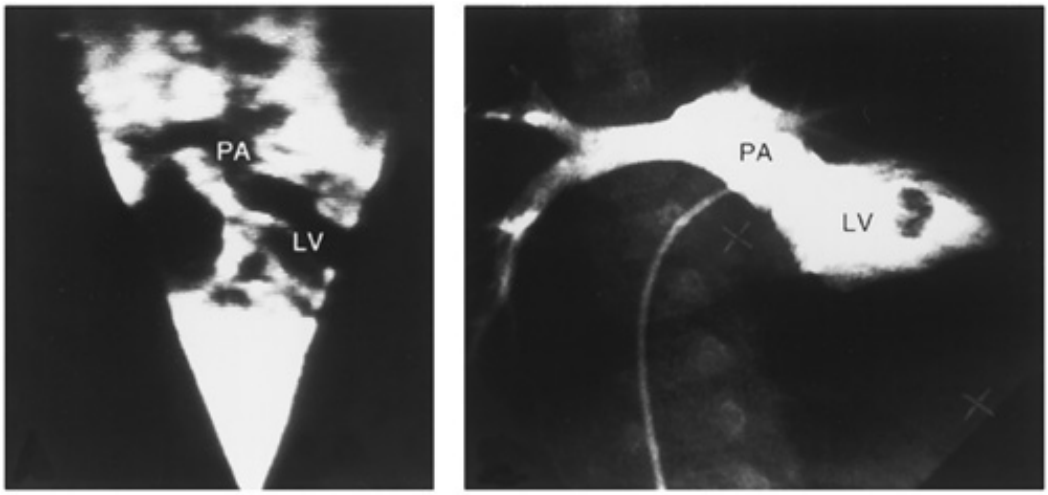


Figure 63-34: *A.* Two-dimensional echocardiogram. The left ventricle leads to a bifurcating great vessel (pulmonary artery, PA), confirming transposition. *B.* Anterolateral projection of an angiogram in the smooth-walled left ventricle (LV). The dye is ejected into the pulmonary artery.

Cardiac Catheterization

Systemic arterial oxygen desaturation is present in all these patients. The pulmonary arterial oxygen saturation is invariably higher than the systemic arterial saturation. The right ventricular systolic pressure will be at systemic levels; the left ventricular pressure also will be at systemic levels if a large VSD, ductus arteriosus, or significant pulmonary stenosis is present. A wide pressure difference between the two ventricles or between the two atria indicates an intact or virtually intact ventricular or atrial septum, but the lack of such a gradient certainly does not guarantee the presence of an adequate opening at either level. Selective ventricular angiography will document the diagnosis and the associated defects (Fig. 63-34*B*). The coronary arterial pattern should be established if it is not visible by echocardiography.[213] *All newborns with transposition can benefit from balloon atrial septostomy at catheterization by virtue of the increased mixing of the pulmonary and systemic venous circulations and the decompression of the left atrium.*

NATURAL HISTORY AND PROGNOSIS

Without balloon septostomy or surgical intervention, 50 percent of infants with transposition die within the first month and 90 percent die within the first year of life.[214] Those with an intact ventricular septum die very early from hypoxemia. Those with a large VSD usually live somewhat longer, but the majority die in the first months of congestive failure; the few survivors have severe PVOD. Those with a large VSD and pulmonary stenosis have the best outlook, but the average life expectancy is barely 5 years even with this combination of defects. With an adequate interatrial opening, whether natural, balloon-induced, or surgically created, infants with an intact ventricular septum do relatively well during the first year. Increasing cyanosis during the first year in these patients may be due to a gradual diminution of the size of the atrial septal opening, narrowing or closure of a persistent PDA or small VSD, the gradual development of subvalvular pulmonary stenosis, or the development of PVOD. Before age 2 years, cerebrovascular accidents are a hazard to these hypoxemic infants and occur almost invariably in a setting of relative anemia rather than extreme polycythemia. The appearance of PVOD is unusual but can occur within the first 12 months of life. It becomes more common, approaching 40 percent, in the second year of life and thereafter. Infants with a large VSD and no significant pulmonary stenosis will develop PVOD and become prohibitive risks for corrective surgery by the end of the first year of life.

Those with a VSD and severe pulmonary stenosis usually become progressively more cyanotic.

Palliative and subsequent corrective operations have enabled a relatively large group of patients to survive beyond infancy and early childhood. Among the survivors of the atrial switch operations, such as the Mustard and Senning procedures, are found residual abnormalities such as pulmonary stenosis and PVOD as well as complications that result from surgery. These complications include residual intraatrial baffle leaks, systemic and/or pulmonary venous obstruction, and arrhythmias. Late sudden death has been described in about 3 percent of survivors and very possibly results from arrhythmias. Finally, right ventricular dysfunction with or without progressive tricuspid regurgitation has been documented in many of the somewhat older survivors of atrial inversion operations and raises the question of whether the right ventricle can function adequately as the systemic arterial ventricle beyond adolescence and early adult life.

While complications have been problematic for some, long-term follow-up of the group as a whole has been good. The Toronto experience is the oldest and largest. Among 534 children who underwent a "Mustard" procedure since 1962, there were 52 early deaths (9.7 percent). Survival at 5 years was 89 percent, and it was 76 percent at 20 years.[215] In a study from New Zealand of 113 hospital survivors of surgery performed between 1964 and 1982, survival at 10, 20, and 28 years was 90 80, and 80 percent, respectively, with 76 percent of survivors being New York Heart Association class I.[216] There has been less long-term follow-up of survivors of the "Senning" type of atrial repair. In a recent study of 100 patients, the actuarial survival at 13 years was 90 percent for those with simple transposition and 78 percent survival for those with complex disease.[217]

MEDICAL MANAGEMENT

The first step in the treatment of infants with an intact ventricular septum is to provide without delay an adequate systemic arterial oxygen saturation. This can be achieved in almost all instances by establishing an adequate interatrial opening with balloon atrial septostomy and providing adequate systemic arterial-to-pulmonary arterial shunting via the ductus with the use of intravenous PGE_1 infusion;[91] the latter procedure frequently is supplemented by endotracheal intubation to compensate for prostaglandin-related apnea. The adequacy of the atrial septostomy opening can be determined by a sustained increase in the systemic arterial oxygen saturation to above 60 percent and verified by direct visualization with two-dimensional echocardiography. If the relief of hypoxemia is unsatisfactory with PGE_1 alone and if the interatrial opening is judged by echocardiography to be small, the alternatives are to perform a balloon atrial septectomy without delay or to proceed directly with corrective surgery in the form of the arterial switch operation.

SURGICAL MANAGEMENT

Arterial switch repair is now the preferred surgical alternative to the atrial inversion procedures for a neonate with an intact ventricular septum and for a slightly older infant with a large VSD and without significant structural pulmonary stenosis (Fig. 63-35). Arterial switching should be performed within the first 2 to 3 weeks of life, before left ventricular systolic pressure falls significantly below that of the right ventricle. For infants beyond 3 weeks of age, if the ratio of left ventricular to right ventricular pressure has fallen below 0.60, a pulmonary arterial band may be applied with or without a systemic-to-pulmonary arterial shunt and the arterial switch operation may be performed approximately 1 week later. Most patterns of coronary arterial origin and course appear to be amenable to the operation, and infants as small as 2.0 kg may be repaired successfully.

In some centers, the surgical risks have been reduced to about 5 to 10 percent,[218] although in other centers, the surgical mortality continues to be higher.[219] Short- and medium-term prognosis is

good,[220] but longer-term studies are awaited. The most common problem has been stenosis at the pulmonary artery anastomotic site.[221] When severe, this usually has been amenable to balloon dilation or stenting.[222]

For infants with transposition, a large VSD, and pulmonary hypertension, the arterial switch technique with VSD closure must be carried out within the first 2 months of life to prevent severe PVOD. Infants with a large VSD and severe pulmonary stenosis usually may be palliated with a systemic-to-pulmonary arterial shunt and repaired in later infancy or as young children,[175] although some centers are doing reparative surgery in infancy.[223] Finally, the severe hypoxemia present in children with a large VSD and severe PVOD may be reduced by an intraatrial repair performed as a palliative procedure, with no attempt at closure of the VSD.[224]

Double-Outlet Right Ventricle

PATHOLOGY

In this malformation, more than 50 percent of the semilunar valve orifices of both great arteries arise from the morphologic right ventricle. In most cases, the ventricles display a d loop, and the pulmonary arterial origin is normally positioned, arising from a conus above the right ventricle. The aorta also arises from the right ventricle above conal tissue. The two semilunar valves are at about the same level, and there is no fibrous continuity between the semilunar and mitral valves (Fig. 63-36).

In most cases, the aortic origin is to the right (d malposition) of the pulmonary arterial origin, with the two vessels usually displaying a side-by-side relationship. Uncommonly, the aortic origin is distinctly anterior to the pulmonary origin or the aorta arises to the left (l malposition) of the pulmonary artery.[225]

With rare exceptions, there is a VSD. The condition may be subdivided further on the basis of the relation of the VSD to the origin of the great arteries. The VSD is subaortic in approximately two-thirds of patients, subpulmonary (*Taussig-Bing heart*) in 18 percent, related to both great arteries (*doubly committed*) in 3 percent, and remote or unrelated to either great artery in about 7 percent.[225]

ASSOCIATED CONDITIONS

Pulmonary stenosis occurs in over half these cases, with the condition usually resulting from a narrow subpulmonary conus. ASD, subaortic stenosis, and coarctation of the aorta are also relatively common, with the latter particularly associated with the subpulmonary defect. Obstruction at the mitral valve may be observed in about one-fifth of cases of double-outlet right ventricle. Mitral valve straddling of the VSD and varying degrees of left ventricular hypoplasia also are encountered.

CLINICAL MANIFESTATIONS

Double-outlet right ventricle, or origin of both great arteries from the right ventricle, is a relatively rare malformation that is found in only 0.8 percent of patients with congenital heart disease. It is of considerable importance, however, because its clinical and laboratory features frequently resemble those of more common and more easily correctable malformations. Double-outlet right ventricle reflects the relationship of the great vessels to the ventricular septum; the presentation and treatment of children with this condition depend on the associated anomalies.

History and Physical Examination

Patients with a subaortic VSD without pulmonary stenosis (Fig. 63-36*A*) have the same findings on examination as do patients with a large isolated VSD. Congestive failure appears within a few weeks of birth, and cyanosis is seldom described. Those with a subaortic VSD and pulmonary stenosis (Fig. 63-36*B*) usually present after the newborn period and follow a course similar to that of patients with tetralogy of Fallot. Patients with a subpulmonary defect without pulmonary stenosis (Fig. 63-36*C*), the Taussig-Bing malformation, resemble patients with transposition of the great arteries and a large VSD without pulmonary stenosis. The findings are those of severe congestive failure and cyanosis.

Chest Roentgenogram

Cardiomegaly with pulmonary overperfusion is characteristic of all types of this anomaly without pulmonary stenosis. Double-outlet right ventricle with subaortic VSD and pulmonary stenosis resembles tetralogy of Fallot. In the case of subpulmonary VSD without pulmonary stenosis, the pulmonary artery usually lies beside rather than posterior to the aorta; this clearly visible, dilated main pulmonary artery may permit distinction of this malformation from transposition, which it mimics so closely.

Electrocardiogram

Right axis deviation and right atrial and right ventricular hypertrophy are characteristic of double-outlet right ventricle.

Echocardiogram

Two-dimensional echocardiography is very useful in demonstrating the anatomic components and associated defects.[225,226]

Cardiac Catheterization

There is an increase in oxygen saturation at the right ventricular level. The pulmonary arterial saturation is lower than that of the aorta in patients with a subaortic VSD and is invariably higher than that of the aorta in those with a subpulmonary septal defect and transposition physiology. Left ventricular systolic pressure may be higher than right pressure if the VSD is small and restrictive. Selective right and left ventricular biplane angiography and an aortogram are recommended.

NATURAL HISTORY AND PROGNOSIS

The clinical course of each variety of double-outlet right ventricle is determined by the associated defects. Without surgical intervention, those with an unguarded pulmonary artery either die in infancy with congestive failure or develop PVOD. Spontaneous narrowing or closure of the VSD may occur and is life-threatening. Increasing dyspnea, increasing intensity of the systolic murmur, and progressive left ventricular hypertrophy suggest this complication. Patients with pulmonary stenosis tend to have progressive obstruction and cyanosis.

MEDICAL MANAGEMENT

Vigorous treatment of heart failure is required for those without pulmonary stenosis. Almost all cases are best treated with surgical palliation or correction in infancy. If there is pulmonary

hypertension, banding or correction should be done by 2 to 3 months of age. Patients with ventricular hypoplasia, mitral stenoses, straddling AV valves, or a remote VSD are usually not candidates for biventricular repair, and initial palliation should prepare the child for a modification of the Fontan operation. Whether or not corrective surgery has been performed, all patients in whom the left ventricular output must pass through the VSD should be observed continuously for the possibility of spontaneous narrowing and obstruction at that site.

SURGICAL MANAGEMENT

Great variability exists in the morphologic spectrum of double-outlet right ventricle. Although primary total repair of most forms of double-outlet right ventricle is now performed and preferred in infancy, palliation (pulmonary arterial banding, repair of aortic coarctation, atrial septal excision, or the creation of a systemic arterial-to-pulmonary arterial or systemic venous-to-pulmonary arterial shunt) to adjust pulmonary blood flow and thus preserve the pulmonary vascular bed, ventricular function, and AV valve competence may be considered in complex variants.

In all forms of double-outlet ventricle, the relation of the VSD to the great arteries and the magnitude of ventricular outflow tract obstruction dictate management. Surgical correction requires (1) obliteration of the interventricular communication, (2) relief of pulmonary stenosis when present, (3) diversion of oxygenated pulmonary venous blood to the aorta, and (4) diversion of hypoxemic systemic venous blood to the pulmonary artery.[227] When the VSD is committed to the aorta, a Dacron semiconduit or tunnel-shaped patch is placed to obliterate the interventricular communication while the left ventricular blood is diverted through the VSD to the aorta. Pulmonary stenosis is corrected by a valvotomy, with excision of obstructive muscle bundles and placement of a transannular patch when necessary. Otherwise, an extracardiac conduit is placed between the right ventricle and the pulmonary artery.[228,229]

When the great arteries are transposed or the VSD is not committed to the aorta, the arterial switch operation, using the concepts of Jatene and Le Compte, permits patch closure of the VSD, directing left ventricular blood into the neoaorta.[230] Further consideration of repair of double-outlet right ventricle associated with more complex defects is beyond the scope of this discussion. For a patient who is not a candidate for biventricular repair because of hypoplasia of a ventricle or a straddling AV valve, initial palliation should prepare the child for a modification of the Fontan operation.

In a 10-year review of repair of double-outlet right ventricle in 73 patients,[228] early mortality was 11 percent, with an overall actuarial survival estimate at 8 years of 81 percent. Twenty-six percent required reoperation, and there was one death; 79 percent of the operative survivors required no restriction of physical activity, and 83 percent required no cardiac medications.

Corrected Transposition of the Great Arteries

DEFINITION

AV discordance and VA discordance form the characteristics of corrected transposition.

PATHOLOGY

Usually situs solitus is present, but the ventricles are inverted (an l loop). The great arteries are transposed and in the l position so that the pulmonary artery arises posteriorly from the right-sided morphologic left ventricle and the l-transposed aorta arises anteriorly from the left-sided right ventricle (SLL) (Fig. 63-37). If situs inversus is present, the segmental pattern is IDD.

Along with the ventricular inversion, there is AV valvular inversion. The two coronary arteries arise from the right and left (posteriorly facing) sinuses, with the right-sided coronary artery giving off the anterior descending and circumflex branches.[231]

ASSOCIATED CONDITIONS

Rarely, no associated conditions are present and the circulation is normal. In the majority of cases (about 75 percent), a VSD is present. It may be in any location, but a perimembranous subpulmonary defect is most common.

The inverted left-sided systemic tricuspid valve frequently shows some degree of abnormality, usually leading to incompetence. The most common abnormality is an Ebstein-like displacement of the septal and posterior leaflets, but dysplasia, clefts, and straddling of the ventricular septum also have been described.

Pulmonary atresia or stenosis is present in about 40 percent of cases, usually associated with a VSD.[231] This obstruction is usually subvalvular, is only rarely valvular, and may characteristically result from attachments of accessory mitral valve tissue.

CLINICAL MANIFESTATIONS

Corrected transposition is an uncommon malformation, occurring in slightly fewer than 1 percent of children with congenital heart disease. The importance of this anomaly lies in its frequent association with serious AV conduction disturbances, the intracardiac malformations, and the medical and surgical implications of the ventricular inversion. The clinical picture is determined primarily by the associated anomalies. At least a third of these patients can be expected to develop complete AV block if followed for a 20-year period.[232]

History

A slow, irregular heart rate often is detected in utero, and 10 percent of patients with congenital complete block prove to have corrected transposition. Patients with a large VSD without pulmonary stenosis usually present within the first month or so of life with symptoms indistinguishable from those of infants with a large VSD alone. Patients with VSD and pulmonary stenosis may present with symptoms of cyanosis and resemble patients with tetralogy of Fallot.

Physical Examination

The murmur of left AV valve regurgitation may be best heard either at the apex or at the lower left sternal border. Most of these patients have a murmur of VSD or pulmonary stenosis. Occasionally, an inordinately accentuated second heart sound at the upper left sternal border suggests the presence of PAH, although in reality it represents a loud aortic valve closure resulting from the anterior and superior displacement of the aorta valve.

Chest Roentgenogram

A straight or gently curved convex upper left heart border representing the contour of the transposed ascending aorta is characteristic and is most easily recognized in patients with a VSD and pulmonary stenosis, in whom there is a mild dilatation of the ascending aorta.

Electrocardiogram

Varying degrees of AV conduction delay are present in almost a third of these patients. The initial forces of ventricular depolarization are characteristically oriented anteriorly and to the left, with Q waves in the right precordial leads and not in leads I, V_5, and V_6 resulting from depolarization of the septum from the left side (right ventricle) to the right side (left ventricle). With normal or nearly normal pressure in the systemic venous or morphologic left ventricle, a QS pattern in the right and an RS pattern in the left precordial leads are usual.

Echocardiogram

Using a segmental approach, two-dimensional echocardiography permits identification of the anatomic components and associated defects.[233]

Cardiac Catheterization

When diagnostic catheterization is performed, the morphologic left ventricle is entered from the right atrium, and in the presence of a VSD, the catheter may cross the defect, traverse the morphologic right ventricle, and enter the ascending aorta in the position normally occupied by the pulmonary artery. Entry into the medially placed pulmonary artery may be much more difficult, but the use of flow-guided catheters permits successful entry for the measurement of pressure. Selective angiography in both ventricles will outline the defects. The ventricular septum usually lies in the anteroposterior plane, and frequently a VSD may be imaged best angiographically in the frontal view (Fig. 63-37). Gentle manipulation of the catheter within the heart is indicated, since the production of varying degrees of transient AV block is not uncommon, and in rare instances, the block may prove permanent.

NATURAL HISTORY AND PROGNOSIS

The clinical course is determined primarily by the severity of the associated defects. It is estimated that only about 1 percent of individuals with corrected transposition have an otherwise normal heart. Even with complicating anomalies, survival to adulthood is possible.[234] Congestive heart failure associated with a large VSD has been the most common cause of death, with most fatalities occurring within the first year of life. AV conduction abnormalities tend to be progressive, and complete AV block may appear at any age. Similarly, left AV valve regurgitation may present at any age and significantly alters the long-term outcome.[235] Finally, the morphologic right ventricle may not be capable of sustaining adequate cardiac output over a normal life span.[236]

MEDICAL MANAGEMENT

Management of corrected transposition includes the treatment of congestive failure, cyanosis, and AV block and the prevention of infective endocarditis. Patients with severe pulmonary hypertension or congestive heart failure should undergo early banding of the pulmonary artery or repair of the defect. Similarly, patients with a VSD, severe pulmonary stenosis, and cyanosis benefit from systemic-to-pulmonary artery shunting procedures or total correction. Those with a congenital block require prompt pacemaker therapy. Patients with significant left AV valve regurgitation require valve replacement. Regularly scheduled follow-up examinations are recommended for all these patients to detect progressive AV conduction disorders and the progression or late appearance of left AV valve incompetence. Antibiotic coverage as protection against infective endocarditis is recommended, as is the introduction of an afterload reducer at the first appearance of AV valve regurgitation.[237]

SURGICAL MANAGEMENT

The conventional approach has been correction of the underlying lesion, closure of the ventricular septal defect in those with an isolated VSD, and closure of the VSD and a conduit from the left (pulmonary) ventricle to the pulmonary artery in those with L-TGA, VSD, and PS.[238] Unfortunately, this approach frequently has led to suboptimal results because of a very high incidence of complete heart block, increasing left AV valve regurgitation, and right systemic ventricular dysfunction and heart failure.[235] Despite recent advances, operative mortality rates for VSD or VSD and pulmonary stenosis or atresia remain in the range of 4 to 15 percent with postoperative heart block in 14 to 33 percent.[239,240] The 10-year actual survival was 83 percent in one study[239] and 55 percent in the other.[240] Replacement of the regurgitant left AV valve at the first sign of progressive ventricular dysfunction has been recommended to preserve ventricular function but has been of limited utility.[241]

In view of the less than optimum results with the standard procedures, more innovative approaches have been suggested.[242] For those with a VSD in association with corrected transposition, an arterial switch can be performed and, since this would create complete transposition, an atrial switch as well. This "double-switch" procedure is clearly a much more complex operation but has the advantage of leaving the left ventricle as the systemic ventricle and leaving the problematic tricuspid valve on the right side of the heart.

For those with corrected transposition, a ventricular septal defect, and pulmonary stenosis, the VSD can be closed in a way that diverts the left ventricle into the aorta and the right ventricle via a conduit into the pulmonary artery. Since this also would create transposition physiology, one needs to do an atrial switch by Mustard's or Senning's technique. Although the early mortality for this approach is about 10 percent,[243,244] it is hoped and expected that the long-term results will be superior to those of the more conventional approach.

Single Ventricle

DEFINITION

The univentricular heart, or single ventricle, is characterized by the entire flow from the two atria being carried directly through the left and/or right AV valves into the single ventricular chamber. The double-inlet type of AV connection may take the form of either one common or two separate AV valves; straddling of one AV valve sometimes is included. The VA connections may be concordant (pulmonary artery from right ventricle and aorta from left ventricle), discordant (pulmonary artery from left ventricle and aorta from right ventricle), double-outlet (both great arteries from either the left or the right ventricle), or single-outlet (atresia of one great artery). Alternatively, one of the AV valves may be atretic. This is associated with normally related great vessels or transposition of the great arteries.

PATHOLOGY

A common type of single ventricle is associated with triscupid atresia in which the ventricle has the morphology of a left ventricle. There may be normally related great vessels (type I), D transposition of the great arteries (type II), or L transposition (type III). Depending on the size of the ventricular communication with the hypoplastic right ventricle, there may be pulmonary atresia (A), pulmonary stenosis (B), or no pulmonary stenosis (C).

In a large series,[245] about two-thirds were type I, and of these about two-thirds had pulmonary stenosis (I B). Among the one-third with transposition, the most common variety is without pulmonary outflow obstruction (II C). L transposition accounts for less than 5 percent in almost all series of children with tricuspid valve atresia.

When the mitral valve is severly stenotic or atretic, the left ventricle and aorta are usually hypoplastic or atretic (hypoplastic left heart syndrome). In this situation, it is the right ventricle that is the predominant ventricle. Depending on the severity of the left-sided hypoplasia, the ascending aorta and aortic arch are usually hypoplastic as well.

When there is one large atrioventricular valve or when both AV valves are present, the valve may straddle the ventricular septum, producing one large ventricle and one small ventricle (Fig. 63-38). The most common situation (65 to 70 percent of cases) is that in which the dominant ventricular chamber has the trabecular pattern of a left ventricle and communicates through an opening, the bulboventricular foramen, with a rudimentary right ventricle.[246] The VA connection is discordant (transposition of the great arteries) in about 90 percent of these patients. In about 20 percent of cases, the dominant ventricle shows the trabecular features of a right ventricle and the rudimentary chamber shows those of a left ventricle. The majority of these patients have a double-outlet VA connection from the main chamber, and a smaller number have a single-outlet connection with pulmonary atresia.[246] In 10 to 14 percent, neither ventricular sinus can be identified; this is the so-called primitive ventricle.

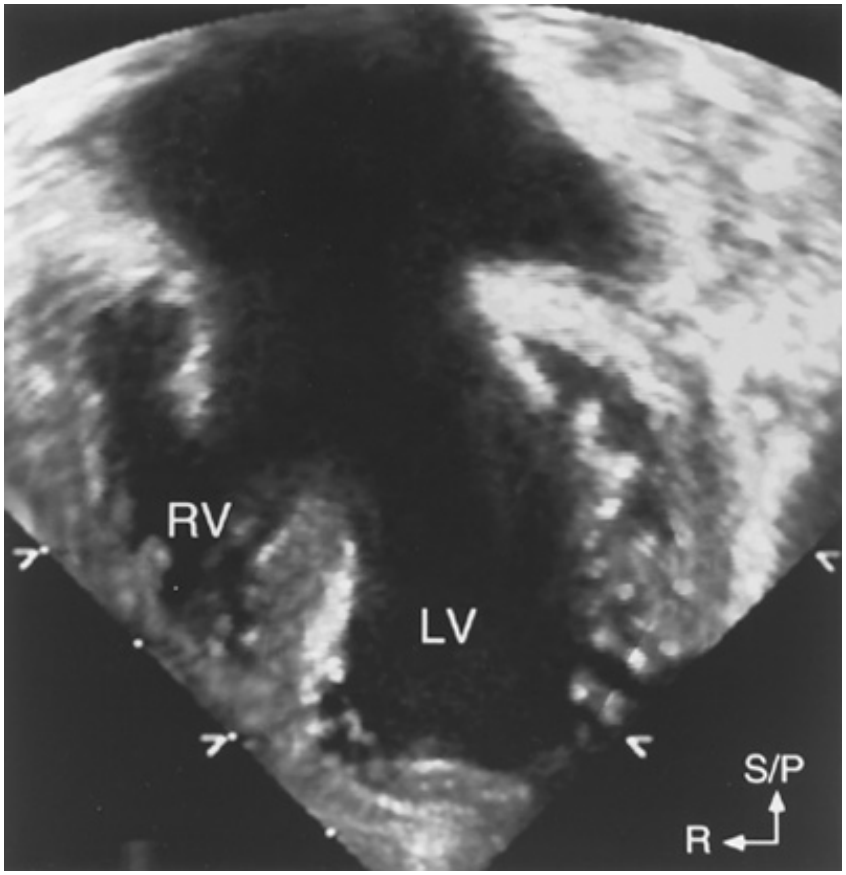


Figure 63-38: A malaligned atrioventricular canal with a large left ventricle (LV) and small right ventricle (RV). This would be repaired by a single ventricle approach (Fontan). (From Levine J and Geva T.[85] Reprinted with permission of the author and publisher.)

The term *Holmes' heart*, which is of historical interest, refers to a double-inlet left ventricle with situs solitus, normally related great arteries (SDS), an absent right ventricular sinus, and a subpulmonary infundibular outlet chamber communicating with the left ventricle via a restrictive bulboventricular foramen.[247]

ASSOCIATED CONDITIONS

Pulmonary stenosis or atresia is common. Subaortic stenosis and coarctation of the aorta occurs in association with L transposition and may result from a narrow bulboventricular foramen. In those with tricuspid or mitral atresia, an atrial communication is present.

CLINICAL MANIFESTATIONS

This complex and challenging malformation is relatively rare. The clinical picture is determined largely by the associated defects, among which pulmonary stenosis or atresia, which is present in a little over half of the patients, and obstruction to aortic flow are the most important.

All these patients have some degree of systemic hypoxemia because of mixing of the two sides of the circulation. If pulmonary stenosis or atresia is present, the presenting symptom is usually cyanosis. Without pulmonary stenosis, the presentation is usually congestive heart failure at 2 to 6 weeks of age as the pulmonary resistance falls. For those with subaortic stenosis and/or coarctation of the aorta, failure can occur within the first days of life as the ductus arteriosus closes. Physical examination depends on the combination of lesions present, but systolic ejection murmurs and a single second heart sound are very common.

Chest Roentgenogram

Almost all these patients have at least some degree of cardiac enlargement. Those with little or no pulmonary stenosis generally have very large hearts with marked pulmonary plethora. Only patients with very severe pulmonary stenosis or atresia show a nearly normal heart size and diminished pulmonary arterial blood flow.

Electrocardiogram

Evidence of right or left ventricular hypertrophy is common depending on which ventricle predominates.

Echocardiography

Two-dimensional echocardiography with Doppler color flow studies can identify the morphologic and functional features of this malformation that are necessary to establish the diagnosis and formulate a plan for clinical management.[248]

Cardiac Catheterization

A degree of systemic arterial oxygen desaturation is present in all these patients, although the severity appears to be related mainly to the volume of pulmonary blood flow. Careful recording of intracardiac and arterial pressures is essential to detect significant or potentially significant obstruction to blood flow across either AV valve, across the atrial septum, or between the ventricle and the aorta or pulmonary artery. The morphologic features of the ventricle, the relation of the aorta and the pulmonary artery, and other features can be established with high-quality selective ventricular angiography, using specially angled views to supplement conventional views.[249]

NATURAL HISTORY AND PROGNOSIS

Since by definition only one ventricle is "usable," treatment must be aimed at preserving the anatomy, physiology, and function to allow this single ventricle to support the circulation and

establishing a method for systemic venous return to go to the lungs without a second pumping chamber.

These patients usually present as newborns with cyanosis, congestive failure, or a combination of both. Those in whom pulmonary arterial pressure and blood flow are increased require surgery to prevent death from congestive heart failure or progressive PVOD. Patients with severe pulmonary stenosis or atresia require systemic-to-pulmonary arterial shunting procedures. Among patients with univentricular heart, there is a propensity for the development of subaortic obstruction[250] and AV valve regurgitation.[251] Both threaten ventricular compliance and diminish the likelihood of successful long-term palliation.[252] Survivors are subject to the threats of infective endocarditis, brain abscess, and progressive PVOD.

MEDICAL MANAGEMENT

Early recognition and identification of patients with these complex defects are important so that successful palliative surgical procedures can be carried out for the relief of congestive failure or cyanosis. PGE_1 is useful in neonates with ductal-dependent defects.[91] An adequate interatrial communication is essential for those with mitral or tricuspid atresia. For those with pulmonary stenosis or atresia, a Blalock-Taussig shunt can be livesaving. Ventricular function and AV valvular competence are preserved by early creation of a bidirectional modified Glenn anastomosis (superior vena cava to undivided pulmonary artery).[253] Subaortic stenosis or obstruction at the bulboventricular foramen can be bypassed by anastomosis of the proximal pulmonary artery to the lateral aspect of the ascending aorta while pulmonary blood flow is delivered to the distal pulmonary arterial tree through a systemic arterial or systemic venous shunt.[254,255] Digitalis and diuretics may be necessary for patients with continuing heart failure. Care should be taken that anemia or severe polycythemia does not develop and that these patients are protected adequately against infective endocarditis. The pulmonary vascular bed must be protected and ventricular function and compliance must be preserved carefully if more definitive procedures are to be considered.

SURGICAL MANAGEMENT

Long-term palliation of children with a single ventricle is usually a three-stage approach: (1) initial palliation in the perinatal period, (2) a bidirectional Glenn at 6 to 18 months of age, and (3) a modified Fontan at 1 to 3 years of age. For complex problems, a heart transplant soon after birth has been suggested.[256]

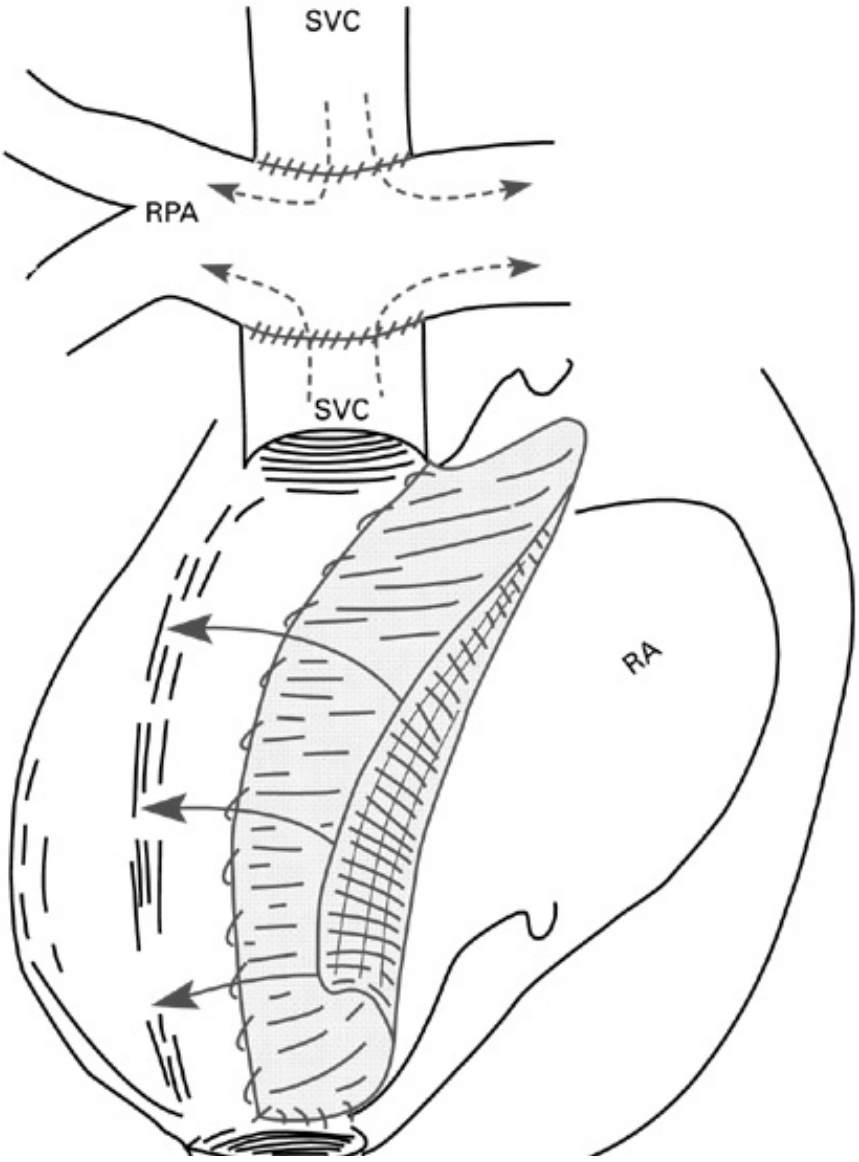
Initial palliation for patients with univentricular AV connections requires adjustment of pulmonary blood flow with a pulmonary arterial band when it is excessive or the creation of a shunt when it is diminished. The modified Blalock-Taussig shunt is preferred in neonates. Relief of aortic stenosis and the creation of an adequate atrial communication frequently are necessary as well. The prognosis is affected adversely by a single ventricle of the right ventricular type[257] and the evolution of AV valvular regurgitation[258] or subaortic obstruction.[259]

Ventricular function and AV valvular competence are preserved by early creation of a bidirectional modified Glenn anastomosis, in which the superior vena cava is divided with the caudad portion patched closed; the cephalad portion is sutured to the top of the right pulmonary artery. If pulmonary atresia is not present, the main pulmonary artery is closed.[260] Subaortic stenosis or obstruction at the bulboventricular foramen can be palliated by anastomosis of the proximal pulmonary artery to the lateral aspect of the ascending aorta, while pulmonary blood flow is delivered to the distal pulmonary arterial tree through a systemic arterial or systemic venous shunt (the Damus-Kaye-Stansel operation). Other surgical options for the relief of subaortic obstruction are direct enlargement of the bulboventricular foramen (VSD), the modified

Norwood operation,[255] and the arterial switch operation.[261]

Although initially some types of single ventricle were repaired by dividing the common chamber into the right and left ventricles, this has largely been abandoned because of unacceptably high initial mortality resulting from problems in connecting the ventricles to the appropriate great vessels without interfering with the atrioventricular valves and the high incidence of complete heart block.

The current approach is a modification of the principal suggested by Fontan and Baudet[262] to bypass the right side of the heart, directing systemic venous blood directly to the pulmonary arteries and allowing the single functioning ventricular chamber to pump blood to the systemic circulation. First, if it has not been done already, a bidirectional Glenn anastomosis is constructed (see above), and then an intraatrial tunnel is constructed to divert the inferior vena caval blood to the caudad portion of the superior vena cava, which then is connected to the underside of the right pulmonary artery (Fig. 63-39). A fenestration in the baffle sometimes is used to decompress the right side in the perioperative period. Recently, instead of tunnelling within the atrium, an external conduit has been used between the inferior vena cava (IVC) and the right pulmonary artery ligating the IVC-right atrial junction. The single ventricle is thus relieved of the burden of the volume overload and ventricular hypertrophy required to maintain the pulmonary circulation and is asked only to deliver systemic cardiac output.[262]



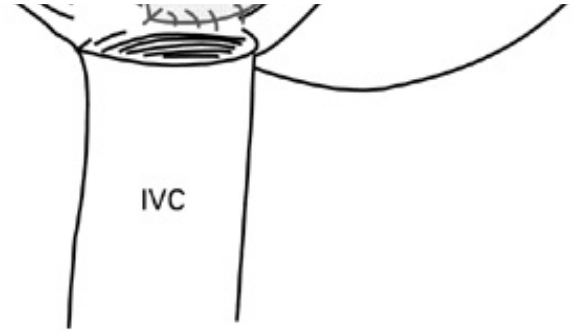


Figure 63-39: The modified Fontan operation. The superior vena cava (SVC) is divided. The cephalad portion is anastomosed to the superior aspect of the right pulmonary artery (RPA), and an intraatrial baffle is constructed from the inferior vena cava (IVC) to the superior vena cava along the lateral wall of the right atrium (RA). The caudad portion of the SVC then is connected to the inferior aspect of the right pulmonary artery.

The surgical risks depend on patient selection. For those with complex forms of single ventricle and those with elevated pulmonary pressure or resistance, ventricular dysfunction, or atrioventricular valve regurgitation, the risks are increased. For those without risk factors and with tricuspid atresia or double-inlet left ventricle, the risks are less than 5 percent.[263] Even for those with some risk factors or with more complex disease, at some centers the mortality is under 10 percent.[263,264]

For children with hypoplastic left heart syndrome, the survival from the three-stage procedure (initial Norwood, bidirectional Glenn, and Fontan) is approximately 50 percent,[265] although some centers are reporting a survival rate as high as 76 percent.[266] There does not seem to be any significant difference in survival in centers that use the three-stage anatomic "repair" from primary heart transplantation in the perinatal period at 36 months of age.[265]

Quality and length of life are clearly improved, but persistent problems (AV valvular regurgitation, systemic embolization, limitation of exercise tolerance, protein-losing enteropathy, atrial arrhythmias, and deterioration of ventricular function) occur with a frequency of about 1 percent per year.[263] For patients with progressive deterioration, cardiac transplantation is recommended.

PREVIOUS | NEXT

Chapter 63: THE PATHOLOGY, PATHOPHYSIOLOGY, RECOGNITION, AND TREATMENT OF CONGENITAL HEART DISEASE

CONGENITAL ABNORMALITIES OF THE CORONARY ARTERIAL CIRCULATION

Coronary Arteriovenous Fistula

PATHOLOGY

A coronary arteriovenous fistula is a fistulous communication between a coronary artery and a cardiac chamber, the coronary sinus, or the pulmonary trunk (Fig. 63-40).

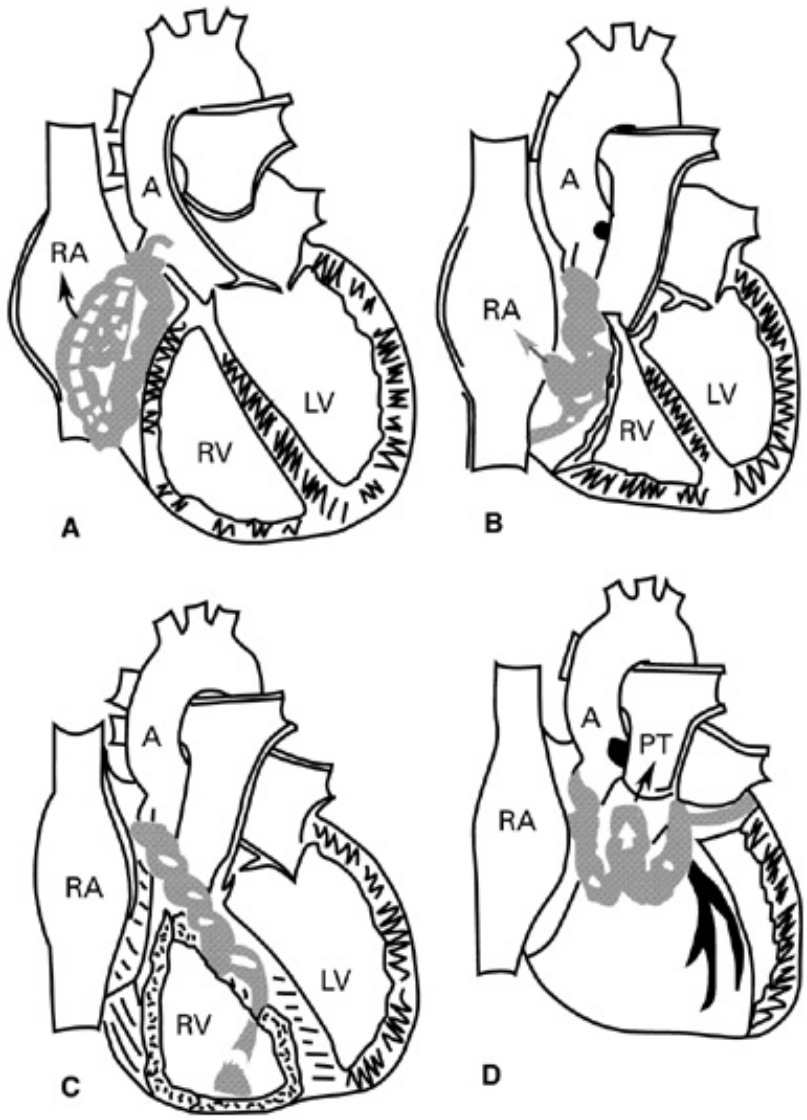


Figure 63-40: Anomalous communications of coronary arteries. *A.* Right coronary artery communicates with coronary sinus. *B.* Right coronary artery communicates with right atrium (RA). *C.* Anomalous communication of right coronary artery with right ventricle (RV). *D.* Two

coronary arteries arise from the aorta (A) and make collateral communication with accessory coronary artery arising from pulmonary trunk (PT). LV = left ventricle.

The site of origin may involve any of the epicardial coronary arteries. *The right coronary artery is the site of origin in somewhat over half the cases, and the two most common sites into which the fistula feeds are a cardiac vein (usually the coronary sinus) and the right ventricle*. Although solitary communication is the rule, there may be multiple sites of termination. A fistula into the pulmonary trunk usually is characterized by one or more vessels opening into the pulmonary trunk and connecting with branches of each of the two main coronary arteries. The artery or arteries feeding the fistula are grossly enlarged and tortuous. Saccular aneurysms may develop in segments of dilated vessels; such aneurysms usually are observed in adults and frequently show calcification of the wall.

CLINICAL MANIFESTATIONS

Many patients with a coronary arteriovenous fistula are asymptomatic.[267,268] In some, the magnitude of the shunt into the right side of the heart is great enough to cause congestive heart failure, with a tendency for this to occur in early infancy or after 40 years of age. The classic finding is that of a continuous murmur with an unusual location, since it is loudest over the fistula. It may have a louder diastolic component, especially if communication is with the right ventricle. In those with large shunts, there may be cardiomegaly and increased pulmonary flow shown by chest roentgenography and right ventricular hypertrophy shown by ECG. Transthoracic echocardiography is usually diagnostic in children;[269] transesophageal studies may be necessary in adults. At cardiac catheterization, an increase in oxygen saturation may be encountered, usually in the right atrium or right ventricle, if the shunt is large enough. Selective coronary arteriography will demonstrate the involved coronary artery and the site of entry of the fistula. The most common complication is infective endocarditis, but thrombosis, myocardial ischemia, and rupture may occur.

SURGICAL MANAGEMENT

Except for very small fistulas, closure is recommended, since the flow tends to increase with age and these patients are at risk for infective endocarditis, congestive heart failure, and myocardial ischemia. Until relatively recently, closure was invariably surgical. Occasionally, closure was done without a coronary bypass by placing obliterating mattress sutures across the fistula beneath the coronary artery as it passes over the surface of the heart.[270] More commonly, cardiopulmonary bypass is preferred for safe exposure of large or multiple fistulas, such as those entering the right atrium near the junction of the superior vena cava and the right atrium, those arising from the artery to the sinoatrial node, and those between the left coronary artery and the left ventricle.[271] The orifice of the fistula is obliterated by direct suture or the placement of a Dacron or pericardial patch. Fistulas have been closed from within the open coronary artery; the artery then is repaired by direct suturing. Surgical mortality should be minimal;[271] the long-term results have been favorable.[272]

Fistulas have been closed by interventional catheterization techniques. Perry and associates[273] attempted to close fistulas in nine patients: four from the left circumflex artery, three from the left anterior descending artery, and two from the right coronary artery. Gianturco coils were used in six patients and a double-umbrella in two, with coils and an umbrella used in one. All were completely occluded. In three patients with multiple fistulas, no attempt was made in the catheterization laboratory and the patients were referred for surgery. This "noninvasive" technique seems to be applicable to some children and adults with coronary AV fistulas, although long-term follow-up is necessary to be certain that the fistulas do not recur.

Origin of the Left Coronary Artery from the Pulmonary Artery

PATHOLOGY AND PATHOPHYSIOLOGY

In this anomaly, the left coronary artery arises from the pulmonary artery rather than from the aorta (Fig. 63-41). In the perinatal period, the pulmonary artery pressure is high and the left coronary is perfused with venous blood. Problems arise when the pulmonary resistance and pulmonary artery pressure fall and the diastolic pressure is insufficient to perfuse the left ventricular myocardium. In the absence of collateral vessels from the right coronary, left ventricular ischemia and eventually infarction of the left ventricular wall and papillary muscles occur. This in turn leads to congestive heart failure, usually by 3 to 8 weeks of age.

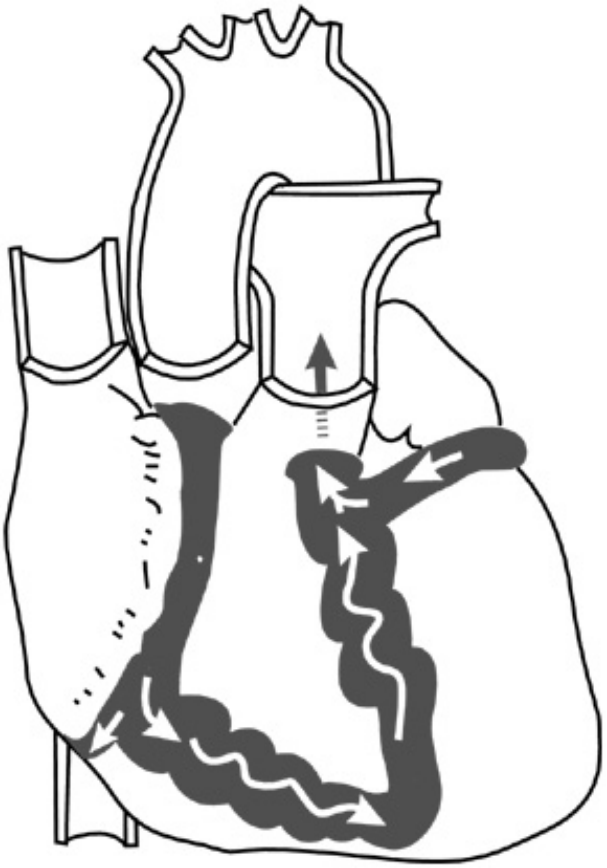


Figure 63-41: Anomalous origin of the left coronary artery from the pulmonary trunk. With time, wide collaterals develop between the two coronary systems so that right coronary arterial blood is shunted into the left coronary system and thence into the pulmonary trunk.

In a small group of children, extensive collaterals between the right coronary (arising normally from the aorta) and the left system develop. Perfusion via the right may be sufficient to oxygenate the left ventricular myocardium so that no ischemia develops. Over time, the higher perfusion pressure in the aorta may allow a left-to-right shunt into the pulmonary artery through the right and then the left coronary system. Eventually this may lead to a "steal" of blood from the myocardium into the lower-resistance pulmonary circuit.

CLINICAL MANIFESTATIONS

The clinical spectrum and mode of presentation in patients with this abnormality vary.[274,275] The majority of these patients present at 6 to 12 weeks of age. Acute episodes of irritability, profuse cold sweating, pallor (? angina), and respiratory distress occur, with evidence of heart failure. Less

often, these patients present at an older age with mitral regurgitation and heart failure. A few reach adolescence or adulthood with no or relatively few symptoms other than occasional exertional angina or palpitations. Sudden death may be the first and only sign of this condition.

On physical examination, the heart is enlarged, with an abnormal left ventricular apex impulse. Other signs of failure are usually present. Pallor and clammy skin are common. In some patients, a soft continuous murmur is heard at the upper left sternal border. This murmur is more prominent in older patients, presumably because of the development of a more extensive collateral circulation. The murmur of mitral regurgitation may be heard at the apex, radiating to the axilla; however, in young infants with heart failure, there can be a surprising degree of regurgitation without a distinctive murmur.

In those with heart failure, the chest roentgenogram typically shows marked enlargement of the heart with posterior displacement of the esophagus by a large left atrium. There is pulmonary edema, and there may be atelectasis of the left lower lobe because of bronchial compression. Those with good collaterals and no left ventricular failure may have a normal x-ray.

In the infant group, the ECG demonstrates the pattern of anterolateral infarction, with deep Q wave in leads I and aV_L and abnormal R-wave progression across the precordium. Arrhythmias are common. The horizontal loop of the vectorcardiogram is clockwise and posteriorly oriented. The echocardiogram shows marked enlargement of the left atrium and ventricle with little or no left ventricular wall motion. The origin of the coronary artery can be imaged, and flow can be seen toward the pulmonary artery instead of toward the heart.[276] Myocardial perfusion imaging with thallium-201 can help distinguish an anomalous coronary artery from congestive cardiomyopathy.[277]

At cardiac catheterization, there may be an increase in saturation in the pulmonary artery if there is enough retrograde flow. There is usually some pulmonary hypertension, with very elevated pulmonary wedge pressure. Aortography or selective right coronary arteriography demonstrates the collateral circulation filling the left coronary artery retrogradely, with at least faint opacification of the main pulmonary artery.

MANAGEMENT

The natural history and prognosis are related by the modes of presentation. Those who present in infancy die without surgical intervention. Medical management is aimed at control of congestive heart failure and arrhythmias before a surgical procedure.

Four approaches have been used for surgical repair. The first, which is of historical interest only, is ligation of the left coronary artery to eliminate the coronary artery-to-pulmonary artery shunt that acts as a coronary artery steal. Many children benefited from this procedure, but there continued to be myocardial ischemia and late sudden death was not eliminated. The second approach was to tunnel the coronary artery inside the pulmonary artery to the wall of the aorta and create an aortopulmonary window.[278] This usually required an external roofing of the pulmonary artery to allow egress of flow from the right ventricle. Although this surgical approach has the advantage of making a two-coronary system, a high proportion of children developed supravalvular pulmonary stenosis at the site of the intrapulmonary artery tunnel. This procedure is now used rarely. More recently, as coronary artery reimplantation has become more common in the arterial switch operation for transposition of the great arteries, surgeons have removed the anomalous coronary artery with a button of pulmonary artery and reimplanted it onto the aorta.[279] Finally, in a few older patients, saphenous vein grafting or internal mammary artery implantation has been used.[280]

The late results after surgery have been quite good.[279,281] The congestive heart failure frequently

improves, the heart becomes smaller, the left ventricular shortening fraction improves, and mitral regurgitation tends to regress. Interestingly, the infarction pattern on ECG with deep anterolateral Q waves frequently disappears, suggesting that the poor function is due to extreme ischemia rather than infarction (hybernating myocardium).[282]

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Figure 63-9: Atrial septal defect at fossa ovalis with left-to-right shunt. SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; PT = main pulmonary arterial trunk; RPA = right pulmonary artery; LPA = left pulmonary artery; RPV = right pulmonary vein; LPV = left pulmonary vein; LA = left atrium; LV = left ventricle; AO = aorta. (From Edwards JE.[66] Reproduced with permission from the publisher and author.)

Figure 63-10: Chest roentgenogram of a 4-year-old child with a secundum atrial septal defect, a large left-to-right shunt, and normal pulmonary arterial pressures. *A*. Frontal. *B*. Lateral. Right ventricular enlargement (seen in the lateral view) accompanies prominence of the main pulmonary arterial segment and increased blood flow. No left atrial dilation is present.

Figure 63-11: Three-dimensional echocardiogram of a secundum atrial septal defect (ASD). This is a right atrial en-face view that shows the size, shape, and position of the defect in relation to the right atrial septal surface. Ao = aortic valve; TV = tricuspid valve; IVC = inferior vena cava. Courtesy of Dr. Gerry Marx.

Figure 63-12: *A*. Sinus venosus type of atrial septal defect, with its constantly accompanying anomalous pulmonary venous connection of superior pulmonary vein (SPV) to superior vena cava (SVC). *B*. Repair is effected with a pericardial patch placed to divert pulmonary venous blood across the defect into the left atrium and to divert superior vena caval blood to the right atrium. (This illustration appeared originally in the first edition of *The Heart*, in 1966, and in all subsequent editions. It is reproduced here by courtesy of Dr. John W. Kirklin, Birmingham, Alabama.)

Figure 63-13: Common AV canal of the partial type. The mitral valve shows a cleft in its anterior leaflet, while the tricuspid valve is undisturbed. SVC = superior vena cava; IVC = inferior vena cava; RA = right pulmonary artery; LPA = left pulmonary artery; RPV = right pulmonary vein; LPV = left pulmonary vein; LV = left ventricle; Ao = aorta. (From Edwards JE.[66] Reproduced with permission from the publisher and author.)

Figure 63-14: Complete form of common AV canal, type A. The common anterior leaflet has a recognizable mitral component (MV) and tricuspid component (TV). In type B, not illustrated, those components are attached by chordae to a papillary muscle in the right ventricle. In type C, not illustrated, the common anterior leaflet is a single unit without any attachment to the underlying ventricular septum. Type A is most amenable to repair. RV = right ventricle; RA = right atrium. (From Rastelli GC et al.[82] Reproduced with permission from the publisher and authors.)

Figure 63-15: Apical four-chamber view of complete common AV canal. Note the large deficiency of both atrial and ventricular septa as well as apical displacement of the AV valves. The arrow points to the attachment of the inferior bridging leaflet to the ventricular septal crest. (From Levine J and Geva T.[85] Reproduced with permission.)

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Figure 63-29: Classic tetralogy of Fallot. There are infundibular and pulmonary valvular stenoses. There is also right-to-left shunting at the atrial level. SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; RPA = right pulmonary artery; LPA = left pulmonary artery; RPV = right pulmonary vein; LPV = left pulmonary vein; LA = left atrium; LV = left ventricle; Ao = aorta. (From Edwards.[66] Reproduced with permission from the publisher and author.)

Figure 63-30: Two-dimensional echocardiogram in parasternal view in a patient with Ebstein's anomaly of the tricuspid valve (TV). Numerous attachments of the tricuspid valve (*arrowheads*) to the interventricular septum and right ventricular apex are seen. LV = left ventricle; LA = left atrium.

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DC Jr, Spencer FC, eds. *Surgery of the Chest.* 5th ed. Philadelphia: Saunders; 1990. Reproduced with permission from the authors and publisher.)

Figure 63-36: Double-outlet right ventricle. *A.* With subaortic ventricular septal defect without pulmonary stenosis. *B.* With subaortic ventricular septal defect and subpulmonary stenosis (Subpul. stenosis). *C.* With subpulmonary, supracristal ventricular septal defect. The so-called Taussig-Bing complex. RA = right atrium; RV = right ventricle; CS = crista supraventricularis; LA = left atrium; PT = main pulmonary arterial trunk.

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Figure 63-38: A malaligned atrioventricular canal with a large left ventricle (LV) and small right ventricle (RV). This would be repaired by a single ventricle approach (Fontan). (From Levine J and Geva T.[85] Reprinted with permission of the author and publisher.)

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Part 10: CONGENITAL HEART DISEASE
Chapter 64:

CONGENITAL HEART DISEASE IN ADULTS

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Congenital heart disease occurs in 5 to 10 per 1000 live births.[1] Without early treatment, the majority of patients would die in infancy or childhood, with only 5 to 15 percent surviving until puberty.[2] The advent of surgical procedures, from ligation of a patent arterial duct[3] in 1939 to the innovations of the 1990s, as well as advances in medical treatment, has transformed the outlook for children with even complex defects. The majority now survive into adolescence and adult life (Chap. 63). This success story has radically altered both the size and complexity of the population of young adults with congenital heart disease. In the United States alone, well over a half-million patients with functionally important congenital cardiac malformations have reached adulthood in the past three decades.[4] Despite the fact that most patients now surviving to adult life will have undergone surgery during childhood, "total correction" is not the rule.[5] The term *total correction* is itself a misnomer, perhaps with the exception of the successfully ligated ductus arteriosus without residua. The misperception of "cure" leads adults not to seek understanding of their anomaly, to fail to follow endocarditis prophylaxis, and to fail in pursuing continued cardiac care. The majority, if not all, require long-term surveillance, and many need reoperation. Other adults may require their first operation for congenital heart lesions that were well tolerated during childhood.

Both the "natural" survivors and the postoperative patients require specialized medical care. Arrhythmia is common, as are residual or deteriorating hemodynamic problems and endocarditis. Although cardiologists specializing in the care of adults may be expert in one or more of these areas, the critical relationship between rhythm and hemodynamic status in hearts with complex circulations (as after a Fontan operation or after intraatrial repair for transposition) may lead to treatment errors by those inexperienced in the treatment of congenital heart defects. Patients with cyanosis require special care because of erythrocytosis, bleeding, renal problems, and arthropathy; moreover, they require specific counseling and management regarding pregnancy. In addition to the medical problems, psychosocial problems such as the search for employment, life and health insurance, participation in sports, sexual activity, and contraception are of great importance to adolescents and young adults with congenital heart disease. Many of the "normal" ordeals of growing up are more difficult for this group, in whom chronic illness, embarrassing scars, and/or exercise limitation may inhibit normal social intercourse and maturation.

Over the last few years, the specialist needs of this growing population have begun to be appreciated. In addition to the challenge of continuing the expert care of their complex cardiac problems from the pediatric environment into the much wider adult medical community, knowledge of the long-term fate of patients with congenital heart disease is essential for pediatric cardiologists in order to refine initial management strategy. A rather short-term view of "success" or "failure" has been encouraged by rapid changes in medical and surgical policies over the last three decades. Nevertheless, there are clear examples, such as the management of transposition of the great arteries, where awareness of long-term problems has altered the primary surgical approach. The Mustard or Senning procedures (see below) provide a physiologic repair at acceptably low risk but may result in long-term systemic ventricular dysfunction, arrhythmias, and sudden death. This has enabled the introduction of anatomic repair by the arterial-switch procedure, despite high surgical mortality in the early series, with the expectation of a more satisfactory long-term outcome. Other debates, over such issues as the place of Fontan operations, cavopulmonary anastomosis, and systemic-to-pulmonary shunts, are not yet resolved and will be strongly influenced by the accumulation of rigorously collected outcome data, not merely for survival but also for morbidity and quality of life.

The optimal solutions for delivery of care to the adult with congenital heart disease will depend on the different medical systems in operation around the world. The common requirements include collaboration between pediatric and adult cardiologists; the establishment of a few specialist centers with appropriate medical, surgical, anesthetic, and nonmedical staff together with investigational facilities; the establishment

of treatment guidelines, and centralization of accumulating knowledge.[6] The report of a consensus conference on adult congenital heart disease commissioned by the Canadian Cardiovascular Society represents an important step forward.[7] This includes recommendations for training and a hierarchy of care from the community to the specialist center. Similar training guidelines have been published in the United States.[8]

MEDICAL CONSIDERATIONS

Many young adults with congenital heart disease have mild lesions that have not required and may not ever require surgery. The commonest defects in this category are small ventricular septal defect, mild pulmonary valve stenosis, mild aortic valve stenosis, and mitral valve prolapse (Table 64-1). Such patients need infrequent follow-up (e.g., biannual) to assess any progression in severity of the lesion, to reinforce the need for antibiotic prophylaxis against infective endocarditis (Chap. 73), and to obtain psychosocial advice. Other patients reach adult life with more complex defects that are still unrepaired. Some may still be candidates for palliative or definitive surgery, whereas in others surgery may no longer be possible, often because of the presence of irreversible pulmonary vascular disease. More and more survivors of surgery in childhood are now reaching adult life; they now form the largest group of patients (Table 64-2). The majority need continuing medical surveillance, since late cardiovascular problems may result from hemodynamic disturbances, arrhythmia, and endocarditis. Such patients can also develop noncardiac problems as a consequence of their heart disease (e.g., secondary to cyanosis) and are, of course, susceptible to all the potential acquired "medical problems" of adulthood.

Table 64-1: Common Congenital Heart Defects Compatible with Survival to Adult Life without Surgery or Interventional Catheterization

Mild pulmonary valve stenosis
Peripheral pulmonary stenosis
Bicuspid aortic valve
Mild subaortic stenosis
Mild supravalvar aortic stenosis
Small atrial septal defect
Small ventricular septal defect
Small patent ductus arteriosus
Mitral valve prolapse
Ostium primum atrial septal defect (atrioventricular septal defect)
Marfan's syndrome
Ebstein's anomaly
Corrected transposition (atrioventricular-ventriculo-arterial discordance)
Balanced complex lesions (e.g, double-inlet ventricle with pulmonary stensosis)
Defects with pulmonary vascular obstructive disease (Eisenmenger's syndrome)

Table 64-2: Common Congenital Heart Defects Surviving to Adult Life after Surgery/Interventional Catheterization

Aortic valve disease, valvotomy or replacement
Pulmonary stenosis, valvotomy
Tetralogy of Fallot
Atrial septal defect
Ventricular septal defect
Atrioventricular septal defect
Transposition of the great arteries, atrial redirection
Complex transposition of the great arteries
Total anomalous pulmonary venous connection
Pulmonary atresia/ventricular septal defect
Fontan operation for complex congenital heart disease
Ebstein's anomaly
Coarctation of the aorta
Mitral valve disease

Hemodynamics

Study of the hemodynamic consequences of repaired and unrepaired congenital heart disease is a crucial aspect of long-term follow-up. Progressive congestive cardiac failure secondary to myocardial deterioration is the most common cause of disability and death in patients whose ventricles may have been subjected to many years of volume and pressure loading, often with chronic hypoxia. A significant number of the adult postoperative patients with congenital heart disease have been repaired at older ages than is the current practice. This may result in greater preoperative damage and pulmonary vascular disease, which may persist postoperatively. In the early era of open-heart surgery, myocardial protection was sometimes less than optimal, resulting in myocardial damage.

It should also be appreciated that postoperative circulations created by the repair of many congenital heart defects result in an adequate physiologic repair (e.g., deoxygenated blood to lungs and oxygenated blood to the body) but often have far from normal anatomy. For example, after the Mustard and Senning operation for transposition of the great arteries, the right ventricle remains on the systemic side of the circulation. Some of these patients have evidence of deteriorating right ventricular function, and there is increasing concern that this will become a major life-threatening problem with longer follow-up.[9] Similar concerns have been expressed for systemic ventricular function after the Fontan operation.[10] The different morphologic characteristics and loading conditions for these ventricles suggest that standard indices of ventricular function, derived from studies of structurally normal hearts, may be inappropriate for such patients (see also Chap. 20).[11] Prospective serial studies are beginning to define "normal ranges" for congenital heart defects and to examine their "natural" and "unnatural" history.[12]

Residual hemodynamic defects are often present in repaired patients and may cause problems even many years after surgery. These may be amenable to further surgery (see below) or require long-term medical treatment. Medical management of cardiac failure in patients with congenital heart disease is adopting therapies shown to be of benefit in large-scale clinical trials of patients with heart failure from predominantly cardiomyopathy or ischemic heart disease.[13-15] Appreciation of ventricular "remodeling" and the effect of neurohumeral responses on symptoms and disease progression has led to increasing and earlier use of angiotensin-converting enzyme inhibitors and, in some cases, beta blockers and long-acting calcium antagonists in addition to standard therapy with digoxin and diuretics (see Chap. 21). These agents

may also slow the rate of progressive deterioration in ventricular function reported in certain congenital heart diseases even when they have been adequately "corrected."

Cyanosis

Adults with congenital heart disease may have central cyanosis from right-to-left shunting secondary to their unrepaired cardiac defect or to pulmonary vascular disease (Eisenmenger's syndrome; see Chap. 63). The latter complication should be seen less frequently in years ahead as a result of the trend toward early recognition and repair of congenital heart disease in infancy. Currently, however, a significant number of patients reach adult life with pulmonary vascular disease as a result of lesions such as large ventricular septal defect, atrioventricular (AV) septal defect, truncus arteriosus, and double-outlet right ventricle. Their pulmonary vascular resistance may already have been too high for surgical repair at the time of diagnosis; in others, pulmonary vascular disease may have progressed despite repair of the congenital heart defect.

Chronic cyanosis may lead to erythrocytosis and hyperviscosity. Many patients with cyanotic congenital heart disease establish a stable high hematocrit but few symptoms of hyperviscosity.[16] They have a low risk of stroke and do not require venesection.[17] In others, the hemoglobin concentration may rise progressively. Once it exceeds 20 g/dL, they are at risk from thromboembolic complications and may suffer from headache, dizziness, and fatigue. Symptoms may be improved with judicious venesection by the removal of 500 mL of blood and volume replacement with normal saline or dextrose solution.[17,18] Overzealous venesection, however, may result in both acute and chronic problems, including cardiovascular collapse in patients with Eisenmenger's syndrome, iron depletion, microcytosis, and hyperviscosity in its own right.[19] The paradoxical anemia of erythrocytotic patients with iron deficiency due to repeated phlebotomy may be missed and indeed has been shown to increase the risk of stroke.[20] It has been demonstrated that phlebotomies and microcytosis were strongly associated with stroke, perhaps due to the fact that iron-deficient red blood cells are less deformable than are normal red blood cells and do not pass through the microcirculation as readily as do iron-replete cells.

Patients with chronic cyanosis also develop defective hemostasis from abnormalities in platelet function and in the coagulation and fibrinolytic systems,[19,20] especially patients with marked erythrocytosis. The risk of hemorrhage, especially at surgery, is well recognized and may be fatal. Hyperuricemia is common because of increased red cell turnover and renal dysfunction. Arthralgia is well recognized, but gouty arthritis is rare and may be misdiagnosed. Renal impairment can deteriorate to renal failure as a result of relatively minor interventions, such as injection of contrast medium at angiography or the injudicious use of nonsteroidal anti-inflammatory agents.[21,22] Patients with right-to-left shunts are at risk of paradoxic embolus, which may cause a cerebrovascular accident or renal infarction. Air filters must be utilized with all intravenous lines. A cerebral abscess is a well-known complication of a septic embolus and must always be considered in the cyanotic patient with any neurologic symptoms, however transient, or low-grade fever. Facial and truncal acne is common, and is not only a cosmetic problem but a potential source of sepsis. A specific concern has been the safety of air travel in adults with cyanotic congenital heart disease, since in-flight atmospheric conditions on commercial jets approach altitude equivalents of 6000 to 8000 ft (1829 to 2438 m). In a recent report, however, only modest (approximately 6 percent) decreases in systemic arterial oxygen saturation were found, with no adverse effects.[23]

Progressive kyphoscoliosis has been recognized for many years as a complication of congenital heart disease.[24] It is common in cyanotic patients and those with previous thoracotomy. The degree of deformity, if left untreated, may become profound and compromise pulmonary function. Treatment with bracing or insertion of a Harrington rod may be indicated, since the kyphoscoliosis may significantly reduce both the quality and quantity of life. Surgical repair is not possible, however, in those with Eisenmenger's syndrome, since the surgical risk is too high.

The prognosis for patients with Eisenmenger's syndrome depends on the site of the lesion and the medical and cardiac care they receive.[25-27] Death may result from right-sided heart failure, pulmonary hemorrhage, or arrhythmia. It can also occur prematurely due to potentially avoidable complication, such as inappropriate drug therapy or injudicious general anesthesia. Special care must be employed during noncardiac surgery, utilizing cardiac anesthesia, maintenance of preload, and cardiac monitoring.[28] Recent data suggest promise for chronic prostacyclin therapy in reducing pulmonary artery pressure, but this is

preliminary.[29]

Infective Endocarditis

Patients with both unoperated and operated congenital heart disease are at risk from infective endocarditis. Lifelong antibiotic prophylaxis is recommended, but the specific indications and optimal regimens are still debated.[30,31] The American Heart Association Special Report on Prevention of Infective Endocarditis has stratified risk groups for the various lesions.[31] Prophylaxis is advocated for all lesions except isolated secundum atrial septal defect and repaired secundum atrial septal defect, ventricular septal defect, or patent ductus arteriosus without residua beyond 6 months (see Chap. 73). The wide variety of portals of entry includes dental work, skin sepsis, obstetric and gynecologic procedures, genitourinary and gastrointestinal interventions, and surgery.[32,33] There is also a risk of bacteremia and infective endocarditis in young adults who have their ears pierced or acquire a tattoo.[34] Patients must be educated and preferably should carry an information card with them. The symptoms of endocarditis may be subtle, and the diagnosis must be considered in any patient who experiences unexplained malaise or fever. Injudicious prescription of antibiotics without previous blood culture may mask the problem and make bacteriologic diagnosis and appropriate treatment difficult. Both general measures, such as oral hygiene as well as skin and nail care, and appropriate antibiotic treatment are important. Among 102 patients with congenital heart disease who filled in a questionnaire, there was a disturbing lack of knowledge about endocarditis prevention measures and indeed about their cardiac lesion in general.[35]

Electrophysiologic Problems

Arrhythmias and conduction defects have a major impact on the prognosis and management of both unoperated and operated patients and have been linked to sudden death in a number of conditions.[36,37] The principles of diagnosis and treatment are similar to those employed in patients with arrhythmia due to other causes (see Chap. 24), with some important exceptions. Rhythm disturbances that may be benign in a structurally normal heart may be life-threatening in congenital heart disease. Restoration of sinus rhythm is usually much more important, and rate control of atrial arrhythmias is usually not a good treatment option. Special consideration must be given before the use of therapies that may have negative inotropic properties. In unoperated patients, chamber dilatation, myocardial hypertrophy, and fibrosis may all contribute to the genesis of arrhythmia. In operated patients, additional sinus or AV node damage and atrial and/or ventricular scarring may cause electrophysiologic problems. The etiology is multifactorial, and the clinical significance of arrhythmia depends very much on the hemodynamic context in which it occurs.

Supraventricular arrhythmia and sinus node injury, not surprisingly, occur most often in conditions with "atrial defects" or those requiring atrial surgery.[38,39] Abnormalities of sinus node function are common in patients with atrial septal defect, particularly the sinus venosus type,[40] and are often seen after Mustard or Senning operation for transposition of the great arteries.[41] Sinus node dysfunction has also been reported after surgery for tetralogy of Fallot, the Fontan procedure, and many other operations for congenital heart lesions.[42] Clinical manifestations include sinus bradycardia, sinoatrial block, sinus arrest, and occasionally the tachybradycardia syndrome with paroxysmal atrial flutter and fibrillation. Although bradycardia has been postulated as the cause of sudden death in some conditions, current evidence indicates that tachyarrhythmia is usually a more likely explanation (see below).[41]

In sinus node disease, insertion of a pacemaker is indicated for patients with symptoms resulting from a slow heart rate, such as tiredness, dizziness, and syncope or for an extremely low heart rate (see Chap. 31). Indications in asymptomatic individuals are still controversial, since the arrhythmia is benign in many cases. It should be noted that pacing may be difficult because of the complex underlying anatomy and lack of a suitable site for endocardial lead fixation.[43] The choice of pacemaker will depend on the precise indication. The simplest VVI pacemaker may be adequate prophylaxis against bradycardia-related sudden death. In general, however, rate-responsive pacemakers are preferable, and dual-chamber pacing may provide the best hemodynamics (see also Chap. 31).[44,45]

Injury to the AV node and proximal conduction tissue may result from surgery for lesions such as ventricular septal defect, AV septal defect, or tetralogy of Fallot. Transient complete AV block in the

postoperative period has been shown to have prognostic significance in some reports, particularly if the site of damage is below the bundle of His. In a 30-year follow-up of ventricular septal defect repair at the Mayo Clinic, the development of transient complete heart block for over 72 h followed by resumption of sinus rhythm was a strong independent predictor of late mortality.[46] Whether transient perioperative AV block warrants permanent pacing and whether an invasive electrophysiologic study can help stratify risk are unresolved.[38] Postoperative right bundle-branch block is frequent after ventriculotomy and may be due to injury related to closure of a ventricular septal defect or to interruption of distal Purkinje fibers by ventriculotomy or muscle resection.[37,38] Occasionally, the electrocardiographic (ECG) pattern of right bundle-branch block with left-axis deviation occurs (bifascicular block), and there may also be PR-interval prolongation (trifascicular block).[47,48] Early reports suggested that these findings were harbingers of sudden cardiac death due to complete heart block.[49] More recent studies, however, have not substantiated this adverse prognosis.[50]

Tachyarrhythmias can be life threatening. Late sudden death has been reported in several lesions, both before and after repair. In general, the worse the disease (i.e., more complex anatomy and/or more extensive surgery), the greater the incidence of sudden death, although aortic stenosis and coarctation are also represented in this group. Studies suggest that the risk increases incrementally 20 years after surgical repair.[51] The identification of patients at risk and their management are important but controversial issues. After the Mustard and Senning operation, atrial flutter with a rapid ventricular response is dangerous, especially when it occurs in association with right ventricular dysfunction or venous pathway obstruction.[52] Medical or electrical cardioversion should be promptly used to restore sinus rhythm, and drug therapy may need to be accompanied by pacemaker insertion. Recently, ablation (surgical or catheter) has been advocated for certain cases of atrial flutter (see Chap. 28). Atrial tachyarrhythmias are also common after the Fontan operation; sinus node injury, atrial suturing, and a dilated hypertensive right atrium probably contribute.[42,51] Modification of the operation to exclude the right atrium from the Fontan circuit, the total cavopulmonary connection, may reduce the incidence of potentially serious early and late rhythm disturbances.[53,54]

Ventricular arrhythmias are known to occur after open-heart surgery, particularly repair of tetralogy of Fallot.[48,55] Studies using ambulatory ECG monitoring in postoperative patients have documented asymptomatic complex ectopy and nonsustained ventricular tachycardia in up to 50 percent of patients,[55-57] and more than 20 percent have inducible ventricular tachycardia at electrophysiologic study.[58,59] Experimental and clinical studies have shown that the electrical substrate for reentry arrhythmia is present in the right ventricle.[60] In several reports, older age at surgery is a predisposing factor,[57,61] an observation that suggests factors present at the time of repair may be involved in the genesis of postoperative arrhythmia, in addition to the myocardial damage occurring at the time of surgery or during postoperative follow-up.[62] This is consistent with morphologic studies that have documented increasing fibrosis of the right ventricle as part of the natural history of defects such as tetralogy of Fallot.[63] The current practice of early surgical repair for tetralogy of Fallot may reduce the incidence of such postoperative ventricular arrhythmia, and encouraging preliminary data support this view.[62,64] Other postulated risk factors include elevated right ventricular systolic pressure, reduced right ventricular ejection fraction, pulmonary regurgitation, and a ventriculotomy scar.[65] The clinical significance of nonsustained ventricular tachycardia and especially the indications for prophylactic antiarrhythmic therapy remain unclear.[52] There is a disparity between the high frequency of ventricular arrhythmia and the much lower incidence of sudden death.[66,67] The predictive value of an abnormal ambulatory ECG or of electrophysiologic study has not been established. Furthermore, prophylactic antiarrhythmic therapy has not been shown to be of value in asymptomatic patients with congenital heart defects. Such therapy may have proarrhythmic potential, be negatively inotropic, or have serious extracardiac side effects. As a result, there is insufficient evidence to advocate prophylactic treatment for asymptomatic individuals with nonsustained arrhythmia. On the other hand, there are a few cases of sudden death, out-of-hospital ventricular fibrillation, and/or sustained ventricular tachycardia in almost all large series of patients after repair of tetralogy of Fallot. Identification of at-risk individuals and appropriate treatment remain a challenge. Recent reports have indicated a link between the electrical and mechanical properties of the right ventricle, which may have clinical relevance.[68] The QRS duration on the surface ECG correlates with cardiothoracic ratio and, in a retrospective review, a QRS greater than 180 ms was a sensitive and specific marker for sudden death or out-of-hospital cardiac arrest.[69] Others have not confirmed this.[70] Further refinements in risk stratification in adults with tetralogy of Fallot or other congenital heart lesions are necessary and probably will involve

hemodynamic and electrophysiologic testing both at rest and after exercise, evaluation of ventricular late potentials (Chap. 26), and heart rate variability.[71] It should be remembered, however, that, despite the attention given to ventricular arrhythmia after repair of tetralogy of Fallot, a major source of morbidity in such patients is from atrial arrhythmia.[72]

Radiofrequency ablation, so successfully used to treat arrhythmia in patients with structurally normal hearts (Chap. 28), is being applied to patients with congenital heart disease. These applications represent some of the most challenging electrophysiologic procedures because of the complex cardiac anatomy, enlarged chamber size, and abnormal localization of the underlying conduction system. Nevertheless, ablation may have a role, not merely in subjects with accessory pathways or AV reentry tachycardia, but also in intraatrial reentry arrhythmias that may be present after operations such as Fontan and Mustard or Senning procedures.[73,74]

Pregnancy

An increasing number of women with complex and postoperative congenital heart defects are reaching childbearing age. Advice is sought on both maternal and fetal risk as well as on the incidence of congenital heart disease in the offspring. In the United States, most maternal cardiac disease is congenital in origin. Data are accumulating regarding outcomes of pregnancy in many complex anomalies.[75-80] Prepregnancy counseling is mandatory for all patients whether operated or unoperated. The evaluation should include a detailed history, physical examination, ECG, and chest x-ray along with a comprehensive echocardiogram to evaluate ventricular function, all valve lesions and defects, and pulmonary artery pressure. If pulmonary artery pressure and resistance is in doubt following noninvasive testing, a cardiac catheterization may be necessary. An exercise test may facilitate a detailed assessment of functional capacity.

There are profound changes in the maternal cardiovascular system during pregnancy, including a large (30 to 40 percent) increase in blood volume, a fall in peripheral vascular resistance, and an increase in cardiac output (approximately 40 percent; see also Chap. 82). In general, women with left-to-right shunts or valvular regurgitation tolerate pregnancy well, whereas those with right-to-left shunts or valvular stenosis do less well.[81,82] Asymptomatic young women with small or moderate left-to-right shunts and normal pulmonary artery pressures can expect an uncomplicated pregnancy and labor. In the presence of a large left-to-right shunt, however, heart failure may be provoked or aggravated by pregnancy. Patients with cyanosis have the most problems in carrying a fetus to term and have a high incidence of early spontaneous abortion. Early studies showed that, with higher degrees of cyanosis (as reflected by the maternal hemoglobin), the incidence of spontaneous abortion increased and the handicap to fetal growth became more pronounced. Infants are unlikely to survive if the maternal hemoglobin level is above 18 g/dL.[83] A study from Presbitero et al. demonstrated a clear relationship between the degree of hypoxia and fetal loss (Table 64-3).[84] When the maternal oxygen saturation was 85 percent, only 2 out of 17 pregnancies (12 percent) resulted in live-born infants. Only 41 of 96 pregnancies (43 percent) produced a live birth in 45 cyanosed mothers. There were 49 spontaneous abortions and 6 stillbirths in this series, again reflecting the high risk that maternal cyanotic congenital heart disease poses for the fetus. Meticulous care during pregnancy and delivery lessened the maternal complication rate, but this was still considerable. Such patients require rest and a short labor as well as avoidance of dehydration and sepsis. In such situations, the decision as to whether to continue with the pregnancy depends on an assessment of the risk to the mother and fetus as compared with the patient's desire to have children.

Table 64-3: Fetal Outcome in Cynotic Congenital Heart Disease and Its Relation with Maternal Cyanosis

Hemoglobin, g/dL[a]	Pregnancy, no.	Live Births, no.	Live Born, %
≤16	28	20	71
17-19	40	18	45
≥20	26	2	8

Arterial Oxygen Saturation, %[b]	Pregnancy, no.	Live Births, no.	Live Born, %
≤85	17	2	12
85-89	22	10	45
≥90	13	12	92

[a]Hemoglobin level unknown in two pregnancies.[b]Arterial oxygen saturation unknown in 44 pregnancies.
SOURCE: From Presbitero P, Somerville J, Stone S, et al. Pregnancy in cyanotic congenital heart disease: Outcome of mother and fetus. *Circulation* 1994; 89:2673-2676. Reproduced with permission from the publisher and authors.

An elevated pulmonary vascular resistance, from either Eisenmenger's syndrome or primary pulmonary hypertension, is a clear contraindication to pregnancy. Pregnancy for women with Eisenmenger's syndrome carries approximately a 50 percent mortality rate.[85] Termination of pregnancy is always preferable; ideally, this should be done with cardiac anesthesia. If such patients are seen late in pregnancy and termination is not feasible, management should concentrate on maintenance of adequate preload and avoidance of vasodilation. The ideal management around the time of delivery for these patients is controversial because individual experience is small. Vaginal delivery is usually associated with less blood loss than is cesarean section. The latter, however, can be done quickly with all medical personnel in attendance. One report has suggested an approach of elective delivery by cesarean section under general anesthesia.[86] The use of prophylactic heparin before and after delivery is also controversial, and there is no established consensus.[86,87] Even after successful delivery, however, death frequently occurs within the few days following from deteriorating hemodynamics or pulmonary infarction.[85] Patients with Marfan's syndrome and aortic root dilation (greater than 40 mm) are at greater risk of aortic dissection and rupture, and while those without preexisting cardiovascular disease whose aortic root is smaller often tolerate pregnancy well, the risk is unpredictable.[88,89] Patients with severe aortic stenosis are also at increased risk because of the fall in afterload that accompanies pregnancy and exaggerates the valve gradient.[90,91] While early reports suggested a high risk of aortic rupture and cerebral hemorrhage in patients with aortic coarctation,[92] recent data have been more encouraging.[93] Fetal risk is increased, however, presumably as a result of compromised placental blood supply.

The management of pregnant women with mechanical prosthetic cardiac valves is a special problem because of the risk to the mother of thromboembolism and the risk to the fetus of anticoagulants (warfarin crosses the placenta and is teratogenic).[94,95] Depending on the condition involved and the mother's motivation and compliance, the use of subcutaneous heparin in the first and third trimesters and warfarin in the midtrimester is one treatment option. Heparin, however, is a poor anticoagulant during pregnancy; even with meticulous control of anticoagulation, there is still an increased risk of valve thrombosis.[96] In addition, there is also an increased risk of fetal loss with this approach. Because of the poor results with heparin, some authors have advocated the use of warfarin throughout pregnancy despite the risk of fetal teratogenicity.[97] This risk may be less if the dose of warfarin is less than 5 mg/day.[98] Nonetheless, this approach is still very controversial, despite the fact that fetal teratogenicity with warfarin may have been overemphasized (see Chap. 44).[99] Before prescribing any cardiovascular drug during pregnancy, the effects

on both mother and fetus must be considered.

Management of labor should be specifically directed toward avoidance of rapid changes in circulatory volume, blood pressure, or cardiac output. In most cases, vaginal delivery is recommended, with careful attention to maternal position and analgesic agents. The American Heart Association no longer recommends endocarditis prophylaxis for vaginal delivery.[31] This recommendation, however, is not based on controlled data, and most cardiologists recommend antibiotics under these circumstances for almost all congenital heart defects.

Genetic Counseling

The risk of recurrence is an increasingly important issue as more males and females with congenital heart disease reach reproductive age, and genetic counseling should be provided for all potential parents. Recent genetic advances are clarifying the etiology of a number of congenital heart diseases. It has been estimated that the cause of congenital heart disease is genetic in approximately 8 percent of cases (e.g., velocardiofacial syndrome and Holt-Oram syndrome with autosomal dominant transmission) and environmental in 2 percent (e.g., congenital rubella syndrome).[100] In the remainder, genetic and environmental factors are thought to interact.[101] The greater the number of affected first-degree relatives within the family, the greater the recurrence risk. Recurrence risks in siblings of patients with congenital heart disease are well documented and range between 1 and 8 percent.[102] For the affected potential parents, however, the risk of recurrence in offspring is the key information, and fewer data exist. Early reports suggested that recurrence risks were considerably higher in offspring compared to siblings. Studies, such as the Second Natural History of Congenital Heart Defects, have suggested a low risk (1.2 percent for aortic stenosis, 2.8 percent for pulmonary stenosis, and 2.9 percent for ventricular septal defects).[103] There is considerable variation in recurrence risks in reported series, and factors inherent in study design, ascertainment bias, and follow-up account for many of the differences. In addition, certain forms of congenital heart disease recur more frequently than others (e.g., left ventricular outflow tract obstruction), and the recurrence risk appears to be higher in pregnancies with affected mothers rather than fathers. Accumulation of further information will be invaluable for counseling of patients. Fetal cardiac ultrasound at approximately 18 weeks of pregnancy facilitates early diagnosis.

Investigation and Imaging

Transthoracic echocardiography and cardiac catheterization with angiocardiography are the principal investigations in pediatric cardiology. Transthoracic echocardiography is an invaluable tool in adults also, although image acquisition is more challenging because of body habitus and chest wall abnormalities as a result of previous surgeries.[104] Transesophageal echocardiography is becoming increasingly important for the definition of cardiac structure and function,[104-106] and multiplane probes with color-flow Doppler imaging allow simultaneous assessment of anatomy and physiology. Specific areas and lesions of the heart that are well imaged in this way include systemic and pulmonary venous drainage, atrial lesions (including baffle function), AV valve morphology and function, left ventricular outflow tract lesions (including the ascending aorta in Marfan's syndrome), and intracavity thrombus or vegetations (Fig. 64-1).[106,107]

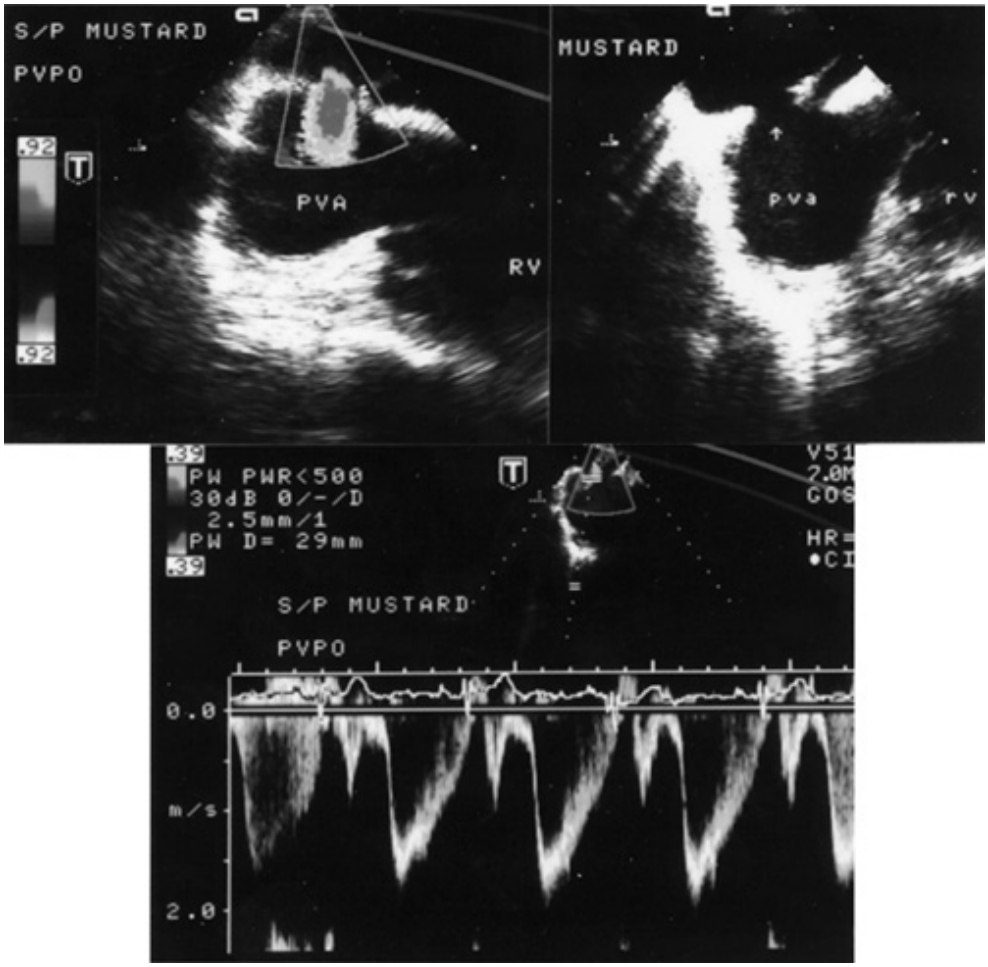

Figure 64-1: Transesophageal echocardiogram and Doppler evaluation after a Mustard operation for transposition of the great arteries. There is moderate pulmonary venous obstruction, indicated by the accelerated flow through the narrowing indicated by the arrow. PVA, pulmonary venous atrium; RV, right ventricle. (Courtesy of Dr. I. D. Sullivan, Great Ormond Street Hospital for Children, London.)

Magnetic resonance imaging (MRI) can also provide valuable anatomic information, which in some cases is superior to that from ultrasound, even via a transesophageal approach. Rapid technologic advances-including three-dimensional image reconstruction; software to study hemodynamics, such as velocity mapping; and cine-MRI-may reduce the need for invasive investigation (Fig. 64-2).[108-110] The expertise required both to acquire and to interpret MRI information is likely to be confined to specialized regional centers, but access to the MRI facility should be available to all units managing adult patients with congenital heart disease.

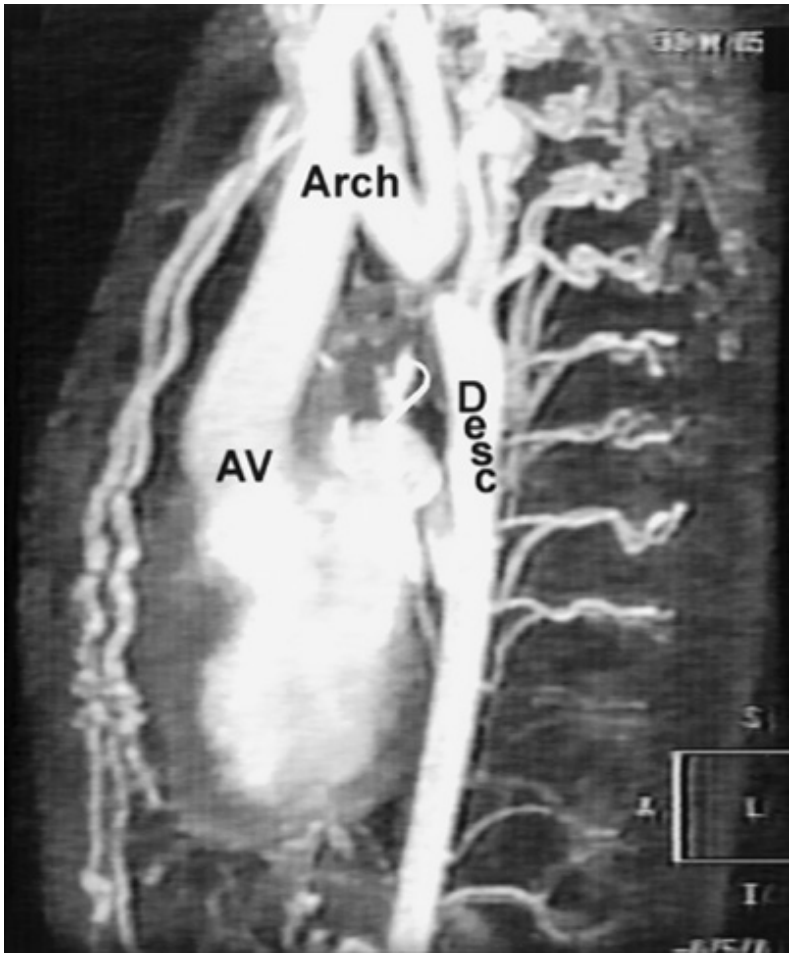

Figure 64-2: MRI angiogram of a 33-year-old man showing a severe coarctation and development of extensive collateralization involving the intercostal and internal mammary arteries. AV, aortic valve; Desc, descending aorta. (From Oh JK, Seward JB, Tajik AJ. Congenital heart disease. In: Oh JK, Seward JB, Tajik AJ, eds: *The Echo Manual*, 2d ed. Philadelphia: Lippincott-Raven, 1999: 233. Reproduced with permission from the publisher and authors.)

In parallel with the decreasing need for diagnostic cardiac catheterization, there has been a dramatic rise in the indications for and scope of interventional procedures in adult patients with congenital heart disease.[111] Residual defects after repair that are amenable to treatment in the catheterization laboratory include coronary fistulas, paravalvular leaks, and pulmonary artery stenoses. Optimum management of patients with complex congenital heart disease can often be achieved by planned collaboration between surgeon and interventional cardiologist. In other patients with a range of relatively simple lesions-including patent ductus arteriosus, pulmonary valve stenosis, atrial septal defect/patent foramen ovale, and certain forms of ventricular septal defect-definitive treatment avoiding surgery may be achieved by interventional catheterization.

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Chapter 64: CONGENITAL HEART DISEASE IN ADULTS

PSYCHOSOCIAL ASPECTS

During adolescence, a crucial transition occurs for the patient with congenital heart disease. By the end of the teenage years, the young adult must understand the nature and implications of his or her heart problem. Sensible advice and guidance must be available regarding employment, insurance, socialization, contraception, exercise, and sports.

Employment

Most patients can work and should have access to employment appropriate to their physical and intellectual capabilities. The report of the Natural History Study of Congenital Heart Defects suggested that, among patients with ventricular septal defect, pulmonary stenosis, and aortic stenosis, in comparison with national normal standards, a greater percentage achieved higher levels of education (college and beyond).[112] No similar data are yet available for large groups of patients with more complex defects, although their situation will undoubtedly prove worse.

Despite the excellent potential of many adults with congenital heart disease, job discrimination is frequently encountered, even when a patient has been cleared by a cardiologist. In the United States, the National Rehabilitation Act of 1973 seeks to prevent job discrimination by employers with 10 or more employees by obliging them to consider only the present capacity of applicants to perform a given job and not projections of future deterioration. In other countries, employers frequently take into account future prospects for absenteeism or premature career curtailment. In these circumstances, young adults with congenital heart defects are often at a disadvantage, particularly if they apply for jobs with long training periods.

Restrictions for employment exist for jobs in which the safety of others is the direct responsibility of an individual, such as driving a bus or truck. Most armed services exclude applicants with a cardiac history. The regulations for commercial airline pilots are clearer and subject to regular review. In Europe, a risk of sudden cardiac death or acute disability below 1 percent per annum is the maximum considered acceptable for multicrew flights and below 0.1 percent per annum for solo flights. The number of congenital heart defects in which low risk rates are clearly defined remains small.[113]

Insurance

Possession of adequate life insurance is often a prerequisite for a home mortgage. Insurance companies are of necessity fiscally conservative. As a result, life insurance is difficult to obtain for many young adults in the absence of adequate long-term survival data for their congenital heart lesions. Most of the data used to assess risk are either incorrect or out of date and do not apply to currently performed medical or surgical procedures. In 1986, a survey in the United States recorded that only patients with very simple lesions were insured at regular rates.[114] These included mild pulmonary valve stenosis, uncomplicated repaired atrial septal defect, ventricular septal defect, and patent ductus arteriosus. A similar survey in the United Kingdom in 1993 evaluated both employment status and insurability of young adults with congenital heart disease.[115] In general, policies were as restrictive as those in the earlier survey, with mitral valve prolapse (without regurgitation), postoperative patent ductus arteriosus, and coarctation insurable at standard rates and all other lesions being either insurable at higher rates or not insurable at all.

Marked inconsistencies were found, making "shopping around" mandatory. This situation is likely to improve when health care professionals are able to provide high-quality follow-up data on morbidity and mortality rates relevant to current treatment protocols (see Chap. 104).

Despite surgical repair, long-term cardiac care into adult life is usually required for patients with congenital heart disease. In many countries, health care provision and financing are changing rapidly, with costs spiraling dramatically.[116] There are particular problems in systems that rely on private health insurance. Medical expenses incurred during childhood are usually reimbursed as part of the parents' policy. This coverage often ceases to be available once the patient reaches the age of majority. A new policy sought at this stage at best excludes benefits for medical or surgical treatment of the cardiac condition itself. As a result, the level of medical surveillance of the adult patient with congenital heart disease drops dramatically after age 21 years. This is a major problem, since, with adequate regular follow-up, costs for adults with congenital heart disease are considerably lower than those for other chronic diseases.

Psychosocial Development

Large controlled longitudinal studies of the psychosocial consequences of congenital heart disease are rare and difficult to interpret.[117] Most patients with congenital heart disease appear well adjusted but have subtle feelings of "difference" from their peers. Lack of self-esteem and fear of isolation are common.[118-120] These feelings are often compounded by frequent reminders that they are different through limitation of their activities compared with those of their peers, the presence of scars, cardiac symptoms, hospital visits, and family anxiety. As a result, adolescents and adults with congenital heart disease should be encouraged to lead as normal a life as possible and to discuss their heart disease openly. Anxieties about sexual activity, marriage, and childbirth are common, but patients often find these aspects difficult to discuss, particularly with the doctor in a regular clinic.[120-122] Often, such issues are best handled by the team caring for the patient, which may include a nurse, social worker, and psychologist. As the child with congenital heart disease matures, one of the most potent effects on his or her life is parental overprotection. In adolescents and young adults, this may result in enormous resentment and rebellion against all adult authority figures, including the doctor. Compliance with medical treatment and advice can be affected.

The impact of congenital heart disease on intellectual development is controversial. Interpretation of testing must take into account the very abnormal childhood experienced by many patients, with absences from school for medical reasons as well as decreased social interaction. In addition, patients have often had an overprotected childhood, and their attitude to testing procedures may be different from those of their peers. All studies of intellect exclude patients with genetic syndromes and other dysmorphic, somatic, or neurologic defects, but subtle abnormalities are easily missed.[123] Certain aspects of development appear to be more specifically affected by congenital heart disease. For example, walking is delayed in cyanotic children, but speech is not. This will affect the relevance of early IQ testing to later performance. Currently, data suggest that cyanosis is associated with mild intellectual impairment.[124-126] This association is reduced by early corrective surgery, even involving cardiopulmonary bypass.

Contraception

Sexually active adolescents and young adults should be given appropriate advice about contraception.[127,128] In general, the low-dose estrogen oral contraceptive pill is safe for young women with congenital heart disease.[129] Exceptions include women with hypertension (e.g., associated with coarctation of the aorta) and those with pulmonary vascular disease or cyanosis with associated erythrocytosis. Progesterone preparations are alternatives, although they have a lower contraceptive efficacy.[130] They are, however, inappropriate for patients with cardiac failure because of the tendency for fluid retention; moreover, progesterone-only pills can cause

depression in adolescents. Barrier methods, either using condom or diaphragm, are safe and effective, but intrauterine devices should probably not be used because of the risk of endocarditis and of increased bleeding, particularly in cyanotic women.[131] In women with severe pulmonary vascular disease or with lesions in which pregnancy would result in high maternal risk, laparoscopic sterilization should be considered.

Exercise and Sports

Exercise is of both physical and psychological benefit. It leads to improved cardiovascular fitness and decreased likelihood of obesity, hypertension, and ischemic heart disease.[132,133] Furthermore, participation in exercise and sports is part of normal socialization in adolescent and adult life. In many adults with congenital heart disease, exercise capacity is diminished, even after surgery. Reduced performance may also reflect lack of regular exercise in protected individuals with congenital heart defects. This is often reinforced by doctors who, if in doubt, tend to limit exercise.

The Twenty-sixth Bethesda Conference provided recommendations for competition in athletics by patients with cardiovascular abnormalities.[134] Sports are broadly categorized into those involving dynamic exercise and those involving static exercise, although these two types of exercise are at two extremes of a continuum. Another important consideration is the danger of bodily injury from collision or the consequences of syncope. Significant disease or death precipitated by exercise in patients with congenital heart disease is rare, but the other consideration is whether prolonged long-term exercise might contribute to progressive hemodynamic deterioration (e.g., left ventricular hypertrophy and aortic stenosis). In some cases, exercise capacity is clearly normal and the risk is minimal, as after closure of a small patent ductus arteriosus. In others, exercise capacity is limited and the risk is high, as in severe pulmonary hypertension. Between these extremes is a gray area in which recommendations must take into account the individual, the underlying cardiac defect, hemodynamic status, and the type of sport and form of exercise contemplated (e.g., social or competitive, or contact or noncontact). Formal testing should be performed (preferably including measurement of oxygen uptake), both as a measure of the effects of submaximal and maximal exercise and also as a reassurance to the patient. A 12-min walking test provides a good guide to functional capacity, whereas a treadmill protocol with more strenuous effort is employed to assess risk by revealing occult arrhythmia, ischemia, or fall in blood pressure (Chap. 14). Subjective estimates of exercise capacity are often inaccurate.

In general, volume overload, valve regurgitation, and left-to-right shunts are associated with good exercise tolerance, while pressure overload, valve stenosis, and right-to-left shunt are not. The recommendations provided by the Bethesda Conference should be considered guidelines only. The physician with knowledge of the severity of the patient's lesion and physiologic and psychologic response to training and competition may choose to modify these recommendations.[134] Those patients with a history of symptomatic arrhythmia, syncope, pulmonary hypertension, or myocardial dysfunction deserve special attention, since they are probably at higher risk. Patients with fixed, elevated pulmonary vascular resistance have limited exercise capacity, and for them exercise has considerable risk. Walking should be encouraged but strenuous exercise avoided. The most controversial recommendations are those for aortic stenosis and Marfan's syndrome. It could be argued that exercise may increase the risk of sudden death or progression of left ventricular hypertrophy in the former (see Chap. 56) and of progressive aortic dilatation in the latter (see Chap. 76). Thus, patients with more than mild aortic stenosis should be counseled against moderate to strenuous activities. Patients with Marfan's syndrome, particularly those with aortic root dilatation, should be counseled against isometric exercise and activities with the potential for bodily collision. Supervised training programs for adults with congenital heart disease can improve aerobic fitness and increase the safe level at which they can participate in sports. Such programs also improve psychological adjustment and self-esteem.

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Chapter 64: CONGENITAL HEART DISEASE IN ADULTS

SURGICAL CONSIDERATIONS

Reoperations

Reoperations in adults with congenital heart disease provide a particular challenge.[135,136] The risks are often higher than for primary procedures. Careful preoperative planning should include complete understanding of the cardiac anatomy and its relationships to neighboring structures, and study of previous operative reports. Sternal reentry is particularly risky when the ventricle immediately beneath the sternum is a high-pressure chamber or when an extracardiac conduit lies in this position. The use of Gore-Tex membranes under the sternum may reduce the difficulties of future repeat procedures. Postoperative hemodynamic and respiratory problems are particularly common after reoperation because of the increased duration of surgery, previously scarred myocardium and/or lung disease, and greater use of blood products. The need for reoperation may come as a shock to patients and relatives who may have believed that childhood surgery was curative. As a result, resentment is frequent, and tact is required. Indications for reoperation are shown in Table 64-4.

Table 64-4: Indications for Reoperation in Adults with Congenital Heart Disease

1. Inevitable reoperation after definitive repair prosthetic valves, extracardiac conduits placed at an early age that become of inadequate size because of body growth
2. Residual defects after definitive repair: ventricular septal defect after tetralogy of Fallot and left AV valve regurgitation after AV septal defect repair
3. New/recurrent defects after definitive repair: subaortic stenosis, restenosis of aortic valve, pulmonary regurgitation in tetralogy of Fallot
4. Staged repair of complex defects: pulmonary atresia with ventricular septal defect
5. Unexpected complications: infective endocarditis
6. Heart/heart-lung transplantation for uncorrectable congenital heart disease
7. Patient operated on for congenital heart disease with new acquired heart disease: coronary disease

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Inevitable Reoperation

Early repair of congenital heart defects that have involved insertion of a prosthetic valve or extracardiac conduit commonly results in a need for reoperation to replace prostheses that are either too small or have undergone degeneration. Extracardiac conduits are commonly used for repair of pulmonary atresia with ventricular septal defect, truncus arteriosus, transposition with left ventricular outflow tract obstruction and/or ventricular septal defect, congenitally corrected transposition with left ventricular outflow tract obstruction, and/or ventricular septal defect and were used in early Fontan operations. Development of obstruction is influenced by the type and size of conduit, technique of insertion, and timing of the original operation. In one series of 143 survivors of heterograft conduit insertion, all had to be replaced by 10 years.[137] A homograft aorta or pulmonary artery and valve have also been used for the repair of pulmonary atresia with

ventricular septal defect.[138] Fresh or frozen homografts in childhood have not performed as well as initially hoped.[139] Calcification and obstruction remain significant complications. However, because of their favorable handling characteristics, homografts remain the conduits of choice for many reconstructions.[140,141] Besides the conduit itself, improved operative technique and the use of a large conduit have clear beneficial influence on the need for early replacement. This may be facilitated by utilizing a prosthetic roof of pericardium placed over the fibrous tissue bed of the explanted conduit, thus permitting a large tissue valve to be inserted.[142] Patients with right-sided conduits need careful follow-up, particularly toward the end of the expected life of the conduit. Although conduit obstruction may be suspected from clinical examination, the signs of severe obstruction may be subtle and may be missed. As a result, replacement may be performed too late. The consequent major deleterious effects on right ventricular function increase the risk of surgery and may not be fully reversible. Regular, noninvasive evaluation by transthoracic or transesophageal echocardiography or MRI is indicated in selected patients and may provide the information usually obtained by cardiac catheterization and angiography. Reoperation is usually indicated if the right ventricular pressure is 75 percent of the systemic or if there is evidence of deteriorating ventricular function.[143]

Residual and Recurrent Defects

Residual and recurrent defects may be difficult to distinguish unless careful assessment after the original repair has been performed. They may have a major impact on morbidity and mortality rates, as when major left AV valve regurgitation persists after repair of AV septal defect.[144] Much more long-term follow-up data are needed before guidelines for reoperation for relatively minor residual abnormalities, such as mild left AV valve regurgitation, in this situation can be established.

The reported need for reoperation after the commonly performed reparative operation for tetralogy of Fallot varies between 1.8 and 13 percent over a follow-up of up to 31 years.[145,146] Ventricular septal defect and right ventricular outflow tract obstruction are the commonest residual abnormalities. Pulmonary regurgitation is extremely common and inevitable after transannular patching as part of the original repair. The hemodynamic consequences of pulmonary regurgitation for the right ventricle are greater in the presence of other defects, such as residual obstruction and/or ventricular septal defect. Pulmonary valve replacement has not been frequently required in the first two decades after repair but may become increasingly performed because of the late deleterious effects of pulmonary regurgitation on the right ventricle.[147] Current indications include progressive right ventricular dilatation and a decrease in exercise tolerance.[148] This is often accompanied by progressive tricuspid regurgitation and atrial arrhythmias. When surgery is performed before the development of right ventricular failure, both clinical status and right ventricular function improve.[149] The optimal method for assessing pulmonary regurgitation in serial follow-up has not been determined; therefore, appropriate guidelines for intervention are still not established.

Several studies have emphasized the palliative nature of aortic valvotomy in childhood.[150-152] Isolated aortic stenosis most frequently results from a bicuspid aortic valve, although in neonates and infants the structural abnormality of the aortic valve is more severe and the results of surgery even worse (see Chap. 63). In a series of 59 patients who underwent open aortic valvotomy at over 1 year of age, the actuarial survival rate was 94 percent at 5 years but only 77 percent at 22 years. Reoperation was carried out in 36 percent, and the actuarial probability of reoperation was 44 percent at 22 years. When serious events, comprising death, reoperation, and endocarditis, were grouped together, 92 percent were free of events at 5 years but only 39 percent at 22 years. Others have reported a similar long-term outcome.[150] The causes of restenosis have not been studied in detail but appear to be related to the degree of residual obstruction.

Staged Repair

For complex congenital heart disease, definitive repair may not be possible until the anatomy and physiology of the circulation have been improved by one or more palliative procedures as part of a staged approach to "correction." This course is often necessary for patients with pulmonary atresia and ventricular septal defect, hypoplastic pulmonary arteries, and multifocal pulmonary blood supply. Palliative procedures to increase flow to the central pulmonary arteries and unifocalization of pulmonary flow by anastomosis (direct or indirect) of collateral vessels to the pulmonary arteries may eventually result in the ability to perform a repair (conduit insertion between the right ventricle and pulmonary artery and ventricular septal defect closure) with an acceptable postoperative right ventricular/left ventricular pressure ratio.[153,154] Good surgical results have been reported from such an approach, but the long-term outcome is not yet known.[155]

Other situations in which definitive repair may be indicated in the young adult include complex congenital heart defects with one functioning ventricle palliated by a systemic-pulmonary shunt or pulmonary artery banding in childhood. In selected patients who fulfill the stringent criteria for a Fontan operation, it is likely that long-term results will be better after a Fontan operation than when the ventricle is left with a chronically increased load resulting from a systemic pulmonary shunt.[12] The Fontan operation, however, should be considered palliative rather than curative: long-term problems are frequent.

Unexpected Reoperations

Indications for unexpected reoperation include thrombosis in a low-flow circulation such as the Fontan, prosthetic valve failure or thrombosis, and infective endocarditis. The latter may be particularly difficult to diagnose in complex congenital heart disease where the site of vegetations may not be easy to image (e.g., in a Blalock-Taussig shunt). Reoperation in the patient with uncontrolled endocarditis carries a particularly high risk.

Heart and Heart-Lung Transplantation

Despite the major successes of the last three decades, an increasing number of patients survive to adult life with deteriorating clinical status. Their only remaining prospect may be a heart or heart-and-lung transplant (see Chap. 22). These patients often present specific surgical problems of multiple previous chest incisions, complex venous anatomy, and borderline pulmonary vascular resistance. In addition, the young adult with end-stage heart disease may not have the ideal social milieu to cope with the demands of transplantation and may require considerable psychological support. Nonetheless, the results in this group of patients may be excellent.[156] The shortage of donors and the ability to monitor rejection in a single organ have stimulated great interest in single-lung transplantation for patients with primary pulmonary hypertension and Eisenmenger's syndrome (in conjunction with closure of the shunt).[157]

First Operations for Congenital Heart Disease in Adults

The first surgical repair of a congenital heart defect may be required in a teenager or an adult because the lesion was mild and of little hemodynamic significance in childhood but progressed in severity with time. Examples of such lesions include a bicuspid aortic valve with progressive stenosis (see Chap. 56), Marfan's syndrome with aortic root dilatation (see Chap. 76), and Ebstein's anomaly with worsening symptoms. Alternatively, lesions such as small to moderate atrial septal defects may have been missed or misdiagnosed until adult life. In certain complex congenital heart defects, the combination of lesions produces a balanced hemodynamic state compatible with prolonged survival without intervention. Patients with double-inlet ventricle and pulmonary stenosis, complex pulmonary atresia, and tetralogy of Fallot may remain well until the second and even third decades of life before deteriorating.[158] The contemplation of heart surgery

in an adolescent or young adult is often terrifying, implying the acceptance of the presence of a serious heart problem by the patient and his or her immediate friends and family. The scar on the chest may cause embarrassment, and the patient may be discriminated against both socially and at work. All these issues need to be dealt with sympathetically by the physician.

Noncardiac Surgery

When performed without adequate preparation, noncardiac surgery in adults with congenital heart disease is a major cause of avoidable morbidity and death. All the anesthetic risks encountered for cardiac reoperation apply equally to noncardiac surgery, but in the latter the patient may be managed by medical staff who may be unfamiliar with the significance of the congenital heart disease. Many patients with congenital heart defects are at increased risk for arrhythmia and from agents that depress ventricular function. The surgeon must be aware of the presence of a pacemaker or pacing leads that may affect the safe use of diathermy. Prophylaxis against infective endocarditis is usually indicated, and the choice of antibiotic regimen is dictated by the surgical procedure or intervention being undertaken (see Chap. 73). In patients with pulmonary vascular disease, general anesthesia may have disastrous consequences, with a sudden fall in systemic vascular resistance.[28] Similar hemodynamic changes may induce a severe hypercyanotic spell in a patient with uncorrected tetralogy of Fallot, and meticulous pre-, intra-, and postoperative hemodynamic monitoring is mandatory, together with the avoidance of vasodilating anesthetic agents, hypoxia, hypoventilation, and blood or volume loss. Cyanotic patients also have impaired hemostasis, and some patients may be taking anticoagulants. Intravenous lines, drugs, and infusions must be managed carefully in patients with intracardiac shunts, since air or emboli may reach the systemic circulation. The safety of noncardiac surgery in adults with congenital heart disease is greatly increased when physicians, anesthesiologists, and surgeons familiarize themselves with these issues, seek specialized advice, and, if necessary, refer the patient to a team with more experience.

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Chapter 64: CONGENITAL HEART DISEASE IN ADULTS

SPECIFIC LESIONS

General Considerations

Some lesions that are commonly seen in adult congenital heart disease, as a result of both natural and unnatural survival, are listed in Tables 64-1 and 64-2.

Interpretation of the literature on long-term outcome of congenital heart defects is hampered by a number of difficulties. First, follow-up is still short, and numbers of survivors are small for many defects. The era of open-heart surgery for congenital heart defects only began in the 1950s, and "correction" has only been attempted much more recently for many categories of patients now beginning to reach adult life (e.g., the Fontan operation). Second, surgical practice has undergone a process of evolution during this time, with new operations for some lesions (e.g., transposition of the great arteries) or major change in operative technique for others (e.g., the Fontan operation). Third, major advances in cardiopulmonary bypass and myocardial protection have accompanied improved preoperative diagnosis and recognition of intracardiac anatomy, particularly of the disposition of the conduction tissues. Finally, for almost all lesions, the management philosophy has changed, with a trend to early primary repair as opposed to initial palliation. For many defects, therefore, long-term outcome data relevant to current practice are not available.

Correct application of survival analysis is essential for interpretation of follow-up data. In particular, the use of hazard functions providing an estimate of *instantaneous risk* is particularly valuable. The following section deals with some specific defects seen in adults with congenital heart disease.

Atrial Septal Defect

Atrial septal defects are among the commonest congenital anomalies in adolescents and adults, accounting for up to 30 percent of congenital heart disease in this age group.[159,160] Approximately 75 percent of defects are ostium secundum defects, 20 percent ostium primum defects (discussed below), and 5 percent sinus venosus defects; defects at other sites are rare (see Chap. 63).[161,162] Associated lesions include pulmonary stenosis, mitral valve prolapse, and mitral regurgitation. Atrial septal defects may be associated with other syndromes, including the Holt-Oram syndrome (see Fig. 10-2)[163] and may be familial.[164] In the latter, conduction disease manifesting as prolongation of the PR interval and, rarely, heart block have been described.[164] Lutembacher syndrome (atrial septal defect coexisting with mitral stenosis) is now very uncommon.

NATURAL HISTORY

Survival into adulthood is the rule, and patients living into their eighties and nineties have been reported.[159] Life expectancy, however, is not normal. Death during the first 20 years of life is infrequent, but after the age of 40 years, the mortality rate increases to about 6 percent per year.[165,166] Defects may go unrecognized for many years because symptoms are rare until later life and physical signs may be subtle. Later, the natural history is characterized by progressive symptoms and cardiomegaly, the development of atrial arrhythmias, right ventricular hypertrophy, and pulmonary hypertension. The mechanisms for the development of symptoms are

multifactorial[159] and include the following:

1. Change in left ventricular compliance from superimposed hypertension or coronary artery disease may increase the shunt with age. Long-standing right ventricular volume overload, although relatively well tolerated, ultimately leads to right ventricular dysfunction and progression of tricuspid regurgitation.
2. Supraventricular arrhythmias, particularly atrial fibrillation and flutter, increase with time and may cause symptoms and cardiac failure (Fig. 64-3).
3. Progressive pulmonary hypertension may become symptomatic after the third decade of life.
4. Rarer complications may occur, including systemic and pulmonary emboli, recurrent chest infections, and infective endocarditis (in patients with coexisting mitral valve disease).

MANAGEMENT

Surgical closure either by direct suture or use of a patch has been performed for more than 40 years (see Chap. 63). Surgery carries a low risk (less than 1 percent operative mortality rate), provided that the pulmonary vascular resistance is not significantly elevated.[162] In older patients, the indication for closure is a little more controversial. Shah et al. compared the outcome of patients treated medically and surgically when diagnosed after the age of 25 years.[167] This unrandomized study followed patients for more than 20 years and concluded that there was no difference in survival or symptoms between the two groups and no difference in the incidence of new arrhythmia, stroke, or other embolic phenomena in the follow-up period. Notably, however, more than 70 percent of patients in both the medical and surgical groups were asymptomatic at presentation, which may partly explain the favorable outcome of the medically treated group, who had a 91 percent survival. Konstantinides et al. evaluated 179 patients with secundum atrial septal defect 40 years of age or older and compared the outcome of medically and surgically treated groups.[168] They demonstrated a reduced mortality rate after surgical closure, with a 95 percent surgical survival versus an 84 percent medical survival at 10 years. Nonfatal cardiovascular complications, however, were similar, with atrial fibrillation and flutter occurring with a similar incidence in both groups. The functional status of the medically treated group deteriorated in 34 percent of patients and improved in many of the surgical patients, particularly those in class III or IV. It thus seems reasonable to conclude that symptomatic adult patients will improve after surgical repair, and the only real contraindication is severe pulmonary vascular disease. When surgery is delayed, symptoms are likely to be progressive, and surgical repair is less likely to prevent problems with atrial fibrillation and thromboembolic events. For those with preexisting atrial fibrillation, a concomitant right-sided maze procedure may facilitate restoration and maintenance of sinus rhythm.[169] The management of the asymptomatic adult patient is less clear, but certainly closure of the defect halts progression of right ventricular volume overload, tricuspid regurgitation, and progression of pulmonary vascular disease, and it can be accomplished with low surgical risk. The standard surgical approach remains a midline sternotomy, but patients should be made aware of the alternatives of thoracotomy or inframammary incision. Although morbidity rates may be higher, the resulting scar may be less offensive, especially to young women.

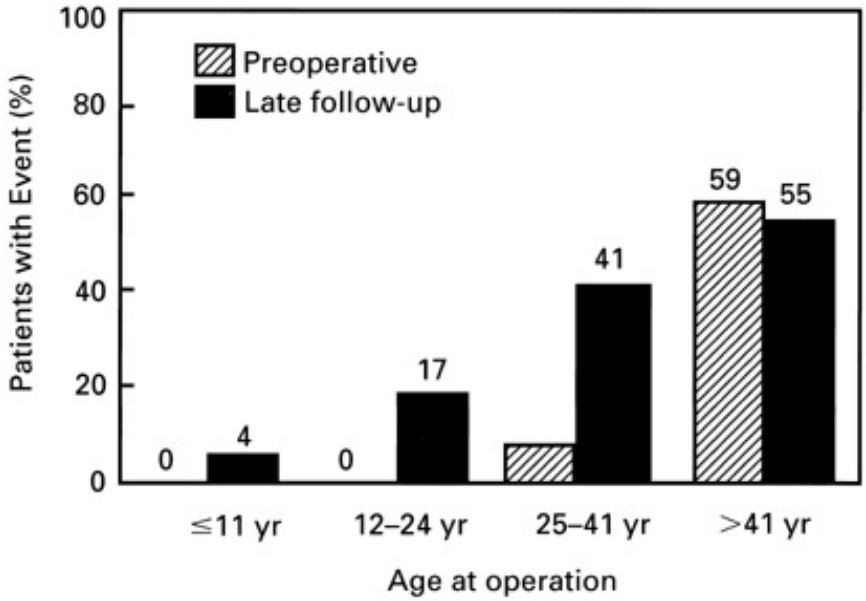

Figure 64-3: Incidence of atrial flutter or atrial fibrillation preoperatively and at late follow-up according to the age at operation after repair of atrial septal defect. (From Murphy JG, Gersh BJ, McGoon MD, et al. Long-term outcome after surgical repair of isolated atrial septal defects: Follow-up at 27-32 years. *N Engl J Med* 1990; 323:1645. Reproduced with permission from the publisher and authors.)

Closure of atrial septal defect has been achieved in selected patients by use of a variety of occlusion devices inserted at cardiac catheterization.[170-174] Several alternatives have been evaluated, but no large series with adequate follow-up are yet available for comparison with surgery. The attractions of closing defects without open-heart surgery are obvious. Eventually, the transcatheter technique may supplant surgery as the method of closure for atrial septal defects of appropriate size, morphologic characteristics, and location. In addition, the presence of a patent foramen ovale has been suggested as a risk factor for cerebral embolus. Determining the risk of clinical events in asymptomatic subjects with patent foramen ovale and indications for treatment are highly controversial areas. Catheter treatment may become the method of choice for patients who have a clear indication for intervention.

LATE RESULTS

In a recent study of patients undergoing surgical repair of an atrial septal defect between 1956 and 1960, late survival of patients undergoing operation at below 24 years of age was not significantly different from that of an age- and sex-matched control population. Late survival in patients aged 25 to 41 years was good but less than that of the control population, while repair after age 41 years was associated with significantly poorer late survival (see Fig. 64-3). The combination of older age at operation and pulmonary hypertension had an additive effect on late mortality rates.[175] In this and other series, the propensity for atrial fibrillation and flutter increased as a function of age both before and after operation (Fig. 64-4).[175,176] Twenty-two percent of late deaths were due to stroke, and all occurred in patients with postoperative atrial fibrillation or flutter. These data support the current policy of repair at a preschool age (Chap. 63). A separate study of 66 patients who underwent closure of atrial septal defect between 60 and 78 years of age implied a benefit in survival in patients discharged from the hospital compared with unoperated historical age- and sex-matched controls.[177] A study of patients over 70 years of age showed improved survival of patients in New York Heart Association (NYHA) class II and III when treated surgically compared to medical treatment. Patients in NYHA class IV did poorly with medical or surgical treatment.

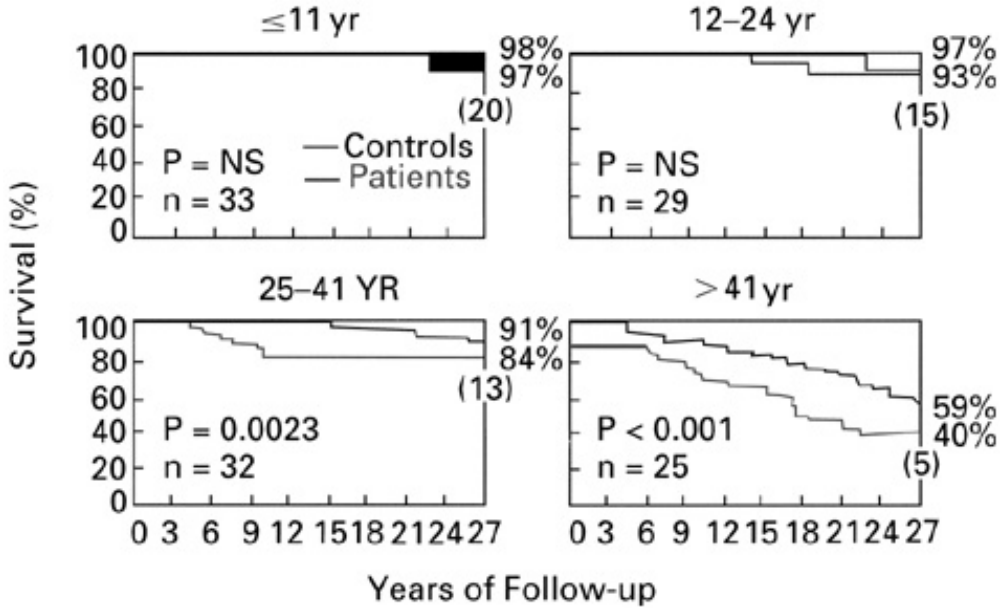

Figure 64-4: Long-term survival of perioperative survivors of atrial septal defect repair by age at time of operation. Controls are survival in an age- and sex-matched population. (From Murphy JG, Gersh BJ, McGoon MD, et al. Long-term outcome after surgical repair of isolated atrial septal defects: Follow-up at 27-32 years. *N Engl J Med* 1990; 323:1645. Reproduced with permission from the publisher and authors.)

The near-normal survival and low morbidity rates in patients undergoing repair within the first two decades of life have important implications for employment and insurance recommendations. Such patients should be encouraged to lead a normal life, and competitive sports should not be restricted in the absence of hemodynamic or electrophysiologic sequelae. Patients who have undergone repair in the third decade of life or later require careful regular surveillance. Although late survival is good, the development of supraventricular arrhythmia and risk of cerebrovascular accident are of concern. Anticoagulation is indicated in patients with atrial fibrillation and should be considered in those with supraventricular tachycardia or atrial flutter in the absence of other contraindications (see also Chaps. 24 and 44). Long-term follow-up is recommended for patients repaired in adult life who have increased pulmonary artery pressure at the end of operation, pre- and postoperative arrhythmia, ventricular dysfunction, or coexisting heart disease.

Ventricular Septal Defect

Isolated ventricular septal defect, although one of the commonest congenital abnormalities in infants and children, is far less frequent in the adolescent and adult for several reasons.[159] First, most patients with a hemodynamically significant defect will have undergone repair in childhood; second, spontaneous decrease in size and closure are common for small or moderate perimembranous or muscular defects (this decreases in frequency with increasing age); finally, patients with large, unoperated defects may die earlier in life.[178] The spectrum of isolated ventricular septal defects in the adult is thus limited to the following four groups of patients: (1) those with small, restrictive defects that were either small to begin with or have partially closed; (2) those with Eisenmenger's syndrome and a predominant right-to-left shunt with cyanosis,[179] who need to be distinguished from those who develop secondary infundibular pulmonary stenosis, which can also decrease the left-to-right shunt and may result in cyanosis with shunt reversal (see Chap. 63);[180] (3) the occasional patient with a moderately restrictive defect in whom the diagnosis has been overlooked or who has not had closure in childhood; and (4) those who have had their defects closed in childhood.

NATURAL HISTORY

The natural history of small, restrictive ventricular septal defects is very favorable. Nevertheless, the risk of infective endocarditis persists (developing in almost 4 percent of patients with ventricular septal defect), and lifelong prophylaxis is required. Spontaneous closure may occasionally still occur in adult life. A subset of patients with perimembranous defects or defects in the outlet septum may develop aortic cusp prolapse and aortic regurgitation. This may be progressive and is often severe by the end of the second decade of life. As incompetence increases, the ventricular septal defect may become "closed" by the prolapsing cusp; if it is left to develop, however, aortic valve replacement may be necessary.[181] Such defects are associated with a high risk of infective endocarditis. Severe and progressive pulmonary vascular disease is a feature of older patients with nonrestrictive large defects. Eisenmenger's syndrome is compatible with survival into young adult life, but the complications of right-sided heart failure, paradoxical emboli, and erythrocytosis usually result in death by the third decade (see Chap. 63). Occasionally, patients with moderate-sized ventricular septal defects and left-to-right shunts who did not develop pulmonary vascular disease present in adolescence and young adult life with symptoms of fatigue, effort intolerance, and respiratory infections.

MANAGEMENT

Patients with small ventricular septal defects are asymptomatic and should be managed conservatively. Continued medical follow-up is, however, helpful to remind patients about the need for prophylaxis against infective endocarditis and to minimize inappropriate discrimination during the search for employment and insurance. Ventricular septal defects associated with aortic cusp prolapse and aortic regurgitation should be repaired even when the shunt is small in an effort to prevent progressive deterioration of the aortic valve. Surgical repair is indicated in the rare adult with a significant left-to-right shunt (pulmonary/systemic flow ratio exceeding 2:1) and a low pulmonary vascular resistance. The management of patients with large defects and infundibular narrowing causing right-to-left shunting and cyanosis is similar to that for tetralogy of Fallot (see below).

Unfortunately, adults are still seen with a large ventricular septal defect and pulmonary vascular disease. In those with borderline pulmonary vascular resistance (7 to 10 U/m^2), surgery may be attempted, but the benefits are unpredictable, since the pulmonary vascular disease may progress despite closure of the defect (see Chap. 63).[182] Medical management and consideration for heart-lung or single-lung transplantation are the only realistic options for patients with established severe pulmonary vascular disease, although prostacyclin may hold some promise.[29]

LATE RESULTS

Late results of surgery are good, but the life expectancy for the whole group is not normal. In a study of 179 operative survivors between 1956 and 1959, 30-year survival was 82 percent, compared with 97 percent in age- and sex-matched controls.[180] Only 25 percent of patients in the series were over 10 years of age at surgery, and their 30-year survival of 70 percent was substantially lower than the 88 percent in patients under 2 years of age at operation. Thirty-year survival was 83 percent for patients aged 3 to 10 years at surgery. Older age at repair and preoperative pulmonary vascular disease are important predictors of late outcome. Postoperative conduction defects, especially right bundle-branch block, are common, but complete heart block, which was seen in the early surgical experience, is now rare. Late ventricular arrhythmia has been reported, as after repair of tetralogy of Fallot.[183] The incidence of late sudden death, however, is extremely low, and prophylactic antiarrhythmic therapy in asymptomatic patients is not indicated.

Certain selected ventricular septal defects may be closed with transcatheter devices. One report

described closure of 21 muscular ventricular septal defects in 12 patients, half of whom had complex heart defects.[184] All the defects were closed successfully, and subsequent cardiac surgery for associated lesions was performed in 11 of 12 patients.

In postoperative patients, the risk of late infective endocarditis is very small, provided that the defect is isolated and is completely closed. Antibiotic prophylaxis, however, is often advised, particularly for 6 months postoperatively. Recommendations regarding physical activity and competitive sports require detailed evaluation, which may include exercise testing, cross-sectional echocardiography, and ambulatory ECG monitoring. The presence of abnormal left ventricular function, a more than trivial residual shunt, arrhythmia, or any degree of pulmonary hypertension mandates some restriction of physical activity.

Atrioventricular Septal Defect

The term *atrioventricular septal defect* describes the spectrum of lesions that involve a defect at the site of the normal AV septum, resulting in an abnormality involving the AV valves, ventricular architecture, and left ventricular outflow tract. A variety of classifications have been used (see Chap. 63), but the defects are usefully divided into "partial" and "complete" forms. In the former, there is a defect in the primum or inferior part of the atrial septum but no direct intraventricular communication (ostium primum defect). In the latter, there is a large ventricular component beneath either or both the superior or inferior bridging leaflets of the AV valve. The deficiency of ventricular septum together with the abnormal AV valve or valves produces an elongated left ventricular outflow tract characteristically described as having a "gooseneck" appearance at angiography. The morphologic and functional features, together with the associated cardiac and noncardiac abnormalities, determine the natural history. Subaortic stenosis is a common association and may occur de novo even after surgical repair.[185]

NATURAL HISTORY

In the New England Regional Cardiac Registry, 5 percent of newborns with cardiac disease had AV septal defects, with two-thirds being the "complete" form.[186] Down's syndrome is very frequently associated, especially with complete defects. The noncardiac features, especially mental retardation, have a major influence on management in adolescence and adult life.

The natural history of partial AV septal defects with little left AV valve regurgitation is similar to that of large secundum atrial septal defects (see above). A small number develop pulmonary vascular disease, and symptomatic deterioration in unoperated adults is often due to the onset of supraventricular arrhythmia. If the left AV valve is more than mildly regurgitant, the natural history is much worse, with a large left-to-right shunt, often with at least moderate pulmonary hypertension, and early symptoms of cardiac failure. Patients with complete defects do even worse. Their course is characterized by the early development of pulmonary vascular disease (especially in patients with Down's syndrome, who may have irreversible damage before their first birthday), with consequent right-to-left shunting and all the problems of patients with Eisenmenger's syndrome. As a result, surgery needs to be undertaken early if it is to be successful, and most uncorrected patients seen by the adolescent or adult cardiologist will have a pulmonary vascular resistance that is too high for repair (greater than 8 to 10 U/m^2; see Chaps. 15 and 63). Their outcome is poor, but survival into their thirties is possible. Uncorrected patients with partial AV septal defects may present to the adult cardiologist for consideration of surgery, which should be recommended for those with a significant left-to-right shunt in the absence of other contraindications.

MANAGEMENT

Surgical repair involves closure of the atrial and ventricular septal defects and restoration of a competent left AV valve as far as is possible (see Chap. 63).[187] The surgical mortality rate in experienced centers is approximately 10 percent for complete defects and less than 5 percent for partial defects.[162]

LATE RESULTS

Patients with repair of both partial and complete forms of AV septal defect have now been followed for more than 20 years. Late results are good in the absence of pulmonary vascular disease and significant residual left AV valve regurgitation. Some patients with complete defects who were corrected later in childhood, before the need for correction in early infancy was appreciated, have developed progressive pulmonary vascular disease. This late complication should be greatly reduced in patients undergoing repair in the first 6 months of life, as is now technically feasible (see Chap. 63). Even patients who are repaired late in adult life (at 40 years of age or more) can have excellent results, with an early mortality rate of only 6 percent and a good chance of left AV valve repair in experienced hands.[188]

During long-term follow-up, careful attention must be paid to the status of the left AV valve. If the regurgitation increases in severity, reoperation and mitral valve replacement may be necessary.[144] Monitoring for arrhythmia at intervals is also currently recommended; in general, little intervention is usually required, apart from lifelong infective endocarditis prophylaxis. Surgically repaired non-Down's patients without pulmonary vascular disease can often enjoy life without cardiovascular disability and should not be discouraged from competitive sports, pregnancy, or employment. Restrictions are clearly required for those with pulmonary vascular disease, left AV valve regurgitation, or mitral valve replacement on anticoagulants. Patients with Down's syndrome, both operated and unoperated, are demanding, and their families require considerable support from the physician as well as from educational and social services. The recurrence risk of congenital heart disease in offspring of mothers with AV septal defect is higher than average, and potential parents should be counseled.

Tetralogy of Fallot

Tetralogy of Fallot is the commonest form of cyanotic congenital heart disease seen in the adult. Nonetheless, in the developed world the unoperated patient with tetralogy of Fallot has, fortunately, become a rarity, since the overwhelming majority of patients will have undergone palliation or, more often, repair in childhood. From an anatomic and pathophysiologic standpoint, the manifestations of tetralogy of Fallot are similar in all age groups, although hypercyanotic spells, which are often seen in infants and young children, are rare in adults. The development of systemic hypertension with age is a problem, since it increases the afterload to both ventricles.[159,189] Although pulmonary blood flow may improve, this occurs at the expense of right ventricular failure. Acquired calcific aortic stenosis has similar effects. Aortic regurgitation may occur as a result of cusp prolapse into the subaortic ventricular septal defect, and the aorta itself may be dilated. The aortic regurgitation may also be exacerbated by infective endocarditis. Since the volume overload is transmitted to both ventricles, patients may present with right ventricular failure as a consequence of aortic regurgitation. The development of chronic obstructive lung disease is another manifestation of an acquired cardiopulmonary disease that may place the adult patient with tetralogy of Fallot at particular risk.

NATURAL HISTORY

Survival into the seventh decade is described,[190] but the natural history in the unoperated patient, which is determined by the severity of obstruction of the right ventricular outflow tract and pulmonary vasculature, is poor. Only 25 percent of patients reach the age of 10 years; 11 percent

are alive at 20 years, 6 percent at age 30 years, and only 3 percent at age 40 years.[159,162,191] Complications of right-to-left shunting and erythrocytosis, which include stroke and cerebral abscess, are common and, in many instances, fatal. Patients are at continuing risk of infective endocarditis; the development of congestive heart failure in adolescence or early adult life is a major cause of death, as is arrhythmia. Myocardial fibrosis resulting from long-standing right ventricular pressure overload and hypoxemia are postulated mechanisms.[192] Prior palliative surgery with a Cooley or Waterston shunt (between the ascending aorta and right pulmonary artery) or a Potts shunt (between the descending aorta and the left pulmonary artery) can lead to the late development of pulmonary vascular disease.[193]

MANAGEMENT

The focus of medical treatment in unoperated patients is on the elevated hematocrit, bleeding disorders, and abnormal uric acid metabolism and the complications of pregnancy. Repair is indicated in all suitable patients, and the principles and techniques are not significantly different in adults than in children (see Chap. 63).[161] Most adults are suitable candidates for repair, but occasionally a patient with an underdeveloped pulmonary vascular bed may require a palliative shunt procedure. Intracardiac repair consists of closure of the ventricular septal defect and relief of right ventricular outflow tract obstruction. In some patients, this may require excision of the pulmonary valve and patch reconstruction of the anulus and outflow tract. In the occasional patient with an anomalous origin of the left coronary artery from the right coronary artery, a conduit between the right ventricle and pulmonary artery may be required.[162]

LATE RESULTS

Late survival is excellent, even in patients who underwent repair during the very early years of open heart surgery.[162] At the Mayo Clinic, the cumulative 30-year survival for patients undergoing successful surgery between 1956 and 1960 was 86 percent compared to 95 percent in age- and sex-matched controls (Fig. 64-4).[194] In a previous series of 396 hospital survivors of repair between 1955 and 1962 at the same institution, 91 percent were alive at 20 years. At 30 years, 77 percent of the initial cohort of 106 patients undergoing surgery between 1954 and 1960 by Lillehei and associates were alive, including 1 patient who was 45 years of age at the time of operation.[195] Surgery cannot be considered "curative," since survival, even in excellent series, is slightly but significantly worse than for a matched control population. The risk factors for an adverse late outcome include older age at surgery, preoperative congestive heart failure, a previous Potts shunt, persistent right ventricular systolic hypertension, and a residual ventricular septal defect.[175,193] Late death may be sudden, due to tachyarrhythmia or, very rarely in the current era, to conduction disease (see above).[50] Left and right ventricular failure due to right ventricular pressure overload or left ventricular volume overload is another important cause of late death in older patients.[159]

The late functional outcome is excellent for the majority of patients. Most lead normal lives, but the results appear to be better in those undergoing surgery at a younger age.[196] Persistent or recurrent symptoms are usually the result of incomplete relief of right ventricular systolic hypertension or recurrent or residual ventricular septal defects. These problems are often manifest within the first few years after surgery and may require reoperation. Progressive aortic dilatation and aortic regurgitation may also occur, requiring aortic valve replacement.[197] Pulmonary regurgitation may be well tolerated for decades but may be associated with late impairment of exercise capacity and, frequently, atrial arrhythmias. Right ventricular volume overload may also be well tolerated for years but ultimately results in right ventricular failure and progressive tricuspid regurgitation. Pulmonary valve replacement can be accomplished with a low risk.[149] In some patients, isolated right ventricular restrictive physiology may paradoxically improve exercise performance and reduce cardiac enlargement, due possibly to shortening of the duration

of pulmonary regurgitation.[68]

Recent information links pulmonary regurgitation, cardiomegaly, QRS duration, and potentially life-threatening ventricular arrhythmia.[68,69] This may be important for identification of risk of late sudden death, which has been a rare event in most long-term follow-up series. Asymptomatic ventricular arrhythmia is very common during long-term follow-up. It is again related to older age at repair, but the link between nonsustained ventricular arrhythmia and adverse clinical outcome is uncertain (see above).[61,62] Objective testing has emphasized the effects of older age at operation on subsequent exercise performance. This is essentially normal for children repaired at below 5 years of age but is usually impaired when surgery is undertaken in adolescence or adulthood.[198]

Before unrestricted physical activity after repair of tetralogy of Fallot can be recommended, careful evaluation-including echocardiography, ECG monitoring, and exercise testing-should be undertaken. Normal activity, including competitive sports, seems reasonable if surgery has been performed at a young age, right and left ventricular function and size are normal, and there are no residual ventricular septal defect, significant right ventricular outflow tract obstruction, or worrisome arrhythmia. In those who do not fulfill these stringent criteria, the degree to which physical activity should be restricted must be individualized. Currently, long-term follow-up of all patients with tetralogy of Fallot is recommended.

Pulmonary Stenosis

Isolated pulmonary valve stenosis is a common form of adult congenital heart disease and is characterized typically by a trileaflet valve with fused commissures. A dysplastic valve without commissural fusion occurs infrequently in otherwise normal children but more commonly in patients with Noonan's syndrome (see Fig. 10-13).[159] Subvalvar stenosis due to infundibular hypertrophy is usually a secondary phenomenon in response to obstruction to right ventricular outflow but may occur as a rare isolated entity. Supravalvar or peripheral pulmonary artery stenosis is also extremely uncommon as an isolated entity but is associated with tetralogy of Fallot and supravalvar aortic stenosis in Williams' syndrome (see Fig. 10-25).

NATURAL HISTORY

Prolonged survival into adult life is common and depends upon the severity of obstruction. In patients with severe pulmonary stenosis, symptoms of right-sided failure increase with time because of progressive obstruction and alterations in right ventricular compliance.[199] In the Joint Study of the Natural History of Congenital Heart Disease, 19 percent of patients with severe stenosis aged 2 to 11 years and 37 percent aged 12 to 21 years were symptomatic. The natural history of moderate pulmonary stenosis in older patients is more favorable, with less tendency to progression.

MANAGEMENT

Patients with mild stenosis are asymptomatic and require no intervention other than antibiotic prophylaxis against infective endocarditis. In patients with more severe stenosis (>140-mm gradient between the right ventricle and pulmonary artery), intervention to reduce severity should be considered even if there are no symptoms.

Surgical valvotomy for isolated pulmonary stenosis has been successfully performed for more than 40 years. Perioperative morbidity and mortality rates are minimal beyond the neonatal period in patients without severe congestive cardiac failure or right ventricular dysplasia.[162] Late results are also excellent. In a study from the Mayo Clinic of patients undergoing surgery between 1956 and 1957, late survival for those undergoing valvotomy who are over 21 years of age was similar

but not identical to that of an age- and sex-matched control population (Fig. 64-5). Among patients undergoing surgery at an older age, late survival, although still good, was less than that of the control population (Fig. 64-6).[200] This effect of age on late outcome, which was independent of the use of ventriculotomy and outflow patches and of pulmonary regurgitation, is likely the result of long-standing pressure overload on the right ventricle. Late functional results are excellent, and pulmonary regurgitation is well tolerated in the short and medium term. More severe pulmonary regurgitation may result when a pulmonary valvectomy or transanular patch is required, as may be the case for a small or dysplastic valve; the long-term consequences on the right ventricle and functional capacity are not yet well documented (see "Tetralogy of Fallot," above).

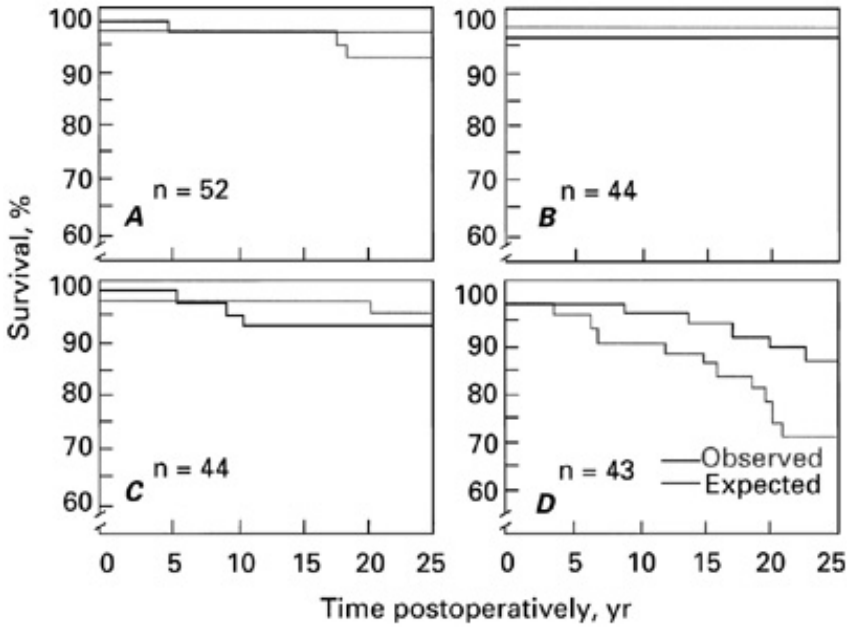

Figure 64-5: Long-term survival of perioperative survivors of surgical repair of pulmonary valve stenosis by age at time of operation. *A*. Ages 0 to 4 years. *B*. Ages 5 to 10 years. *C*. Ages 11 to 20 years. *D*. Ages 21 to 68 years. Expected is survival in an age- and sex-matched population. Values of *p* for comparison between the expected and observed survivals: .07, .34, .16, and <.002 for panels *A*, *B*, *C*, and *D*, respectively. (From Kopecky SL, Gersh BJ, McGoon MD, et al. Long-term outcome of patients undergoing surgical repair of isolated pulmonary valve stenosis: Follow-up at 20-30 years. *Circulation* 1988; 78:1150. Reproduced with permission from the publisher and authors.)

Surgical valvotomy is now rarely required after infancy because of the advent of catheter balloon pulmonary valvotomy. In most institutions, balloon valvotomy is the initial procedure of choice at all ages. In the series of 822 patients in the Valvuloplasty and Angioplasty of Congenital Heart Abnormalities registry, gradient reduction was substantially worse in patients with dysplastic valves.[201] Interventional catheter procedures should be confined to centers with experienced operators.

Long-term follow-up data are not yet available. It appears that the excellent early results are maintained for at least 5 years. The late effects of pulmonary regurgitation resulting from the use of large balloons need to be determined. The risk of infective endocarditis in patients with mild pulmonary stenosis or in those with mild gradients after surgical or balloon valvotomy is low. Long-term follow-up is recommended to evaluate not only the right ventricular outflow tract gradient but also pulmonary regurgitation, right ventricular function, and exercise performance. In patients with good relief of pulmonary stenosis, no restriction of physical activities, including

competitive sports, is required. In those with moderate residual obstruction or right ventricular dysfunction, exercise intensity should be reduced (see also Chap. 77).

Left Ventricular Outflow Tract Obstruction

Congenital left ventricular outflow tract obstruction may occur at valvar, subvalvar, and supravalvar levels (see Chap. 85). Aortic valve stenosis is a common abnormality in adults with congenital heart disease. It may either be an isolated defect or be associated with other lesions, such as coarctation or ventricular septal defect. It is usually due to a bicuspid aortic valve, which may be present in 1 to 2 percent of the total adult population and is three to four times more common in males than in females.[202] Unicuspid and tricuspid stenotic valves are less common.[162] Subvalvar stenosis encompasses a morphologic spectrum of fibrous or fibromuscular obstructions; it can be a discrete "membrane" below the aortic valve, a discrete fibromuscular ridge, or a diffuse narrowing extending well into the left ventricular cavity forming a "tunnel."[203] The condition occurs more commonly in patients with long and narrow left ventricular outflow tracts,[204] and perhaps this morphologic feature promotes turbulence and shear stresses that stimulate cellular proliferation.[205] Abnormal ventricular bands or chords may also contribute to obstruction, along with abnormal chordal attachments of the anterior mitral valve leaflet. A dynamic component of obstruction may also occur as left ventricular hypertrophy progresses. Common associated anomalies include ventricular septal defect and coarctation of the aorta. Supravalvar stenosis is the least common variety of left ventricular outflow tract obstruction in adolescents and adults, except in the context of Williams' syndrome.[206]

NATURAL HISTORY

The natural history of congenital valvar aortic stenosis in adults is variable but is characterized by progressive stenosis with time (Fig. 64-7; see Chap. 56).[159] By the age of 45 years, approximately half of all bicuspid aortic valves have some degree of narrowing. The severity of obstruction at the time of diagnosis correlates with the pattern of progression (Fig. 64-8).[207] Bacterial endocarditis is relatively uncommon (1.8 to 2.7 cases per 100 patient-years),[208] but antibiotic prophylaxis is necessary, even for functionally normal valves. Slowly progressive aortic regurgitation is well recognized in young adulthood, but sudden deterioration is rare, except as a sequel to infection.[209,210] Associated abnormalities of the aorta are not uncommon, and aneurysmal dilatation and dissection of the ascending aorta may be seen even with functionally normal valves. Fragmentation of the elastic fibers in the media has been noted histologically, and, recently, premature smooth muscle cell apoptosis has been implicated. These findings suggest a common genetic abnormality involving both the aortic valve and the ascending aortic wall.[211]

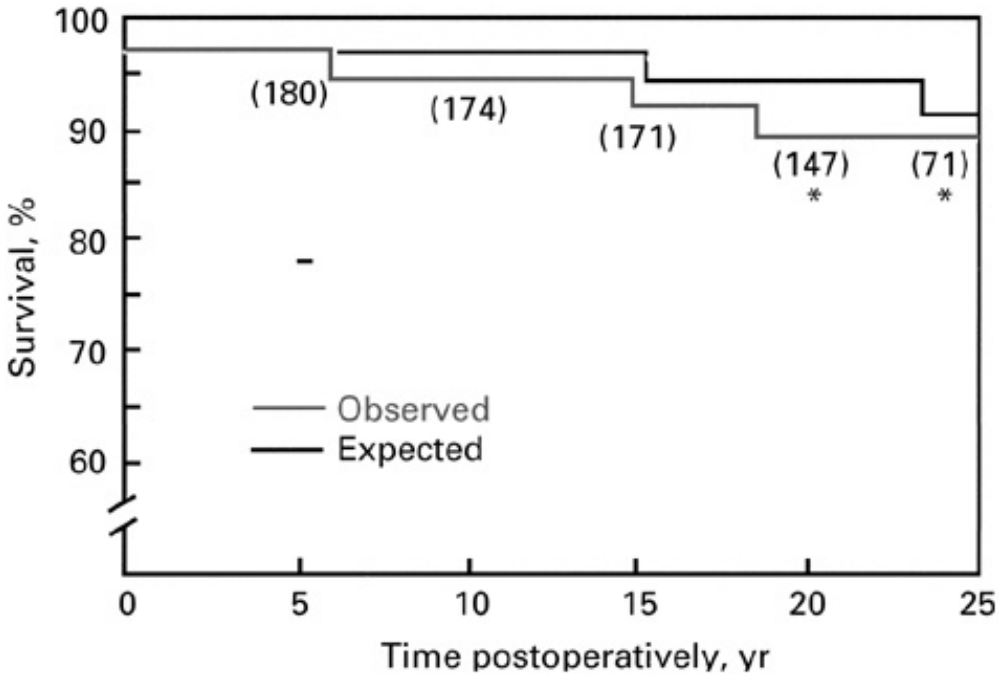

Figure 64-7: Long-term survival of perioperative survivors following surgical repair of isolated pulmonary stenosis and expected survival of age- and sex-matched control populations. Difference between expected and observed $p < .002$. (From Kopecky SL, Gersh BJ, McGoon MD, et al. Long-term outcome of patients undergoing surgical repair of isolated pulmonary valve stenosis: Follow-up at 20-30 years. *Circulation* 1988; 78:1150. Reproduced with permission from the American Heart Association and authors.)

Discrete subaortic stenosis may cause rapidly progressive obstruction in childhood and young adulthood. Progressive aortic regurgitation is common, and infective endocarditis is considered to be a particular hazard (see Chap. 63).[209,210] The natural history of supravalvar aortic stenosis is poor, and survival to adulthood is exceptional.[159] The presence of associated congenital abnormalities and possibly premature coronary artery disease with systolic hypertension is likely a contributory factor to this adverse outcome.

MANAGEMENT

The development of symptoms (e.g., angina, exertional dyspnea, and syncope) mandates prompt intervention in aortic valve stenosis (see Chap. 56). In asymptomatic younger individuals, however, the documentation of severe aortic stenosis may in itself be considered an indication for intervention.[212,213] Mild aortic stenosis in asymptomatic patients with gradients below 50 mmHg warrants careful surveillance. The management of patients in the intermediate group (gradients 50 to 75 mmHg) is more controversial, but evidence argues in favor of elective intervention. Calculation of aortic valve area is important, since left ventricular-aortic gradients may be misleading if there is reduced cardiac output.

Surgery in the young adult with congenital aortic stenosis must be considered palliative.[152,214] In the absence of calcification, young patients may be candidates for aortic valvotomy (see also Chaps. 56 and 63). Perioperative mortality rates in adolescents and adults are extremely low, and late survival is excellent. A large proportion (35 to 45 percent), however, will require reoperation, including aortic valve replacement, over a follow-up period of 20 to 25 years.[150,152] Catheter balloon valvotomy (see Chap. 63) has been utilized in adolescents and young adults with mobile noncalcified valves, but the results are also palliative.[215]

Valve replacement is the only option for valves unsuitable for valvotomy, including those with significant calcification and regurgitation. The pulmonary autograft (Ross) operation represents an attractive surgical alternative to prosthetic or homograft aortic valve replacement. The choice of operation is discussed elsewhere (see Chap. 56), but the age and size of the patient are major considerations, as are individual characteristics that determine the safety of anticoagulation, such as the desire for future pregnancies.

Subaortic stenosis is usually amenable to more definitive surgical repair. This fact, in conjunction with the potential for progressive aortic regurgitation, justifies a more aggressive approach even in asymptomatic patients with lesser gradients.[216,217] Excision of the obstructive membrane, together with a myectomy or myotomy, is usually required. Subaortic stenosis occasionally recurs, and persistent or progressive aortic regurgitation may develop. Operative mortality rates are low, but the risks are greater in patients with "tunnel" forms of obstruction and in patients with obstruction at several levels. Such situations usually require a more aggressive surgical intervention with extensive myectomy, a Konno procedure, or modification thereof.[218]

Hospital mortality rates for repair of supravalvular aortic stenosis are low, and late morbidity and mortality rates are also excellent. Nevertheless, residual abnormality, such as aortic regurgitation or stenosis, may persist after aortoplasty.

Medical follow-up of patients who have undergone surgical or balloon valvotomy should focus on the development of restenosis, the severity and progression of aortic regurgitation, and the constant hazard of infective endocarditis. Echocardiography has facilitated serial evaluation of gradients, valve areas, ventricular dimensions, function, and mass. The acceptable level of physical activity in patients with left ventricular outflow tract obstruction remains very controversial. It is debatable whether any patient who has had significant obstruction should be allowed to participate in competitive sports. We consider a residual gradient greater than 20 mmHg or persistent left ventricular hypertrophy to be contraindications to vigorous physical activity. Before one approves strenuous activity in others, evaluation should include ECG monitoring and maximal exercise testing (see Chap. 14).

Coarctation of the Aorta

Although coarctation of the aorta is a congenital malformation, nearly 20 percent of the cases presenting at the Mayo Clinic over a 20-year period were diagnosed initially in adolescence or adulthood. Most commonly, coarctation diagnosed at ages beyond childhood was discovered in asymptomatic patients in whom a routine physical examination for athletic participation or employment disclosed upper limb hypertension with diminished or absent femoral pulses. Coarctation of the aorta may occur anywhere along the descending aorta, even below the diaphragm, but in more than 95 percent of cases it is located below the origin of the left subclavian artery, and may involve the origin of this vessel. Usually, there is a discrete infolding of the aortic wall, causing eccentric narrowing of the lumen. Frequently, there is secondary aortic dilatation proximal and distal to the coarcted area.

NATURAL HISTORY

Isolated, severe aortic coarctation may cause congestive heart failure as early as the neonatal period. More frequently, however, coarctation producing symptoms during early infancy is associated with other congenital cardiovascular abnormalities, such as ventricular septal defect, left ventricular outflow tract obstruction, or mitral valve abnormality. Many patients with undetected coarctation will remain symptom-free until adolescence or early adulthood, when symptoms such as headaches related to hypertension, leg fatigue, or leg cramps may develop. Occasionally, a major catastrophic event, such as a cerebrovascular accident, infective endocarditis, or even rupture of the aorta, is the first recognized symptom. A bicuspid aortic valve

is found in approximately 25 to 50 percent of patients with coarctation, and these abnormal valves have a tendency to calcify in early or middle adult life, producing aortic stenosis. Aortic stenosis may be the presenting condition, and subsequent investigation may disclose an additional coarctation of the aorta. In the era before surgical intervention, approximately 50 percent of patients with coarctation died within the first three decades, and 75 percent were dead by age 50.[219] Death was most frequently caused by a complication of hypertension, such as stroke or aortic dissection, but other causes included endocarditis, endarteritis, and congestive heart failure.

MANAGEMENT

Infrequently, a mild degree of coarctation may be present that would not justify intervention. In the great majority of cases, however, symptoms or the presence of significant upper-body hypertension mandate surgical repair. On occasion, an asymptomatic adolescent or adult patient with a severe coarctation will be normotensive at rest because of well-developed collaterals around the coarctation site. Such patients have inappropriate hypertension with exercise, however, and should be repaired. There is evidence that residual hypertension and late complications are directly related to age at the time of repair.[220]

Surgery for coarctation has been available since 1945.[221] Various techniques have been used, including end-to-end anastomosis, patch grafting, and the use of the subclavian flap technique.[222] Aneurysmal or atherosclerotic changes in the aorta found in adolescents or adults may occasionally mandate the use of an interposition prosthetic graft. Surgery is performed without cardiopulmonary bypass, and the risk of death from operation is small, although it is higher in adults than in children. Serious morbidity is rare, but occasionally paraplegia secondary to spinal cord ischemia and bowel ischemia or infarction occur.[223] For patients who require concomitant surgical procedures, such as aortic valve replacement, an ascending-to-descending aortic bypass may be utilized through a median sternotomy.[224] Some patients require antihypertensive medication because of transient postoperative hypertension for a short period, whereas in others hypertension may persist, requiring long-term treatment.

Balloon angioplasty of native coarctation has been utilized, but the role of this technique remains controversial.[225] Immediate reduction of the degree of obstruction and gradient is usually possible but is achieved at the price of tearing both the aortic intima and media. Late aneurysm formation, presumably secondary to the disruption of the media, has been observed.[226] Currently, most centers do not perform catheter balloon angioplasty as the primary procedure for coarctation, reserving it for recoarctation, where it appears to have a much greater role.[227] Balloon-expandable stents have also been utilized recently with good results, although long-term follow-up data are not available.[228-231]

LATE RESULTS

The Mayo Clinic has published late results in 646 patients with coarctation operated upon between 1946 and 1981.[220] The median age at operation was 16 years (range 1 week to 72 years) with 72 patients (11 percent) over age 35 years of age. Although survival was good (91 percent at 10 years and 72 percent at 30 years), the mean age of death was 38 years, confirming the previous finding that life expectancy is reduced, even after repair. In this and other series reporting long-term follow-up, the most common cause of death was premature coronary artery disease with secondary myocardial infarction.[232,233] Other causes included congestive heart failure, stroke, and ruptured aortic aneurysm. Age at operation was a powerful prognostic factor. The older the patient at the time of repair, the greater the probability of premature death, making it highly likely that the duration of preoperative obstruction and hypertension is important in the etiology of arterial disease and subsequent cardiovascular events.

The incidence of recoarctation with all surgical techniques is low for repairs performed after

infancy, but surgery in later years for associated abnormalities, such as aortic and mitral valve disease, may be required. The majority of survivors are asymptomatic, but there is a high incidence of late hypertension, despite satisfactory early fall in blood pressure after surgery and good relief of obstruction. In one series, only 32 percent of patients were normotensive 30 years after repair, and 25 percent were significantly hypertensive.[233] Long-term blood pressure surveillance, including blood pressures with exercise, is therefore mandatory, since hypertension is directly related to many of the late vascular complications.[220,232,233] This incidence may decline significantly as more patients are diagnosed and repaired during infancy or early childhood. Long-term regular follow-up should also include surveillance of the repaired aorta (MRI imaging is very suitable), assessment of the aortic valve, and endocarditis prophylaxis.

Transposition of the Great Arteries

In complete transposition of the great arteries, the aorta arises from the right ventricle and the pulmonary artery from the left ventricle (discordant ventriculoarterial connection). As a result, the systemic and arterial circulations run "in parallel" rather than "in series," and predominantly desaturated blood enters the aorta. Oxygenation and survival depend on mixing between the systemic and pulmonary circulations at the atrial level in simple transposition (via a patent foramen ovale or atrial septal defect; see Chap. 63). In approximately half the cases, there are associated anomalies: ventricular septal defect (30 percent), left ventricular outflow tract obstruction (5 to 10 percent), ventricular septal defect with left ventricular outflow tract obstruction (10 percent), patent ductus arteriosus, and, more rarely, coarctation of the aorta or AV valve anomalies.[234] These associated conditions affect both the natural history and surgical management.

NATURAL HISTORY

Transposition of the great arteries is relatively common, but the natural history is so poor that very few patients survive past childhood without intervention. Death is usually due to profound hypoxia and its hematologic consequences. In transposition of the great arteries with large ventricular septal defect, severe hypoxia is rare, but patients do badly as a result of heart failure from excessive pulmonary flow and early pulmonary vascular disease.[129] Transposition with ventricular septal defect and left ventricular outflow tract obstruction presents with early hypoxia. Occasionally, prolonged survival into adult life may occur with a large atrial septal defect, ventricular septal defect, and/or patent ductus arteriosus, with the development of pulmonary vascular disease (Eisenmenger's syndrome) or with associated ventricular septal defect and left ventricular outflow tract obstruction.

MANAGEMENT

The outlook has been transformed by the use of catheter balloon atrial septostomy.[235] In the late 1950s and early 1960s, the Senning[236] and Mustard[237] operations, involving atrial redirection of the systemic and pulmonary venous returns, were introduced. These operations are usually performed between 3 and 12 months of age, with a trend over the years to earlier surgery. Both procedures have been undertaken with excellent early mortality rates (approximately 2 percent operative mortality rate and less than 10 percent for the whole early-management protocol). Long-term follow-up for both procedures is now available, with comparable late results, apart from a lower incidence of baffle obstruction after the Senning operation.[238] Follow-up now extends to 30 years in some patients.[239] A recent study reported actuarial survival rates of 90 percent, 80 percent, and 80 percent at 10, 20, and 28 years, respectively, after the Mustard repair.[240,241] Seventy-six percent of the survivors were in NYHA class I. Thus, cardiologists are likely to see patients who have undergone these types of atrial redirection. Late problems, however, are now recognized, with sudden death, arrhythmia, tricuspid regurgitation, and right (systemic)

ventricular dysfunction being the major concerns.[240] These late complications have led to the increasing acceptance of the arterial switch operation as the operation of choice.[242] This procedure involves transection and reanastomosis of the great arteries (aorta to left ventricle and pulmonary artery to right ventricle) with coronary artery transfer. The mortality rate for this procedure has decreased, but the long-term results into adult life are not yet available. For transposition with ventricular septal defect, the mortality rate for atrial repair with ventricular septal defect closure has always been higher than for simple transposition, and arterial switch is the operation of choice. Transposition with ventricular septal defect and left ventricular outflow tract obstruction is usually palliated in infancy with a systemic-to-pulmonary shunt followed by repair by the Rastelli procedure in later childhood.[243] This operation involves closure of the ventricular septal defect to connect the left ventricle to the aorta and insertion of a valved conduit from the right ventricle to the pulmonary artery. Long-term results are good, but further surgery to replace the extracardiac conduit in adolescent and adult life is inevitable (see "Surgical Considerations," above).

LATE RESULTS

Two specific problems after atrial redirection have caused concern during long-term follow-up: arrhythmia and systemic ventricular dysfunction. Loss of sinus rhythm is progressive and has not been prevented by modification of surgical technique for either the Mustard or the Senning operation.[41,244] In most cases, it is asymptomatic, but occasionally profound bradycardia may necessitate pacemaker insertion. There appears, however, to be no relationship between loss of sinus rhythm and risk of sudden death. More worrisome is the development of atrial tachyarrhythmias, including atrial flutter. This arrhythmia has profound hemodynamic consequences after intraatrial repair and is a risk factor for sudden death, especially in the presence of right ventricular dysfunction. Deteriorating performance of the right ventricle supporting the systemic circulation has been reported in some patients, but the precise basis for this problem remains unclear.[9] Although a major concern, it is not yet known whether or not ventricular performance will inevitably deteriorate in the majority of patients and, if so, over what period.[9]

Risk stratification for sudden death remains a clinical challenge. Late death cannot be predicted merely from serial ECGs or ambulatory monitoring.[41] This difficulty underscores the need for a more sophisticated approach involving both electrophysiologic and hemodynamic measurements. Assessment should include evaluation of cardiac performance at rest and exercise, and evaluation of systemic and venous pathways. Transesophageal echocardiography is particularly useful in this situation. Heart transplantation should be considered in the patient who has severe right ventricular failure or disabling arrhythmias. An alternative approach is to perform pulmonary artery banding as preparation for conversion of the atrial repair to an arterial switch. Published results have indicated a significant surgical mortality rate for this approach. As a result, case selection and timing, as well as optimal surgical strategy, remain unclear.[245] The rather limited information after arterial switch operation suggests that electrophysiologic problems are much less prevalent.[246] More recent studies confirm the theoretical advantages of anatomic repair over atrial repair with respect to preservation of sinus node function and lower prevalence of clinically relevant tachyarrhythmias.[247] The systemic left ventricle after the switch is at risk from the surgical procedure itself, potential myocardial ischemia from coronary distortion, and aortic regurgitation. Early results, however, are encouraging, but few patients have yet reached adult life.[248] Because of the high incidence of observed and potential medical problems, all patients who have had both atrial and arterial repair of transposition of the great arteries should have lifelong follow-up by a cardiologist at a center specializing in adult congenital heart disease.

Congenitally Corrected Transposition (Atrioventricular and Ventriculoarterial Discordance)

In congenitally corrected transposition of the great arteries, there is a discordant AV connection

(right atrium to left ventricle and left atrium to right ventricle) and a discordant ventriculoarterial connection (left ventricle to pulmonary artery and right ventricle to aorta). As a result of this "double discordance," the systemic and pulmonary venous returns flow to the appropriate great arteries, giving rise to the potentially confusing term *corrected transposition*.[249]

NATURAL HISTORY

In a small proportion of cases (approximately 10 percent in reported series, but this is probably an underestimate), there are no associated cardiac defects.[250,251] Such individuals are pink and asymptomatic, and survival to the ninth decade has been reported.[76] The only specific difference from normal hearts is the tendency to develop AV conduction problems and complete heart block. Complete heart block may be present from birth (approximately 10 percent of patients)[252] and is said to develop in about 2 percent of patients per year.[253] It is not clear whether the systemic right ventricle in patients with corrected transposition can maintain function over extended periods or whether this has an impact on outcome, since few studies have examined enough patients without associated defects over a long enough period. The majority of patients have a ventricular septal defect (90 percent) and/or pulmonary stenosis (80 percent).[250] The combination of these lesions may cause cyanosis. Abnormalities of the tricuspid valve (systemic AV valve) are common and may be due to an intrinsic tricuspid valve abnormality, such as Ebstein's malformation. These defects influence the natural history and surgical strategy required.

MANAGEMENT

Strategies and indications for surgery differ from those in patients with normal connections because of the potential for the operation to aggravate systemic ventricular dysfunction, systemic AV valve incompetence, or conduction problems. Palliative surgery in childhood is sometimes performed, since definitive repair may involve insertion of an extracardiac conduit. In a large retrospective study of 111 patients managed over a 20-year period, it was concluded that patients with symptomatic heart failure should be repaired before the systemic ventricle dilates and the tricuspid regurgitation becomes severe.[251] Patients with more than mild tricuspid regurgitation whose valves were not replaced did very poorly. In contrast, the patients with cyanosis did much better, and the timing of intracardiac surgery can be delayed and be determined by the patient's symptoms. In one recent series of surgical repair of 127 patients, 56 percent required reoperation within 20 years for AV valve regurgitation, pulmonary stenosis, or both.[254] Left AV valve regurgitation is common in adults with congenitally corrected transposition[255] and tends to be progressive.[256] It may be related to an Ebstein-like malformation of the left AV valve, but these valves, in contrast to Ebstein's anomaly of the right AV valve, cannot be repaired adequately and always need to be replaced. Left AV valve replacement should always be performed before there is compromise of systemic (morphologic right) ventricular function. In one series of 40 patients, left AV valve replacement was accomplished without surgically induced complete heart block, with an early mortality rate of 10 percent (n = 4) and 8 late deaths.[257] The principal cause of death in all 12 patients was systemic ventricular failure. Survival correlated with preoperative systemic ventricular ejection fraction of 44 percent or greater. It thus seems appropriate to refer these patients for valve replacement at the earliest signs of ventricular dysfunction.

Recently, alternative surgical strategies involving a "double switch" have been adopted by some units. These involve an atrial repair by a Mustard or Senning operation together with connection of the left ventricle to the aorta (via a patch through the ventricular septal defect) or an arterial switch.[258,259] The advantage of these approaches is that the morphologic left ventricle (with mitral valve) supports the systemic circulation. While this is an attractive option, it should be stressed that few patients who have received double-switch procedures have reached adolescence, and long-term follow-up data are not yet available for comparison with the conventional surgical approach.

LATE RESULTS

The long-term outcome for well-repaired patients is good, but those with severe symptomatic heart failure preoperatively do badly. Atrial arrhythmias are common in long-term follow-up and in one recent series occurred in 36 percent of survivors.[260] Since repairs may involve insertion of an extracardiac conduit, prosthetic AV valve, and pacemaker, careful long-term follow-up is mandatory.

Complex Lesions

A number of complex congenital heart defects involve structural abnormalities that preclude the creation of a biventricular circulation. The changing nomenclature and classification that have been applied to these defects over the years are a major source of confusion (see Chap. 63). This group of patients includes those with double-inlet ventricle (single ventricle), absent right or left AV connection (tricuspid or mitral atresia), some cases of pulmonary atresia/intact ventricular septum, and cases with straddling of an AV valve and hypoplastic left or right ventricles. The natural history of these defects is highly variable and depends to a large extent on the impact of the associated defects. In a recent report of 191 patients with double-inlet ventricle presenting in the first year of life, the actuarial survival rate before definitive repair for the whole group was 57 percent at 1 year and 42 percent at 10 years.[158] On multivariate analysis, pulmonary stenosis, balanced pulmonary flow, and older age at presentation were factors favoring survival, while right atrial isomerism, common AV orifice, pulmonary atresia, obstruction to systemic output, and anomalous pulmonary venous return were detrimental. Despite the complex morphologic defects, prolonged natural survival is possible, particularly if the physiology is well balanced.[261] The patients with double-inlet left ventricle with discordant ventriculoarterial connection and pulmonary stenosis with balanced pulmonary flow do best, with predicted actuarial survivals of 96 percent at 1 year and 91 percent at 10 years.

MANAGEMENT

For most patients with complex congenital heart disease, prolonged survival into adult life is possible only with one or more palliative operations (e.g., systemic to pulmonary shunt, Glenn shunt, pulmonary artery banding, and relief of systemic outflow obstruction) or after a Fontan-type procedure. With palliative surgery alone, clinical deterioration usually begins in the second decade of life and is often due to progressive ventricular dysfunction and/or AV valve regurgitation.[262-264]

The goals of management during childhood have been to maintain suitable anatomy and physiology for the Fontan circulation. A number of modifications of Fontan's original operation have been introduced (Fig. 64-9).[265-268] The basic principle is to separate the systemic and pulmonary circuits by returning systemic venous blood to the pulmonary artery without incorporating a subpulmonary ventricle. This circulation is less "flexible" than one with two functioning ventricles; the operative risk and postoperative status are largely dependent on the patient's suitability. Most important are a low pulmonary vascular resistance and adequate ventricular function (both systolic and diastolic), allowing the circulation to operate with an acceptably low systemic venous pressure. Careful preoperative hemodynamic assessment is vital to optimize patient selection. The operative risk varies considerably among institutions.

LONG-TERM RESULTS

The early and medium-term results of the successful Fontan operation are excellent when compared to the preoperative status of the patients. Improvements in arterial saturation and

exercise tolerance have been confirmed by objective testing.[268] The patients with the best hemodynamics can perform well at submaximal levels of exercise equivalent to most normal daily activities.[269] With longer follow-up, however, increasing problems develop (Table 64-5).[270,271] Fontan's own analysis of 334 patients revealed a premature decline in survival and functional status and a late rise in hazard for which no risk factors could be identified other than the Fontan state per se.[271] Arrhythmia is a particularly common problem and occurs in approximately 20 percent at 10-year follow-up (Table 64-6).[270] Other problems include thrombus in the atria and declining ventricular function.[270-272] Anticoagulation policy differs widely even among specialist centers. The increasing concerns regarding stasis of blood in the right atrium and thrombus formation have led to wider routine use of long-term anticoagulants, but this is not standard practice. Patients with a history of documented atrial arrhythmias, a fenestration in the Fontan connection, and "smoke" in the right atrium on echocardiography have the strongest indications for anticoagulation. Protein-losing enteropathy (PLE) is another important complication and probably results from elevated systemic venous pressure, which subsequently causes lymphangiectasia. PLE is associated with fluid accumulation, such as pleural effusion, ascites, and peripheral edema. The diagnosis can be confirmed by quantifying gastrointestinal protein loss utilizing $alpha_1$ antitrypsin clearance. The cumulative risk for the development of PLE by 10 years in one reported large series was approximately 13 percent;[273] once this complication had developed, the 5-year survival rate was approximately 50 percent. Therapy includes sodium restriction, dietary modification, and anticongestive measures such as diuretics and afterload-reducing agents. Many patients require periodic albumin infusion, but medical management of PLE is usually only partially successful. Obstruction in the Fontan circuit should always be ruled out as a potential cause, since reoperation may result in resolution of the PLE. Chronic subcutaneous heparin therapy may also resolve the PLE,[274,275] as may percutaneous atrial fenestration.[265,276] Occasional reports suggest improvement with steroid therapy.[277] Cardiac transplantation appears to pose a high risk and does not always resolve the protein loss.[274] Other concerns are the effects of nonpulsatile pulmonary flow, favoring the development of pulmonary arteriovenous malformations, as seen after the Glenn anastomosis.[278] Extrapolation of these data to current practice is difficult, but the Fontan procedure should be considered palliative, not curative.

Despite these complications, more and more modifications of the Fontan operation are being performed, and more long-term data are necessary to see whether important complications can be reduced in this way. Much recent interest has involved conversion of the Fontan to a more "hydrodynamically efficient" circuit to improve atrial arrhythmias and PLE.[279] A high mortality rate, however, is associated with PLE surgery, and in one series only 50 percent of the survivors were cured.[274] Atrial arrhythmias may also persist after Fontan conversion[279,280] even though hydrodynamics are improved. Perhaps concomitant arrhythmia circuit cryoablation may improve the results.[281]

Some surgical modifications that have been introduced may improve early and late hemodynamics and the functional results. Perforation of the patch at surgery (fenestrated Fontan) allows a hypertensive right atrium to decompress via a right-to-left shunt at the atrial level.[282] These holes may be closed later with an occlusion device at catheterization. Recent "Fontan" operations have excluded the right atrium from the circulation, creating a total cavopulmonary connection (superior vena cava to right pulmonary artery via a bidirectional Glenn anastomosis and inferior vena cava blood channeled to the pulmonary artery).[283] Data suggest improved flow and energy characteristics compared to the standard atriopulmonary connection and fewer early supraventricular arrhythmias.[46] Other modifications have created an extracardiac Fontan connection using a tube graft in the hope of preventing atrial distention and atrial arrhythmias.[284,285]

All patients who have complex congenital heart defects palliated by systemic-to-pulmonary shunt, cavopulmonary anastomosis (bidirectional Glenn), or Fontan should have lifelong regular cardiac follow-up at a specialist center. Particular attention should be paid to ventricular function, detection of thrombus in the right atrium, residual shunts, systemic AV valve regurgitation, AV malformations in the lung, obstruction at the Fontan anastomosis (especially in early operations involving a right atrium-to-pulmonary artery conduit), and PLE (see above).

Ebstein's Anomaly of the Tricuspid Valve

Ebstein's anomaly is characterized by displacement of the proximal attachments of the tricuspid valve from the AV ring into the right ventricle (see Chap. 63). This structural abnormality divides the right ventricle into an "atrialized" portion and a distal "ventricularized" portion. The severity is variable and accounts for the broad clinical spectrum, from severe disease causing fetal or neonatal death to mild disease compatible with natural survival as late as the eighth decade of life.[286] Ebstein's anomaly is an uncommon defect occurring in less than 1 percent of patients with congenital heart disease, but it is disproportionately represented in the adult congenital heart disease population because of its favorable natural history.

The diagnosis of Ebstein's anomaly is now much easier with echocardiography, which has altered our understanding of the natural history. In a large collaborative study of Ebstein's anomaly reported in 1974, only 7 percent of patients were under 1 year of age.[286] It is not surprising that neonates presenting with Ebstein's anomaly represent the worst end of the spectrum, with a severe anatomic defect and a high incidence of associated abnormalities, particularly right ventricular outflow tract obstruction. Their poor outcome is predictable from their anatomy.[287] Those who survive this period with or without surgery may live into adult life, although there is continued morbidity and death throughout childhood. Many patients are minimally symptomatic in childhood and do not present until adolescence or adult life. Symptoms and signs, when they develop, include cyanosis due to right-to-left shunting at the atrial level, dyspnea and fatigue secondary to hypoxia and low cardiac output, and palpitation due to supraventricular arrhythmia. Ebstein's anomaly is often associated with ventricular preexcitation, which may involve one or more, usually right-sided, accessory pathways. Approximately 25 to 30 percent of adults will have symptomatic arrhythmias that may be difficult to treat and can result in sudden death.[288] Progressive heart failure may develop with time and may be related not only to right-sided problems but also to left-sided abnormalities. Excessive fibrosis has been reported in the left ventricle, and left ventricular dysfunction may be induced on exercise.[287,289] Early cyanosis is an adverse risk factor for survival, as is congestive cardiac failure.[290]

MANAGEMENT

Surgery may consist of repair or replacement of the tricuspid valve together with closure of the atrial septal defect to prevent cyanosis (Fig. 64-10).[291] In 189 patients aged 11 months to 64 years (mean 19.1 years), a tricuspid valve reconstruction was possible in 58.2 percent, and in 36.5 percent a prosthetic valve, usually a bioprosthesis, was inserted. In the occasional patient, the atrial septal defect may be responsible for a left-to-right shunt and can be closed as the sole procedure. In others, the functioning right ventricle is too small for a biventricular circulation, and a Fontan procedure may be the only option. Cross-sectional echocardiography is very useful in determining whether the tricuspid valve is amenable to repair, delineating the mobility or tethering of the elongated anterior leaflet and the presence or absence of fenestration. The results of surgery are affected by the presence of arrhythmia. Uncontrolled preoperative supraventricular arrhythmia is a risk factor for early postoperative rhythm problems that may have serious hemodynamic consequences.[288] It is usually recommended that division of an accessory pathway be performed at the time of tricuspid valve surgery. The pathways are usually in the posteroseptal or right free-wall position and may be multiple. An alternative approach is to perform catheter radiofrequency ablation of the accessory pathway (see Chap. 28) before surgery. Thus far, few such procedures

have been performed in patients with Ebstein's anomaly. In hearts with marked enlargement of the right atrium, catheter ablation is challenging and, in the setting of an atrial communication, poses the additional risk of a paradoxical embolus and stroke. If there are no accessory pathways, a right-sided maze procedure at the time of tricuspid valve surgery may successfully control supraventricular arrhythmia.[169]

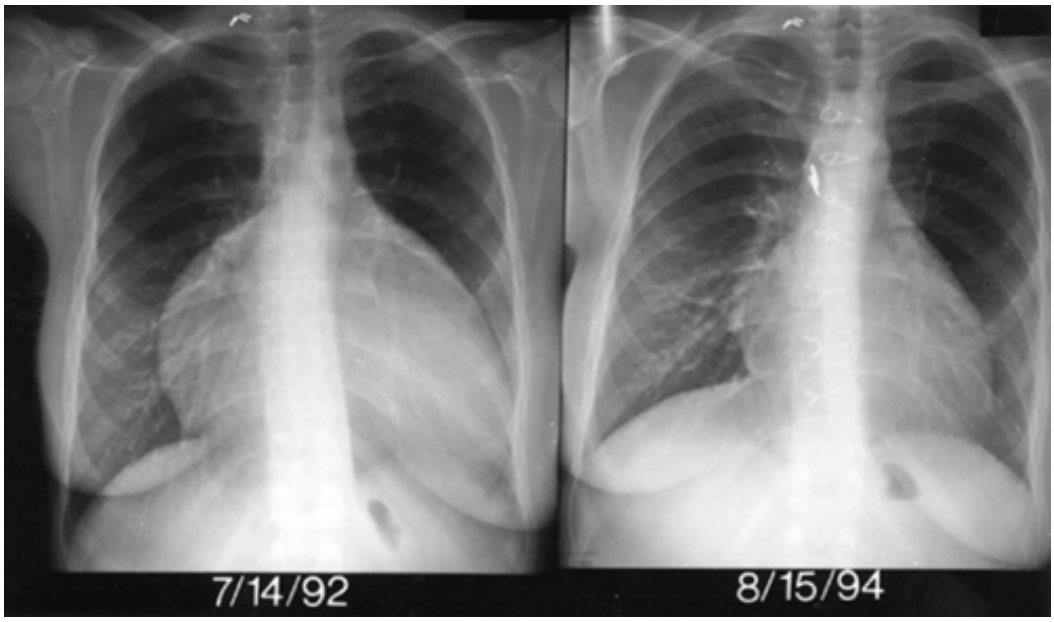

Figure 64-10: (*Left*). The chest radiograph shows severe cardiac enlargement associated with Ebstein's anomaly in a 32-year-old woman. She had had a right Blalock-Taussig shunt at age 12. (*Right*). Following tricuspid valve repair and closure of a secundum atrial septal defect, there has been dramatic reduction in the size of the heart.

LATE RESULTS

The long-term outlook for well-repaired patients is good; reduction in heart size is usual (see Fig. 64-10), and atrial arrhythmias are reduced. Exercise capacity improves postoperatively, particularly in those who are cyanotic before surgery.[292] Of 149 patients receiving a porcine bioprosthesis in the Mayo Clinic series, the 10-year survival was 92.5 percent, and 92 percent of the survivors were NYHA class I or II. Bioprosthesis durability in the tricuspid position performs favorably, with freedom from bioprosthesis replacement being 80.6 percent at 10 and 15 years.[293]

Marfan's Syndrome

Although the autosomally dominant Marfan's syndrome is congenital in the sense that the patient is born with an abnormal gene or genes, the heart defect is usually acquired. Mutations of fibrillin 1, the main constituent of extracellular microfibrils, are the cause of the pleiotropic manifestations of Marfan's syndrome.[294] The typical phenotypic features-tall, thin stature; pectus deformities; arachnodactyly; and high-arched palate-by which the condition is currently diagnosed, may be obvious, subtle, or absent (see Fig. 10-7). Cardiovascular complications occur in 30 to 60 percent of patients and are the cause of a decreased life expectancy.[295] Mitral valve prolapse is the commonest finding in the pediatric population,[296] but aortic root dilation with a potential for aortic dissection or severe aortic valve regurgitation is the most serious later complication.[297] In a review of 257 patients seen between 1939 and 1972, the median age of death was reported to be about 45 years, with aortic root problems accounting for three-fourths of the deaths (see also

Chap. 76).[295] By 1995, a multicenter study reported that the median survival had improved to 72 years.[298]

MANAGEMENT

The risk of dissection is broadly related to the degree of dilation of the aortic root. Dilation can be followed serially by regular cross-sectional echocardiography, which should be performed at least annually. Particularly close monitoring is necessary during puberty and the rapid-growth phase of adolescence. Treatment with beta blockade has been advocated for patients with evidence of aortic root enlargement. Elective aortic root replacement has a low operative mortality rate, but, in contrast, emergency repair, usually for acute aortic dissection, carries a much higher early mortality rate. In a recent multicenter study of 675 patients having aortic root replacement, the 30-day mortality rate was 1.5 percent for those having elective repair, 2.6 percent for those having urgent repair (within 7 days of a surgical consultation), and 11.7 percent for those having emergency repair (within 24 h of a surgical consultation).[297] Forty-six percent of the 158 patients with aortic dissection had an aneurysm with a diameter of 6.5 cm or less. Elective aortic root surgery, therefore, is generally recommended when the aorta exceeds 5.5 cm in diameter.[299] The aortic valve itself may also need to be replaced, although preliminary results from valve-sparing procedures, which eliminate the need for long-term anticoagulants necessary for conventional mechanical valve replacements, suggest cautious optimism.[297,300] It is important to note that more than 10 percent of patients in the multicenter study had problems with the residual aorta, emphasizing the need for continued vigilance of the aorta with MRI or computed tomographic scanning and meticulous control of blood pressure. Since regular, long-term follow-up visits are required, patients with Marfan's syndrome are not uncommon in adult congenital heart clinics. In addition to cardiac care, such patients need expert help with skeletal and ocular problems, genetic counseling, advice on physical activity (see above), and general psychosocial support.

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Chapter 64: CONGENITAL HEART DISEASE IN ADULTS

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Chapter 64: CONGENITAL HEART DISEASE IN ADULTS

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Figure 64-8: (*Left*) Cumulative actuarial curves of 153 patients presenting with *mild* aortic stenosis. Bars show ±1 standard error in age at presentation 6.5 years (range 1 to 25 years); mean follow-up was 8.8 years (range 1 to 26 years). (*Right*) Cumulative actuarial curves of 54 patients presenting with *moderate* aortic stenosis. Conventions are as in the left-hand figure. Mean age at presentation was 11.8 years (range 1 to 25 years). Mean follow-up was 8.5 years (range 1 to 24 years). (From Hossack KF, Neutze JM, Lowe JB, Barratt-Boyes BG. Congenital valvar aortic stenosis: Natural history and assessment for operation. *Br Heart J* 1980; 43:561. Reproduced with permission from the publisher and authors.)

Figure 64-9: Angiograms. *A.* Fontan conduit from right atrium to pulmonary artery. There is dilatation of the right atrium with filling of the inferior vena cava, superior vena cava, and coronary sinus. *B.* Total cavopulmonary connection. The superior vena cava is connected to the right pulmonary artery ("bidirectional Glenn"), and the inferior vena cava is baffled to the pulmonary artery. (Courtesy of Dr. I. D. Sullivan, Great Ormond Street Hospital for Children, London.)

Figure 64-10: (*Left*). The chest radiograph shows severe cardiac enlargement associated with Ebstein's anomaly in a 32-year-old woman. She had had a right Blalock-Taussig shunt at age 12. (*Right*). Following tricuspid valve repair and closure of a secundum atrial septal defect, there has been dramatic reduction in the size of the heart.

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Part 11: CARDIOMYOPATHY AND SPECIFIC HEART MUSCLE DISEASES
Chapter 65:

CLASSIFICATION OF CARDIOMYOPATHIES

Author: Jay W. Mason

Despite controversy in classifying the cardiomyopathies, there is general agreement on the definition. Cardiomyopathy is a primary disorder of the heart muscle that causes abnormal myocardial performance and is not the result of disease or dysfunction of other cardiac structures. Thus, the term *cardiomyopathy* excludes cases of myocardial failure due to myocardial infarction (so-called ischemic cardiomyopathy, a misnomer), systemic arterial hypertension, and valvular stenosis or regurgitation. Although cardiomyopathy is easily defined, classification of its various forms is difficult. This difficulty results because the great majority of cases of cardiomyopathy are associated with generalized cardiac dilatation and ventricular systolic dysfunction, in which the etiology is unknown.

CLASSIFICATION SCIENCE

Physicians and biomedical scientists use classification schemes to draw relations and distinctions between diseases. This process promotes understanding and aids recollection. Even disorders we know little about can be understood if appropriately placed in a class with other disorders we do know about.

The science of classification requires that all items within the classified domain be included and that each item appear in only one class. Inability to make clear distinctions between biologic systems makes this latter requirement the most demanding. Classification must be based on those features of the individual units within the domain that are understood or recognizable and that permit a useful distinction between groups.

Thus, the classification of cardiomyopathies should be based on an extensive, current category of knowledge about heart diseases and should be as useful as possible to physicians and scientists.

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CATEGORIES OF KNOWLEDGE ABOUT CARDIOMYOPATHIES

Knowledge about cardiomyopathies falls into several categories: Etiology, gross anatomy, histology, genetics, biochemistry, immunology, hemodynamic function, prognosis, treatment, and others. No single classification scheme can utilize all of these areas of knowledge because there is so much overlap between them.[1]

The best classifications use a single category of knowledge with which to separate items in the domain. However, the most useful knowledge category differs among users of the classification. A histologic classification will be useful to the pathologist, while a functional categorization is more valuable to the treating physician. If only one classification is to be used by both clinicians and scientists, etiologic categorization seems to be most successful. It must be recognized, however, that no single classification can serve all users and all purposes.

Several commonly employed classifications of cardiomyopathy are discussed below. For clarity, the primary categories of each classification are displayed in Tables 65-1 to 65-6, but only a few representative diseases are mentioned within each category. The exceptions are the etiologic classification (Table 65-3) and the *International Classification of Disease,* **Ninth Revision (ICD-9)** classification (Table 65-5), in which more nearly complete listings are provided.

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THE WORLD HEALTH ORGANIZATION CLASSIFICATION

The only currently used clinical classification of cardiomyopathy that was developed by consensus is that of the *World Health Organization* (WHO) and the International Society and Federation of Cardiology.[2,3] This scheme is outlined in Table 65-1. Because it was developed by a panel of experts and has the implied backing of the WHO, it is widely recognized and frequently used. Although it has been in existence since 1980, it has not gained general acceptance.

The 1980 WHO committee[2] reserved the term *cardiomyopathy* for myocardial disease of unknown cause. This somewhat restricted usage has not been adopted widely and is not fully adhered to in this text. The more common usage includes all forms of heart disease in which the myocardium is primarily involved, as defined at the start of this chapter, but excludes valvular heart disease, systemic arterial hypertension, and coronary atherosclerosis. In its 1995 classification, the WHO committee (entirely new except for one member) moved toward this more common usage, stating, "With increasing understanding of etiology and pathogenesis, the difference between cardiomyopathy and specific heart muscle disease has become indistinct."[3]

Examination of the 1980 and 1995 WHO classifications reveals that they are, in fact, somewhat awkward schemes that employ two separate categorizations in series, one based primarily on left ventricular morphology and function and the other based on etiology. A resultant disadvantage is that diseases are placed in two schema that overlap.

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FUNCTIONAL CLASSIFICATION OF CARDIOMYOPATHIES

The most widely used functional classification of cardiomyopathy recognizes three disturbances of function: dilatation, hypertrophy, and restriction (Table 65-2). *Dilatation* is dominated by left ventricular cavity enlargement and systolic failure. *Hypertrophy* includes both obstructive and nonobstructive forms. *Restriction* is characterized by inadequate compliance causing restriction of diastolic filling. The value of this scheme is that virtually all cardiomyopathies are readily placed in one of the three categories, and the therapeutic approaches to each category are distinctly different. For example, left ventricular afterload reduction is a cornerstone of therapy for dilated cardiomyopathies with systolic failure, but is of little benefit in the restrictive forms. There are some shortcomings of the functional classification however. Many diseases are physiologically heterogeneous. Almost all hypertrophic conditions have an element of diastolic restriction. Most dilated ventricles display myocyte hypertrophy. Some diseases change from one category to another during their course; the best example is cardiac amyloidosis, which initially exhibits diastolic stiffness, with complete preservation of systolic performance, followed years later by dilatation and systolic failure.

The functional scheme also associates diseases that have vastly different causes, some of which require special therapeutic interventions. For example, the primary therapy for cardiac hemochromatosis, often an initially restrictive disease, is removal of excessive iron stores; this would not, of course, be effective treatment for other diseases similarly classified. Despite its shortcomings, the functional classification of cardiomyopathy remains the most popular among clinicians because it is based on easily understood physiology and is relevant to therapy.

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ETIOLOGIC CLASSIFICATION

This scheme utilizes knowledge about cardiomyopathies more extensively than all the others. It has the most primary categories because there are numerous known causes that are not interrelated. Table 65-3 categorizes the diseases covered in Chaps. 69, 73 to 80, 85, 86, and 91 to 94. The general outline established by WHO in 1980 is followed roughly. In many cases the etiologic agent is poorly understood (e.g., uremic "cardiomyopathy"), or the cardiomyopathy is associated with another disease, but the mechanism responsible for heart failure is not known (e.g., cardiomyopathy of systemic neoplasia).

While this classification has the advantage of being inclusive, it has the disadvantage of being awkwardly long. It has 7 primary and 42 secondary categories. In addition, most similarly classified disorders are anatomically, physiologically, and therapeutically unrelated. Thus, this classification is not used routinely by clinicians. It has been used most frequently as an organizational scheme in textbooks and reviews concerning heart muscle disease and cardiomyopathy.

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ENDOMYOCARDIAL BIOPSY CLASSIFICATION

Because the heart can be safely biopsied, antemortem histologic diagnosis can be used to classify cardiomyopathies. Dozens of specific myocardial diseases can be detected by biopsy (Table 65-4). The great strength of histologic diagnosis is that it is definitive and unequivocal when a specific disease is observed. In contrast, numerous deficiencies make this method of classification relatively restricted in use. The foremost problem is that, although the number of specific histologic diagnoses is large, they represent a small proportion of all cases-certainly fewer than 15 percent. The histology in most patients with cardiomyopathy is nonspecific and nondiagnostic. Hypertrophy, or fiber attenuation, and fibrosis may be seen in varying degrees in almost any disorder and are the only findings in most cases of idiopathic dilated cardiomyopathy and hypertrophic cardiomyopathy (as well as in many instances of heart failure due to myocardial infarction and valvular dysfunction). Furthermore, completely normal histology may occasionally be seen on biopsy in cases of severe dilatation and systolic failure.

Myocardial biopsy samples can be subjected to several additional analytic techniques that expand the potential for classification using endomyocardial biopsy. While at present these analyses are only investigational and none can be generally applied, it is likely that one or more of them will become clinically useful in the future and could form the basis of a classification with wide appeal.

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ICD-9 CLASSIFICATION

ICD-9-CM stands for *International Classification of Disease*, Ninth Revision, Clinical Modification. This system was developed by WHO in 1948 for registering disease incidences. In 1977, the United States National Center for Health Statistics modified the ICD-9 code to allow coding of medical records. That modification is the current ICD-9-CM. In 1989 it became mandatory for physicians in the United States to include an ICD-9-CM code on their Medicare claims. It is fascinating to see how utterly different a classification system intended for governmental statistics and claims payment is in comparison to those intended for scientific or clinical purposes. The code is a remarkable hodgepodge, combining multiple categories of knowledge into one classification system. Diseases are variously defined according to one or more features such as etiology, anatomy, physiology, comorbidity, symptoms, and even method and extent of diagnosis. It is no wonder that this code is impossible to remember and notoriously ambiguous and difficult to use. In Table 65-5, the codes describing cardiomyopathies have been extracted from the 1999 version of the ICD-9-CM, where they appear in several groups scattered throughout the listing. Relatively few-25-cardiomyopathy diagnoses are coded, and these represent only 9 specific entities. Some well-recognized myocardial diseases are completely ignored, such as arrhythmogenic right ventricular dysplasia. This classification system and the method of classification it represents are certainly not recommended to physicians and scientists. ICD-9-CM should remain in the bailiwick of bureaucrats and serve as a paragon of classification chaos.

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THERAPEUTIC CLASSIFICATION

A classification based on specific therapies borrows heavily from the functional and the etiologic classifications of cardiomyopathy. This classification adds information regarding treatment that is not available in other schemes and therefore may be useful to clinicians.

Nevertheless, this classification has several shortcomings. First, often more than one class of therapy is appropriate for a disease. Therefore, the classification must categorize diseases on the basis of their *primary* therapy. This introduces some instability to the classification, since therapeutic preferences are subject to variance in opinion and to change with new research. The greatest fault of therapeutic categorization is that when new therapies are introduced, the existing classification becomes obsolete. The therapeutic classification shown in Table 65-6 illustrates the sensitivity of this approach to opinion. Some might argue, for example, that diuretic therapy remains the primary treatment for dilated cardiomyopathy.

Note that some commonly employed therapies, such as inotropic agents and cardiac transplantation, do not appear in Table 65-6 because they are often not the initial or primary therapies.

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GENE-BASED CLASSIFICATION

Aside from traumatic, iatrogenic, infectious, and certain other secondary cardiac disorders, most heart diseases result from an abnormality of gene function. Many diseases caused by adverse gene behavior are due to inherited or acquired genetic mutations. Several diseases are now defined genetically, including hypertrophic cardiomyopathy, long QT syndrome, forms of dilated cardiomyopathy, muscular dystrophies involving the heart, and arrhythmogenic right ventricular dysplasia. A genetic classification of cardiomyopathies would specify the type of genetic disorder (chromosomal, single genic, polygenic, mitochondrial, or somatic cellular) and the mode of inheritance (autosomal or X-linked, and dominant or recessive), the chromosomes or chromosomal locations involved, and the genes involved. A complete genetic classification might also specify the specific mutation or the regional location of the mutation within the gene, since phenotype does and therapy might vary with each specific mutation or region of mutation. A classification system based upon genetic mutations is diagnostically and therapeutically useless unless the biochemical and resultant physiologic aberrations are understood. Thus, the classification should specify the affected protein products of the mutations, as well as the affected functions provided by the proteins.

In the future, many cardiac diseases will be shown to be due to genes functioning at the extremes of normal behavior, and these behavior abnormalities could be classified in much the same way as inherited mutations. Gene-based classification will become the best classification system for cardiomyopathies, because it will at once precisely and uniquely define the disease, and make evident the necessary diagnostic and therapeutic actions.[4]

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SUMMARY

No single classification of cardiomyopathy is generally accepted within the biomedical community. An attempt to gain a consensus for one of the many classifications in current use is not likely to succeed because we are unable to subdivide meaningfully cases of idiopathic dilated cardiomyopathy, which constitute the large majority of all cases. At present, it seems best for the individual health practitioner or scientist to use the classification scheme that best serves his or her purpose. For clinicians, this will often be the functional classification.

In the future, a widely acceptable classification may develop that is based on the molecular genetics of myocardial disease. Although this field is only beginning to develop, it is the discipline most likely to contribute to the understanding of causes and the development of new treatments for myocardial disease.

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Part 11: CARDIOMYOPATHY AND SPECIFIC HEART MUSCLE DISEASES
Chapter 66:

DILATED CARDIOMYOPATHIES

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This chapter describes the phenotypic and clinical characteristics of the primary and secondary dilated cardiomyopathies, the most common cause of the clinical syndrome of chronic heart failure.[1] Heart failure is an enormously important clinical problem that, if not contained or solved, ultimately may overwhelm health care resources.[2] The clinical syndrome of heart failure is a complex process where the primary pathophysiology is quickly obscured by a variety of superimposed secondary adaptive, maladaptive, and counterregulatory processes (see also Chap. 20). Heart failure is best understood and approached from the vantage point of *myocardial failure*, most commonly associated with a dilated cardiomyopathy phenotype.[3] As an indication of the importance of the problems of cardiomyopathy and heart failure, the cardiomyopathies have been reclassified recently by a World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) task force[3] (and elaborated on further below).

IMPORTANCE OF HEART FAILURE

Due to its high prevalence (1-1.5 percent of the adult population) and high morbidity, including frequent hospitalizations, the clinical syndrome of heart failure is among the most costly medical problems in the United States.[2] Despite improvements in the treatment of heart failure introduced in the last 10 years, including the general availability of cardiac transplantation and better medical treatment, clinical outcome following the onset of symptoms has not changed substantially.[1] That is, mortality remains high (median survival of 1.7 years for men and 3.2 years for women),[1] the natural history remains progressive,[1] the cost is excessive,[2] and disability[2] and morbidity[2,4] are among the highest of any disease or disease syndrome.

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RELATIONSHIP OF MYOCARDIAL FAILURE AND DILATED CARDIOMYOPATHIES TO THE CLINICAL SYNDROME OF HEART FAILURE

The vast majority of the cases of heart failure are caused by heart muscle disease (cardiomyopathy). Within the WHO categorization[3] of cardiomyopathy (Table 66-1), the most common cause of the clinical syndrome of heart failure is a secondary (ischemic, valvular, hypertensive, etc.) or a primary (e.g., idiopathic or familial) *dilated cardiomyopathy*, defined as a ventricular chamber exhibiting increased diastolic and systolic volumes and a low (<40 percent) ejection fraction. The natural history of the clinical syndrome of heart failure depends on the course of myocardial failure, since (1) the most powerful single predictor of outcome is the degree of left ventricular (LV) dysfunction, as assessed by the LV ejection fraction,[5] (2) treatment that improves intrinsic ventricular function improves heart failure natural history,[6] and (3) treatment that ultimately worsens intrinsic function, such as many types of positive inotropic agents, is associated with an adverse effect on outcome.[6]

Table 66-1: The World Health Organization/International Society and Federation of Cardiology Classification of the Cardiomyopathies[3]

Category	Definition
I. Dilated (DCM) 1. Primary 2. Secondary	↑ EDV, ↑ ESV; low EF
II. Restrictive (RCM) 1. Primary 2. Secondary	↓ EDV, ↔ ESV; ↑ FP, ↔ EF
III. Hypertrophic (HCM)	↑↑ Septal and ↑ posterior wall thickness, myofibrillar disarray Mutation in sarcomeric protein, autosomal dominant inheritance
IV. Arrhythmogenic RV Dysplasia (ARVC)	Fibrofatty replacement of RV myocardium Autosomal dominant (most) and recessive inheritance
V. Unclassified 1. Primary 2. Secondary	Not meeting criteria for other categories Features of > one category

ABBREVIATIONS: EDV = end-diastolic volume; ESV = end systolic volume; EF = LV ejection fraction; FP = LV filling pressure; CM = cardiomyopathy.

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THE WHO/ISFC CLASSIFICATION OF CARDIOMYOPATHIES

The WHO/ISFC classification of cardiomyopathies was revised recently[3] to accommodate several rapidly emerging realities. The first was that the molecular genetic basis of previously unknown types of heart muscle disease is rapidly being elucidated, and so it really makes no sense to reserve the classification for "unknown etiologies" of cardiomyopathy.[7] The second consideration was that many of the mechanisms responsible for the natural history of myocardial dysfunction are qualitatively similar in primary versus secondary dilated cardiomyopathies,[8] which accurately predicted a qualitatively similar response to treatment targeted at these mechanisms.[9,10] This made the exclusion of secondary or "known cause"[7] cardiomyopathies gratuitous, and their inclusion in the new classification allows all cardiomyopathies to be classified under one scheme.

As shown in Table 66-1, the WHO/ISFC cardiomyopathy classification uses two separate methods to define the individual categories. The first is based on the global anatomic description of chamber dimensions in systole and diastole. Thus the dilated and restrictive categories have definitions based on LV dimensions or volume, which also define function via calculated ejection fraction (see Table 66-1). The justification for this is that these two groups have distinct natural histories and respond distinctly differently to medical treatment. The second method of creating individual categories within the WHO/ISFC classification is for cardiomyopathies that are genetically based, have unique myocardial phenotypic features, and do not exhibit extracardiac phenotypes. Thus hypertrophic cardiomyopathy (HCM), caused by mutations in contractile proteins manifesting as a unique phenotype, merits a separate category. The same is true for arrhythmogenic right ventricular dysplasia (ARVC), which also has a unique phenotype and likely will turn out to be completely genetic in basis, as has HCM. On the other hand, genetic cardiomyopathies without unique phenotypes, such as the dilated cardiomyopathy of Becker-Duchenne, are included as one form of the anatomic/chamber dimension category (category I).

The WHO/ISFC classification includes another assignment of nomenclature in "secondary" cardiomyopathies, i.e., those associated with known cardiac or systemic processes.[3] These are referred to as *specific cardiomyopathies,* named for the disease process with which they are associated. Thus an ischemic cardiomyopathy would be a specific cardiomyopathy related to previous myocardial infarction (MI) and the subsequent remodeling process, which usually would fall within the dilated class. On the other hand, a hypertensive cardiomyopathy might be classified as either dilated or restrictive depending on the chamber dimensions. Therefore, the correct term for these cardiomyopathies would be *ischemic dilated cardiomyopathy* and *hypertensive dilated* (or *restrictive*) *cardiomyopathy.*

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MOLECULAR MECHANISMS IN CARDIOMYOPATHIES AND MYOCARDIAL FAILURE: DISEASE PHENOTYPE PRODUCED BY ALTERATIONS IN GENE EXPRESSION

As shown in Table 66-2, there are three general categories of mechanisms whereby altered gene expression can lead to a phenotypic change in cardiac myocytes.[11] These are (1) a single-gene defect, e.g., as present in β-myosin heavy-chain codon 403 in familial HCM[12] and in an analogous region of the α-myosin heavy chain in HCM transgenic mouse models,[13,14] (2) polymorphic variation in modifier genes, such as is present in many components of the renin-angiotensin system,[15-19] and (3) maladaptive regulated expression of completely normal genes, such as for the mechanisms responsible for progressive myocardial dysfunction and remodeling in secondary dilated cardiomyopathies.[6,11]

Table 66-2: Three General Mechanisms by Which Alterations in Gene Expression Can Influence the Development or Progression of a Dilated Cardiomyopathy

Type of Process	Examples
Gene mutation	Cardiac α-actin,[34] desmin,[35] dystrophin,[36,37] lamin[38,39]
Polymorphic variation in modifier genes	Angiotensin converting enzyme (ACE),[16,43,44] β_2-adrenergic receptor[46]
Altered expression of a completely normal, wild type gene	Decreased expression: β_1-adrenergic receptors,[8] α-MHC,[47,48] SERCA-2[49]
	Increased expression: ANP,[50] β-MHC,[47] ACE,[51,52] TNF-α,[53] endothelin,[54] βARK[55]

ABBREVIATIONS: MHC = myosin heavy chain; TNF = tumor necrosis factor; βARK = β-adrenergic receptor kinase; SERCA = sarcoplasmic reticulum calcium ATPase; ANP = atrial natriuretic peptide.

Genetic Causes of Cardiomyopathies in Humans and Animal Models

The ability to genetically manipulate the cardiovascular system has made it possible to investigate the role of a number of genes in the developing and adult mouse heart (for a review, see Robbins[20]). The discovery that mutations in sarcomeric proteins lead to HCM has made it possible to generate animal models for this disease.[13,14] In the case of myosin mutations, a single genetic defect initiates a pathway that ultimately leads to hypertrophy and then in males results in late decompensation and ventricular dilatation.[14] Multiple gene mutations have now been associated causally with familial dilated cardiomyopathies, as discussed later in this chapter.

A serendipitous genetic model of dilated cardiomyopathy and heart failure (*myf*5 mice) has been generated by activation of a skeletal muscle genetic program in the heart.[21] These mice have a dilated cardiomyopathy phenotype characterized by progressive myocardial dysfunction and dilatation. They develop the clinical syndrome of heart failure, and they have an extraordinarily high (>90 percent at 260 days) heart failure-related mortality.[21] Another serendipitous genetic model of dilated cardiomyopathy is the muscle LIM protein (MLP) knockout mouse.[22] MLP is a positive regulator of muscle differentiation that is ordinarily expressed at high levels in the heart and which may be involved in myofibrillar protein

assembly along the actin-based cytoskeleton.[22] MLP knockout mice exhibit typical features of dilated cardiomyopathy, including decreased systolic and diastolic function and β-adrenergic receptor pathway desensitization.[22]

These characteristics make this model very useful in assessing the mechanisms that lead to the development and progression of myocardial failure. Thus, in transgenic mouse models, both altered expression of contractile proteins and perturbation of myocyte cytoarchitecture can lead to the dilated cardiomyopathy phenotype.

There are several additional transgenic mouse models of cardiomyopathy that may be more relevant to the production of a dilated phenotype in humans. Three of them involve overexpression of components of the adrenergic receptor pathway, the heterodimeric G-protein α_s subunit ($G\alpha_s$)[23,24] and the β_1-[25,26] and β_2-adrenergic receptors.[27] These β-adrenergic pathway transgenic mouse models exhibit similar histopathology consisting of myocyte hypertrophy and increased fibrosis, evidence of apoptosis, systolic and diastolic dysfunction, and ultimately, development of LV dilatation.[23-28]

Several transgenic models of concentric or symmetrical LV hypertrophy have now been reported, including overexpression of the protooncogenes *ras*[29] and *myc*,[30] α_1-adrenergic receptors,[31] the heterodimeric G-protein α subunit ($G\alpha_q$),[32] and protein kinase C (PKC).[33] The mechanisms for the induction of increased ventricular wall thickness are diverse, inasmuch as the *ras*, α_1-receptor, $G\alpha_q$, and PKC overexpressors exhibit true cellular hypertrophy with an increase in cell size,[29,31-33] whereas the *myc* animal exhibits cardiac myocyte hyperplasia.[30] The HCM phenotypes discussed earlier illustrate the principle that apparently diverse signals can culminate in the same phenotype, presumably by converging on final common pathways.

Multiple gene defects have been identified that can produce a dilated cardiomyopathy in humans, as discussed in more detail in the section on familial forms of dilated cardiomyopathy. As listed in Table 66-2, these include mutations in the cardiac α-actin,[34] desmin,[35] dystrophin,[36,37] and lamin[38,39] genes.

Polymorphic Variation in Modifier Genes

Genes exhibit polymorphic variation; i.e., normal variants of genes exist in the population that are of slightly different size or sequence.[40] Some gene polymorphisms are associated with differences in function of the expressed protein gene product, and some of these differences in function likely account for "biologic variation" routinely encountered in population studies of disease susceptibility or clinical response to treatment.

Examples of "modifier" genes that may have an impact on the natural history of a dilated cardiomyopathy (see Table 66-2) include the angiotensin-converting enzyme (ACE) *DD* genotype, where individuals are homozygous for the "deletion" variant, which is associated with increased circulating[15] and cardiac tissue[41] ACE activity. The *DD* genotype appears to increase the extent of hypertrophy in HCM[42] and may be a risk factor for early remodeling after MI[43] and for the development of end-stage ischemic or idiopathic dilated cardiomyopathy.[16,44] Other potentially important polymorphic variants that may influence the natural history of a cardiomyopathy involve the angiotensin AT_1 receptor[18,45] and β_2-adrenergic receptors.[46]

Altered, Maladaptive Expression of a Completely Normal Gene

The third way in which altered gene expression can contribute to the development of a cardiomyopathy is altered, maladaptive expression of a completely normal "wild type" gene.[11] This occurs most commonly in the context of progression of heart muscle disease and myocardial failure, which is the natural history of virtually all cardiomyopathies once they are established. Examples in this category (see Table 66-2) include downregulation of β_1-adrenergic receptors,[8] α-myosin heavy chain (α-MHC),[47,48] and sarcoplasmic reticulum Ca^{2+} ATPase[49] genes and upregulation in the atrial natriuretic peptide (ANP),[50] β-myosin heavy chain (β-MHC),[47] ACE,[51,52] tumor necrosis factor (TNF-α),[53] endothelin,[54] β-adrenergic receptor kinase

(βARK)[55] genes. These concepts are discussed further below.

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PATHOPHYSIOLOGIC PROCESSES INVOLVED IN MYOCARDIAL DYSFUNCTION, REMODELING, AND THEIR PROGRESSION

Tissue preparations and myocytes isolated from failing human hearts exhibit evidence of decreased contractile function.[56] Assuming that loading conditions and ischemia are not adversely affecting cardiac myocyte function, in the setting of chronic systolic dysfunction from a dilated cardiomyopathy, progressive myocardial failure is most likely caused by myocardial cell loss or changes in the gene expression of proteins that regulate or produce muscle contraction. Figures 66-1 and 66-2 summarize these general points and emphasize the central roles of the renin-angiotensin system (RAS) and the adrenergic nervous system (ANS) in promoting cell loss, growth and remodeling, and altered gene expression.[6]

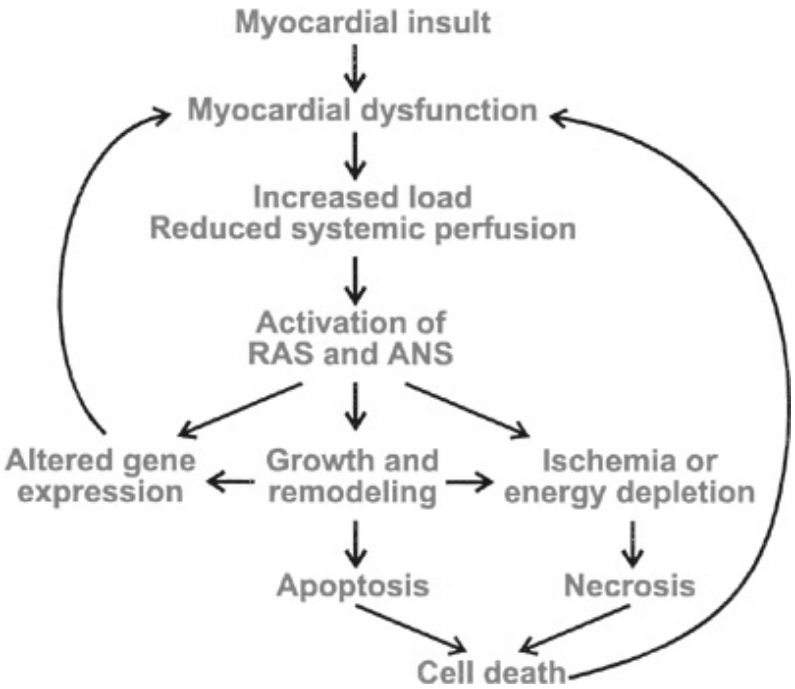

Figure 66-1: Relationship of neurohormonal activation and production of cardiac myocyte loss due to apoptosis and necrosis and altered gene expression. Cell loss and altered gene expression result in more myocardial dysfunction, and a vicious cycle is established. RAS = renin angiotensin system; ANS = adrenergic nervous system.

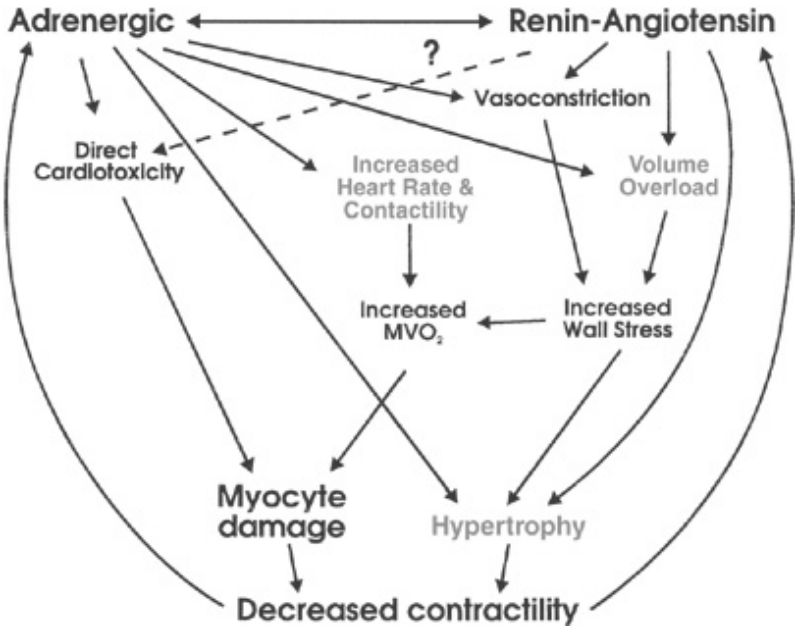

Figure 66-2: Heart failure compensatory mechanisms that are activated to support the failing heart. Light-colored areas indicate physiologic mechanisms that stabilize pump function.

Myocardial Dysfunction and Remodeling due to Altered Expression of Contractility Regulating Genes and Changes in Sarcomeric Assembly

Gene expression can be defined, broadly, as the expression of a fully or normally functioning protein gene product or, more narrowly (and commonly), as the steady-state abundance of a gene's mRNA transcript. Using either definition, numerous abnormalities of gene expression of normal, wild-type genes have been demonstrated in the failing human heart, as discussed earlier, with examples listed in Table 66-2. In order to characterize the abnormalities that may account for progressive myocardial dysfunction and remodeling, it is useful to subdivide them into two general categories,[57] as shown in Table 66-3. The first category encompasses mechanisms that subserve *intrinsic* function, or the mechanisms responsible for contraction and relaxation of the heart in the basal or resting state. *Intrinsic function* is defined as myocardial contraction and relaxation in the absence of extrinsic influences, such as neurotransmitters or hormones. The second general category is *modulated* function, which comprises the mechanisms responsible for the remarkable ability of the heart to increase or decrease its performance dramatically (by 2- to 10-fold) and rapidly in response to various physiologic or physical stimuli. Other critical organs such as the brain, kidney, and liver do not exhibit this quality. *Modulated function* is defined as stimulation or inhibition of myocardial contraction or relaxation by endogenous bioactive compounds, including neurotransmitters, cytokines, autocrine/paracrine substances, and hormones.

Table 66-3: General Categorization of Myocardial Function

Intrinsic (Function in the Absence of Neural or Hormonal Influence)	Modulated (Function that May Be Stimulated or Inhibited by Extrinsic Factors Including Neurotransmitters, Cytokines, or Hormone)
• Contractile proteins • E-C coupling mechanisms • R-G-adenylyl cyclase pathways • Bioenergetics • Cytoskeleton • Sarcomere and cell remodeling	• R-G-adenylyl cyclase pathways • R-G-phospholipase C pathways

ABBREVIATIONS: E-C = excitation-contraction; R-G = receptor-G-protein.

In the failing human heart, changes are present in the expression of genes potentially responsible for both general types of myocardial function depicted in Table 66-2.[6,57] Abnormalities of intrinsic function include the factors responsible for an altered length-tension relation,[58-60] a blunted force-frequency response,[61,62] and/or the signals responsible for abnormal cellular and chamber remodeling.[63,64] In the case of the abnormal force-frequency and length-tension responses, the evidence favors abnormal contractile function of individual cardiac myocytes.[56] As shown in Table 66-3, these abnormalities likely reside in the contractile proteins or their regulatory elements,[47,48,65-67] mechanisms involved in excitation-contraction coupling,[49] or the cytoskeleton.[22,68-70] However, within these possibilities for altered intrinsic function, there is not currently a consensus as to which specific abnormalities are present in idiopathic dilated cardiomyopathy (IDC), the most common form of heart failure studied in humans. For cellular remodeling, in both human ventricles[71,72] and animal models,[64,73] the assembly of sarcomeres in series leads to a myocyte that is markedly increased in length but not in diameter, which contributes to remodeling at the chamber level. Such remodeling places the chamber and the myocyte at an energetic disadvantage because of the attendant increase in wall stress,[74] which is one of the major determinants of myocardial oxygen consumption. Inadequate myocyte energy production, particularly associated with key subcellular ion flux mechanisms or the myosin ATPase cycle,[75] in turn would contribute to myocyte contractile dysfunction. Moreover, the hypertrophy process itself leads to a qualitative change in contractile protein gene expression (induction of a "fetal" gene program) that reduces contractile function.[11,47,48,65] On the other hand, cardiac myocyte contractile dysfunction likely plays a role in the remodeling process, inasmuch as medical treatment that improves intrinsic myocardial function can reverse remodeling.[6] Thus contractile dysfunction and remodeling at the cellular level are intimately related to the progressive contractile dysfunction and chamber enlargement that define the natural history of myocardial failure.[76] These concepts are summarized in Fig. 66-3.

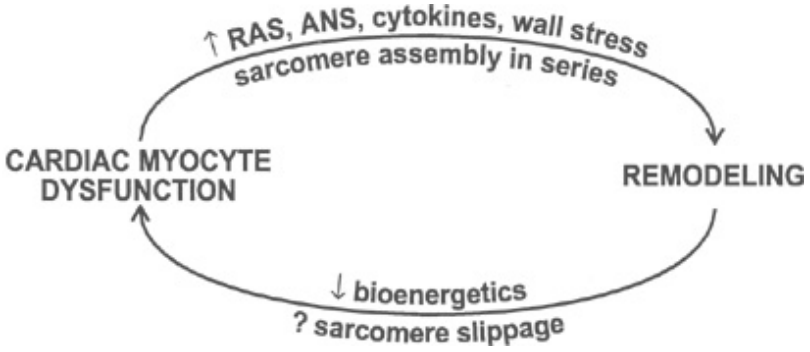

Figure 66-3: Relationship between progressive myocardial dysfunction and remodeling. RAS = renin angiotensin system; ANS = adrenergic nervous system.

In contrast to abnormalities of intrinsic function, a consensus has been reached on several specific abnormalities in the stimulation component of modulated function. Most of these changes concern β-adrenergic signal transduction.[8,11,57] The ability of β-adrenergic stimulation to increase heart rate and contractility is markedly attenuated in the failing heart due to multiple changes at the level of receptors, G-proteins, and adenylyl cyclase. This produces a major abnormality in the stimulation component of modulated function. In addition, the inhibition component of modulated function is also abnormal in the failing heart, due to a reduction in parasympathetic drive.[77]

There is obviously overlap between the two major subdivisions of myocardial function. Recent data indicate that even in the absence of adrenergic stimulation, β-adrenergic receptors have intrinsic activity.[78-81] That is, a small number of receptors are in an activated state without agonist occupancy and as such can support intrinsic myocardial function.[79,80] Thus overexpression of human β_2-adrenergic receptors is able to markedly increase intrinsic myocardial function,[80] as is enhancement of sarcoplasmic reticulum calcium uptake and release by genetic ablation of the phospholamban gene.[82] The recent realization that active state,

agonist-unoccupied β-adrenergic receptors can modulate intrinsic myocardial function is the reason why the "R-G-adenylyl cyclase" mechanism appears in both categories in Table 66-3.

Progressive Myocardial Dysfunction and Remodeling due to Loss of Cardiac Myocytes

The second general mechanism by which myocardial function may be adversely affected is by loss of cardiac myocytes, which also may play a role in the progression of ventricular dysfunction in dilated cardiomyopathies. Cardiac myocyte loss can occur via toxic mechanisms producing necrosis or by "programmed cell death" producing apoptosis. Apoptosis, which is likely due to a combination of growth signaling and cell cycle dysregulation, has been described in end-stage IDC,[83] as well as in the β_1-adrenergic receptor,[25] the $G\alpha_s$ overexpressor transgenic mice,[28] and in models of hypertrophy.[84] However, the human hearts with IDC or ischemic cardiomyopathy were taken from very late stage, literally dying patients maintained on multiple powerful intravenous inotropic medications,[83] and it is not clear if apoptosis plays a significant role in remodeling and/or chamber systolic dysfunction until this point in the natural history of the dilated cardiomyopathies.

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IMPORTANCE OF "COMPENSATORY" MECHANISMS IN THE PROGRESSION OF MYOCARDIAL FAILURE

As depicted in Figs. 66-1 and 66-2, there is now a large body of information supporting the idea that *activation of the ANS and RAS compensatory mechanisms contributes to, or is responsible for, the progressive nature of both myocardial failure and the natural history of the heart failure clinical syndrome*.[6] This evidence includes the observations that activation of both these systems is associated with progression of myocardial dysfunction and the heart failure syndrome and clinical trial data that consistently demonstrate that inhibition of these systems can prevent deterioration in or improve myocardial function as well as reduce mortality.[6,10] Despite the fact that in human heart failure we now know that chronic activation of the ANS and RAS contributes to the progressive nature of myocardial dysfunction, we know virtually nothing about how these systems adversely affect the biology of the cardiac myocyte. What we do know is that mechanisms within both general categories outlined in Table 66-3 must be involved in the adverse myocardial effects mediated by the ANS and RAS. This is so because modulated function may be improved by treatment with ACE inhibitors or β-blocking agents. Progressive myocardial dysfunction and remodeling are attenuated by both β-blocking agents and ACE inhibitors, and in cardiomyopathies, intrinsic myocardial function is improved and remodeling is reversed by chronic treatment with β-blocking agents.[6] Additionally, mortality in chronic heart failure is directly related to activation of the ANS[85,86] and RAS[87] and may be related to activation of other neurohormonal or autocrine/paracrine systems as well.

Regardless of the type or cause of dilated cardiomyopathy, an initial myocardial insult resulting in this phenotype exhibits common pathophysiologic features that are summarized in Fig. 66-1. That is, a myocardial insult that produces systolic dysfunction will be followed by the initiation of processes designed to temporarily stabilize pump function. The possible mechanisms available for such stabilization are in fact limited. As shown in Fig. 66-2, in chronological order of their action, they are an increase in heart rate and contractility mediated by an increase in cardiac β-adrenergic signaling (produced within seconds of the onset of pump dysfunction), volume expansion in order to use the Frank-Starling mechanism to increase stroke volume (evident within hours of the onset of pump dysfunction), and cardiac myocyte hypertrophy to increase the number of contractile elements (evident within days to weeks of the onset of pump dysfunction). As shown in Fig. 66-2, these compensatory adjustments are largely accomplished by activation of the RAS and ANS. However, despite the short-term (days to months) stability achieved via these mechanisms, they ultimately prove harmful.[6] The best evidence that chronic, continued activation of the RAS and ANS contributes to progressive myocardial dysfunction and remodeling comes from clinical trials where both inhibitors of the RAS (ACE inhibitors) and ANS (β-adrenergic receptor-blocking agents) prevent these two phenomena, and β-blocking agents actually may reverse remodeling and progressive systolic dysfunction,[6] as alluded to.

Much current work is focused on the precise pathophysiologic mechanisms by which activation of the RAS and ANS produces remodeling and adverse effects on myocardial function. Some of the possibilities are given in Fig. 66-1, and they include an exacerbation of ischemia and/or energy depletion leading to cell loss via necrosis, cell loss by programmed cell death, direct promotion of hypertrophy and remodeling through stimulation of cell growth, and alterations in cardiac

myocyte gene expression.[6] A key feature of the schema shown in Fig. 66-1 is the process of remodeling, which is discussed in more detail in Chap. 20. Virtually all dilated cardiomyopathies undergo this process, which is characterized by progressive dilatation, progressive myocardial systolic dysfunction in viable segments, and a chamber shape change whereby the ventricle becomes less elliptical and more round.[6,63] As shown in Fig. 66-3, this places the ventricle at an energetic disadvantage,[6,63,74] which likely contributes to further myocardial dysfunction, which then contributes to progressive remodeling. The latter observation is based on data obtained with β-adrenergic blocking agents, which produce an improvement in systolic dysfunction that can be detected prior to a reversal in remodeling.[6] As emphasized by Fig. 66-3, each myocardial degenerative process likely begets the other, leading to an inexorably progressive deterioration in myocardial performance and clinical condition.

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SCOPE OF DILATED CARDIOMYOPATHIES

The number of cardiac or systemic processes that can produce or are associated with a dilated cardiomyopathy are plentiful and remarkably varied, as shown in Table 66-4. The dilated phenotype is by far the most common form of cardiomyopathy, comprising over 90 percent of subjects referred to specialized centers.[88] In the United States, the most common dilated cardiomyopathy is ischemic dilated cardiomyopathy,[1] or the cardiomyopathy that follows MI. Other common secondary dilated cardiomyopathies are hypertensive and valvular dilated cardiomyopathies, both produced in part by chronically increased wall stress. The primary cardiomyopathy, IDC, is another relatively common dilated phenotype,[89,90] as discussed below.

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SELECTED, COMMON TYPES OF DILATED CARDIOMYOPATHIES

Ischemic Cardiomyopathy

DEFINITION/DIAGNOSIS

Ischemic cardiomyopathy is defined as a dilated cardiomyopathy in a subject with a history of MI or evidence of clinically significant (i.e., ≥70 percent narrowing of a major epicardial artery) coronary artery disease, in whom the degree of myocardial dysfunction and ventricular dilatation is not explained solely by the extent of previous infarction or the degree of ongoing ischemia.[3] In other words, *an ischemic dilated cardiomyopathy is present when a post-MI left ventricle experiences remodeling and a drop in ejection fraction.*

DISTINCT PATHOPHYSIOLOGY

Dilatation of the left ventricle and a decrease in ejection fraction occurs in 15 to 40 percent of subjects within 12 to 24 months following an anterior MI[91,92] and in a smaller percentage of subjects following an inferior MI.[92] Based on limited data,[43] it is tempting to speculate that the subjects who undergo the remodeling process and develop an ischemic dilated cardiomyopathy are individuals with particularly heightened compensatory mechanisms (see Figs. 66-1 and 66-2), perhaps as a result in polymorphic variation in these systems.[16] As discussed earlier, the remodeling process is an attempt by the compromised ventricle to increase its performance by increasing stroke volume, but ultimately, it correlates with an adverse outcome[6,63] in the long term.

The gross pathology of ischemic cardiomyopathy includes transmural or subendocardial scarring, representing old MIs, that may comprise up to 50 percent of the LV chamber. The histopathology of the noninfarcted regions is similar to changes that occur in IDC,[71] as discussed below.

PROGNOSIS

Several studies have concluded that ischemic cardiomyopathy patients have a worse prognosis than subjects with a "nonischemic" dilated cardiomyopathy,[93,94] probably because the risk of ischemic events is added to the risk of having a dilated cardiomyopathy.

TREATMENT

The treatment of ischemic dilated cardiomyopathy and chronic heart failure is covered in detail in Chap. 21. In general, treatment consists of the use of ACE inhibitors in asymptomatic or symptomatic patients, the use of diuretics in volume-overloaded subjects, and the use of digoxin in subjects who remain symptomatic on the former medications. An emerging treatment strategy is the use of β-adrenergic blocking agents in mild to moderately symptomatic subjects,[6,10] whereas in both ischemic and nonischemic dilated cardiomyopathies,[9,10,95-97] second- and third-generation compounds improve LV function,[6,9-11] reduce hospitalizations,[9,10,95-97] and lower mortality.[9,10] Additionally, adjunctive therapy includes anticoagulation in subjects with lower LV

ejection fractions to prevent thromboembolic complications, amiodarone to treat symptomatic arrhythmias, maintaining potassium levels in the high normal (4.3-5.0 meq/L) range to prevent sudden death, frequent clinic visits to adjust medications, and an aggressive approach to treating ischemia, including revascularization.

Hypertensive Cardiomyopathy

DEFINITION/DIAGNOSIS

A *hypertensive dilated cardiomyopathy* is diagnosed when myocardial systolic function is depressed out of proportion to the increase in wall stress. In other words, a subject presenting in heart failure with a hypertensive crisis would not carry this diagnosis unless ventricular dilatation and depressed systolic function remained after correction of the hypertension. In addition to producing a "pure" form of hypertensive cardiomyopathy, hypertension is a major risk factor for heart failure from any cause.[98] Within the WHO/ISFC classification, "hypertensive heart disease" may present in the "dilated," "restrictive," or "unclassified" categories.

DISTINCT PATHOPHYSIOLOGY

The most important pathophysiologic element in hypertension in dilated cardiomyopathy is sustained increased systolic wall stress. Interestingly, in both systolic pressure overloaded right and left ventricles, phenotypic expression is qualitatively variable[99,100] and can include dilatation and systolic dysfunction without increased wall thickness, increased wall thickness, concentric hypertrophy with or without systolic dysfunction, and systolic dysfunction without concentric hypertrophy. Other contributors to the pathophysiology of hypertensive cardiomyopathies are local neurohormonal mechanisms.[101]

PROGNOSIS

The prognosis depends on the presence of other comorbid conditions such as diabetes mellitus and coronary artery disease, as well as the extent of control of afterload. Compared with other forms of cardiomyopathy, in the absence of comorbid conditions, the prognosis of hypertensive cardiomyopathy in subjects whose afterload is controlled is probably better than for most other types of dilated cardiomyopathy.[102]

TREATMENT

The treatment is as for ischemic dilated cardiomyopathy, except that afterload must be vigorously controlled.[101] This consists of the addition of pure antihypertensive vasodilators such as amlodipine or α-blocking agents to standard heart failure therapy.

Valvular Cardiomyopathy

DEFINITION/DIAGNOSIS

A *valvular cardiomyopathy* occurs when a valvular abnormality is present and myocardial systolic function is depressed out of proportion to the increase in wall stress. This most commonly occurs with left-sided regurgitant lesions (mitral regurgitation and aortic regurgitation), less commonly occurs with aortic stenosis, and never occurs as a consequence of pure mitral stenosis.

DISTINCT PATHOPYSIOLOGY

The classic explanation for the typical phenotypes observed in valvular cardiomyopathies relates

to exposure to different types of wall stress.[103] Within this construct, the pattern of eccentric hypertrophy derives from increased diastolic wall stress.[103] Thus long-standing mitral regurgitation most commonly results in compensated eccentric hypertrophy that can progress to a dilated failing phenotype. Aortic regurgitation is a particularly poorly tolerated hemodynamic insult because wall stress is increased in both systole and diastole,[103] and when decompensation occurs, ventricular volume will be increased with or without increased wall thickness. Aortic stenosis classically results in compensated concentric hypertrophy, but when decompensation occurs, a variety of phenotypes can be observed that are similar to hypertensive cardiomyopathies. A disturbing and fairly commonly observed phenomenon is the development of a dilated cardiomyopathy after surgical correction of mitral and sometimes aortic valve disease in subjects who preoperatively had only mild LV dysfunction. These cases are likely due to the superimposition of myocardial damage resulting from open heart surgery and/or underlying dysfunction that was likely greater than appreciated preoperatively.

PROGNOSIS

The prognosis is variable and depends on the number of associated conditions, the nature and extent of the valvular abnormality, and most important, the severity of the cardiomyopathy at the time of surgical correction (see below). In general, *severely depressed myocardial function will not improve much with surgical repair of aortic regurgitation or mitral regurgitation, but the prognosis is likely to be improved because of elimination of some of the hemodynamic insult.* Replacement of the mitral valve should not be attempted in the majority of subjects with severe mitral regurgitation and LV ejection fractions less than 25 percent because of prohibitively high operative/perioperative mortality rates. On the other hand, there is no impairment of LV systolic function severe enough to preclude valve replacement of severe aortic stenosis, since function invariably will improve on relief of the hemodynamic insult, and the prognosis is relatively good.

TREATMENT

The treatment of a valvular dilated cardiomyopathy is surgical valve replacement or repair as soon as the cardiomyopathy is detected. Catheter valvuloplasty may be an option for severe aortic stenosis (AS) patients who are not good surgical candidates for reasons other than heart failure.[104] Medical treatment may be the only option in subjects with aortic insufficiency or mitral regurgitation whose LV function is severely impaired. The medical treatment of either disorder should be as mentioned earlier for ischemic cardiomyopathy plus aggressive afterload reduction, usually hydralazine/nitrates on top of ACE inhibitors. The calcium channel blocker amlodipine is another option for afterload reduction,[105] particularly for aortic insufficiency, where calcium channel blocker therapy has been shown to improve survival.[106]

Idiopathic Dilated Cardiomyopathy, Including Familial Forms

DEFINITION/DIAGNOSIS

IDC is diagnosed by excluding significant coronary artery disease, valvular abnormalities, and other causes. IDC is a relatively common cause of heart failure, with an estimated prevalence rate of 0.04 percent[89] and incidence rates varying from 0.005 to 0.006 percent.[89,90] The true incidence of IDC is undoubtedly higher, owing to the fact that subjects may remain asymptomatic until marked ventricular dysfunction has occurred. The incidence of IDC increases with age, and males are afflicted at a higher rate than are females.[89] As discussed below, histologic features are nonspecific and consist of myocardial cell hypertrophy and varying amounts of increased interstitial fibrosis. Although the diagnosis is not difficult, problems arise when an apparent IDC presents in someone with a history of hypertension or excessive alcohol intake. In such cases, it is best to reassign the etiology to alcohol only when the intake has exceeded 80 g/day for males and

40 g/day for females for more than 5 years and to hypertensive heart disease when blood pressure has been uncontrolled and high (>160/100 mmHg), as well as sustained (for years). All subjects with an unexplained dilated cardiomyopathy need a thyroid-stimulating hormone (TSH) determination done to exclude hypo- or hyperthyroidism, and subjects with diastolic dysfunction need to have an infiltrative process excluded. As discussed below, this is best done by performing an endomyocardial biopsy.

DISTINCT PATHOPHYSIOLOGY

IDC may be familial in as many as 35 to 50 percent of the patients when first-degree relatives are carefully screened.[107,108] The analysis of the phenotype identifies a wide range of clinical and pathologic forms indicating genetic heterogeneity. Accordingly, several chromosomal assignments for gene location have been made, and recently, as shown in Table 66-2, several genes have been identified.[34-39,109-118] The majority of familial patients present with autosomal dominant inheritance and a phenotype characterized by low and age-related penetrance (which is the proportion of carriers who manifest the disease). It is estimated that only 20 percent of gene carriers under the age of 20 display the disease phenotype.[119] Autosomal dominant dilated cardiomyopathy can be due to mutations of the cardiac actin[34] or desmin gene,[35] but in the majority of cases the disease gene is still unknown. The detection of an altered creatine kinase level can indicate the existence of a subclinical skeletal muscle disease. In these patients, an X-linked inheritance suggests mutations in the dystrophin gene,[36,37,120-122] whereas an autosomal dominant transmission and the presence of conduction defects and arrhythmia suggests mutations in the lamin A/C gene.[38,39] In *laminopathy*, the phenotype of the affected relatives can be very variable, from a pure IDC to a mild Emery-Dreifuss-like or limb-girdle-like muscle dystrophy[39] (see Chap. 62). Skeletal muscle and endomyocardial biopsy are diagnostic in X-linked dilated cardiomyopathy, showing abnormalities of dystrophin protein expression by immunocytochemistry.[123,124] Finally, autosomal recessive transmission of dilated cardiomyopathy occurs in mutations of sarcoglycan genes, which encode for dystrophin complex-associated proteins.[125]

Dystrophin, sarcoglycans, desmin, and lamin are cytoskeletal proteins. The contractile protein cardiac α-actin also has a force-transmission or cytoskeletal role.[34] Other data support the hypothesis that IDC could represent, in the majority of cases, a disease of the cytoskeleton; absence of the protein metavinculin in the myocardium was reported in one IDC patient,[70] and as discussed earlier, a dilated cardiomyopathy can be created in mice[22] or is present in a hamster line[126] related to mutations in cytoskeletal genes. However, as discussed earlier, it appears that other genetic abnormalities such as mutations in contractile proteins[14,21,34,127,128] and overexpression of β-adrenergic receptors[25-27] or $G\alpha_s$[24] also can produce a dilated phenotype.

In children, X-linked familial IDC suggests mutation in the G4.5 or tafazzin gene, particularly if associated with certain other signs (such as endocardial fibroelastosis, neutropenia, short stature, or skeletal muscle abnormalities).[116] The function of tafazzin is still unknown. In mitochondrial DNA (mtDNA) mutations, myocardial dysfunction usually is associated with multiorgan involvement (encephalopathy, lactic acidosis, skeletal muscle abnormalities, retinitis pigmentosa, etc.).[129] It is still unclear whether a mtDNA mutation can lead to an isolated IDC phenotype in adults.

Although still incomplete, new knowledge on the genetics of IDC has important clinical implications. The frequency of familial forms indicates the need of family screening in IDC, which can allow genetic counseling, an early detection of the disease, and early therapeutic interventions in affected relatives. The complexity of the phenotype requires an accurate skeletal muscle investigation, which can direct the diagnosis toward a specific type of familial myopathy.

Finally, family investigations require more sensitive diagnostic criteria[130] that are able to detect minor cardiac abnormalities as initial signs of the disease. These include initial dilatation without marked systolic dysfunction, arrhythmia, and isolated wall and other abnormalities.[39,108,131]

The major morphologic feature of IDC on postmortem examination is dilatation of the cardiac chambers.[130,131] One ventricle (usually the left) may be more dilated than the other ventricle. The weight of the heart is increased in IDC, with a mean cardiac weight of 551 g for women and 632 g for men.[131] Although there is an increase in muscle mass and myocyte cell volume in IDC, LV wall thickness is usually not increased because of the marked dilatation of the ventricular cavities. Grossly visible scars may be present in either ventricle, and while most scars are small, some may be large and transmural. Scarring occurs in the absence of significant narrowing of the epicardial coronary arteries. In most cases, the degree of fibrosis does not appear to be extensive enough to cause changes in systolic or diastolic function. Intracardiac thrombi and mural endocardial plaques (from the organization of thrombi) are present at necropsy in more than 50 percent of patients with IDC.[132,133] The effect of anticoagulation on the incidence of thrombi has not been studied carefully, but systemic and pulmonary emboli are more frequent in patients with ventricular thrombi or plaques.[134]

The characteristic findings of IDC on microscopy are marked myocyte hypertrophy, very large, bizarrely shaped nuclei[135-137] (Fig. 66-4), increased interstitial fibrosis (see Fig. 66-4), myocyte atrophy, and myofilament loss.[133,138] In isolated cardiac myocytes, the major cellular phenotypic change is marked increase in cell length without a concomitant increase in diameter.[72] As described earlier, this cellular lengthening or remodeling contributes to the chamber remodeling/dilatation that characterizes IDC and other cardiomyopathies. These morphologic changes in IDC are not specific and are generally found in secondary cardiomyopathies such as in the noninfarcted regions of ischemic dilated cardiomyopathy.[71] Also, the morphometric changes in IDC do not correlate with the severity of illness.[137,138] Ultrastructural abnormalities such as mitochondrial changes, T-tubular dilatation, and intracellular lipid droplets may be observed in IDC but also can be observed in other forms of heart disease.[137] There may be interstitial parenchymal and perivascular focal infiltrates of small lymphocytes.[136-140] The lymphocytic infiltrates that are present on histologic examination in IDC are not associated with adjacent myocyte damage, in contrast to myocarditis where adjacent myocyte necrosis is observed. Fibrosis is nearly always present in IDC,[136-140] and its pattern is quite variable from a fine perimyocytic distribution to coarse scars indistinguishable from those present in chronic ischemia. However, small intramural arteries and capillaries are structurally normal in IDC.[137]

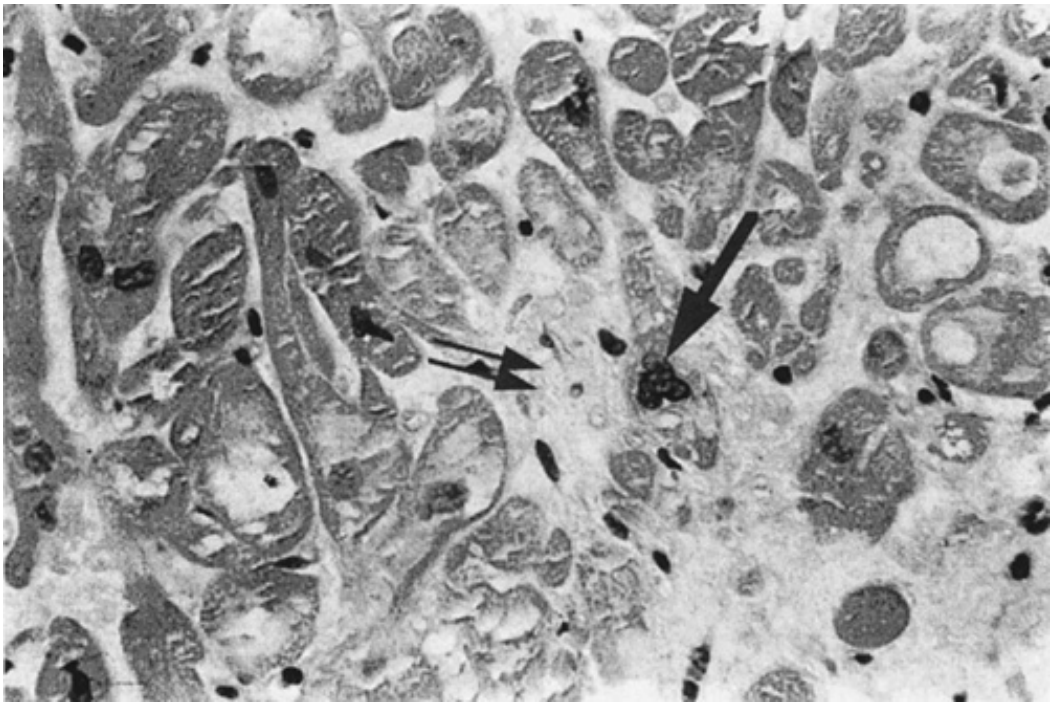

Figure 66-4: Right ventricular endomyocardial biopsy from a subject with IDC. Note the increased nuclear size (*arrow*) and the increased interstitial fibrosis.

A number of immune regulatory abnormalities have been identified in IDC, including humoral and cellular autoimmune reactivity against myocytes,[141] decreased natural killer cell activity,[142] and abnormal suppressor cell activity.[143,144] These abnormalities suggest that immune defects may be important etiologic factors in the development of IDC. These findings, however, are not universally present in patients with IDC, and some abnormalities are also present in other types of heart muscle disease. For example, an increase in the cardioselective M7 antimitochondrial antibodies is found in both IDC and hypertrophic cardiomyopathy but not in heart failure from coronary artery disease.[145] The incidence of some autoreactive antibodies, such as antinuclear and antifibrillary antibodies, increases with the severity of heart failure.[146] It is likely that many of the antibodies detected in IDC and other myocardial diseases do not have pathogenic relevance, but rather are secondary to the primary degenerative process. However, it is possible that certain antibodies present in IDC may have important functional implications. For example, anti-β_1-adrenergic receptor antibodies[147,148] could modify β-adrenergic receptor activity[149] and produce chronic increases in signal transduction that are harmful to the failing heart. Disturbed energy metabolism from antibodies to the ADP/ATP carrier of the inner mitochondrial membrane is another potential pathogenetic autoimmune mechanism[150,151]; these antibodies are present in some individuals with IDC[150] and have been shown to impair metabolism and myocardial function.[151]

There has been great interest in histocompatibility locus antigens (HLAs) in IDC because these antigens are known to be associated with immune regulatory functions, and many autoimmune diseases are found to have positive HLA antigenic associations. HLA associations also have been identified in IDC; the frequency of HLA-B27, HLA-A2, HLA-DR4, and HLA-DQ4 is increased compared with controls, and the frequency of HLA-DRw6 is decreased compared with controls.[152] Genetic abnormalities in the HLA region potentially could alter immune response and thereby increase disease susceptibility to infectious agents such as enteroviruses. Thus the association in IDC with specific HLAs suggest a possible immunologic etiology for this disease. However, these specific HLAs are present in less than 50 percent of patients with IDC, and the heterogeneity of these antigens does not point to a unique site for a putative disease-associated

gene. Thus, while the autoimmune hypothesis is an attractive candidate for the etiology of some cases of IDC, it remains unproved.

A clinical and pathologic syndrome that is similar to IDC may develop after resolution of viral myocarditis in animal models and biopsy-proven myocarditis in human subjects.[153] This has led to speculation that IDC may develop in some individuals as a result of subclinical viral myocarditis. Theoretically, an episode of myocarditis could initiate a number of autoimmune reactions that injure the myocardium and ultimately result in the development of IDC. The abnormalities in immune regulation and the variety of antimyocardial antibodies present in IDC are consistent with this hypothesis. However, it is generally not possible to isolate an infectious virus or to demonstrate the presence of viral antigens in the myocardium of patients with IDC.[153,154] Enteroviral RNA sequences are found in heart biopsy samples in IDC, but only in approximately one-third of patients.[154-156] Furthermore, active myocardial inflammation is usually not detected in IDC.[139,140] However, in controlled trials, corticosteroid therapy of patients with IDC does not result in significant clinical improvements.[157] Importantly, recent experimental data have shown in vitro and in vivo that the enteroviral protease 2A is able to cleave dystrophin and disrupt the cytoskeleton in cardiac myocytes, providing a potential link between viral infection and a genetic model of the disease.[158] Furthermore, analysis of human viruses other than enteroviruses suggests that adenoviruses, herpesvirus, and cytomegalovirus also can cause myocarditis and potentially IDC, particularly in children and young subjects.[159,160] Further investigation will be necessary to understand the significance of these findings, particularly in the adult population.

As also discussed in Chap. 22, endomyocardial biopsy of the right or left ventricle may be a valuable diagnostic adjunct for diagnosing specific myocardial processes that can produce a dilated phenotype, such as myocarditis and infiltrative cardiomyopathies. Since several of these other dilated cardiomyopathies may have specific treatments and/or a different prognosis than IDC, endomyocardial biopsy may be warranted in many individuals presenting with a dilated cardiomyopathy. In the future, biopsy may be used more frequently to identify genetic disorders resulting in abnormal gene or protein expression,[50] such as now can be done to diagnose Becker-Duchenne cardiomyopathy.[123,124] Since special staining, electron microscopy, or molecular analysis of the biopsy material may be necessary, endomyocardial biopsy is best performed in specialized cardiomyopathy/heart failure centers.

PROGNOSIS

Several studies of the natural history of IDC have been conducted.[159,160] The prognosis is generally better than for ischemic cardiomyopathy,[93,94] and prior to the routine use of ACE inhibitors, survival was approximately 50 percent in 5 years.[161] The prognosis has been improved substantially since then,[162] inasmuch as ACE inhibition,[163] cardiac transplantation[164] and β-adrenergic blockade[10] are all effective treatments in this cardiomyopathy.

TREATMENT

The treatment of IDC is similar to that discussed earlier for ischemic cardiomyopathy, except that there is no issue of revascularization. The risk of thromboembolic complications may be higher than in ischemic cardiomyopathy, resulting in a lower threshhold for anticoagulation. β-Adrenergic blockade produces a quantitatively greater degree of improvement in LV function compared with ischemic cardiomyopathy[165,166] either because there is a greater degree of adrenergic activation[8] or there is more viable myocardium to work with in IDC. Approximately 10 percent of IDC subjects treated with β-adrenergic blockade will normalize their myocardial

function, and this form of treatment should be offered to all IDC patients who do not have a contraindication before considering cardiac transplantation.[167]

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Chapter 66: DILATED CARDIOMYOPATHIES

SELECTED SPECIFIC DILATED CARDIOMYOPATHIES WITH UNIQUE MANAGEMENT ISSUES

Anthracycline Cardiomyopathy

DEFINITION/DIAGNOSIS

The commonly used and highly efficacious anthracycline antibiotic anticancer agents doxorubicin and daunorubicin produce a dose-related cardiomyopathy[168-173] that may limit their clinical application. Within the WHO/ISFC classification, an anthracycline cardiomyopathy would most likely be in the "dilated" category, but because the extent of dilatation initially may be minimal (see below), it also could be in the "unclassified" category. The cardiomyopathy produced by these agents depends on the total cumulative dose, and for the more widely used compound doxorubicin (Adriamycin), the incidence of heart failure due to cardiomyopathy dramatically increases above total cumulative doses of 450 mg/m^2 in subjects without underlying cardiac problems or other risk factors.[169] *Prior mediastinal radiation involving the heart is a powerful risk factor for anthracycline cardiomyopathy,*[170] *and the risk is also evident if radiation treatment follows chemotherapy.*[172,173] In subjects with risk factors, anthracycline cardiomyopathy can present at lower cumulative doses than 450 mg/m^2.[170-172]

Although the diagnosis of anthracycline cardiomyopathy can be made clinically, the definitive diagnosis depends on the demonstration of a substantial number of cardiac myocytes exhibiting the characteristic anthracycline effect.[168,170-173] Tissue sampling is best done by endomyocardial biopsy, which allows for "thin section" electron microscopic processing of the sample and more definitive resolution of the anthracycline effect with light microscopy.[168,170-173]

DISTINCT PATHOPHYSIOLOGY

In the absence of a tissue diagnosis, anthracycline cardiomyopathy may be diagnosed clinically by exclusion of other causes of cardiomyopathy in a subject who has had at least 350 mg/m^2 of doxorubicin or the equivalent amount of another anthracycline. As shown in Fig. 66-5, the anthracycline cardiac myocytic lesion consists of cell vacuolization progressing to cell dropout, and when 16 to 25 percent of the total number of sampled cells exhibit this morphology, myocardial dysfunction results.[170]

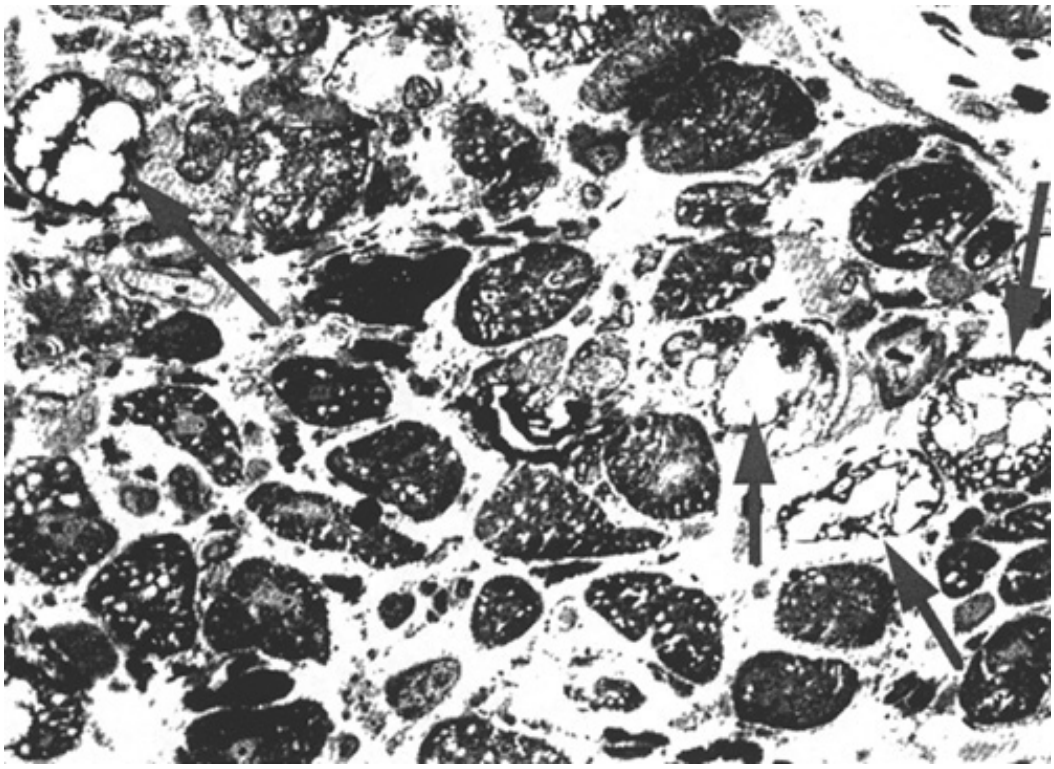


Figure 66-5: Cardiac myocyte vacuolization in cases of Adriamycin cardiomyopathy classified on endomyocardial biopsy as grade 3 by the Billingham classification.[170,171,178]

There are some distinguishing clinical features of anthracycline cardiomyopathy that may relate to its pathophysiology. These include a relative absence of hypertrophy and dilatation and a higher heart rate (110-130 beats per minute) than is usually encountered in ambulatory heart failure. The reasons for these features are that the onset of symptoms may be relatively acute (remodeling takes time to develop), and the anthracycline inhibits contractile protein synthesis,[174] reducing the amount of compensatory dilatation and remodeling. In this situation, the only option available for stabilizing cardiac output is increasing the heart rate, since increasing stroke volume via a larger end-diastolic volume has been precluded. The increased heart rate is produced by a greater than expected hyperadrenergic state, and so these subjects may be exceptionally dependent on adrenergic support.

PROGNOSIS

The prognosis of anthracycline cardiomyopathy is variable and depends on numerous factors, including the age and underlying prechemotherapy cardiac status of the patient and the time of presentation relative to the last dose of drug. Subjects who present late (several months) or very late (years) after the last dose have a better prognosis because the anthracycline myocardial effect takes at least 60 days to become fully manifest.[175] That is, subjects who develop heart failure within a few days of the last dose of drug have an additional cardiomyopathic burden to face, since the last one to two doses produce their full morphologic effect over the next 1 to 2 months.

TREATMENT/PREVENTION

Subjects who develop anthracycline cardiomyopathy should be treated aggressively with conventional heart failure treatment, since some degree of reversibility is likely. Conventional treatment consists of ACE inhibitors, digoxin, and diuretics. β-Adrenergic blockade has been used successfully in some subjects,[176,177] but because of the high adrenergic drive, it may be difficult to administer. On the other hand, the heightened adrenergic mechanism may be producing a

commensurate amount of adverse effect on the myocardium, and so the potential for a favorable response may be even greater than in other kinds of cardiomyopathy. In severe refractory cases, cardiac transplantation may be performed provided that the patient's cancer is in complete remission and is not likely to recur (≈70 percent chance of cure).

Several strategies have been shown to lower the risk of developing anthracycline cardiomyopathy without compromising the chemotherapy response rate. These include using endomyocardial biopsy and right-sided heart catheterization with exercise to assess risk, which virtually eliminates clinical cardiomyopathy and allows more anthracycline to be administered to less susceptible subjects[178]; using serial radionuclide angiography with[179] or without[180] exercise as a monitoring strategy, which may be somewhat helpful but because of a low specificity reduces the total amount of chemotherapy that can be administered safely to some subjects[178,179]; giving the agents as low-dose weekly[181] or as 48- to 72-h infusions[182] rather than as every 3- to 4-week boluses; using a liposomal formulation[183]; or concomitantly administering a second agent that reduces toxicity.[184] Unfortunately, none of these strategies completely eliminates the risk of developing a clinical cardiomyopathy.

Postpartum Cardiomyopathy

DEFINITION/DIAGNOSIS

Postpartum or *peripartum cardiomyopathy* is defined as the presentation of systolic dysfunction and clinical heart failure during the last trimester of pregnancy or within 6 months of delivery.[185] Given the extreme hemodynamic load produced by pregnancy, it is perhaps surprising that postpartum cardiomyopathy is not more common.

DISTINCT PATHOPHYSIOLOGY

Postpartum cardiomyopathy most likely will be classified within the "dilated" WHO/ISFC category but occasionally will be "unclassified" because dilatation and remodeling have not had time to occur. Postpartum cardiomyopathy is likely a heterogeneous group of disorders consisting of the addition of the hemodynamic load of pregnancy to a variety of underlying myocardial processes, including hypertensive heart disease, familial or idiopathic dilated cardiomyopathy, and myocarditis.[185,186]

PROGNOSIS

Approximately half of subjects who develop postpartum cardiomyopathy will recover completely,[187] and the majority of the rest will improve. Subjects who have developed a postpartum cardiomyopathy should never become pregnant again, even if myocardial function has recovered fully.

TREATMENT

Treatment should be aggressive and as for IDC. Cardiac transplantation may be required in severely compromised patients who do not improve.

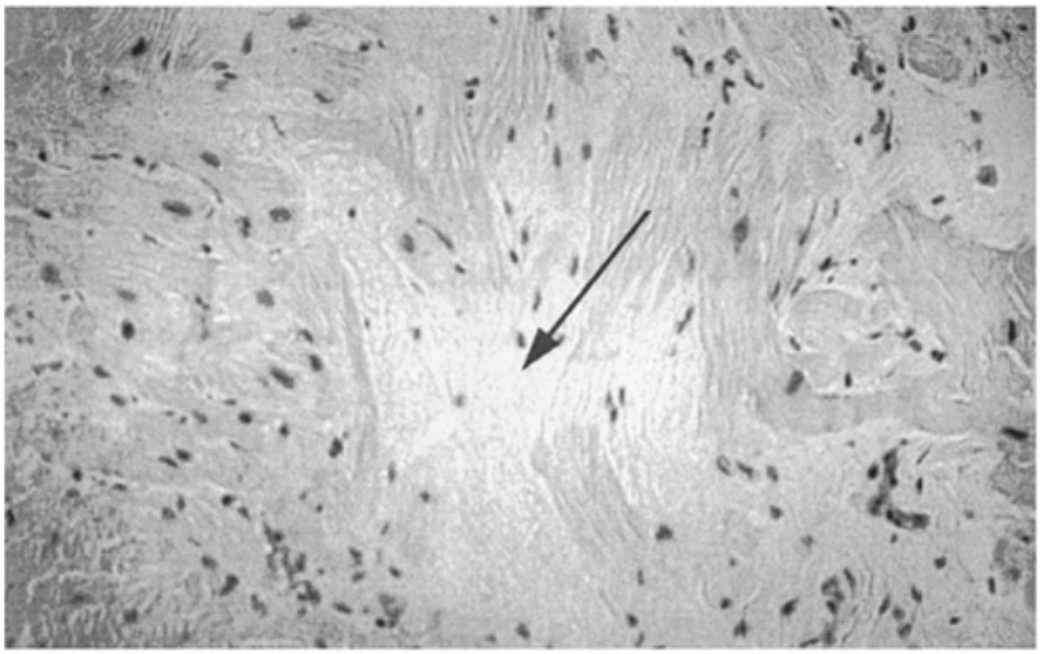
Amyloid Cardiomyopathy

DEFINITION/DIAGNOSIS

As discussed in Chap. 68, amyloidosis is a group of diseases characterized by extracellular

deposition of proteins characterized by their unique β-pleated sheet conformation and recognized electron microscopically as randomly arranged nonbranching fibers ranging from 8 to 14 nm in length. Amyloidosis is classified according to the type of amyloid protein involved.[188] Amyloidosis involving the heart is not rare and accounts for up to 10 percent of all nonischemic cardiomyopathies in autopsy studies.[189,190]

Amyloid cardiomyopathy may present in the WHO/ISFC "restrictive," "dilated," or "unclassified" categories. Most commonly it presents as a restrictive cardiomyopathy with conduction system abnormalities. In the setting of systemic amyloidosis (secondary or primary forms), the presence of increased wall thickness on echocardiogram plus low electrocardiographic voltage is highly suggestive of cardiac involvement.[191] In primary systemic amyloidosis, a monoclonal immunoglobulin spike is detectable in urine or serum in approximately 80 percent of subjects.[192] The definitive diagnosis of amyloid cardiomyopathy is made by tissue examination, ideally premortem by endomyocardial biopsy.[191] In systemic forms, the tissue diagnosis may be made by rectal, skin, or tongue biopsy of any abnormal tissue in these locations coupled with an unexplained myocardial process. As shown in Fig. 66-6, the characteristic histologic signature of amyloid is extracellular deposition of a fibrillar protein with a characteristic periodicity on electron microscopy.[193] Although a Congo Red stain can identify most cases, electron microscopy is more sensitive and specific and should be used routinely when amyloid is suspected.



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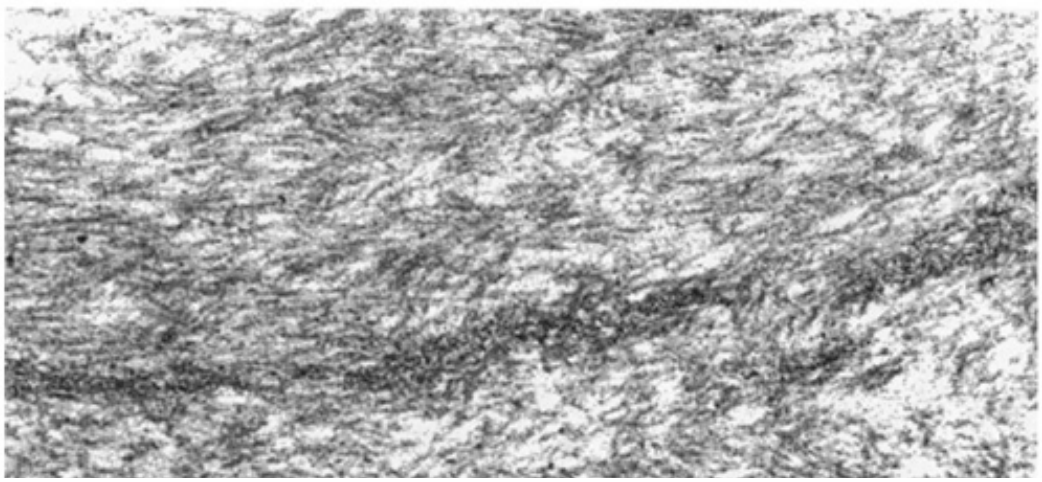

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Figure 66-6: *A.* Right ventricular biopsy demonstrating interstitial amyloid deposition (H&E stain, ×100). *B.* Electron micrograph of the same biopsy specimen illustrating the characteristic 8- to 14-nm, nonbranching, randomly oriented amyloid fibrils.

DISTINCT PATHOPHYSIOLOGY

Although the source and chemical nature of amyloid protein differs among the various types of amyloidosis, the tissue/organ pathophysiology is the same, i.e., the slow destruction of the heart by the inexorable deposition of a β-pleated sheet fibril that is insoluble and impervious to proteolytic digestion.[190]

PROGNOSIS

The prognosis is uniformly bad regardless of the type of amyloidosis, and the majority of patients with amyloid cardiomyopathy are dead within 2 years of diagnosis.

TREATMENT

There is no definitive treatment of amyloid cardiomyopathy. Treatment is completely empirical and consists of diuretics when needed, pacemaker treatment of bradyarrhythmias, and the avoidance of digoxin, which may be arrhythmogenic in any infiltrative cardiomyopathy. There is limited evidence that chemotherapy directed at amyloid secretion by abnormal β-lymphocytes can produce favorable effects in some patients.[194] Cardiac transplantation should be avoided even in primary localized amyloid cardiomyopathy because it will invariably recur in the heart or in other organs. The exception may be familial forms of amyloidosis, where the abnormal protein is a transthyretin or prealbumin variant synthesized in the liver. Combined liver and heart transplantation can be curative in this situation.[195]

Alcohol Cardiomyopathy

DEFINITION/DIAGNOSIS

An *alcohol cardiomyopathy* is said to be present when other causes of a dilated cardiomyopathy have been excluded and there is a history of heavy, sustained alcohol intake. The usual requirement in terms of alcohol amount is 100 g alcohol per day, typically over several years. However, in susceptible individuals it is likely that lower amounts of intake can produce a cardiomyopathy. The histologic features of alcohol cardiomyopathy are nonspecific and do not differ from IDC. Other than history, the only potentially distinguishing feature between IDC and alcohol cardiomyopathy is that the latter may present with a relatively high cardiac output.

DISTINCT PATHOPHYSIOLOGY

The pathophysiology of alcohol cardiomyopathy is thought to be related to the toxic effects of alcohol, plus in some subjects nutritional components such as thiamine deficiency.

PROGNOSIS

The prognosis depends on the degree of impairment of myocardial function and the extent of

abstinence from alcohol and, in an extremely compromised patient, the administration of thiamine. There is evidence that the prognosis is somewhat better for alcohol cardiomyopathy than for IDC.[196]

TREATMENT

The treatment of alcohol cardiomyopathy does not differ from IDC, except the inclusion of total abstinence from alcohol. Obviously, these subjects are not good candidates for cardiac transplantation because of the high relapse rate to alcoholism.

Chagas' Cardiomyopathy

DEFINITION/DIAGNOSIS

Chagas' disease is discussed in Chap. 69 as a cause of myocarditis. In addition, Chagas' disease is the most common cause of nonischemic cardiomyopathy in South and Central America, with over 10 million people afflicted.[197] It is caused by a parasite, the leishmanial or tissue form of the protozoan *Trypanosoma cruzi*. Although in the United States the vector (*Triatoma*, or kissing bug) is found only in the Southwest, Chagas' disease may be transmitted by blood transfusions, and as a result, it could become relatively more important in this country. The natural history consists of an initial myocarditis most commonly presenting in childhood, associated with acute myocardial infection followed by recovery and in some individuals the development of a dilated cardiomyopathy 10 to 30 years later.

The diagnosis of Chagas' cardiomyopathy is based on clinical (history, LV functional, and electrocardiographic) criteria and a positive serologic test for *T. cruzi*.[198] Electrocardiographic abnormalities consist of bundle-branch or hemiblocks (indeed, hemiblocks were first described by Rosenbaum et al.[199] in Chagas' afflicted hearts with discrete foci of involvement), LV hypertrophy, and first- or second-degree atrioventricular (AV) block.[200] The histologic lesion of chronic Chagas' consists of mononuclear infiltrates, fibrosis, and as shown in Fig. 66-7, foci of the leishmanial form of *T. cruzi* in myocardial fibers. The LV functional abnormalities initially may be segmental and may include an apical aneurysm but later become more global.[198,200]

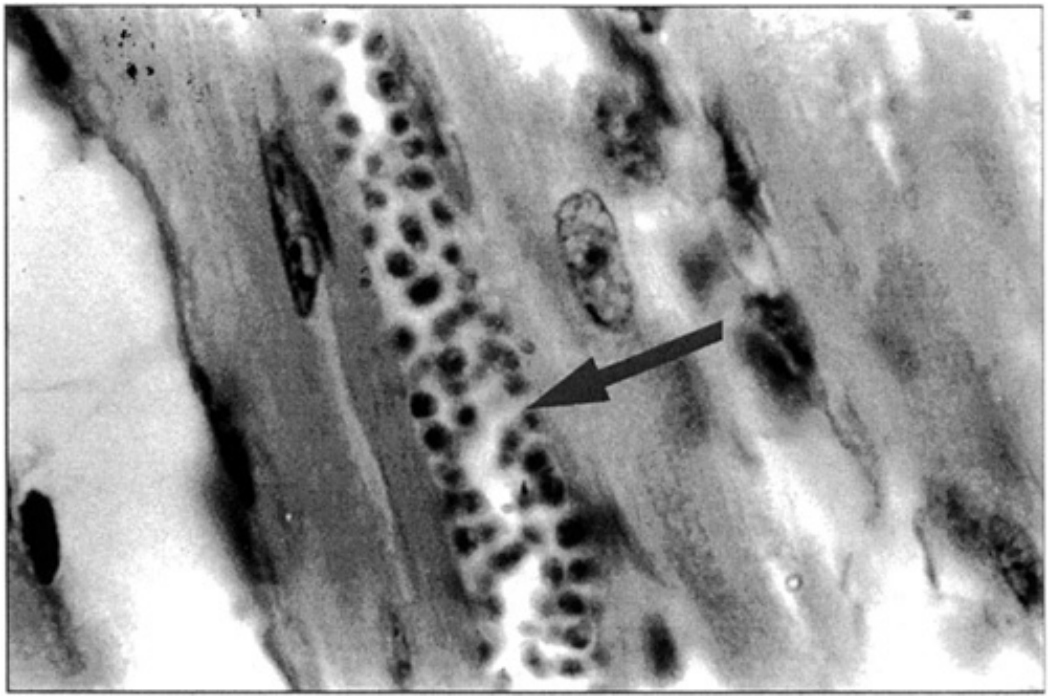

Figure 66-7: Leishmanial forms of *T. cruzi* within the swollen cytoplasm of a cardiac myocyte (Chagas' cardiomyopathy) (H&E stain, ×250). (Courtesy Dr. Elmer Koneman.)

DISTINCT PATHOPHYSIOLOGY

The basis for Chagas' cardiomyopathy is unknown but may be immunologic, whereby antibodies generated against *T. cruzi* crossreact with cardiac myocyte antigens including myosin.[201]

PROGNOSIS

The prognosis is relatively good for a dilated cardiomyopathy and similar to IDC; the 5-year survival in Chagas' cardiomyopathy with heart failure is around 50 percent.[198] Compared with IDC, death likely occurs more commonly due to an arrhythmic mechanism.[198] However, as for IDC and most other dilated cardiomyopathies, mortality risk depends directly on the degrees of ventricular dysfunction and exercise intolerance.[198]

TREATMENT

There is no definitive treatment for Chagas' cardiomyopathy, and nonspecific treatment includes pacemaker implantation for heart block and heart failure treatment as for IDC. The one exception may be the more frequent use of amiodarone, which appears to be particularly effective in treating arrhythmias associated with Chagas' cardiomyopathy and in one study reduced mortality compared with standard treatment.[202] The role of cardiac transplantation is still somewhat uncertain, but it can be done at acceptable risk,[203] especially when coupled with trypanocidal agents.[204]

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Chapter 66: DILATED CARDIOMYOPATHIES

SUMMARY

Dilated cardiomyopathies are important because they are the most common cause of heart failure, which is the single most costly medical problem in the adult U.S. population. Cardiomyopathies in general are a heterogeneous group of diseases, but they can be classified under a newly modified WHO/ISFC classification system, which, although imperfect, should be of great value in standardizing the terminology and encouraging systematic investigative and clinical approaches to diagnosis and treatment. Within this classification system, primary and secondary dilated cardiomyopathies comprise the single largest and most important group. Current diagnosis and treatment of dilated cardiomyopathies vary somewhat among the various types, but the cornerstones of medical management are similar in most cases.

Genetic causes and influences on the natural history of dilated cardiomyopathies are the new frontier in this field, and their elucidation is almost certain to lead to new therapeutic and diagnostic approaches. In the near future, molecular genetic testing will be done routinely for many cardiomyopathies that may have a single gene defect as the cause. As we learn more about the influence of polymorphic genetic variation on the natural history and selection of specific medical therapy, genetic testing will be performed in most patients with cardiomyopathies.

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Part 11: CARDIOMYOPATHY AND SPECIFIC HEART MUSCLE DISEASES
Chapter 67:

HYPERTROPHIC CARDIOMYOPATHY

Author: Barry J. Maron

Hypertrophic cardiomyopathy (HCM) is a genetically transmitted primary cardiac disease that has been of great interest to clinicians and laboratory scientists because of its particularly diverse clinical, morphologic, pathophysiologic, and molecular genetic manifestations.[1-22] Because of the broad and heterogeneous HCM disease spectrum as well as the relatively low prevalence in cardiologic practice, a measure of confusion and uncertainty has persisted regarding this condition.

HISTORICAL CONSIDERATIONS

There is some uncertainty regarding the first gross anatomic description of HCM. About 1900, French and German authors reported four patients at autopsy in whom striking hypertrophy involving the ventricular septum appeared to be responsible for obstruction to left ventricular ejection.[23,24] The first unequivocal description of HCM was the detailed pathologic report of Teare,[25] which stimulated widespread interest in this disease among cardiologists, pathologists, and surgeons. Teare described a condition in eight patients (seven of whom died suddenly) characterized by an asymmetric pattern of left ventricular wall thickening and nondilated ventricular cavities. The striking ventricular septal hypertrophy and bizarre arrangement of muscle bundles observed in these patients was initially thought to represent a benign tumor of the heart.

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

NOMENCLATURE AND PREVALENCE

Over the past 40 years, numerous studies have led to a dramatic evolution of our concepts concerning the clinical and pathologic spectrum of HCM; in the process, the disease has acquired a myriad of names[7] (Fig. 67-1). This multiplicity of descriptive terms largely reflects the enormous clinical, functional, and morphologic diversity of this disease. However, many of the terms that have been used to describe HCM are somewhat misleading by emphasizing the presence of left ventricular outflow obstruction at rest, a clinical feature that occurs in only a minority of HCM patients (about 20 to 25 percent).[1,3,5] The prevalence of HCM appears to be about 0.2 percent in the general population[26] and 1 percent in primary medical practice[27] based on identification of the disease phenotype with two-dimensional (2D) echocardiography. It is possible, however, that many individuals with HCM go undetected in the community because they manifest no or only mild symptoms and are not referred for echocardiographic studies.[28-31] Reports from a large number of diverse geographic areas suggest that HCM has extensive if not worldwide occurrence; there is also some evidence that the morphologic expression of the disease may differ in certain ethnic or racial groups (such as Japanese).[32-34]

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

DEFINITION AND CRITERIA FOR DIAGNOSIS

The clinical diagnosis of HCM is based on definition of the most characteristic morphologic feature of the disease-i.e., thickening of the left ventricular wall associated with a nondilated cavity in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident (e.g., systemic hypertension or aortic stenosis)[7] (Fig. 67-2). Because the nonobstructive form of HCM is predominant, the well-described clinical features of dynamic obstruction to left ventricular outflow-such as systolic anterior motion of the mitral valve, partial premature closure of the aortic valve, and a loud systolic ejection murmur-are not required for diagnosis.[1] Also, not all individuals harboring a genetic abnormality capable of producing the clinical and morphologic abnormalities of HCM show left ventricular hypertrophy at all phases of life.[10,22,31,35-37] For example, some children with HCM will not have left ventricular wall thickening identifiable by 2D echocardiogram prior to about age 16[35] and a few adults with incomplete penetrance may also show little or no hypertrophy.[10,36,38-40]

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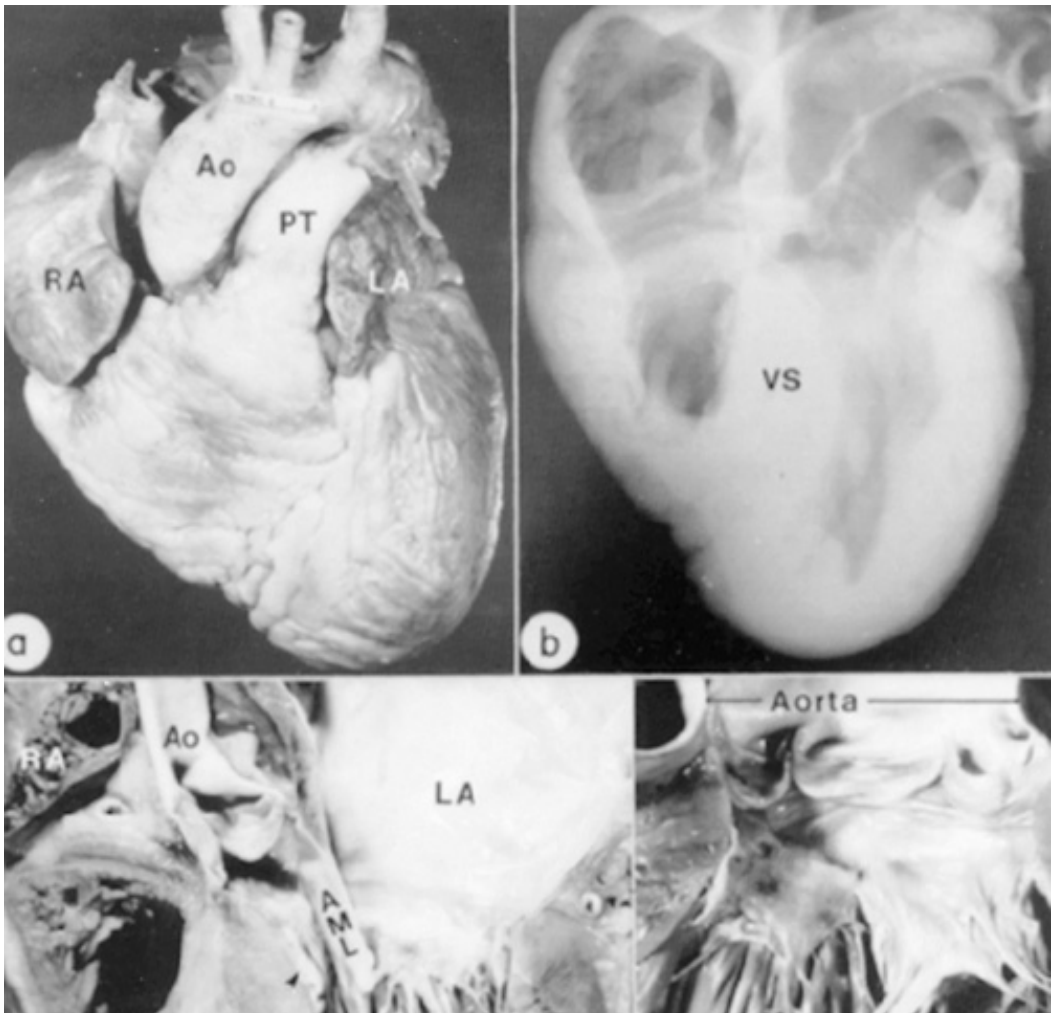
Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

MORPHOLOGIC CHARACTERISTICS

Gross Features

Left ventricular hypertrophy is the gross anatomic marker of HCM and the likely determinant of many of the clinical features identifiable in most patients with this disease[1-7,16-18] (Figs. 67-3 and 67-4). Since the left ventricular cavity is usually small or normal in size, the increased left ventricular mass is due almost entirely to an increase in wall thickness. Although a symmetric (concentric) pattern of left ventricular hypertrophy can be observed,[12,18,41] the distribution of hypertrophy is almost always asymmetric; i.e., with segments of the left ventricular wall thickened to a dissimilar degree, and with the ventricular septum showing disproportionate magnitude of hypertrophy.[12,18] Examination of the heart at necropsy also typically shows dilatation of the atria, enlargement and elongation of the mitral valve leaflets, and areas of replacement fibrosis (scarring) in the left ventricular wall.[16,17,20,42,43] In addition, most hearts show a characteristic fibrous plaque on the mural endocardium of the leftventricular outflow tract in apposition to the thickened anterior mitral leaflet, presumably resulting from systolic (or diastolic) contact between mitral valve and septum[16] (Fig. 67-3).



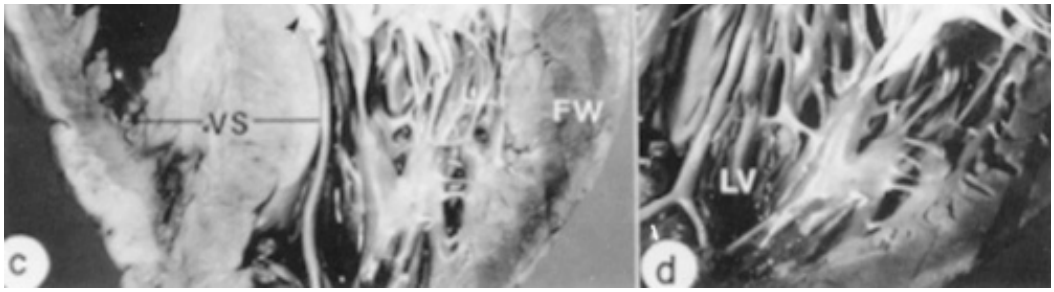


Figure 67-3: Anatomic features of HCM are demonstrated in the heart of a 26-year-old man. *A.* Exterior view; both right atrium (RA) and left atrium (LA) are dilated. Ao = aorta; PT = pulmonary trunk. *B.* Radiography of specimen showing asymmetric thickening of ventricular septum (VS). *C.* Coronal section; the septum is clearly thicker than left ventricular free wall (F); an endocardial mural contact plaque (*arrowhead*) is present in the left ventricular outflow tract in apposition to the anterior mitral leaflet (AML). *D.* Closer view of plaque and thickened anterior leaflet. (From Roberts WC et al.[16] with permission from the authors and publisher.)

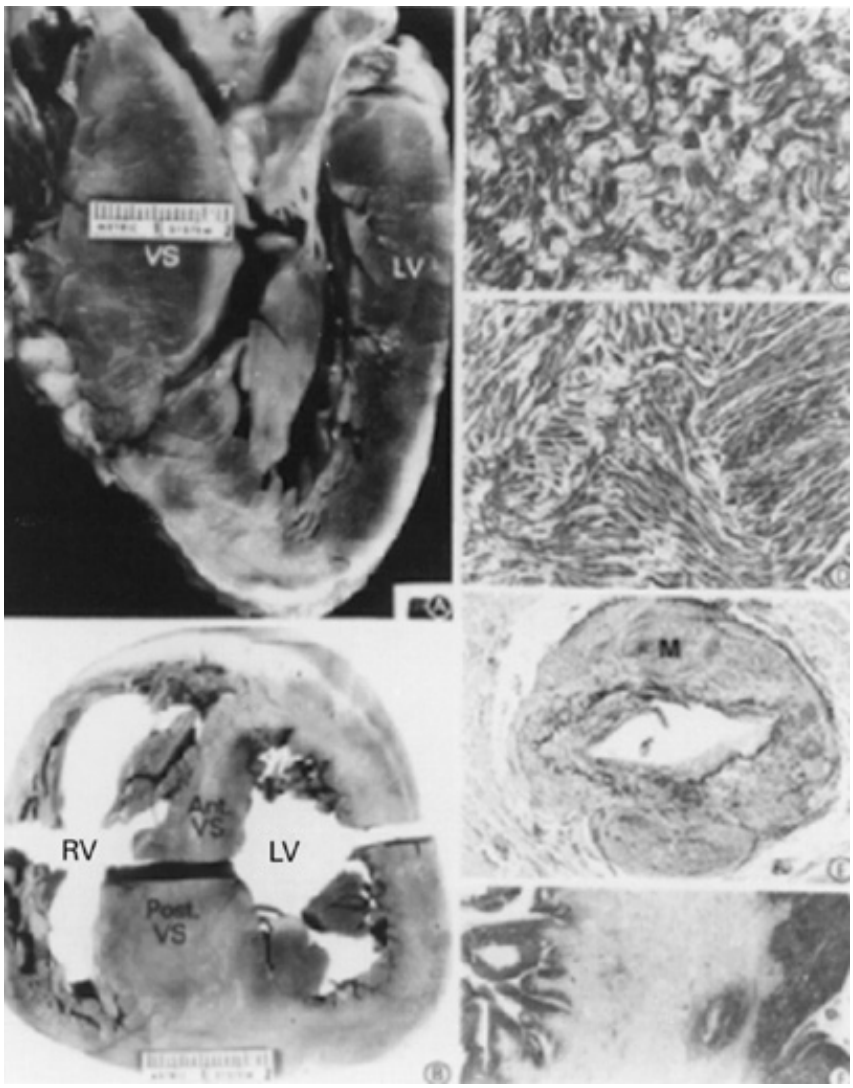


Figure 67-4: Morphologic components of the underlying disease process in HCM. *A.* Gross heart specimen sectioned in a cross-sectional plane similar to that of the echocardiographic (parasternal) long axis. The pattern of left ventricular hypertrophy is asymmetric, with wall thickening confined primarily to the anterior ventricular septum (VS), which bulges into the left ventricular outflow

tract. *B.* Heart specimen illustrating a different pattern of hypertrophy, in which marked left ventricular wall thickening is localized to the posterior portion of the ventricular septum (Post. VS), while the anterior septum (Ant. VS) is only mildly thickened. *C* and *D.* Histopathology characteristic of the left ventricle in HCM. *C.* Septal myocardium shows markedly disordered architecture, with adjacent hypertrophied cardiac muscle cells arranged at perpendicular and oblique angles to each other. *D.* Bundles of hypertrophied cells show a disorganized, "interwoven" arrangement. *E.* Intramural coronary artery with apparently narrowed lumen and thickened wall due primarily to medial (M) hypertrophy. *F.* Extensive scarring of ventricular septum, which is transmural in distribution. LV = left ventricular free wall. (From Maron BJ et al.[3] with permission from the authors and publisher.)

Based on both echocardiographic and necropsy analyses of large numbers of patients, it is apparent that the HCM disease spectrum is characterized by vast structural diversity with regard to the patterns and extent of left ventricular hypertrophy [12,18,41,43] (Figs. 67-5 and 67-6). Indeed, no single phenotypic expression can be considered "classic" or particularly typical of this disease. While maximal thickness of the left ventricular wall varies greatly, the average value in a population is usually 21 to 22 mm. Wall thickness is markedly increased in many patients, with some showing the most severe hypertrophy observed in any cardiac disease (60 mm is the most extreme dimension).[44,45] On the other hand, the HCM phenotype is not always expressed as a particularly thickened left ventricle; some patients may show only a mild increase of 15 to 18 mm, and a few genotyped affected individuals have been observed with normal thicknesses (≤12 mm).[10,36,40,46] Often the pattern of wall thickening is strikingly heterogeneous, involving noncontiguous segments of left ventricle (i.e., with areas of normal thickness evident in between), or with marked differences in wall thickness in adjacent segments of the wall. Transitions between thickened areas and regions of normal thickness are often sharp and abrupt, not infrequently creating right-angled contours of the wall.

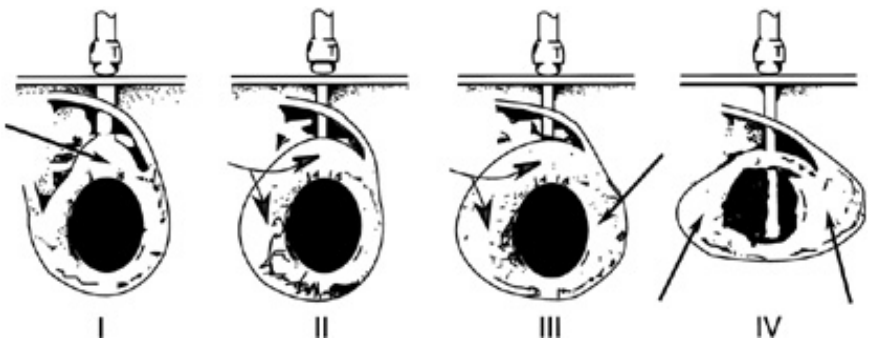


Figure 67-5: Morphologic variability in HCM, based on observations made from two-dimensional echocardiography; areas of hypertrophy are indicated by arrows. All images are drawn in the standard short-axis cross-sectional plane at mitral valve level with anterior chest wall and transducer to the top, posterior free wall to the bottom, posterior septum to the left, and anterolateral free wall to the right. *I.* Relatively mild left ventricular hypertrophy confined to anterior portion of ventricular septum. *II.* Hypertrophy of anterior and posterior septum in the absence of free wall thickening. *III.* Diffuse hypertrophy of substantial portions of both ventricular septum and anterolateral free wall. *IV.* Included are more unusual patterns of hypertrophy in which the thickened portions of left ventricle are present in the posterior septum or anterolateral free wall (as shown here) or at the left ventricular apex. (From Maron BJ[12] with permission from the author and publisher.)

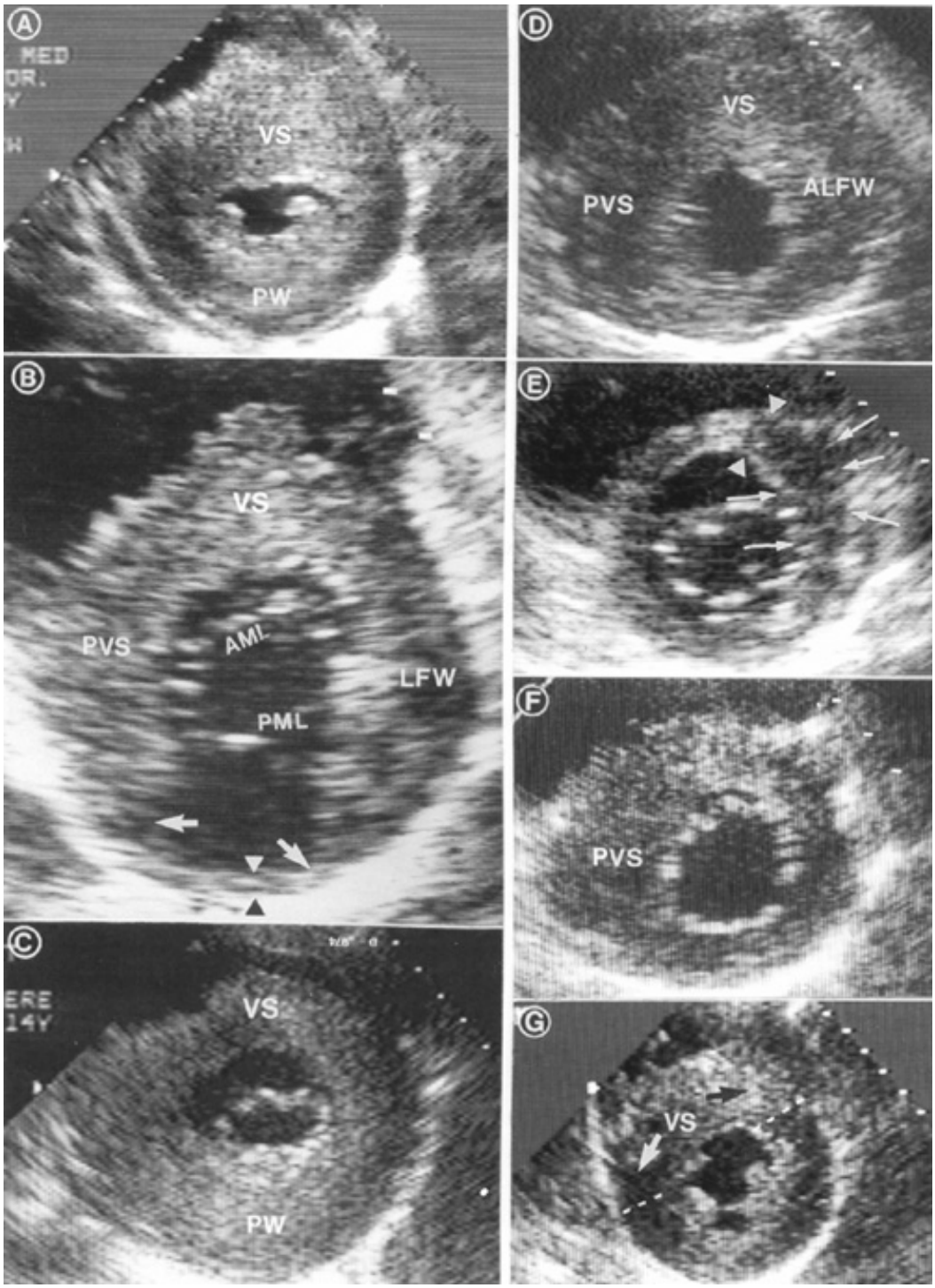


Figure 67-6: Variability of patterns of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy, shown in a composite of diastolic stop-frame images in the parasternal short-axis plane. *A, B,* and *D.* Wall thickening is diffuse, involving substantial portions of ventricular septum and free wall. At the papillary muscle level (*A*), all segments of the left ventricular wall are hypertrophied, including the posterior free wall (PW), but the pattern of thickening is asymmetric, with the anterior portion of ventricular septum (VS) massive (i.e., 50 mm). *B.* Hypertrophy is diffuse, involving three segments of the left ventricle but with the posterior wall spared and thin (<10 mm) (*arrowheads*) and with particularly abrupt changes in wall thickness evident (*arrows*). *C.* Marked hypertrophy in a pattern distinctly different from that in *A, B,* and *D,* in which the thickening of the posterior wall is predominant and the ventricular septum is of nearly normal thickness. *D.* Diffuse distribution of hypertrophy involving three segments of the left ventricle similar to that in *B* but without sharp changes in the contour of the wall. *E.* Hypertrophy predominantly of lateral free wall (*arrows*) and only a small portion of the contiguous anterior

septum (*arrowheads*). *F.* Hypertrophy predominantly of posterior ventricular septum (PVS) and, to a lesser extent, the contiguous portion of the anterior septum. *G.* Thickening of anterior and posterior septum to a similar degree but with sparing of the free wall. Calibration dots are 1 cm apart. AML = anterior mitral leaflet; LVW = lateral free wall; PML = posterior mitral leaflet. (From Klues HG et al.[18] with permission from the authors and publisher.)

In most patients the pattern of hypertrophy is diffuse, involving both septum and substantial portions of the lateral free wall, while the posterior segment of free wall is usually least affected by the hypertrophic process.[12,18] In others, hypertrophy involves only the ventricular septum while sparing the free wall. Of note, in an important proportion of patients (about one-third), wall thickening may be relatively mild and confined to a single segment of left ventricle.[12,13,18] Such segmental hypertrophy is usually localized to the anterior septum but may also be limited to the posterior septum,[12,18] anterolateral free wall,[12,18] posterior free wall,[47] or even the most apical portion of the left ventricle.[14,15,32,48-50] Therefore, the ventricular septum is usually, but not always, prominently involved in the hypertrophic process. Infiltrative and myocardial storage diseases such as cardiac amyloid and Fabry's disease may occasionally mimic HCM morphologically (Chap. 10).

Hypertrophy confined to the left ventricular apex ("apical HCM") has been reported most commonly by Japanese investigators,[32,34,49] who have described this subgroup of HCM patients to be clinically benign and with a "spade" deformity of the left ventricular cavity on angiography and a distinctive electrocardiographic (ECG) pattern of deep ("giant") T-wave inversion. Reports from outside Asia would suggest, however, that apical hypertrophy is uncommonly accompanied by marked T-wave inversion and associated with adverse outcome in some patients.[14,15,48,50] This heterogeneous morphologic expression described for HCM is underlined by the fact that even first-degree relatives with the disease usually show great dissimilarity in the pattern of left ventricular wall thickening.[11]

In some young athletes, segmental hypertrophy of the anterior ventricular septum (wall thicknesses of 13 to 15 mm), consistent with a relatively mild morphologic expression of HCM, may often be difficult to distinguish from the physiologic left ventricular hypertrophy that can represent an adaptation to intense forms of athletic training.[51,52] In asymptomatic individuals within this morphologic "gray zone," the differential diagnosis between athlete's heart and nonobstructive HCM can often be resolved by clinical assessment and noninvasive testing[52] (Fig. 67-7).

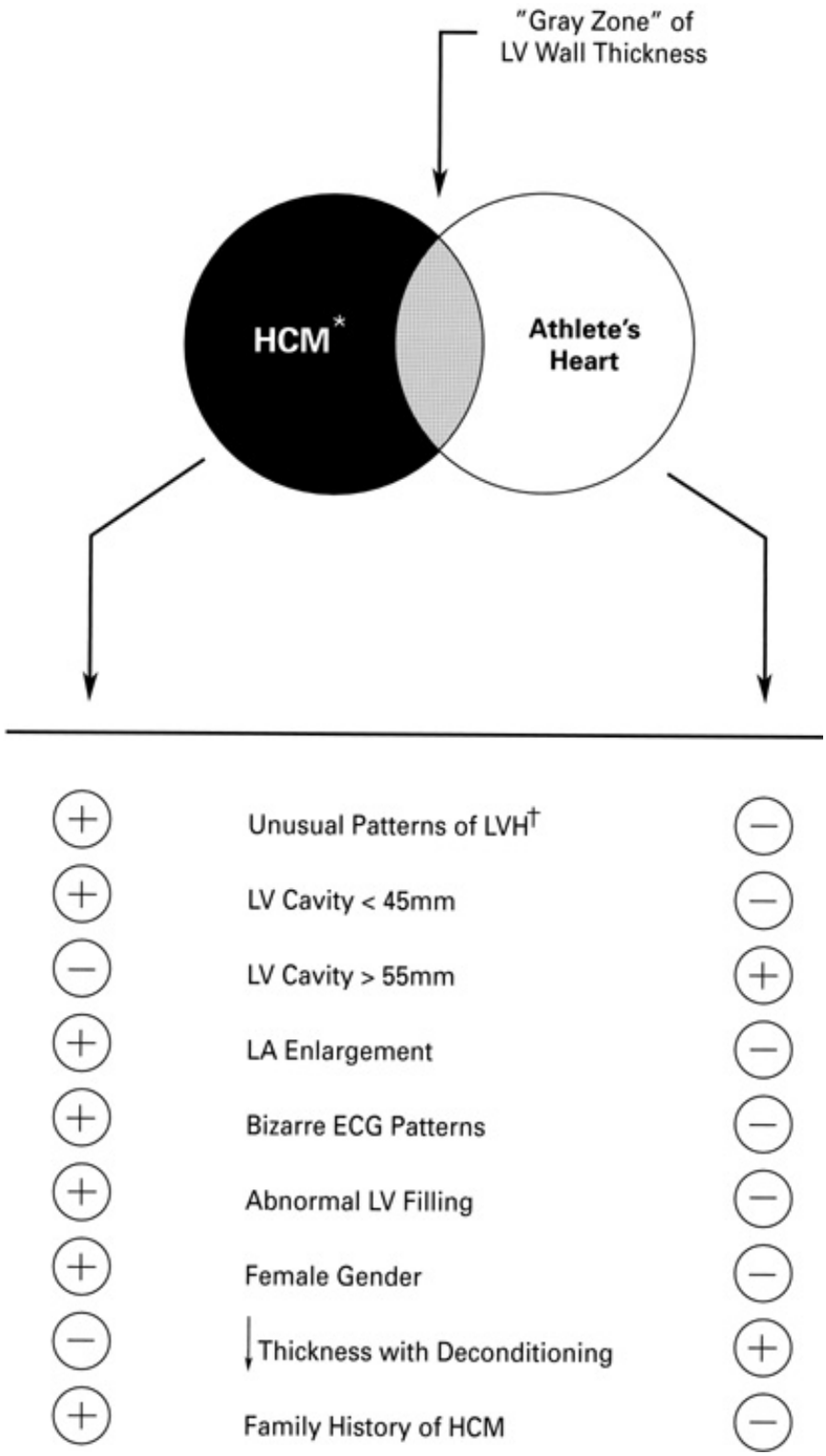
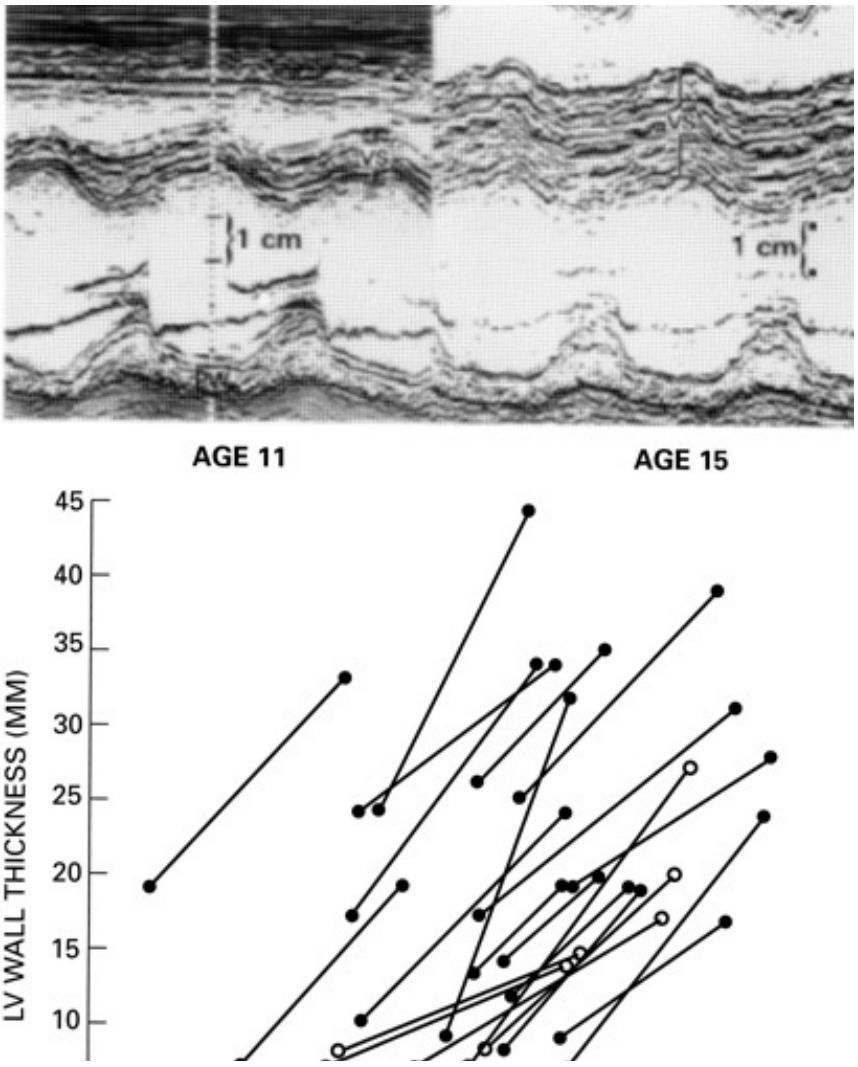


Figure 67-7: Criteria used to distinguish HCM from athlete's heart when left ventricular (LV) wall thickness is within the shaded gray zone of overlap, consistent with both diagnoses. *Assumed to be the nonobstructive form, since substantial mitral valve systolic anterior motion would confirm, per se, the diagnosis of HCM in an athlete. †May involve a variety of abnormalities, including heterogeneous distribution of LV hypertrophy in which adjacent regions may be of greatly different thicknesses, with sharp transitions evident between segments; also, asymmetric patterns in which anterior ventricular septum is spared from the hypertrophic process and the region of predominant thickening may be in the posterior septum or anterolateral or posterior free wall. ↓ = decreased; LA = left atrial. (From Maron BJ et al.[52] with permission from the authors and Williams & Wilkins.)

HCM can represent a congenital heart malformation in which phenotypic expression in the form of left ventricular wall thickening begins during fetal development[53] and is evident at or shortly after birth.[54-56] Indeed, HCM has been reported in a small number of very young children, including a few infants under 6 months of age.[54-56] When HCM presents in infancy, the disease is usually associated with marked septal hypertrophy as well as severe progressive congestive heart failure and biventricular outflow obstruction.[54,55,57] However, most cases of idiopathic left ventricular hypertrophy presenting in the first 2 years are not true HCM due to sarcomere protein mutations, but are often associated with other conditions such as Noonan syndrome.[57]

Later in childhood, serial echocardiographic investigations have shown prominent left ventricular remodeling. The morphologic expression of HCM is not usually complete until adulthood,[35,58] and during adolescence children often show striking spontaneous increases in wall thicknesses (i.e., of about 100 percent) and more widespread distribution of hypertrophy, including de novo development of wall thickening, when body growth and maturation are accelerated (Fig. 67-8). Progression of basal septal hypertrophy associated with a developmentally small left ventricular outflow tract appears to be the major determinant for the development of mitral valve systolic anterior motion and outflow obstruction during childhood.[59] In some young children, abnormalities on the 12-lead ECG may be the initial clinical manifestation of HCM, even preceding the appearance of hypertrophy on the echocardiogram.[31,60] Such left ventricular remodeling is usually not associated with development or progression of symptoms or sudden death and appears to be an expression of the genetically predetermined morphologic evolution of the disease.[35,61]



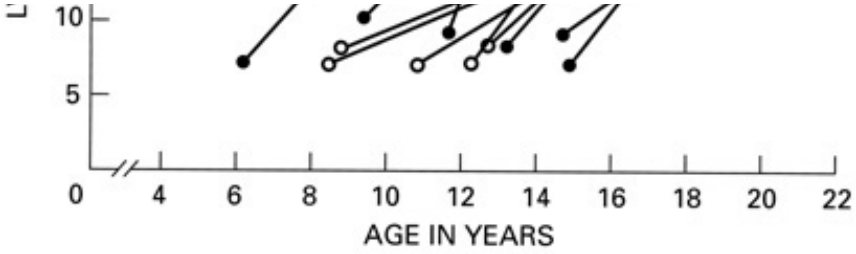


Figure 67-8: Development and progression of left ventricular hypertrophy in children with HCM. *Upper panel:* Development of marked hypertrophy of the anterior basal ventricular septum (VS). M-mode echocardiograms shown here were obtained at the same cross-sectional level in a girl with a family history of HCM. At age 11, ventricular septal thickness was at upper limit of normal (10 mm); at age 15, septal thickness had increased markedly (to 33 mm), and appearance of the echocardiogram is typical of HCM. The patient remained asymptomatic throughout this period of time but died suddenly and unexpectedly at age 17. PW = posterior left ventricular free wall. *Lower panel:* Dynamic, striking changes in left ventricular wall thickness with age in 22 children; each patient is represented by the left ventricular segment that showed the greatest change in wall thickness. Open symbols denote 5 patients who had no evidence of hypertrophy in any segment of the left ventricle at the initial evaluation but subsequently developed de novo hypertrophy typical of HCM. (From Maron BJ et al.[35] with permission of the authors and the Massachusetts Medical Society.)

In symptomatic adult patients with HCM, the magnitude of left ventricular hypertrophy may *decrease* with aging.[62] Very marked degrees of hypertrophy (e.g., maximum wall thickness ≥30 mm) are largely limited to patients under age 40, while older patients over age 60 generally have more modest hypertrophy and rarely show wall thicknesses >25 mm. The explanation for this inverse relation between age and magnitude of hypertrophy could be a higher rate of premature death in younger patients with severe morphologic forms or, alternatively, to a process of wall thinning and remodeling occurring very gradually over long periods of time in many patients.[61]

Histologic Features

Several histologic features of left ventricular myocardium represent components of the primary cardiomyopathic disease process in HCM[1,3,42,63-73]: (1) disarray of cardiac muscle cells (myocytes) (Fig. 67-4*C* and *D*); (2) replacement fibrosis (Fig. 67-4*F*); (3) expansion of the interstitial (matrix) collagen compartment; and (4) abnormally small intramural coronary arteries (Fig. 67-4*E*). Marked distortion of cellular architecture with myocyte disarray, described prominently by Teare in his initial report of HCM,[25] is a characteristic feature of the left ventricle.[64-68,71] Many cardiac muscle cells in both the ventricular septum and left ventricular free wall show increased transverse diameter and bizarre shapes, maintain intercellular connections with several adjacent cells, and are arranged in a disorganized pattern at oblique and perpendicular angles to each other. This myocyte disarray is present in about 95 percent of patients dying of HCM and usually occupies substantial portions of both septum (i.e., about 33 percent) and left ventricular free wall (i.e., 25 percent) (see Fig. 74-4*C* and *D*). However, there is little correlation between absolute wall thickness and amount of disorganized myocardium in segments of the left ventricular wall.[71] Therefore areas of normal or only mildly increased left ventricular wall thickness may also show evidence of the cardiomyopathic process in HCM, in the form of cellular disarray.[71]

Dispersion of disorganized cardiac muscle cells throughout the left ventricular myocardium may impair intercellular transmission of normal electrophysiologic impulses, predispose to electrical instability, and thereby serve as an arrhythmogenic substrate responsible for the genesis of primary ventricular tachycardia/fibrillation.[74]

Patients with HCM (and without atherosclerotic coronary artery disease) often exhibit myocyte necrosis and replacement fibrosis in the left ventricle at necropsy.[42,63,69,72] A spectrum of severity and distribution is observed ranging from isolated small scars to extensive, grossly visible replacement scarring that may even be transmural[42] (Fig. 67-4*F*). These areas of fibrosis, which likely result from repetitive bursts of myocardial ischemia or are related in some other way to the underlying cardiomyopathic disease process, can be identifiable during life as irreversible thallium-201 myocardial perfusion abnormalities[75] and may well contribute to the increased ventricular chamber stiffness and impaired relaxation identifiable in most patients with HCM as well as representing a nidus for the genesis of ventricular arrhythmias.[1,3,5,74] In addition, the interstitial collagen matrix of the left ventricle is substantially increased in size; its components (perimysial coils, pericellular weaves, and struts) are increased in number and morphologically abnormal, often showing a disorganized arrangement.[73]

Abnormal intramural coronary arteries are present in about 80 percent of patients with HCM studied at necropsy and are most commonly evident in the ventricular septum.[69,70] The walls of these arterioles are thickened (because of increased smooth muscle cells, collagen, elastic fibers, and mucoid deposits in the media and intima), and frequently the lumen appears narrowed and compromised (Fig. 67-4*E*). Increased numbers or clusters of abnormal intramural arteries are often observed within or at the margins of sizable areas of fibrosis.[42,69] This association between abnormal intramural coronary arteries and myocardial scarring suggests that a form of "small-vessel disease" present in patients with HCM may be responsible for myocardial ischemia and necrosis.[69]

Mitral Valve Abnormalities

Morphometric analysis of mitral valves removed at operation or necropsy from patients with outflow obstruction supports the concept that primary structural abnormalities of the mitral valve are also characteristic of many patients with HCM[20,43] (Fig. 67-9). About two-thirds of patients show alterations in mitral valve size and shape, with an increased mitral valve tissue area (up to twice normal) due primarily to leaflet elongation (but without evidence of myxomatous degeneration). These enlarged valves demonstrate considerable structural heterogeneity, either with both the anterior and posterior leaflets increased in size or asymmetric and segmental enlargement of one leaflet.[20] Mitral valve systolic anterior motion and outflow obstruction may occur both with normal or enlarged mitral valves but show age-related morphologic and functional features. In younger patients with obstruction, the leaflets are usually elongated and the valve is situated more posterior in the left ventricular outflow tract (at end-diastole), in contrast to elderly patients in whom the mitral valve is often normal-sized and situated much closer to the ventricular septum.[43]

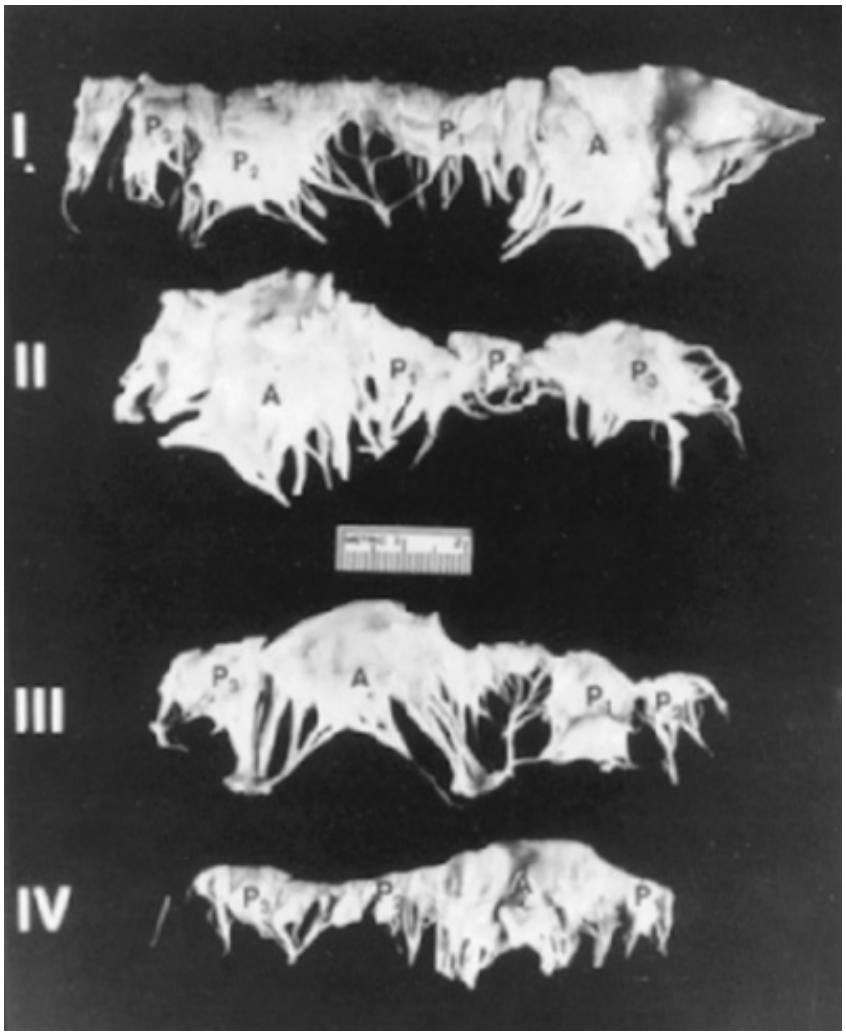
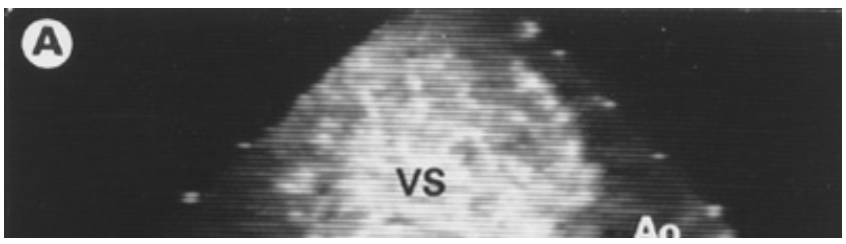


Figure 67-9: Mitral valves from three patients with obstructive HCM, aged 31, 29, and 60 years (I, II, and III), and from a normal control patient without cardiovascular disease (IV), showing variation in valvular size and structure present in HCM. Valves are opened with the circumference displayed in a horizontal orientation, exposing the atrial surface, with annular margin to top and chordal attachments to bottom. *I.* Large valve (area 22 cm2) in which both the anterior (A) and posterior (P) leaflets are greatly elongated and increased in area. *II.* Large valve in which increased valve size (area 18 cm2) is due primarily to elongation and enlargement of the anterior leaflet (A). *III.* Segmental elongation and increased area confined to a scallop of posterior leaflet. (From Klues HG et al.[20] with permission of the authors and Lippincott Williams & Wilkins.)

In addition, other HCM patients show a congenital malformation of the mitral apparatus due to an arrest in embryonic development, with anomalous insertion of papillary muscle directly into the anterior mitral leaflet (without the interposition of chordae tendineae)[19] (Fig. 67-10). Greatly enlarged mitral valves and anomalous papillary muscle insertion represent a constellation of structural malformations of the mitral apparatus (in >50 percent of patients studied at necropsy) that expand the morphologic definition of HCM.[19,20,43]



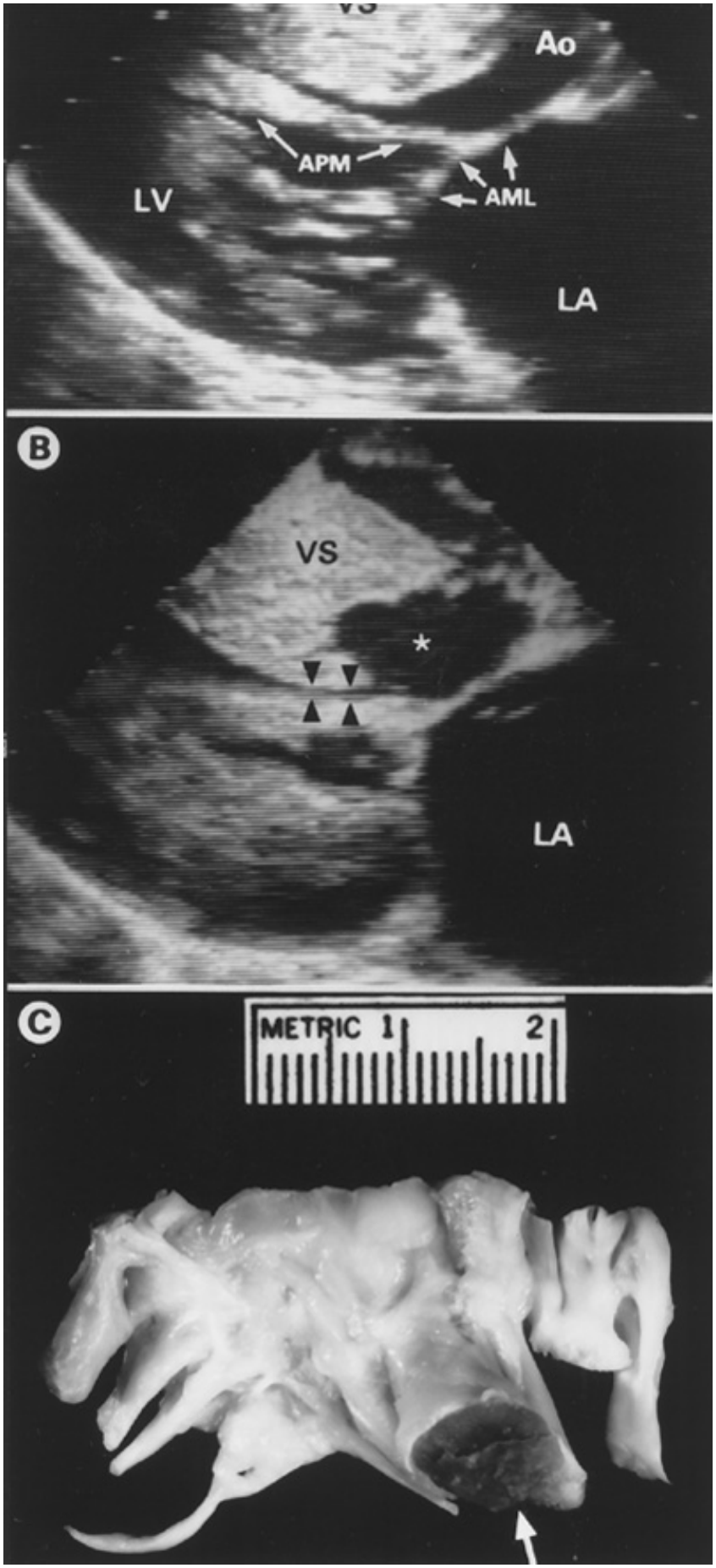


Figure 67-10: Anomalous papillary muscle insertion directly into anterior mitral leaflet (*AML*) in patient with obstructive HCM. *A. Before myotomy-myectomy:* parasternal long-axis

echocardiogram shows AML in direct continuity with the hypertrophied anomalous anterolateral papillary muscle (*APM*), which displaced anteriorly within the left ventricular cavity, producing a long area of midcavity muscular contact with the ventricular septum (VS) and outflow obstruction (*arrows*); tips of the mitral leaflets coapt in the usual position, and typical systolic anterior motion is absent (*small arrows*). *B. After myotomy-myectomy:* Long-axis echocardiogram shows extensive muscular resection (*), extending from base of the septum to beyond the distal margins of the anterior mitral leaflet; nevertheless, a large area of direct muscular contact remains after operation between papillary muscle and ventricular septum (*arrowheads*), which is responsible for persistent and marked obstruction to left ventricular outflow. *C.* Mitral valve specimen excised at operation; a massively hypertrophied anterolateral anomalous papillary muscle (*arrow*) inserted directly into the body of the anterior leaflet. Ao = aorta; LA = left atrial; LV = left ventricle. (From Klues HG et al.[19] with permission of the authors and Lippincott Williams & Wilkins.)

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

ETIOLOGY AND GENETICS

HCM is a mendelian trait with an autosomal dominant pattern of familial inheritance.[1-5,8-11,22,38-40,76-83] Based on 10 years of molecular genetic studies, it is now known that HCM is genetically heterogeneous and caused by mutations in any one of nine genes that encode contractile proteins of the cardiac sarcomere, involving thick filaments (myosin subunits-i.e., beta-myosin heavy chain and essential and regulatory myosin light chains), thin filaments (cardiac troponin T, cardiac troponin I, α-tropomyosin, and α-actin), and-in the case of titin cardiac myosin-binding protein C-the structural network that joins thick and thin filaments.[5,8-11,22,38-40,76-83] Clinical and laboratory data are largely restricted to three disease genes that, together, explain most occurrences of familial HCM: β-myosin heavy chain, myosin-binding protein C, and cardiac troponin T. Overall, more than 100 individual disease-causing HCM mutations have been reported, either of the missense type (with the replacement of one amino acid by another) or mutations leading to truncated proteins. Indeed, most genotyped pedigrees show a mutation apparently unique to that family. Undoubtedly, numerous other genes and mutations await identification. The fact that all mutations known to cause HCM involve genes encoding proteins of the sarcomere represents a unifying principle that permits us to regard this heterogeneous condition as a single disease entity (and as a disease of the sarcomere).[5,8-10,84]

It has been suggested that the prognosis of HCM varies considerably with respect to many of the mutations reported. For example, some β-myosin heavy chain point mutations appear benign (e.g., Val606Met), whereas others are more virulent and associated with reduced survival (e.g., Arg403Gln, Arg453Cys, and Arg719Trp).[8,9,22,76,82] In addition, cardiac troponin-T mutations may have malignant forms associated with reduced survival even though cardiac hypertrophy is often relatively mild.[5,22,38,39] Although, collectively, these observations suggest that genetic data may ultimately predict prognosis and influence clinical management, at present such a risk stratification strategy should be regarded as preliminary considering the relatively small number of genotyped families and the aforementioned genetic heterogeneity.

Occurrence of premature sudden cardiac death in a family should dictate a genetic and/or echocardiographic evaluation in surviving relatives, since the clinical expression of HCM may be particularly virulent in certain families (e.g., "malignant" HCM).[85] Also, because HCM is the most common cause of sudden unexpected death in young competitive athletes,[86] youthful family members should be screened for HCM prior to participation in intense athletic training. Because phenotypic (i.e., morphologic) expression of HCM may not be complete until 17 to 18 years of age,[35] a single screening echocardiogram during early childhood may not definitively exclude HCM. Therefore, children in families with HCM in whom left ventricular hypertrophy is absent on 2D echocardiography should continue to have examinations periodically until they achieve full growth and maturation. There now appears to be one clear exception to the tenet that development or progression of left ventricular hypertrophy does not occur in adulthood-i.e., myosin-binding protein-C mutations[10,46] (Fig. 67-11), which are associated with age-related penetrance; in some young adults, the HCM phenotype may not be evident on echocardiography, and is delayed until much later in life[10,46] (Fig. 67-12).

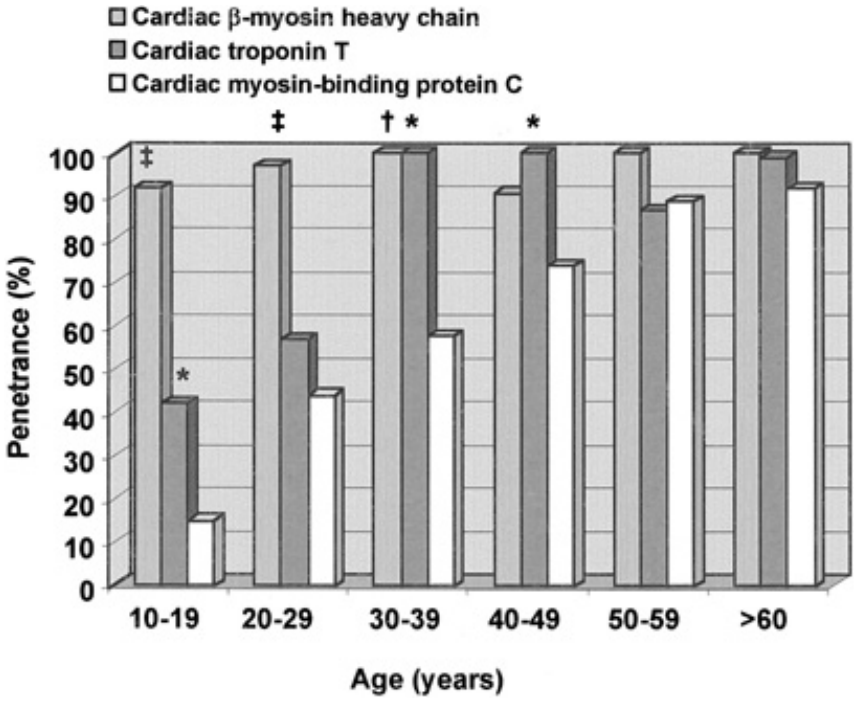

Figure 67-12: Age-related penetrance of familial HCM caused by mutations in the genes for cardiac myosin-binding protein C, cardiac troponin T, and cardiac β-myosin heavy chain. Solid bars denote the percentage of persons with both cardiac myosin-binding protein C mutations and left ventricular hypertrophy. Comparable clinical data for cardiac troponin T and β-myosin heavy chain are shown. Significant differences in the penetrance of familial HCM caused by cardiac myosin-binding protein C mutations and by mutations in cardiac troponin T or cardiac β-myosin heavy chain are indicated as follows: * = $p < 0.05$; = $p < 0.005$; $fy2$æ = $p < 0.001$. (From Niimura H et al. [10] with permission of the authors and the Massachusetts Medical Society.)

Routine echocardiographic screening at ≤12 years of age is usually unproductive, since phenotypic expression of the mutant gene is rarely present at that age.[31,35,59,77] Family screening can usually be deferred in young children until adolescence unless they are involved in intense sports programs (such as swimming and tennis) or are members of families with HCM-related sudden deaths.[85]

With the advent of preclinical genetic diagnosis of HCM, a number of asymptomatic youthful family members havebeen identified as affected on the basis of a DNA diagnosisin the absence of typical phenotypic features of their disease(as assessed with echocardiography and electrocardiography).[5,10,22,31,36,37,40] The increasing availability of gene-based diagnosis will lead to the identification of greater numbers of children and adults with a preclinical diagnosis of HCM (i.e., who have a gene defect but no phenotypic manifestations of HCM).[5,10,22,31,36,37,40] At present, the clinical implications of such gene abnormalities and the appropriate management are largely unresolved issues, although-of note-very few such patients have been reported with adverse outcome.[87,88] Therefore there is not sufficient evidence available at present to preclude such individuals from competitive athletics in the absence of cardiac symptoms or risk factors such as family history of sudden cardiac death.[89] It should be emphasized that, at present, due to the substantial genetic heterogeneity of HCM and the complex, time-consuming, and expensive techniques required for genetic screening, DNA diagnosis is quite demanding, permits only research-oriented genotyping of selected pedigrees, and is not routinely available for clinical practice.[22]

Although the reported sarcomeric protein mutations are regarded as disease-causing for HCM,

many of the abnormal and primary structural features of this disease are not confined to protein abnormalities of the sarcomere but extend to alterations in connective tissue elements-e.g., mitral valve enlargement and elongation as well as other anomalies of the mitral apparatus,[19,20,43] abnormal small intramural coronary arteries,[69,70] and an expanded collagen matrix.[72,73] This fact, together with the observations that the patterns of left ventricular hypertrophy in closely related family members are usually dissimilar[11] and that hypertrophy is frequently confined to only a portion of the wall,[11-13,18] suggests that phenotypic expression is importantly influenced by genetic factors other than the causal mutation (e.g., by modifier genes)[90] or by undefined environmental influences.

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

PATHOPHYSIOLOGY

The symptoms of HCM are varied and include those of pulmonary congestion-such as exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea-as well as fatigue, chest pain (which may be atypical of angina pectoris), palpitations, and impaired consciousness, including dizziness, near syncope, and syncope. The onset of symptoms is often in early adulthood between 20 and 40 years of age, although they can become evident at any age.

A number of pathophysiologic components of the HCM disease process dictate the clinical course and outcome experienced by patients[1,3-5,91-101]: (1) left ventricular outflow tract obstruction; (2) diastolic dysfunction; (3) myocardial ischemia; and (4) supraventricular and ventricular arrhythmias. However, consistent with the heterogeneity of HCM, cardiac symptoms do not always show a direct (one-to-one) correlation with a particular pathophysiologic mechanism in the individual patient, and the relative contributions of each component to symptoms appear to vary considerably among patients. Among patients with outflow gradients, no consistent correlation has been identified between the frequency and severity of symptoms and the magnitude of the gradient. Furthermore, the severity and character of symptoms may be similar in those patients with or without outflow obstruction.

Outflow Obstruction

Obstruction to left ventricular outflow exhibited by patients with HCM (due to systolic anterior motion of the mitral valve and midsystolic contact with the ventricular septum)[4,6,94-97,102,104] is characteristically dynamic, showing spontaneous variability.[2] Interventions or circumstances that decrease myocardial contractility (e.g., beta-blocking drugs) or increase ventricular volume or arterial pressure (squatting or vasoconstrictor agents) have the effect of reducing or abolishing subaortic obstruction. Interventions or circumstances that increase contractility (exercise or infusion of isoproterenol) or decrease arterial pressure or ventricular volume (Valsalva maneuver or a hypotension-producing agent) will increase or provoke obstruction. Not uncommonly, patients with little or no obstruction to left ventricular outflow under basal conditions are capable of generating substantial labile gradients with physiologic or pharmacologic provocations[2-4] or just after the cessation of exercise.[98]

The increase in systolic intraventricular pressure associated with outflow obstruction may increase myocardial wall stress and oxygen demand. It is generally conceded that outflow obstruction in HCM can, in some patients, have long-term detrimental consequences on left ventricular function and be responsible for the genesis of symptoms.[1-6,95] The magnitude of the systolic pressure gradient can be reliably estimated noninvasively by the magnitude and duration of mitral valve systolic anterior motion on M-mode echocardiogram[4,6,94,95] or, more easily and quantitatively, by continuous-wave Doppler interrogation, obviating the necessity of performing serial cardiac catheterizations.[105] The combined use of color-coded, pulsed, and continuous-wave Doppler echocardiography allows assessment of the site and severity of outflow obstruction[104] (Chap. 13).

For the subaortic gradient to occur in HCM, several of the following morphologic and hemodynamic factors will be present: (1) reduced outflow tract dimension at end-diastole; (2) substantial hypertrophy involving the basal anterior ventricular septum; (3) displacement of mitral

valve and papillary muscles anteriorly within the ventricular cavity; (4) increased length of the mitral leaflets; and (5) hyperdynamic left ventricular ejection, creating a high-velocity jet which streams through the narrowed outflow tract, pulling the mitral leaflets forward toward the septum (i.e., Venturi effect), or perhaps more likely due to drag (the hydrodynamic pushing force of flow) on the leaflets as they protrude into the outflow tract.[90] While mitral regurgitation due to outflow obstruction is usually mild-to-moderate in HCM, it may occasionally be much more severe when associated with primary intrinsic abnormalities of the valve (e.g., myxomatous mitral valve with prolapse).[106] Although outflow obstruction is due to mitral systolic anterior motion in most patients with HCM (>95 percent)-with septal contact usually effected by the anterior leaflet and only occasionally by the posterior leaflet preferentially[103]-a small subset of patients demonstrate a peak systolic outflow gradient due primarily to muscular midcavity obstruction; such gradients may result from anomalous papillary muscle insertion directly into the anterior mitral leaflet[19] (Fig. 67-10) or from other forms of muscular apposition, which in some instances are associated with segmental apical or more generalized ventricular hypokinesia.[107]

In infants and young children with HCM, obstruction to right ventricular outflow is common and occurs in association with subaortic obstruction.[54,55,95,108] Right ventricular outflow obstruction in HCM is produced by greatly hypertrophied right ventricular musculature (crista supraventricularis, moderator band, or trabeculae), reflecting an excessive hypertrophic process, and projecting into the relatively small outflow tract.[109]

Diastolic Dysfunction

Echocardiographic, Doppler, contrast, or radionuclide angiographic and hemodynamic studies of left ventricular diastolic function have identified characteristic abnormalities in relaxation and filling that are present in about 80 percent of patients with HCM[1,3,4,6,92,93,99,110-113] and are presumed to have an important role in the genesis of fatigue, exertional dyspnea, and angina pectoris. Therefore, considering the overall HCM disease spectrum, diastolic dysfunction is probably the single most important pathophysiologic mechanism responsible for symptoms. Prior studies have shown that the early filling phase of diastole is significantly prolonged and associated with a decreased rate and volume of rapid filling.[1,4,92,93] Associated with this alteration is a compensatory increase in the contribution of late diastolic filling associated with atrial systole.[1,4,92,93] Diastolic dysfunction may occur in the absence or presence of symptoms or outflow obstruction and appears unrelated to the severity or distribution of left ventricular hypertrophy.[92,113,]

Myocardial Ischemia

There is abundant evidence that myocardial ischemia occurs in HCM as part of the underlying cardiomyopathic process and unrelated to atherosclerotic coronary artery disease.[1,3,69,70,91,114] For example, the presence of regional ischemia can be inferred clinically; patients with HCM may have typical angina chest pain and ECG abnormalities consistent with ischemia and infarction.[115,116] Furthermore, when patients with HCM and a history of anginal chest pain undergo right atrial pacing, the characteristic chest pain usually develops, the induced increase in coronary flow is reduced, and lactate is frequently produced.[91] Also, such patients may have fixed or exercise-induced reversible thallium-201 defects indistinguishable from those of patients with myocardial ischemia secondary to coronary artery disease.[75] Nevertheless, it has proven exceedingly difficult to measure or quantitate precisely the extent and location of such ischemia or to consistently derive clinical correlations or prognostic information for this finding.[110]

Myocardial ischemia and impaired vasodilator reserve in HCM may be due to several potential mechanisms: (1) compromised coronary blood flow to the left ventricular myocardium because of

abnormal intramural coronary arteries (i.e., "small vessel disease"); (2) excessive myocardial oxygen demand that exceeds the capacity of the coronary system to deliver oxygen; or (3) prolonged diastolic relaxation, resulting in elevated myocardial wall tension.

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

ELECTROCARDIOGRAPHIC FEATURES

The 12-lead ECG is abnormal in about 90 percent of patients with HCM and shows a wide variety of patterns, often bizarre in appearance.[2,4,48-50,116] However, no particular ECG alteration is characteristic of most patients with HCM; common abnormalities are increased precordial voltages consistent with left ventricular hypertrophy, ST-segment changes and T-wave inversion, left atrial enlargement, abnormally deep Q waves, and diminished or absent R waves in the right precordial leads. Infants and young children often have the paradoxic finding of right ventricular hypertrophy on ECG, which may reflect obstruction to right ventricular outflow.

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

PREPARTICIPATION SCREENING FOR HCM IN ATHLETIC POPULATIONS

Detection of preexisting cardiovascular abnormalities (such as HCM) with the potential for significant morbidity or sudden death during intense physical activity is an important objective of the widespread practice of preparticipation screening of high school[117,118] and college-aged athletes.[119] In the United States, customary screening practice dictates a personal and family history and physical examination.[117-119] However, under the conditions of standard screening, it is difficult to identify or raise the suspicion of HCM, given that the vast majority of patients have the nonobstructive form of the disease with either no or only a soft systolic heart murmur, and that historical clues such as syncope or family history of sudden death are also uncommon.[1m118] Ideally, the detection of HCM would be enhanced by the incorporation of noninvasive testing during screening, such as 12-lead ECG[120] or echocardiography.[118] However, cost-efficacy and other considerations make the routine application of such tests impractical throughout the United States.[118] Echocardiographic screening for HCM is also limited by the frequency of borderline wall-thickness measurements (and the uncertainty and anxiety created by such findings), as well as the fact that the HCM phenotype may not always be detectable with echocardiography prior to about age 16.[35]

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NATURAL HISTORY INCLUDING SUDDEN CARDIAC DEATH

HCM may be identified clinically at virtually any age, from infancy to old age (with even a few patients >90 years of age). Understanding the clinical course of HCM, particularly when viewed in the context of predicting outcome for individualpatients, has for 40 years been constrained by three obstacles:(1) uncommon occurrence of the disease (i.e., 0.2 percent inthe general population)[26]; (2) heterogeneity of disease expression[1-22,29,32-34,37-46,58-62,77-83,121]; and (3) tertiary center referral bias.[28,122,123]

Indeed, because much of the considerable published literature on HCM is based on studies performed at tertiary referral centers,[28,124-130] the overall clinical picture of HCM that has emerged is profoundly influenced by the biases created by highly selective patient referral patterns,[28,122,123] which has led to an overestimation of the overall risk for premature death and morbidity. This concept is substantiated by the fact that annual mortality figures from such referral centers are considerably higher (3 to 4 percent and up to 6 percent in children)[108,125,126,128,129] than those more recently reported in relatively unselected regional populations (about 1 percent per year).[122,131-136] Indeed, patient referral patterns are probably the strongest determinants of our prevailing perceptions regarding the clinicalexpression and impact of HCM.[122,123]

In general terms, it is reasonable to characterize HCM as a complex disorder capable of important clinical consequences, including causing premature death in some patients. However, the disease has a more favorable overall clinical course than previously thought, as many patients achieve normal life expectancy with little or no disability and often without the aid of therapeutic interventions. These observations emphasize the need to provide many HCM patients, including many children, with reassurance regarding their clinical outlook, as well as prudence concerning possible adverse consequences.

On the other hand, when HCM is viewed in terms of patient subgroups (rather than the overall disease), some individuals are clearly at much higher risk and may be subject to three modes of death: (1) sudden and unexpected, often in the young; (2) progressive heart failure in midlife; and (3) stroke associated with atrial fibrillation, largely in the elderly.

While frequent in children and young adults, sudden death is not confined to these age groups and may also occur in midlife and beyond, without a statistically significant predilection for any particular age group. Therefore the potential risk period in HCM is particularly long. However, reports of sudden death in infants and very young children are exceedingly rare. Sudden death in HCM usually occurs in previously asymptomatic (or only mildly symptomatic) patients, and such catastrophes are often the first clinical manifestation of the disease.[124] Although most patients die in the morning hours[137] while engaged in sedentary pursuits or during mild exertion, a substantial proportion collapse during or just after vigorous physical activity.[86,124] The latter observation-as well as the fact that HCM is the most common cause of sudden death among young competitive athletes[86] (Fig. 67-13)-supports the view that intense physical activity can act as a trigger for sudden death in the presence of underlying cardiovascular disease.[138] Therefore it is prudent to recommend the disqualification of young athletes with HCM from intense competitive sports, in

accord with the standards of the 26th Bethesda Conference,[89] in an effort to decrease the risk of exercise-related sudden death.

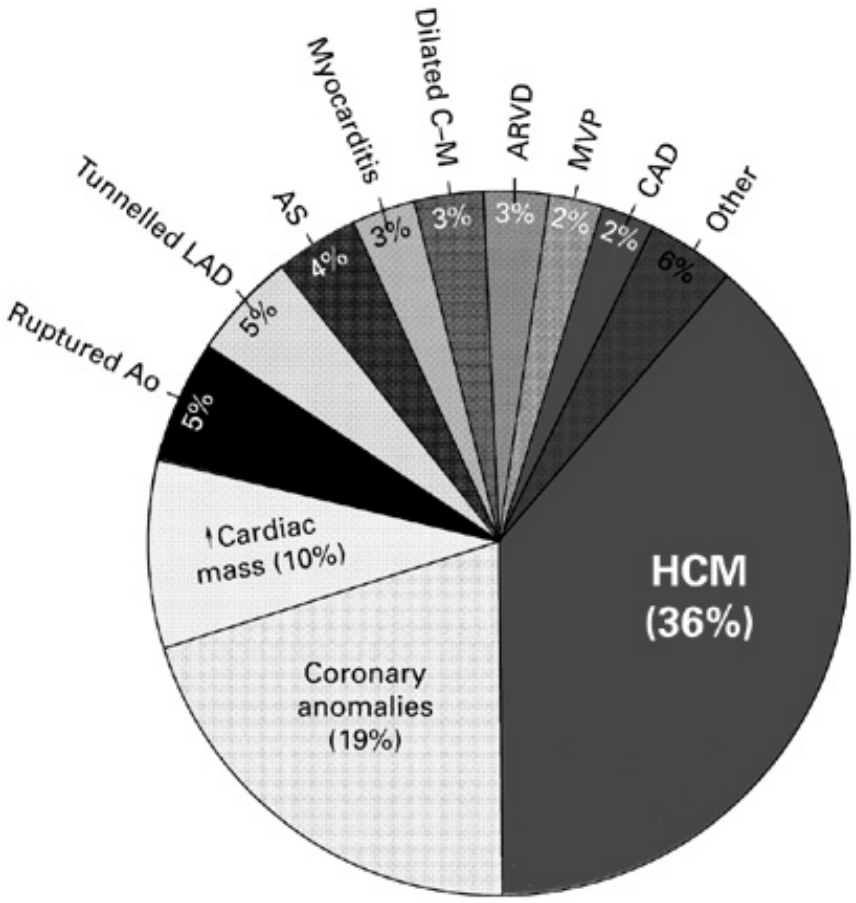

Figure 67-13: Causes of sudden cardiac death in young competitive athletes (median age, 17), based on systematic tracking of 158 athletes in the United States, 1985 to 1995. In an additional 2 percent, no evidence of cardiovascular disease sufficient to explain death was found at necropsy; ↔(increased) cardiac mass = hearts with increased weight and some morphologic features consistent with (but not diagnostic of) HCM. Ao = aorta; LAD = left anterior descending coronary artery; AS = aortic stenosis; C-M = cardiomyopathy; ARVD = arrhythmogenic right ventricular dysplasia; MVP = mitral valve prolapse; CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy. (Adapted from Maron BJ et al.[86] with permission of Lippincott Williams & Wilkins.)

Based on stored electrogram data from HCM patients experiencing appropriate implantable cardioverter-defibrillator discharges, ventricular tachycardia/fibrillation appears to be the primary mechanism most commonly responsible for sudden death in HCM,[74] although a number of other mechanisms may also be involved.[139-146] No particular symptom complex has been shown to be reliably associated with subsequent sudden death in HCM with the exception of recurrent or exertional syncope, particularly in the young.[5] Furthermore, patients with or without subaortic obstruction may die suddenly, and some patients appear to tolerate marked outflow obstruction for virtually their entire lives without adverse consequences.[122] Indeed, the presence or magnitude of the outflow gradient has not been independently associated with increased risk for sudden death, although an association with heart failure-related or total cardiovascular mortality has been cited.[122,136,148]

However, other disease variables have been associated with an increased likelihood of sudden death. The most important of these proposed risk factors include[1,5,8,9,22,38,74,82,85,145,147-149] (Fig. 67-14) the following: prior cardiac arrest or sustained ventricular tachycardia, "malignant" genotype or family history of premature HCM death, multiple-repetitive (or prolonged) bursts of nonsustained ventricular tachycardia on ambulatory ECGs, massive degree of left ventricular hypertrophy (wall thickness, ≥30 mm). A hypotensive blood pressure response to exercise may also be informative regarding risk but is encumbered by a low positive predictive accuracy and is much more powerful as a negative predictor of outcome.[139,140]

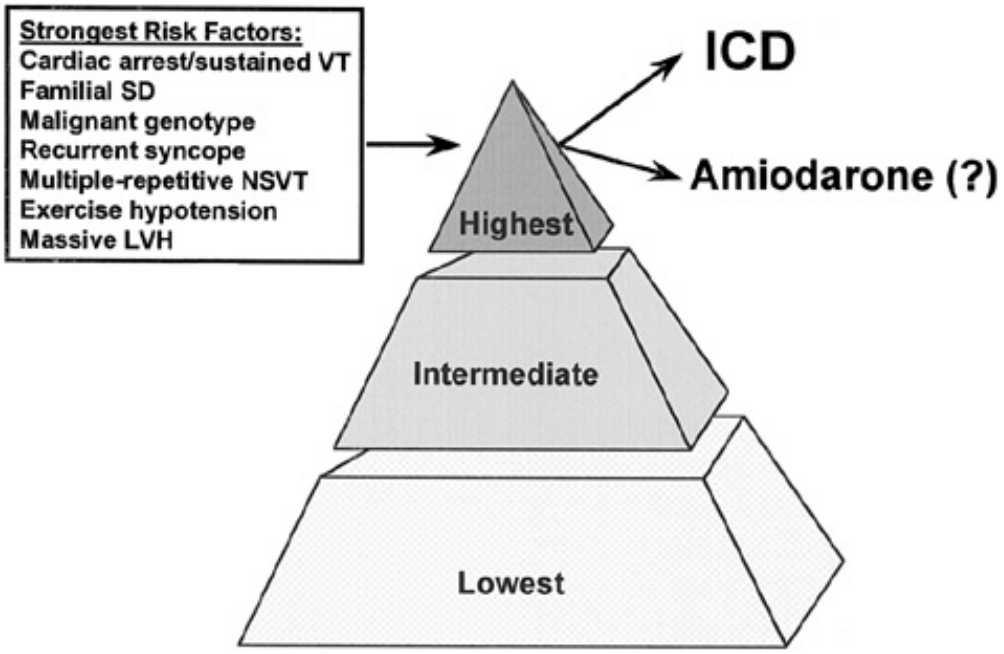

Figure 67-14: Assessment of risk for sudden cardiac death in HCM population. Treatment for the prevention for sudden death is limited to that small subset perceived to be at highest risk compared to all other patients with HCM, based on the presence of ≥1 of the risk factors shown. Patients regarded as low risk are asymptomatic with mild left ventricular hypertrophy and *without* either ventricular tachycardia on ambulatory Holter ECG, hypotensive blood pressure response to exercise, and family history of premature HCM-related death, ICD = implantable cardioverter-defibrillator; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SD = sudden death; VT = ventricular tachycardia. (From Maron,1 with permission of the author and *Lancet*.)

A recent retrospective analysis of children with HCM suggested that an intramural course of a segment of the proximal left anterior descending coronary artery (i.e., myocardial bridging) constitutes a risk factor for sudden cardiac arrest.[145] It was proposed that such muscular bridges could produce systolic coronary arterial narrowing, residual diastolic compression, and myocardial ischemia, thereby justifying surgical unroofing when detected.

The data available at this time do not provide convincing evidence that programmed electrical stimulation has a major role in risk stratification in HCM. Particularly aggressive programmed stimulation protocols with triple ventricular premature depolarizations seldom induce monomorphic ventricular tachycardia but frequently trigger polymorphic ventricular tachycardia or ventricular fibrillation in patients with HCM.[5,150] Based on experience in HCM as well as in coronary artery disease and dilated cardiomyopathy, these latter arrhythmias are generally regarded as nonspecific responses.[5]

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

END-STAGE PHASE

A final phase of disease evolution occurring in about 10 percent of symptomatic patients in a referral-based population has been variously referred to as the "end-stage," "burned-out," or "dilated" phase of HCM[61] (Fig. 67-15). This distinctive clinical course is characterized by progressive congestive symptoms with marked exercise limitation and atrial arrhythmias, associated with substantial left ventricular remodeling-i.e., enlarging left ventricular cavity size (occasionally with marked absolute dilatation), thinning of portions of the wall, systolic dysfunction, and-in a few patients-spontaneous reduction of the subaortic gradient. Therefore, the disease in end-stage patients is transformed from the typical morphologic and functional appearance of HCM (hyperdynamic, hypertrophied, and nondilated left ventricle) to a clinical state that is more suggestive of a dilated form of cardiomyopathy (Chap. 66) in which the thickness of the left ventricular wall may be virtually normal. Many such patients exhibit irreversible myocardial perfusion abnormalities, which undoubtedly represent areas of extensive myocardial scarring.[42,63,69,75]

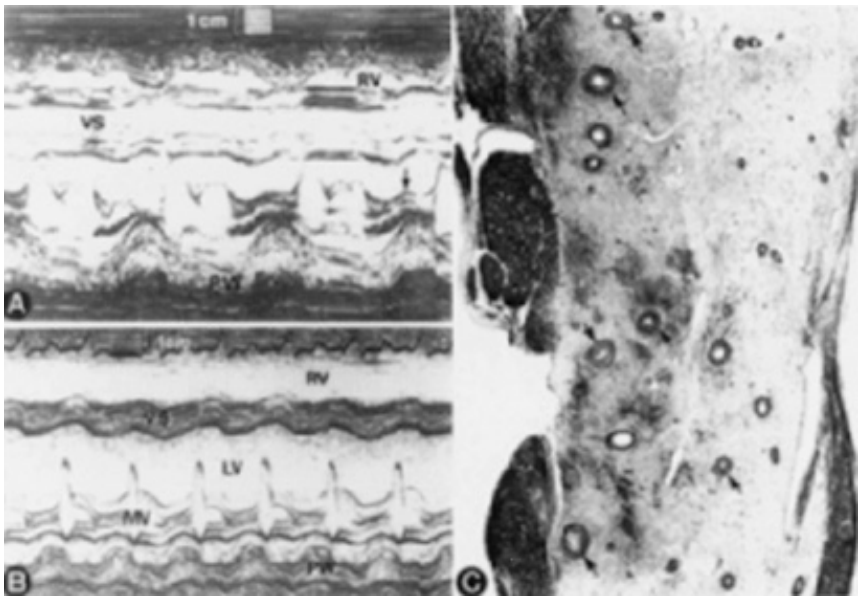

Figure 67-15: Studies in patients with HCM and normal extramural coronary arteries showing changes occurring in association with progressive congestive cardiac failure and transmural myocardial infarction (end-stage phase). *A.* Echocardiographic study from a 26-year-old patient with exertional chest pain and dyspnea. Ventricular septum (VS) is markedly thickened (23 min) and pattern of hypertrophy is asymmetric. Left ventricular end-diastolic dimesion is reduced (38 min), and there is a trivial degree of mitral systolic anterior motion (*arrow*). PW = posterior wall; RV = right ventricular. *B.* From same patient at 30 years of age (9 months before death) after clinical deterioration with progressive cardiac failure, pulmonary edema associated with chronic atrial fibrillation, and cardiopulmonary collapse. Appearance of left ventricular has changed dramatically. Septum has thinned considerably (to 13 mm) and is about as thick as the posterior wall; left ventricular (LV) and right ventricular cavities have enlarged substantially. MV = mitral valve. *C.* Low-power photomicrograph of a specimen from a patient with a clinical course similar

to that of the patient in *A* and *B* showing transmural scarring of the septum and numerous abnormal intramural coronary arteries, some with thickened walls and narrowed lumen (*arrows*) (Magnification ×6). (From Maron BJ et al.3 with permission of the authors and the Massachusetts Medical Society.)

It is possible that the morphologic and functional changes that result in end-stage depression of left ventricular contractile function are due to impaired coronary blood flow and myocardial ischemia resulting from small-vessel coronary artery disease. Patients evolving into the end-stage phase of HCM or experiencing sudden and unexpected cardiac death may coexist in the same family (and share the identical disease-causing mutation).[151] Also, a few patients with aborted episodes of cardiac arrest have themselves died many years later in the end-stage phase.[152]

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HYPERTROPHIC CARDIOMYOPATHY IN THE ELDERLY

Older patients (over age 60 to 65) with morphologic and clinical features consistent with HCM have been reported.[1,21,153,154] In certain of these patients, HCM may be well tolerated to particularly advanced ages (i.e., 80 to 90 years) and therefore should be regarded as a disease compatible with normal longevity. In an unselected HCM population, about 20 percent of patients had achieved the age of ≥75 years.[122] In other elderly patients, symptoms are not present early in life, but severe functional limitation and heart failure may intervene abruptly for the first time after age 60 to 65.[21,153,155] This prolonged period of symptomatic latency is notable for a disease usually expressed morphologically by age 20 and in which symptoms are usually evident by age 40 to 50.

Older patients with HCM differ in many respects from many younger patients with regard to certain morphologic features.[21,153-155,156] Older patients characteristically have relatively small hearts with only modestly increased left ventricular wall thickness (usually 20 mm)[21,62,122,155] and severely distorted outflow tract morphology, with greatly reduced size, and exaggerated anterior displacement of a normal-sized mitral valve. Substantial deposits of calcium in the mitral annular region are frequently present and may contribute to anterior displacement of the valve in some patients. Outflow obstruction often occurs in the presence of restricted mitral valve systolic anterior motion, with contact between ventricular septum and anterior mitral leaflet produced by a combination of anterior excursion of the mitral valve toward the septum and posterior movement of septum toward the mitral valve.[43] It is uncertain whether the HCM phenotype in such older patients always conveys the same genetic etiology as in younger patients; however, some older patients have been documented to carry the same mutant genes encoding sarcomeric proteins characteristic of other (younger) HCM patients.

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

MEDICAL TREATMENT

Asymptomatic Patients and Prevention of Sudden Cardiac Death

Those patients with clear evidence of high risk should be offered treatment for the prevention of sudden cardiac death.[1,5] The implantable cardioverter-defibrillator (ICD) has proved effective and reliable in relatively young and high-risk HCM patients by virtue of sensing ventricular tachycardia/fibrillation and restoring sinus rhythm by appropriate defibrillation shocks or antitachycardia pacing at an overall rate of 7 percent per year.[74] The ICD may be lifesaving,[74,157] both in the context of secondary prevention after cardiac arrest or in sustained ventricular tachycardia (11 percent per year) or for primary (prophylactic) prevention due to the perception of high risk based on ≥1 sudden death risk factors.[74] Alternatively, long-term prophylactic treatment with amiodarone[158] would seem less realistic in relatively young HCM patients, given the potential side effects and the long risk period in HCM as well as the paucity of data substantiating amiodarone as affording effective protection against sudden cardiac death specifically in this disease. Prophylactic and empiric administration of beta blockers or verapamil to asymptomatic patients for the primary purpose of reducing the risk for sudden death, for which there are no or little data, now seems outdated in view of the availability of more definitive therapeutic measures such as the ICD. Drug treatment to prevent or delay progression of congestive symptoms is empiric, with a complete lack of any controlled data.

Alleviation of Symptoms

Therapeutic strategies for symptomatic patients with HCM are summarized in Fig. 67-16. Responses of HCM patients to medical treatment are highly variable; consequently, therapy must often be tailored to the individual requirements of symptomatic patients.[1,5,159] Historically, beta-adrenergic blocking drugs (propranolol or more cardioselective agents such as atenolol, metoprolol, or nadolol) have been utilized extensively to relieve symptoms in patients with either the obstructive or nonobstructive form of HCM.[1,3-6,159] The beneficial effects of beta blockers on symptoms (principally exertional dyspnea and chest pain) and exercise capacity appear to be due largely to decreased heart rate, with consequent prolongation of diastole, increased passive left ventricular filling, and decreased filling pressures. By reducing inotropic state, beta blockers may also lessen myocardial oxygen demand and decrease the left ventricular outflow gradient during exercise when sympathetic tone is increased.

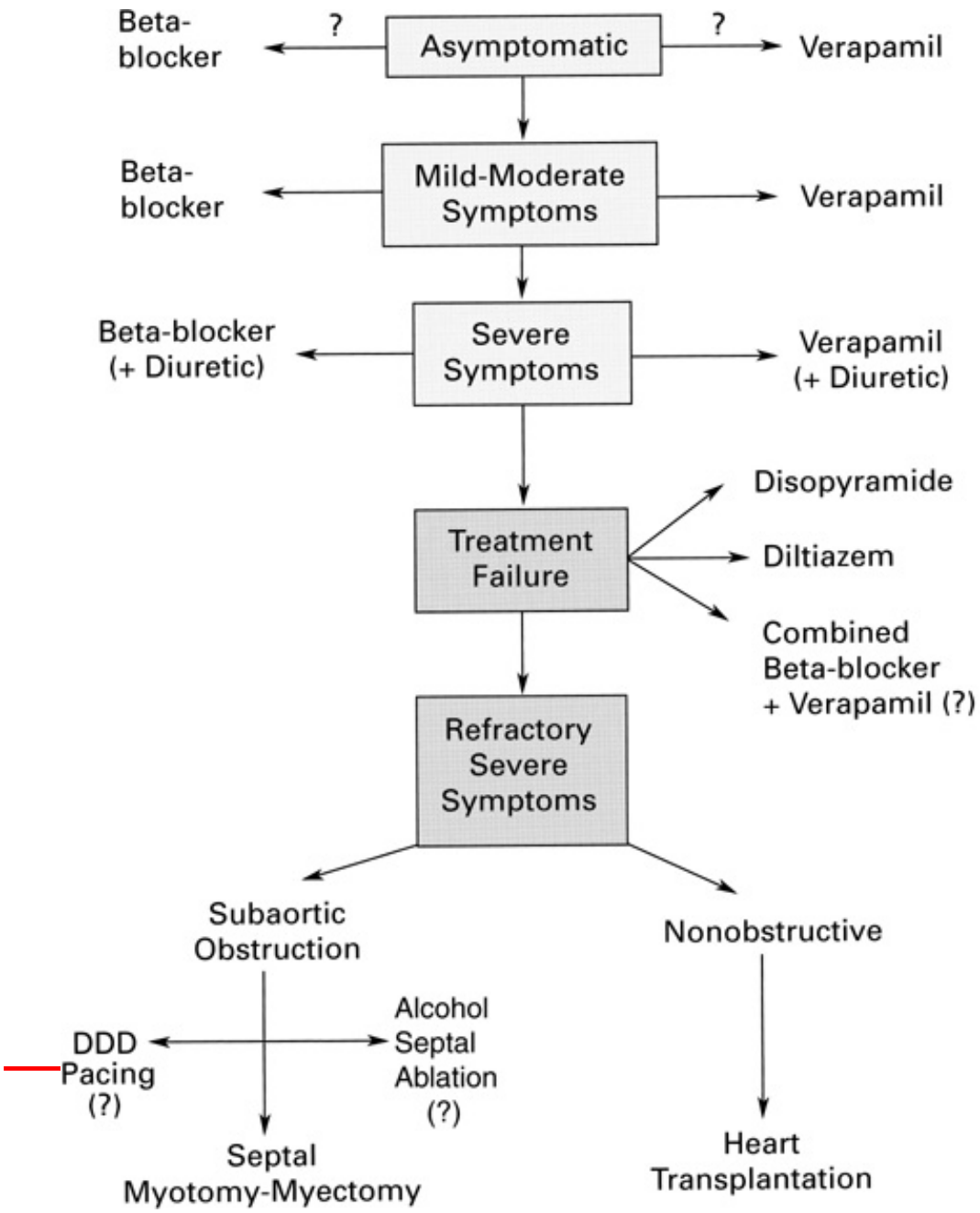

Figure 67-16: Therapeutic strategies for patients with HCM. Question marks indicate treatment recommendations that are largely unresolved.

Calcium channel blockers (principally verapamil) are also important therapeutic agents in the management of symptomatic patients with HCM.[1,160,161] Orally administered verapamil provides improvement in cardiac symptoms and exercise tolerance for many patients with HCM, including those who have failed to benefit from beta blockers. This symptomatic improvement with verapamil appears to be due largely to normalization of left ventricular filling parameters.[1,5]

Beta blockers and verapamil are usually administered empirically at the onset of symptoms by titrating drug dosage to the historical assessment of functional disability, although some investigators utilize exercise testing with or without measurement of oxygen consumption to gauge the effect of medications on symptoms. Furthermore, there is no consensus on the sequence with which beta blockers and verapamil should be administered; usually a trial with one or the other drug is initiated and should a benefit fail to result, the patient is converted to the other drug. Excessive dosages of either a beta blocker or verapamil should be avoided (e.g., >480 mg/day of

verapamil), since such drug levels rarely achieve beneficial results and can incur side effects. There is no evidence that the effect of using beta blockers and verapamil together is superior to that of either drug alone, and this combination should be avoided.

At selected centers, disopyramide has been an alternative medication for patients with obstructive HCM and severe symptoms otherwise unresponsive to standard therapy.[6,162-164] Disopyramide may reduce outflow gradient and improve symptoms by virtue of its negative inotropic properties, although the potential for proarrhythmia has constituted an obstacle to its use in HCM for some investigators. The aforementioned negative inotropic agents have been shown to reduce outflow gradient in HCM by slowing left ventricular ejection acceleration.[164]

Some patients with particularly severe symptoms of heart failure despite treatment with beta blockers or verapamil may show symptomatic improvement with the judicious addition of diuretic agents.[3] The aforementioned therapeutic considerations apply to those patients with HCM in whom symptoms of congestive failure typically occur in the presence of normal or hyperdynamic systolic performance. Conversely, in the subgroup of patients experiencing congestive symptoms secondary to systolic dysfunction (i.e., end-stage HCM)[1,4-6,61,159] therapeutic strategy is similar to that employed for heart failure in other diseases with impaired systolic function, including the use of diuretics, angiotensin-converting enzyme inhibitors, and digitalis; ultimately, heart transplantation should be considered in this subgroup of patients[61,165] (see Chap. 22).

Prevention of Infective Endocarditis

Bacterial endocarditis, a recognized complication of HCM, is virtually confined to patients with the obstructive form of the disease (and mitral valve systolic anterior motion) with a prevalence of about 0.5 percent.[166] Vegetations most commonly involve the anterior mitral leaflet or septal endocardium at the site of mitral valve contact (likely a consequence of the high-velocity outflow jet) and less commonly the aortic valve.[166,167]

Atrial Fibrillation

Atrial fibrillation is a particularly important arrhythmia in HCM,[134,168,169] reportedly occurring in up to about 20 percent of patients followed longitudinally with this disease.[122,134] Atrial fibrillation is associated with an increased risk for systemic thromboembolism, heart failure, and death.[1,3-6] Of note, HCM patients with atrial fibrillation usually show substantial left atrial enlargement but, paradoxically, usually only relatively mild left ventricular hypertrophy.[168] Onset of atrial fibrillation may importantly impair the clinical course in HCM, probably because absence of the atrial systolic contribution to ventricular filling is critical to cardiac function in patients with such poorly compliant ventricles. In many patients, however, chronic atrial fibrillation appears to be reasonably well tolerated as long as ventricular rate is controlled.[169] Beta-adrenergic blocking agents or verapamil are usually efficacious in controlling heart rate in patients with chronic atrial fibrillation. Recurrent atrial fibrillation is managed by restoring sinus rhythm with electrical cardioversion, if necessary, or alternatively by drugs-with amiodarone probably the most effective antiarrhythmic agent for the prevention of recurrent atrial fibrillation. Because of the risk of peripheral embolism and stroke, anticoagulant therapy should be administered (and continued indefinitely) in most patients once atrial fibrillation has been documented.

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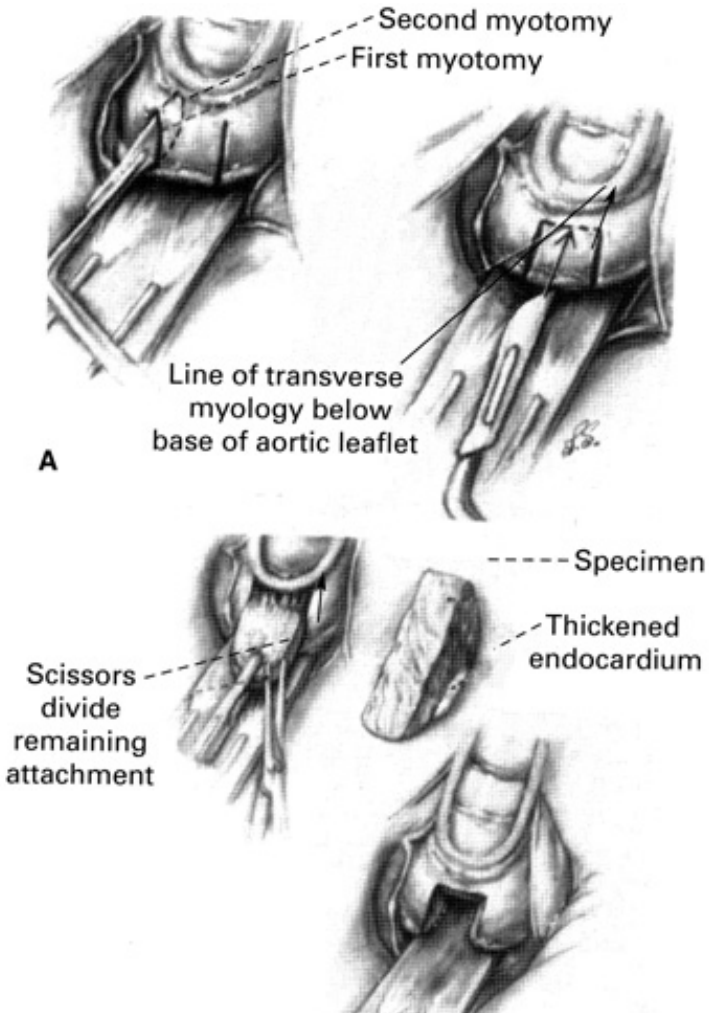
SURGICAL TREATMENT

Operation is regarded as the standard treatment for those HCM patients with obstruction to left ventricular outflow under basal conditions (gradient ≥50 mmHg), and severe drug-refractory symptoms.[1,3-6,159,170-186] Therefore surgery is performed to relieve incapacitating symptoms and subaortic obstruction by normalizing the markedly increased systolic intraventricular pressures.[1,3-6,159,170-186] General agreement is lacking, however, as to whether symptomatic patients with marked outflow gradients-which are present solely or predominantly under provokable conditions such as exercise or with maneuvers in the catheterization laboratory (e.g., isoproterenol infusion, amyl nitrite inhalation, or Valsalva maneuver)-are appropriate operative candidates.[2,4,6,171,179]

Ventricular septal myotomy-myectomy (Morrow operation)[170] (Fig. 67-17) is the surgical procedure of choice; a small amount of muscle is removed from the basal anterior septum (usually about 2 to 6 g) through an aortotomy. However, mitral valve replacement has been employed[177,179,184] in selected patients when the operative site for muscular resection in the basal anterior portion of the septum is relatively thin (i.e., ≤18 mm) or when the distribution of septal hypertrophy is atypical.[179]



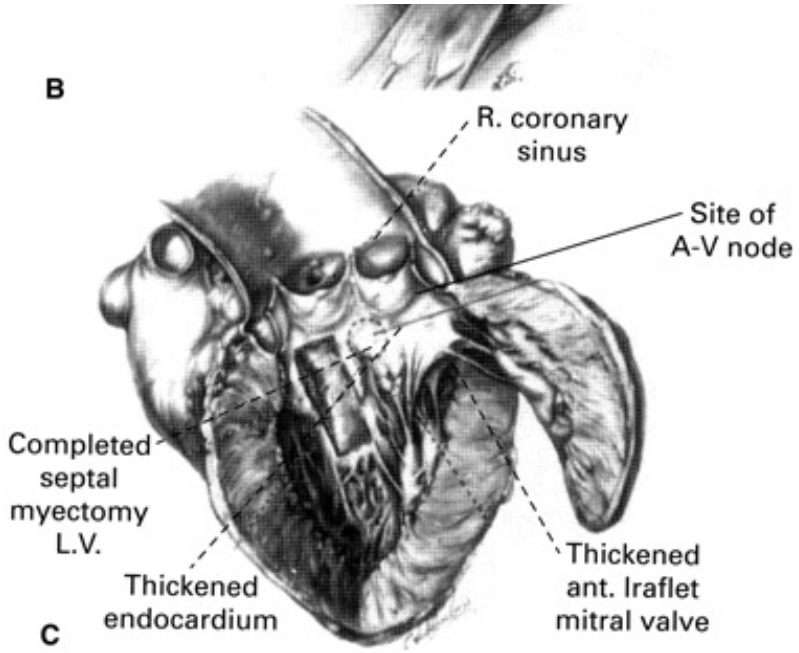


Figure 67-17: Illustration of ventricular septal myotomy-myectomy operation (Morrow procedure). *A.* Two vertical, parallel myotomies are made in the cephalad portion of the septum about 1 cm apart. Transverse incision is then made, connecting the two parallel myotomies. *B.* Attachments of the muscle bar to the septum are divided; this segment of muscle is isolated and then excised. *C.* After completion of the myotomy-myectomy, a rectangular channel about 4 cm long and 2 cm wide is evident extending from the aortic annulus to a point just distal to the caudal margins of the mitral leaflets. (From Maron BJ et al.[176] with permission from the authors and the *European Heart Journal*.)

Occasionally, patients have outflow obstruction from a mechanism other than mitral valve systolic anterior motion. For example, anomalous papillary muscle insertion directly into anterior mitral leaflet without the interposition of the chordae tendineae (Fig. 67-10) producing muscular mid-ventricular obstruction[19] should always be contemplated prior to surgery, since the operative strategy may require a more extensive myectomy[186] or possibly mitral valve replacement.[19] Suture plication of the anterior mitral leaflet (in combination with myotomy-myectomy) has also been introduced in patients judged to have a greatly enlarged mitral valve, so as to reduce the likelihood that mitral valve systolic anterior motion will persist postoperatively.[185]

Intraoperative 2D echocardiography is an important guide to mapping the distribution and magnitude of septal hypertrophy [179,187,188] and determining how the muscle resection should be tailored to the distribution of septal hypertrophy in the individual patient to achieve the desired hemodynamic result and avoid iatrogenic complications such as ventricular septal defect. Transesophageal echocardiography (chap. 13) may also be useful in assessing morphologic and functional abnormalities during surgery, particularly of the mitral valve.[187,188]

Results from a number of North American and European centers employing septal myotomy-myectomy over the past 40 years, in about 2000 patients, have demonstrated salutary hemodynamic as well as symptomatic effects.[1,3-6,159,170-183,189] Operative mortality at the most experienced centers has improved over the past several years and is presently less than 1 to 2 percent.[1,5] Older patients with associated cardiac lesions, such as coronary artery disease requiring bypass grafting, may be at greater operative risk.[190]

Several important effects of operation have been defined in patients with HCM.[1,3-6,159,170-183,189] First, in more than 90 percent of patients, myotomy-myectomy (or mitral valve replacement)

abolishes or substantially reduces the basal subaortic gradient and mitral valve systolic anterior motion without importantly compromising left ventricular function; this consequence of surgery appears to be permanent, with no evidence that the gradient recurs postoperatively or that spontaneous growth of septal musculature recurs in the area of the resection. Second, the reduction in left ventricular systolic pressure is associated with a significant and persistent improvement in symptoms and exercise capacity in 70 percent of patients ≥5 years after operation as well as with a demonstrable increase in myocardial oxygen consumption and improvement in lactate metabolism.[191]

In a minority of patients, even after surgical relief of outflow obstruction, symptoms may nevertheless return (presumably due to persistently impaired left ventricular filling or ischemia, atrial fibrillation, or conduction abnormalities), and premature cardiac death can still ensue many years postoperatively.[189,191] Traditionally, surgery has not been recommended for asymptomatic (or mildly symptomatic) patients with outflow obstruction since, in addition to the operative risk, definitive evidence is lacking that prophylactic relief of outflow obstruction prolongs survival, diminishes risk for sudden death, or mediates the development of symptoms.

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

ALTERNATIVES TO SURGERY

Dual-Chamber Pacing

Although the septal myotomy-myectomy operation is the first therapeutic option for severely limited patients without obstructive HCM, perhaps the major limitation of surgery is the restricted availability of surgeons with the necessary experience to readily afford patients with low operative mortality and a high expectation of hemodynamic and symptomatic success with myotomy-myectomy. In addition, some patients are not ideal surgical candidates, either due to advanced age, insufficient personal motivation, or a limiting medical disability unrelated to HCM. Therefore it is a reasonable aspiration to develop and pursue alternatives to operation for this small but important subgroup of patients. However, proper patient selection for such procedures is a paramount consideration.

Over the past several years there has been some interest in the application of permanent dual-chamber pacing, as an alternative to operative intervention, for severely symptomatic patients with obstructive HCM who are refractory to drug therapy.[192-194] Observational and uncontrolled studies have reported pacing to be associated with reduction in outflow gradient and amelioration of symptoms in many patients over relatively short time periods.[172-174] However, this reported symptomatic benefit has not been consistently accompanied by improved exercise tolerance documented by objective parameters (e.g., treadmill exercise duration and measured oxygen consumption). Randomized, double-blind, crossover pacing studies have shown that the subjectively perceived symptomatic improvement reported by patients is largely due to a placebo effect.[195-197] In addition, the effect of pacing on outflow gradient and symptoms is variable and reduction in obstruction is often much more modest than that achieved with surgery.[196,198] Other laboratory catheterization studies report dual-chamber pacing to have deleterious effects on left ventricular systolic and diastolic function.[199-201] For these reasons and because the underlying HCM disease process and the risk for sudden death do not appear to be altered by permanent dual-chamber pacing, this potential treatment modality cannot be regarded as a primary treatment for the diverse clinical and functional spectrum of HCM.[196] However, there may well be a therapeutic role for certain subsets of patients with this disease.[196,201] In one randomized study, those patients ≥65 years old showed the most convincing benefit from pacing.[196]

Alcohol Septal Ablation

A second, recently introduced potential alternative to surgery is alcohol septal ablation, in which about 2 mL of alcohol is injected directly into the first septal perforator coronary artery for the purpose of producing an MI, septal thinning, and reduced mitral valve systolic anterior motion.[202-205] This procedure is intended to mimic the morphologic and functional consequences of ventricular septal myotomy-myectomy. At present the septal ablation technique is associated with a risk similar to that of surgery but is capable of producing a substantial reduction in the basal gradient. As yet, there is little objective substantiation for the improvement in symptoms reported by many patients over short-term follow-up. This is of particular importance in assessing symptomatic and functional changes for a disease in which pathophysiology is complex and symptoms are variable, often difficult to assess by history, and subject to a placebo effect.[196] As is the case with pacing, alcohol ablation should not be regarded as a primary treatment for the

disease or one capable of reducing the risk of sudden death. Indeed, there is concern[206,207] that this intervention could paradoxically increase the future long-term risk for life-threatening ventricular tachyarrhythmias and sudden death-a risk directly attributable to the intramyocardial scar produced by alcohol ablation (which is not present following myotomy-myectomy) in a patient population that already harbors an arrhythmogenic substrate and often a particularly long period of risk.

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Chapter 67: HYPERTROPHIC CARDIOMYOPATHY

List of Figures

Figure 67-6: Variability of patterns of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy, shown in a composite of diastolic stop-frame images in the parasternal short-axis plane. *A, B,* and *D.* Wall thickening is diffuse, involving substantial portions of ventricular septum and free wall. At the papillary muscle level (*A*), all segments of the left ventricular wall are hypertrophied, including the posterior free wall (PW), but the pattern of thickening is asymmetric, with the anterior portion of ventricular septum (VS) massive (i.e., 50 mm). *B.* Hypertrophy is diffuse, involving three segments of the left ventricle but with the posterior wall spared and thin (<10 mm) (*arrowheads*) and with particularly abrupt changes in wall thickness evident (*arrows*). *C.* Marked hypertrophy in a pattern distinctly different from that in *A, B,* and *D,* in which the thickening of the posterior wall is predominant and the ventricular septum is of nearly normal thickness. *D.* Diffuse distribution of hypertrophy involving three segments of the left ventricle similar to that in *B* but without sharp changes in the contour of the wall. *E.* Hypertrophy predominantly of lateral free wall (*arrows*) and only a small portion of the contiguous anterior septum (*arrowheads*). *F.* Hypertrophy predominantly of posterior ventricular septum (PVS) and, to a lesser extent, the contiguous portion of the anterior septum. *G.* Thickening of anterior and posterior septum to a similar degree but with sparing of the free wall. Calibration dots are 1 cm apart. AML = anterior mitral leaflet; LVW = lateral free wall; PML = posterior mitral leaflet. (From Klues HG et al.[18] with permission from the authors and publisher.)

Figure 67-7: Criteria used to distinguish HCM from athlete's heart when left ventricular (LV) wall thickness is within the shaded gray zone of overlap, consistent with both diagnoses. *Assumed to be the nonobstructive form, since substantial mitral valve systolic anterior motion would confirm, per se, the diagnosis of HCM in an athlete. †May involve a variety of abnormalities, including heterogeneous distribution of LV hypertrophy in which adjacent regions may be of greatly different thicknesses, with sharp transitions evident between segments; also, asymmetric patterns in which anterior ventricular septum is spared from the hypertrophic process and the region of predominant thickening may be in the posterior septum or anterolateral or posterior free wall. ↓ = decreased; LA = left atrial. (From Maron BJ et al.[52] with permission from the authors and Williams & Wilkins.)

Figure 67-8: Development and progression of left ventricular hypertrophy in children with HCM. *Upper panel:* Development of marked hypertrophy of the anterior basal ventricular septum (VS). M-mode echocardiograms shown here were obtained at the same cross-sectional level in a girl with a family history of HCM. At age 11, ventricular septal thickness was at upper limit of normal (10 mm); at age 15, septal thickness had increased markedly (to 33 mm), and appearance of the echocardiogram is typical of HCM. The patient remained asymptomatic throughout this period of time but died suddenly and unexpectedly at age 17. PW = posterior left ventricular free wall. *Lower panel:* Dynamic, striking changes in left ventricular wall thickness with age in 22 children; each patient is represented by the left ventricular segment that showed the greatest change in wall thickness. Open symbols denote 5 patients who had no evidence of hypertrophy in any segment of the left ventricle at the initial evaluation but subsequently developed de novo hypertrophy typical of HCM. (From Maron BJ et al.[35] with permission of the authors and the Massachusetts Medical Society.)

Figure 67-9: Mitral valves from three patients with obstructive HCM, aged 31, 29, and 60 years (I, II, and III), and from a normal control patient without cardiovascular disease (IV), showing variation in valvular size and structure present in HCM. Valves are opened with the circumference displayed in a horizontal orientation, exposing the atrial surface, with annular margin to top and chordal attachments to bottom. *I.* Large valve (area 22 cm2) in which both the anterior (A) and posterior (P) leaflets are greatly elongated and increased in area. *II.* Large valve in which increased valve size (area 18 cm2) is due primarily to elongation and enlargement of the anterior leaflet (A). *III.* Segmental elongation and increased area confined to a scallop of posterior leaflet. (From Klues HG et al.[20] with permission of the authors and Lippincott Williams & Wilkins.)

Figure 67-10: Anomalous papillary muscle insertion directly into anterior mitral leaflet (*AML*) in patient with obstructive HCM. *A. Before myotomy-myectomy:* parasternal long-axis echocardiogram shows AML in direct continuity with the hypertrophied anomalous anterolateral papillary muscle (*APM*), which displaced anteriorly within the left ventricular cavity, producing a long area of midcavity muscular contact with the ventricular septum (VS) and outflow obstruction (*arrows*); tips of the mitral leaflets coapt in the usual position, and typical systolic anterior motion is absent (*small arrows*). *B. After myotomy-myectomy:* Long-axis echocardiogram shows extensive muscular resection (*), extending from base of the septum to beyond the distal margins of the anterior mitral leaflet; nevertheless, a large area of direct muscular contact remains after operation between papillary muscle and ventricular septum (*arrowheads*), which is responsible for persistent and marked obstruction to left ventricular outflow. *C.* Mitral valve specimen excised at operation; a massively hypertrophied anterolateral anomalous papillary muscle (*arrow*) inserted directly into the body of the anterior leaflet. Ao = aorta; LA = left atrial; LV = left ventricle. (From Klues HG et al.[19] with permission of the authors and Lippincott Williams & Wilkins.)

Figure 67-11: Pedigree of HCM family with a myosin-binding protein C mutation and variable penetrance. The genetically affected 42-year-old woman (II.2) is both the offspring of an affected parent (I.2), the mother of a 16-year-old affected child (III.4), and the sister of an affected 40-year-old sibling (II.3). In contrast to her father, child, and sister, this woman (II.2) showed no evidence of left ventricular hypertrophy and the HCM phenotype by two-dimensional echocardiography (or 12-lead ECG).

Figure 67-12: Age-related penetrance of familial HCM caused by mutations in the genes for cardiac myosin-binding protein C, cardiac troponin T, and cardiac β-myosin heavy chain. Solid bars denote the percentage of persons with both cardiac myosin-binding protein C mutations and left ventricular hypertrophy. Comparable clinical data for cardiac troponin T and β-myosin heavy chain are shown. Significant differences in the penetrance of familial HCM caused by cardiac myosin-binding protein C mutations and by mutations in cardiac troponin T or cardiac β-myosin heavy chain are indicated as follows: * = $p < 0.05$; = $p < 0.005$; $fy2$æ = $p < 0.001$. (From Niimura H et al. [10] with permission of the authors and the Massachusetts Medical Society.)

Figure 67-13: Causes of sudden cardiac death in young competitive athletes (median age, 17), based on systematic tracking of 158 athletes in the United States, 1985 to 1995. In an additional 2 percent, no evidence of cardiovascular disease sufficient to explain death was found at necropsy; ↔(increased) cardiac mass = hearts with increased weight and some morphologic features consistent with (but not diagnostic of) HCM. Ao = aorta; LAD = left anterior descending coronary artery; AS = aortic stenosis; C-M = cardiomyopathy; ARVD = arrhythmogenic right ventricular dysplasia; MVP = mitral valve prolapse; CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy. (Adapted from Maron BJ et al.[86] with permission of Lippincott Williams & Wilkins.)

Figure 67-14: Assessment of risk for sudden cardiac death in HCM population. Treatment for the prevention for sudden death is limited to that small subset perceived to be at highest risk compared to all other patients with HCM, based on the presence of ≥1 of the risk factors shown. Patients regarded as low risk are asymptomatic with mild left ventricular hypertrophy and *without* either ventricular tachycardia on ambulatory Holter ECG, hypotensive blood pressure response to exercise, and family history of premature HCM-related death, ICD = implantable cardioverter-defibrillator; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SD = sudden death; VT = ventricular tachycardia. (From Maron,1 with permission of the author and *Lancet*.)

Figure 67-15: Studies in patients with HCM and normal extramural coronary arteries showing changes occurring in association with progressive congestive cardiac failure and transmural myocardial infarction (end-stage phase). *A.* Echocardiographic study from a 26-year-old patient with exertional chest pain and dyspnea. Ventricular septum (VS) is markedly thickened (23 min) and pattern of hypertrophy is asymmetric. Left ventricular end-diastolic dimesion is reduced (38 min), and there is a trivial degree of mitral systolic anterior motion (*arrow*). PW = posterior wall; RV = right ventricular. *B.* From same patient at 30 years of age (9 months before death) after clinical deterioration with progressive cardiac failure, pulmonary edema associated with chronic atrial fibrillation, and cardiopulmonary collapse. Appearance of left ventricular has changed dramatically. Septum has thinned considerably (to 13 mm) and is about as thick as the posterior wall; left ventricular (LV) and right ventricular cavities have enlarged substantially. MV = mitral valve. *C.* Low-power photomicrograph of a specimen from a patient with a clinical course similar to that of the patient in *A* and *B* showing transmural scarring of the septum and numerous abnormal intramural coronary arteries, some with thickened walls and narrowed lumen (*arrows*) (Magnification ×6). (From Maron BJ et al.3 with permission of the authors and the Massachusetts Medical Society.)

Figure 67-16: Therapeutic strategies for patients with HCM. Question marks indicate treatment recommendations that are largely unresolved.

Figure 67-17: Illustration of ventricular septal myotomy-myectomy operation (Morrow procedure). *A.* Two vertical, parallel myotomies are made in the cephalad portion of the septum about 1 cm apart. Transverse incision is then made, connecting the two parallel myotomies. *B.* Attachments of the muscle bar to the septum are divided; this segment of muscle is isolated and then excised. *C.* After completion of the myotomy-myectomy, a rectangular channel about 4 cm long and 2 cm wide is evident extending from the aortic annulus to a point just distal to the caudal margins of the mitral leaflets. (From Maron BJ et al.[176] with permission from the authors and the *European Heart Journal*.)

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Part 11: CARDIOMYOPATHY AND SPECIFIC HEART MUSCLE DISEASES
Chapter 68:

RESTRICTIVE, OBLITERATIVE, AND INFILTRATIVE CARDIOMYOPATHIES

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RESTRICTIVE CARDIOMYOPATHY

Definition of Restrictive Cardiomyopathy

The World Health Organization (WHO) and World Heart Foundation define cardiomyopathies as heart muscle diseases of unknown etiology and classify them according to hemodynamic and pathophysiologic criteria.[1] Although this definition differentiates primary cardiomyopathies from other pathologic processes that disturb myocardial function-such as ischemic, hypertensive, valvular, and congenital heart diseases-the WHO classification, despite recent modifications, remains controversial. The clinicopathologic classification scheme initially proposed by Goodwin is similar and includes dilated or congestive, hypertrophic, and restrictive forms.[2] *Restrictive cardiomyopathy* refers to either an idiopathic or systemic myocardial disorder characterized by restrictive filling, normal or reduced left ventricular (LV) and right ventricular (RV) volumes, and normal or nearly normal systolic (LV and RV) function. Thus, the clinical and hemodynamic picture thus simulates constrictive pericarditis and is characterized by elevated venous pressure with prominent X and Y descents, a small or normal sized LV, and pulmonary congestion. Restrictive cardiomyopathy may be noninfiltrative or infiltrative and occurs with or without obliteration; infiltration may be interstitial (e.g., amyloid, sarcoid) or cellular (e.g., hemochromatosis).

Restrictive cardiomyopathy has assumed importance in clinical cardiology for several reasons. First, these myocardial disorders epitomize diastolic heart failure; thus, abnormal ventricular diastolic compliance and impaired ventricular filling constitute their central pathophysiologic components and congestion and elevated diastolic pressure are their major clinical and hemodynamic manifestations. Second, the hemodynamic and clinical manifestations may mimic those produced by constrictive pericarditis, which, in contrast to restrictive cardiomyopathy, is a surgically curable disorder. Accordingly, its lack of recognition may have dire consequences. Third, restrictive cardiomyopathy may present with interventricular conduction delays, heart block, or skeletal muscle disease, often making the diagnosis difficult. Fourth, diagnostic criteria for restriction are not universally accepted, and the morphologic spectrum overlaps with hypertrophic cardiomyopathy challenges our traditional concepts of classification.[3] Finally, a comprehensive echo Doppler assessment has become an important, noninvasive means of detecting the pathophysiology, morphology, and prognosis of the restrictive cardiomyopathies.[4,5]

Clinical Features of Restrictive Cardiomyopathy

Involvement of the myocardium (or endomyocardium), and ventricular obliteration, may occur either in isolation or in the setting of systemic or iatrogenic disease (Table 68-1). Thus, in the strictest sense, restrictive cardiomyopathy is not necessarily a primary disease of heart muscle. Irrespective of the etiology, terminology, or the nature of myocardial process, the ventricles are small (generally <110 mL/m^2), and stiff, restricting ventricular filling. Despite normal (or near normal) systolic function, ventricular diastolic, jugular, and pulmonary venous pressures are

increased. Typically, LV filling pressures exceed RV filling pressures by more than 5 mmHg, but equalization of the diastolic pressures and a "square root" dip and plateau of early diastolic pressures of the RV and LV may be seen if the compliances of these chambers are similarly affected. Importantly, the hemodynamics of constrictive pericarditis may be simulated. Moreover, elevated atrial pressures produce symptoms of systemic and pulmonary venous congestion (dyspnea, orthopnea, edema, abdominal discomfort), and relatively underfilled ventricles are responsible for reduced cardiac output and fatigue. In patients with restrictive cardiomyopathy as part of a systemic disorder, cardiac symptoms may dominate or overshadow symptoms referable to other organ systems. Patients with constrictive cardiomyopathy generally have lower RV systolic pressures (<40 mmHg) and an RV end-diastolic pressure greater than one-third of the pressure RV systolic pressure as opposed to patients with restrictive cardiomyopathy but these differences are far from absolute.

Table 68-1: Classification of the Restrictive Cardiomyopathies

Myocardial

1. Noninfiltrative cardiomyopathies
   - Idiopathic
   - Familial
   - Pseudoxanthoma elasticum
   - Scleroderma
2. Infiltrative cardiomyopathies
   - Amyloidosis
   - Sarcoidosis
   - Gaucher's disease
3. Storage disease
   - Hemochromatosis
   - Fabry's disease
   - Glycogen storage diseases

Endomyocardial

1. Obliterative
   - Endomyocardial fibrosis
   - Hypereosinophilic syndrome
2. Nonobliterative
   - Carcinoid
   - Malignant infiltration
   - Iatrogenic (radiation, drugs)

Physical Findings

Physical examination reflects the elevated systemic and pulmonary venous pressure. Striking elevation of the jugular venous pulse and prominent X and especially Y descents are characteristic (see Chap. 10). A *diastolic* arterial pulse, owing to a reduced stroke volume and tachycardia, may be seen in severe cases. The apical impulse is not displaced and systolic murmurs of atrioventricular regurgitation and filling sounds marking the abrupt cessation of rapid early diastolic filling may be present.

Diagnostic/Imaging Studies

Electrocardiographic (ECG) abnormalities such as abnormal voltage, atrial and ventricular arrhythmias, and conduction disturbances are frequent; when restrictive cardiomyopathy is due to amyloid infiltration, low voltage is usual (Fig. 68-1). The chest radiograph usually reveals normal-sized ventricles, although atrial enlargement and pericardial effusion may produce an enlarged cardiac silhouette. Pleural effusions and signs of pulmonary congestion may also be present. Echocardiographic findings are nonspecific but in many cases are useful to exculpate other, more common causes of heart failure.

DIFFERENTIATION FROM CONSTRICTIVE PERICARDITIS

Although several clinical, imaging, and hemodynamic features are helpful in distinguishing restrictive cardiomyopathy from constrictive pericarditis (Table 68-2), considerable overlap and diagnostic confusion exist. The pathophysiologic basis for this distinction includes (1) transmission of intrathoracic pressure to the ventricles (limited by the stiff pericardium in constrictive pericarditis but not in restrictive cardiomyopathy); (2) the principal determinant of the diastolic ventricular pressure-volume relation (ventricular versus pericardial compliance in restrictive cardiomyopathy as compared to constrictive pericarditis, itself); and (3) involvement of the ventricular septum in restrictive cardiomyopathy versus the capacity for ventricular interdependence in constrictive pericarditis.

Table 68-2: Clinical and Hemodynamic Features That Help Distinguish Restrictive Cardiomyopathy from Constrictive Pericarditis

	Restrictive Cardiomyopathy	Constrictive Pericarditis
History	Systemic disease that involves the myocardium, multiple myeloma, amyloidosis, cardiac transplant	Acute pericarditis, cardiac surgery, radiation therapy, chest trauma, systemic disease involving the pericardium
Chest radiograph	Absence of calcification Massive atrial enlargement	Helpful when calcification persistsModerate atrial enlargement
Electrocardiogram	Bundle branch blocks, AV block	Abnormal repolarization
CT/MRI	Normal pericardium	Helpful if thickened (>4 mm) pericardium
Hemodynamics	Helpful if unequal diastolic pressures	Diastolic equilibration
	Concordant effect of respiration on diastolic pressures	Dip and plateau
Biopsy	Fibrosis, hypertrophy, infiltration	Normal

Recently, Doppler techniques (spectral Doppler, color M-mode, and Doppler tissue imaging) have assumed an important role in characterizing the nature of transvalvular filling and in clinically distinguishing between constrictive pericarditis and restrictive cardiomyopathy (see also Chap. 13).[5-7] These Doppler flow patterns and the associated respiratory changes are illustrated in Fig. 68-2. In the *normal subject,* the early filling wave (E) of mitral flow is greater than the late, atrial systolic wave (A), and neither change significantly with respiration. In contrast, the E and A

velocities of tricuspid valve flow increase slightly with inspiration. The deceleration time of the LV early diastolic wave ranges from 150 to 240 ms, and the LV isovolumic relaxation time ranges from 70 to 110 ms. Pulmonary venous flow is generally biphasic, with a dominant wave during systole (S) and a smaller wave during diastole (D); respiratory changes are minimal and atrial systolic reversals are generally small. Hepatic vein flow consists of a larger S and smaller D wave with small reversals (V_r and A_r) after each wave, respectively. With expiration, S and D waves decrease and V_r and A_r increase. Doppler tissue imaging (DTI) shows a prominent longitudinal axis velocity in early diastole (E_a >8 cm/s) and a smaller velocity after atrial contraction (A_a). The slope of early diastolic LV filling on color M-mode (Vp) is >45 cm/s. In the patient with *restrictive cardiomyopathy*, mitral valve flow shows an increased E/A ratio (≥2) with a short (<150 ms) deceleration time and a short (<70 ms) isovolumic relaxation time (a "restrictive" pattern of filling) without respiratory variation. The tricuspid valve flow shows an increased E/A ratio without respiratory variation, a shortened deceleration time, and a short isovolumic relaxation time that shortens further with inspiration. The S/D ratio of pulmonary venous flow is <1, atrial reversals are increased (not shown in Fig. 68-1), and there is little respiratory variation. The S/D ratio of hepatic venous flow is <1 and prominent reversals are seen during inspiration. Doppler tissue imaging shows a striking decrease in E_a (<8 cm/s) and the propagation velocity on color M-mode is <45 cm/s.

In *constrictive pericarditis*, mitral and tricuspid valve flows are also "restrictive," but unlike those in restrictive cardiomyopathy, they display marked respiratory variation. The isovolumic relaxation time shortens during expiration. The S/D of pulmonary venous flow is <1, with increased velocities (especially diastolic) in expiration, resulting in a further decrease in the S/D ratio. In contrast to restrictive cardiomyopathy, hepatic venous flow reversals occur in expiration, early diastolic tissue velocities (E_a) are normal on DTI, and the transmitral propagation velocity is >45 cm/s.

Despite the considerable interest and potential clinical value in the ability to discriminate restrictive cardiomyopathy from constrictive pericarditis, there is no uniform agreement regarding the characteristic features of the Doppler indices, especially those of venous flows. Moreover, rigorous studies of the sensitivity and specificity of these Doppler findings are lacking and relatively few patients have been examined. Thus, the diagnostic certainty is related to the number of "pathognomonic" findings in concert with clinical information and additional imaging studies.

One report suggested that radionuclide ventriculographic indices of LV diastolic function could differentiate constrictive pericarditis and restrictive cardiomyopathy.[8] However, measurements of LV filling-such as the peak filling rate, time to peak filling, and various filling fractions-require careful attention to technical detail. The need for stable heart rates, the lack of venous flows, and the inability to observe the influence of respiration on cardiac blood flows are important limitations of the radionuclide ventriculographic technique.

Magnetic resonance imaging (MRI) and computed tomography (CT) are useful for accurately assessing pericardial thickness (Fig. 68-3); a pericardium >4.0 mm thick can distinguish the two entities (see also Chap. 18A).[9] Recent preliminary data suggest that constrictive pericarditis is associated with severe autonomic dysfunction that involves all segments of the autonomic nervous system, whereas in restrictive cardiomyopathy the autonomic dysfunction is localized to the parasympathetic efferent pathway.[10] Invasive hemodynamics may be helpful (below), and occasionally a histologic diagnosis is necessary.

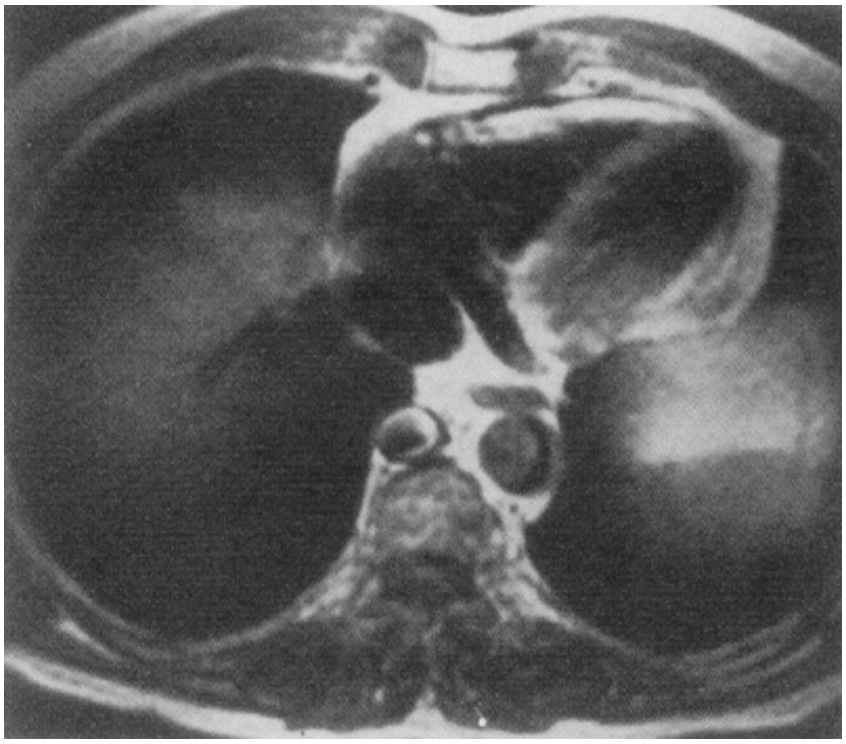

Figure 68-3: Magnetic resonance image showing normal pericardium as a low-intensity (*black*) line anterior to the right ventricle between high-intensity (*white*) epicardial and mediastinal fat. (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:588. Reproduced with permission.)

It is important to remember that clinical and laboratory testing, including imaging and pathologic studies, may produce results consistent with mixed constrictive pericarditis and restrictive cardiomyopathy; indeed, the two entities may coexist [for example, after mediastinal irradiation or after coronary artery bypass grafting (CABG)]. In these cases, a decision to treat conservatively or surgically explore a patient requires experienced clinical judgment.

Cardiac Catheterization

Most patients in whom restrictive cardiomyopathy is a serious consideration should undergo right- and left-sided heart catheterization to document the diagnosis, assess severity, and, in some patients, establish the etiology by means of endomyocardial biopsy. As in patients with constrictive pericarditis, extra care must be taken to obtain high-quality pressure recordings with appropriate gain and optimal damping conditions, and to attend to details such as the transducer height and system calibration. The venous pressure is elevated and the deep and rapid fall of the right atrial Y descent is striking. During inspiration, the descent of the V wave in the right atrium becomes deeper, steeper, and more pointed, whereas the other waves of the venous pulse and the mean atrial pressure do not vary throughout the respiratory cycle.[11] The RV systolic pressure is often within the range of 35 to 45 mmHg, and the early portion of diastole is characterized by a deep, sharp dip followed by a plateau, during which no further increase in RV pressure occurs (Fig. 68-4). These hemo dynamic features are identical to those of constrictive pericarditis and may cause diagnostic confusion. There is usually only modest pulmonary hypertension and the pulmonary arterial diastolic pressure is a few millimeters higher than the pulmonary wedge pressure, which is often quite elevated. It is not uncommon for the pulmonary wedge and the right atrial pressures to be identical and to simulate further the hemodynamics of constrictive pericarditis; however, a higher LV than RV filling pressure strongly favors the diagnosis of restrictive cardiomyopathy rather than constrictive pericarditis. LV systolic pressure is normal, while the LV diastolic pressure tracing shows the same abnormalities as those of the RV (Fig. 68-

4).

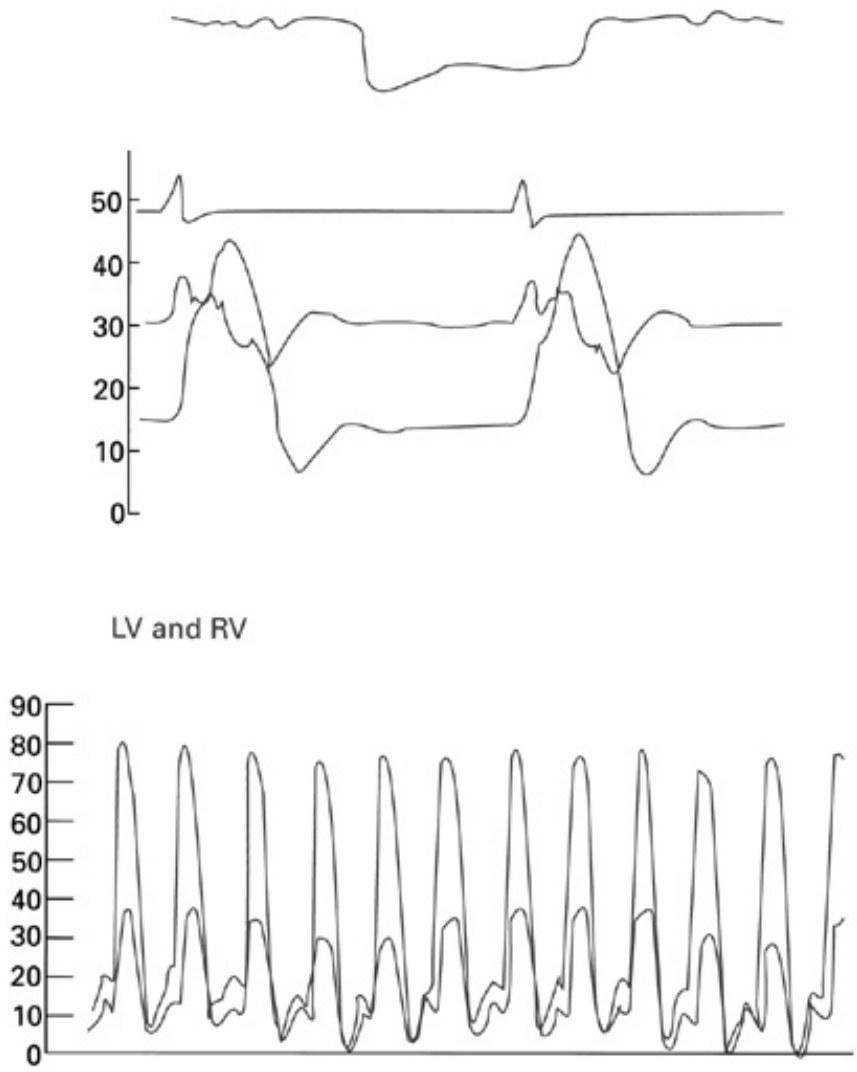

Figure 68-4: *Top:* Right-sided heart hemodynamic data from a patient with amyloidosis recorded with a high-fidelity catheter. From the top tracing down is a respirometer, electrocardiogram, right ventricular (RV) dP/dt, and RV pressure. Note the characteristic dip-and-plateau configuration. *Bottom:* Simultaneous RV and LV pressure tracings from another patient with cardiac amyloidosis. In this patient, the typical dip-and-plateau pattern was not present, but during inspiration LV and RV diastolic pressures equilibrated. (From Shabetai R. Restrictive, obliterative, and infiltrative cardiomyopathies. In: Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2079. Reproduced with permission.)

Left ventriculography usually shows a normal ejection fraction and the absence of major regional wall motion abnormalities. Endomyocardial biopsy is an integral part of the workup of many patients with restrictive cardiomyopathy. When distinction from constrictive pericarditis is particularly difficult, the biopsy may furnish proof of myocardial disease and establish the cause of restrictive cardiomyopathy (e.g., amyloidosis), or (by virtue of unremarkable histology) suggest the need for surgical exploration, even in the absence of a thickened pericardium.

Treatment of Restrictive Cardiomyopathy (General Considerations)

Except in certain instances described below ("Specific Restrictive Cardiomyopathic Diseases"),

the treatment of restrictive cardiomyopathy is empiric and directed toward the treatment of diastolic heart failure. Reduction in the elevated ventricular diastolic pressures produces substantial improvement in pulmonary and systemic congestion, but judicious use of diuretics is warranted in view of the steep pressure-volume relation of the ventricles and the need to maintain a relatively high filling pressure. Vasodilators may also jeopardize ventricular filling and should be used cautiously. Calcium channel blockers are used by some because of their beneficial effect in hypertrophic cardiomyopathies, but improvement in ventricular compliance with their use has not been demonstrated in restrictive cardiomyopathy.

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Chapter 68: RESTRICTIVE, OBLITERATIVE, AND INFILTRATIVE CARDIOMYOPATHIES

SPECIFIC RESTRICTIVE CARDIOMYOPATHIC DISEASES

A useful classification of the restrictive cardiopathies is shown in Table 68-1. This scheme is based upon the cardiac compartment predominantly involved (i.e., myocardial versus endomyocardial) and subdivides the myocardial diseases into the noninfiltrative, infiltrative, and storage and the endomyocardial diseases into obliterative (i.e., endomyocardial fibrosis and the hypereosinophilic syndrome), carcinoid, infiltrative, and iatrogenic.

Myocardial Diseases

NONINFILTRATIVE CARDIOMYOPATHIES

Idiopathic and Familial Restrictive Cardiomyopathy

Recent data suggest that idiopathic restrictive cardiomyopathy may be an autosomal dominant disorder involving myocardium, conduction tissue, and skeletal muscle, with resultant restrictive ventricular filling and heart failure, AV block, and distal skeletal myopathy. Deposition of the intermediate filament desmin has been linked to this syndrome and may represent a distinct pathologic entity; accumulation of desmin immunoreactive material on heart biopsy may be confirmed ultrastructurally.[12,13] Changes in collagen subtypes and matrix metalloproteinase activity may play an important role in the genesis of increased LV stiffness.[14]

Myocyte hypertrophy and fibrosis on endomyocardial biopsy characterize idiopathic restrictive cardiomyopathy, and the absence of myocyte disarray is an important pathologic distinction from hypertrophic cardiomyopathy. However, overlap syndromes characterized by physiologic evidence of restriction and myocyte hypertrophy but without myocyte disarray or LV hypertrophy on echocardiography are reported.[15] Moreover, it was recently postulated that primary restrictive and hypertrophic cardiomyopathies may represent different phenotypic expressions of the same genetic disease.[16] An echocardiographic feature distinguishing primary restrictive cardiomyopathy from cardiac amyloidosis (in addition to the associated clinical features) is the increased LV wall thickness in the latter. In both disorders (and restrictive cardiomyopathies in general), ventricular dimensions are normal or reduced, systolic function is variable, and atrial dimensions are increased.

Two-dimensional and Doppler echocardiography are reliable, noninvasive techniques for diagnosing primary restrictive cardiomyopathy (see Chap. 13).[17] A dominant mitral early diastolic "E" velocity, an increased pulmonary venous atrial systolic "A" reversal velocity and duration, and shortened mitral deceleration time are present in both children and adults with primary restrictive cardiomyopathy (Fig. 68-5). On CT or MRI scans, evidence of restrictive filling (e.g., right atrial and caval enlargement) are common in both restrictive cardiomyopathy and constrictive pericarditis. MRI may differentiate primary restrictive cardiomyopathy from amyloidosis on the basis of tissue characterization.[18]

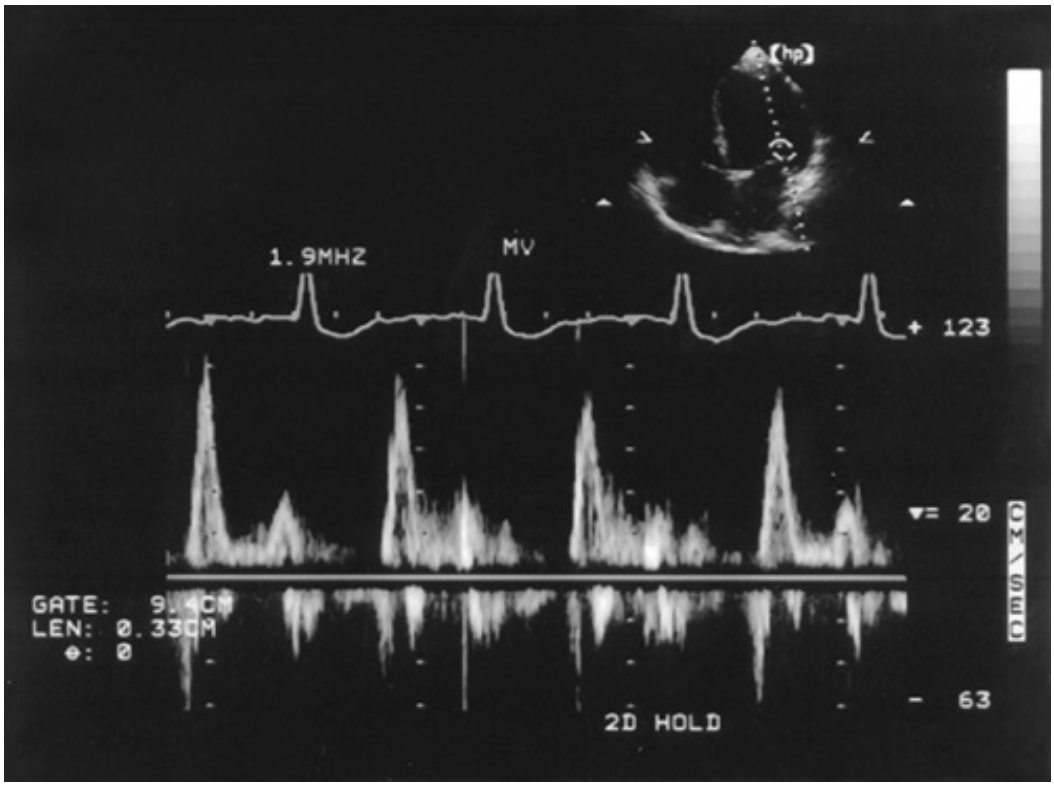

Figure 68-5: Doppler record of mitral inflow velocity from a patient with idiopathic restrictive cardiomyopathy. Note the dominant early diastolic wave. (From Shabetai R. Restrictive, obliterative, and infiltrative cardiomyopathies. In: Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2077. Reproduced with permission.)

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum is a rare, genetically heterogeneous disorder characterized by fragmentation and calcification of elastic fibers involving the skin, eyes, and gastrointestinal and cardiovascular systems. Although endocardial fibroelastosis uncommonly causes restrictive cardiomyopathy (Fig. 68-6), coronary artery disease with premature death is a major problem in these patients.[19]

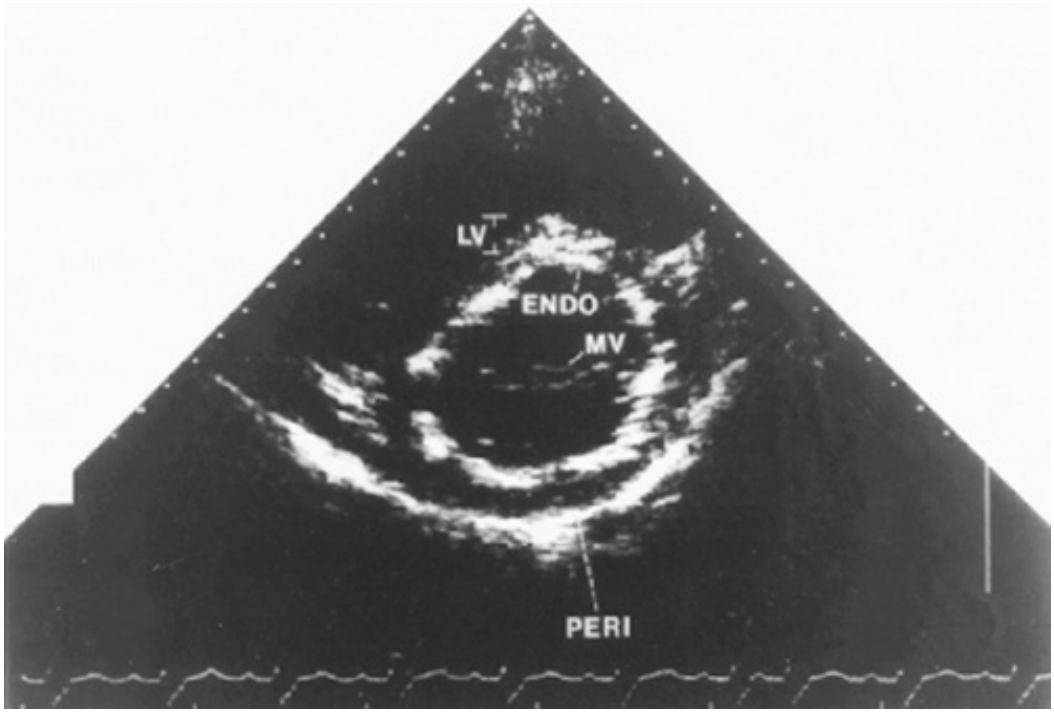

Figure 68-6: Short-axis view of the left ventricle (LV) at the mitral valve (MV) level in a patient with pseudoxanthoma elasticum. Note the calcified endomyocardium (ENDO) and echodense pericardium (PERI). The endocardial calcification was clearly visible by fluoroscopy. (From Shabetai R. Restrictive, obliterative, and infiltrative cardiomyopathies. In: Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2085. Reproduced with permission.)

Progressive Systmic Sclerosis

Myocardial fibrosis, which may have a patchy distribution and be present in both ventricles, is found in the majority of patients with scleroderma at autopsy. On echocardiography, LV wall thickening in the absence of hypertension and evidence of LV dysfunction may be seen, but heart failure due to either restrictive or dilated cardiomyopathy is rare.[20] Pericardial involvement and electrocardiographic abnormalites (heart block, supraventricular and ventricular tachycardia, and pseudoinfarction patterns) are common. Pulmonary hypertension is a leading cause of morbidity and mortality in patients with scleroderma.

INFILTRATIVE CARDIOMYOPATHIES

Amyloidosis

Amyloidosis is a systemic disorder characterized by interstitial deposition of linear, rigid, nonbranching amyloid protein fibrils in multiple organs (e.g., heart, kidney, liver, nerve). Although there are several types of amyloidosis, cardiac involvement is most common in primary amyloidosis (AL type), which is caused by plasma cell production of immunoglobulin light chains; the latter occurs often in association with multiple myeloma. Multiple myeloma is also reported to cause diastolic heart failure in the absence of amyloidosis.[18,21] Cardiac deposition of amyloid protein (protein A, a nonimmunoglobin) mayalso occur in secondary amyloidosis due to chronic inflammation (such as tuberculosis or rheumatoid arthritis). Amyloidois may also be familial and is commonly present (especially at postmortem examination) in the elderly as senile amyloidosis.

Mutations of the protein transthyretin (formerly prealbumin) are usually inherited as an autosomal

dominant trait and produce peripheral and autonomic neuropathy in addition to cardiac disease; over 50 mutations have been described.[22] Cardiac involvement occurs late in the disease and, although present in less than one-third of cases, it is responsible for over half of the deaths.[23] A transthyretin mutation at isoleucine 122 was recently reported as a cause of late-onset cardiac amyloidosis in African Americans.[24]

CLINICAL FEATURES

Amyloid deposits may be interstitial and widespread, resulting in restrictive cardiomyopathy, or localized to (1) conduction tissue, resulting in heart block and ventricular arrhythmias (especially familial amyloid); (2) the cardiac valves, causing valvular regurgitation; (3) the pericardium, producing constriction; and (4) the coronary arteries, resulting in ischemia. Amyloid may be isolated to the subendocardium in senile amyloid and amyloid secondary to chronic disease. Deposition of amyloid and atrial natriuretic factor (ANF) in the atria is frequent in aged hearts.[25] Despite sinus rhythm, atrial mechanical failure and thrombus formation may result due to electromechanical dissociation.[26] Atrial and brain natriuretic peptide are expressed in ventricular myocytes in patients with cardiac amyloidosis.[27] In some cases, the clinical picture is dominated by autonomic neuropathy (orthostatic hypotension, syncope, diarrhea, lack of sweating, and impotence) and nephropathy and cardiac involvement are unrecognized. Cardiac manifestations define a spectrum, often progressive through stages of severity, from the asymptomatic to biventricular failure.

DIAGNOSTIC/IMAGING STUDIES

The cardiac silhouette on the chest radiograph may be normal or moderately enlarged. The ECG typically shows decreased voltage, a pseudoinfarction pattern, left axis deviation; arrhythmias and conduction disturbances may predominate the clinical course.

The M-mode echocardiogram may reveal symmetrical wall thickness involving the right and left ventricles, a small or normal LV cavity, variable (but often depressed) systolic function, left atrial enlargement, and a small pericardial effusion (Fig. 68-7). Digitized M-mode tracings may reveal decreased rates of systolic wall thickening and diastolic wall thinning and increased isovolumic relaxation time,[28] especially in the early stages.

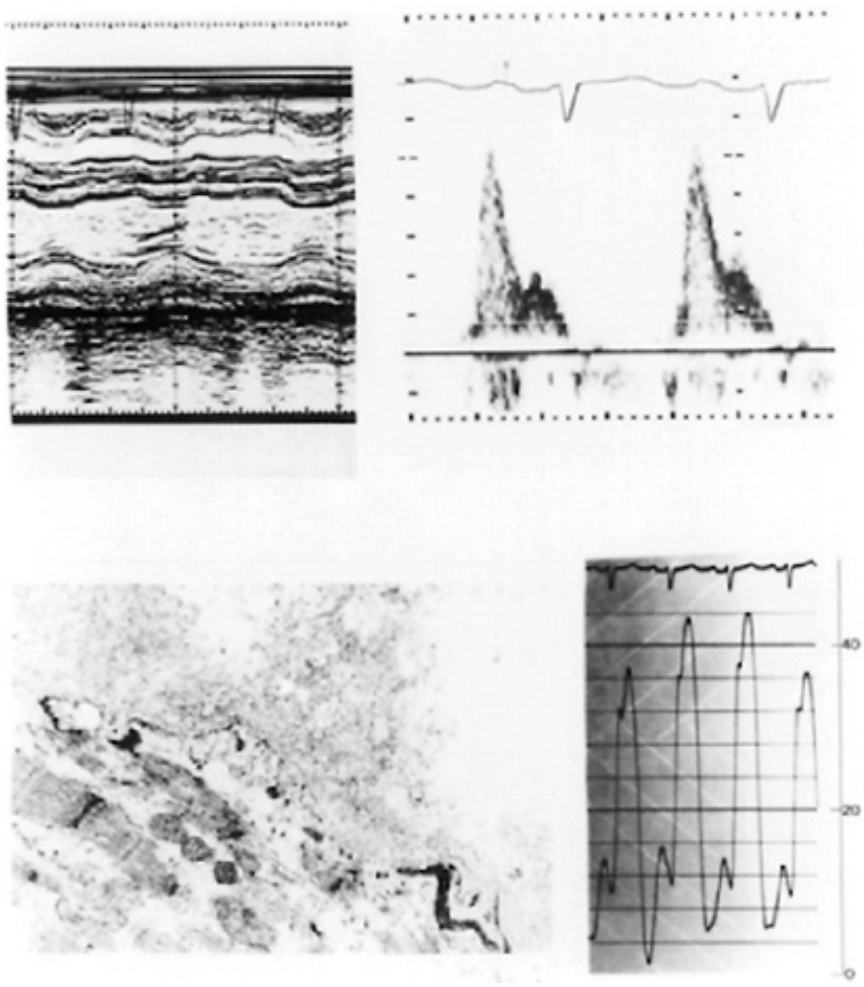

Figure 68-7: Amyloidosis. *Top left:* M-mode echocardiogram showing increased thickness of the left ventricular myocardium (calibration mark = 1 cm). *Top right:* Doppler tracing of mitral inflow velocity. Note that the atrial contribution to mitral blood flow velocity is markedly reduced (calibration mark = 20 cm/s). *Bottom left:* electromicrograph showing extensive replacement of myocardium by amyloid. *Bottom right:* Right ventricular pressure tracing. A diastolic dip-plateau pattern is absent because of tachycardia. (From Shabetai R. Restrictive, obliterative, and infiltrative cardiomyopathies. In: Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2083. Reproduced with permission.)

Two-dimensional echo findings include thickening of the ventricular myocardium, the interatrial septum and valves (especially the AV valves), enlarged papillary muscles, and dilated atria and inferior vena cava (Fig. 68-8). LV wall thickness is an important prognostic variable; in one study, patients with biopsy-proven amyloidosis having a mean wall thickness ≥15 mm had a median survival of 0.4 years, whereas patients with a mean wall thickness ≤12 mm had a median survival of 2.4 years.[29] Highly reflective echoes producing a granular or sparkling appearance and occurring in a patchy distribution are characteristic echocardiographic findings but are neither sensitive nor specific; concentric hypertrophy, as occurs in hypertension or aortic stenosis, may produce a uniformly speckled or echolucent appearance of the myocardium; and idiopathic hypertrophic cardiomyopathy may display a patchy, granular sparkling. Although they correlate with wall thickness, granular echoes may not be seen. Importantly, their recognition is subjective and is affected by ultrasound instrument settings. Thus, granular sparkling alone is an unreliable finding. The infiltrative pathology associated with amyloidosis may be detected by tissue characterization using MRI.[18] Amyloid cardiomyopathy may exist despite the absence of echocardiographic evidence of infiltration.[30]

Doppler studies may show the restrictive pattern of LV filling-i.e., a transmitral E/A ratio ≥2 without respiratory variation, transmitral diastolic deceleration time <150 ms, and an isovolumic relaxation time ≤70 ms (Fig. 68-7). The RV filling pattern is often abnormal. The systolic-to-diastolic pulmonary venous flow ratio is <1 and atrial reversals increase with inspiration in the pulmonary and hepatic veins. However, the *earliest sign* of amyloid cardiomyopathy is impaired LV relaxation, manifest by an E/A ratio <1, and increased isovolumic relaxation and transmitral diastolic deceleration times. The severity of combined systolic and diastolic abnormalities can be determined with an echo Doppler index using isovolumic contraction and relaxation and ejection times.[31] In addition, Doppler has shown utility in prognosis; a deceleration time <150 ms and an increased E/A transmitral ratio are strong predictors of cardiac death.[32]

Abnormalities of LV filling are also demonstrated with the LV time-activity curve from radionuclide ventriculography.[33] Moreover, radionuclide imaging using technetium-99m pyrophosphate or Indium-111 antimyosin may be useful in diagnosis. The variable clinical, diagnostic, and prognostic features reflect the location, nature, and extent of amyloid deposition and the temporal course of the disease. Serum and urine protein electrophoresis is diagnostic in most cases of primarily amyloidosis, but monoclonal protein is not secreted in 10 percent of cases.[23] Endomyocardial biopsy of the RV (most helpful if an abdominal fat aspirate is negative) provides the diagnosis, establishes the histochemistry, and quantifies myocardial damage and atrophy.[34]

TREATMENT OF AMYLOIDOSIS

The treatment of amyloidosis is unrewarding and symptomatic therapy is fraught with hazard; patients are sensitive to digoxin and calcium channel blockers, and hypotension with vasodilators and diuretics is a threat due to the steep LV pressure-volume relation. Immunosuppressive therapy with melphalan and prednisone is the established treatment regimen for primary (AL) amyloidosis. In a recent study, multiple alkylating agents failed to increase the response rate or survival time over this conventional regimen.[35] Orthotopic cardiac transplantation is generally not recommended because of the systemic nature of amyloidosis and the possibility of recurrence in the transplant, but successful cases have been reported.[36] Liver transplantation may be lifesaving in patients with familial amyloidosis,[37] since the liver is the site of transthyretin production.

Sarcoidosis

Sarcoidosis is a disorder of unknown etiology characterized by the presence of noncaseating granulomas that involve many organs (e.g., lung, skin, lymph nodes, liver, spleen). Granulomas involve the heart in sarcoidosis in as many as 25 percent of patients but are frequently subclinical.[38] Nevertheless, in approximately half of the fatalities, cardiac involvement is responsible.[39] Rarely, sarcoid is confined to the heart. The combination of extracardiac manifestations and cardiac abnormalities favors a presumptive diagnosis of sarcoidosis without biopsy.

Interstitial granulomatous inflammation initially produces diastolic dysfunction, but later, when the disease is more extensive, it may produce systolic (at times focal) abnormalities. Localized thinning and dilatation of the basilar LV resembling ischemic heart disease are characteristic. Restrictive cardiomyopathy is uncommon. However, sarcoid pulmonary involvement is frequent and produces echo and Doppler findings of pulmonary hypertension and right heart failure. High-grade AV block, due to involvement of the conduction system, and ventricular arrhythmias are the principal manifestations and may result in sudden cardiac death; syncope is common. The ECG commonly demonstrates T-wave and conduction abnormalities. Pseudoinfarct patterns may appear with extensive myocardial involvement.

Echocardiographic findings include evidence of systolic and diastolic LV dysfunction, LV aneurysm formation, abnormal ventricular wall thickness, pericardial effusion, regional wall motion abnormalities in the basal septum with apical sparing, and evidence of cor pulmonale. Thallium 201 and gallium 67 have been used to indicate areas of myocardial involvement and serve to predict the response to corticosteroids. MRI may detect mass lesions due to sarcoid granuloma or scar.[40] Endomyocardial biopsy is useful but may be falsely negative. An important entity in the differential diagnosis is giant-cell myocarditis, which is characterized by a more aggressive and fatal course than cardiac sarcoid.[41]

Treatment with prednisone is warranted in highly suspicious or proven cases because the cardiac granuloma may be sensitive. In patients at high risk for sudden cardiac death, an automatic implantable cardioverter defibrillator (AICD) may be appropriate,[42] and cardiac transplantation is an appropriate consideration in some cases.[43]

Gaucher's Disease

Gaucher's disease is due to an inherited deficiency of the enzyme β-glucocerebroside, which results in accumulation of cerebroside in the reticuloendothelial system, brain, and heart. Diffuse interstitial infiltration of the left ventricle occurs, with reduced LV wall compliance and cardiac output, but is often subclinical. LV and left-sided valvular thickening and pericardial effusion are seen on echo.[44]

STORAGE DISEASES

Hemochromatosis

Primary hemochromatosis is an autosomal recessive iron-storage disease that involves the heart, pancreas, skin, liver, and gonads. Myocardial iron deposition in hemochromatosis, either primary or secondary (e.g., resulting from multiple transfusions, ineffective erythropoesis), usually produces dilated cardiomyopathy but may cause restrictive cardiomyopathy. Arrhythmia and conduction disturbances are common; indeed, congestive heart failure, conduction abnormalities, and supraventricular and ventricular arrhythmias occur in one-third of patients.[45] Interstitial fibrosis is variable and unrelated to the extent of iron deposition, which occurs in the myocyte; secondarily, myocardial fibrosis may develop. Bronze diabetes and hepatic dysfunction, reflecting iron deposition in the skin, pancreas and liver are frequent associated manifestations.

One report suggests that cardiac involvement progresses temporally from a small, concentrically hypertrophied LV with diastolic dysfunction to a dilated LV with systolic dysfunction.[46] However, this sequence of events is not universally accepted, and systolic abnormalities may require provocation.[47] Findings consistent with either dilated or restrictive cardiomyopathy may be seen; the presence of systolic dysfunction indicates a poor prognosis (Fig. 68-9). Granular sparkling and atrial enlargement may be observed, but these are nonspecific signs. Quantitative ultrasonic analysis of integrated backscatter has been used experimentally to detect changes in the echo reflectivity of the myocardium due to iron deposition in thalassemia major.[48] Computed tomography and magnetic resonance imaging may demonstrate subclinical cardiac involvement, and tissue characterization may be possible with MRI. Endomyocardial biopsy is confirmatory; in selected instances, it may be useful in excluding the diagnosis.

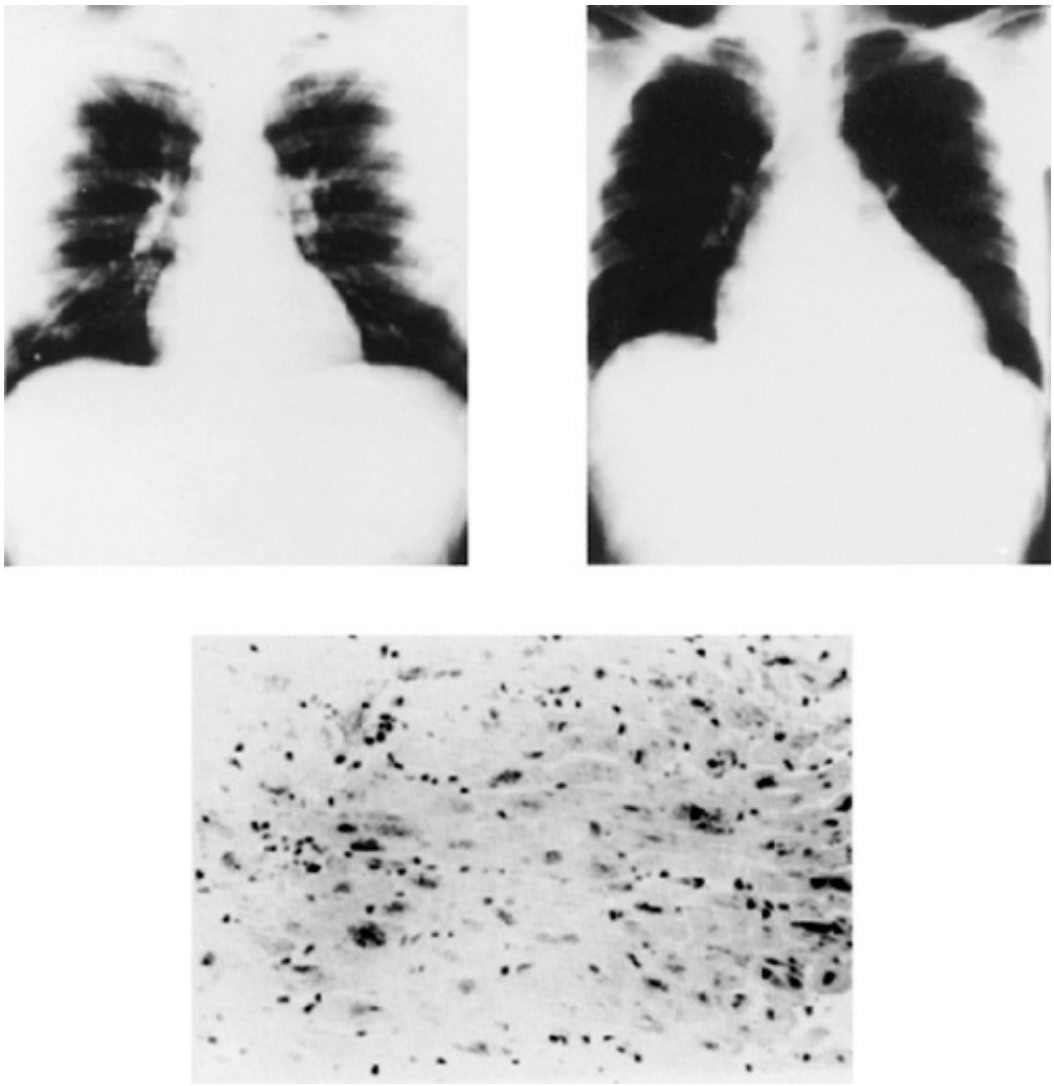

Figure 68-9: Chest radiograph of a patient with cardiac hemochromatosis before (*top right*) and after (*top left*) several months of treatment with phlebotomy. *Bottom:* Endomyocardial biopsy that established the diagnosis. (From Shabetai R. Restrictive, obliterative, and infiltrative cardiomyopathies. In: Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2084. Reproduced with permission.)

Repeated phlebotomy is recommended for primary hemochromatosis, and the chelating agent desferrioxamine is often beneficial in secondary hemochromatosis. Cardiac transplantation (with or without liver transplantation) may be considered in selected cases.

Fabry's Disease

Fabry's disease is an X-linked, genetically heterogeneous disorder of glycosphingolipid metabolism caused by lysosomal ceramide (α-galactosidase) deficiency that leads to accumulation of glycolipid in the heart, skin, and kidneys. Glycolipid accumulation in the myocardium and vascular and valvular endothelium may present with either a restrictive, hypertrophic, or dilated cardiomyopathy, mitral regurgitation, ischemic heart disease, or aortic degeneration. Echocardiographic findings in restrictive cardiomyopathy mimic those seen in amyloid, and LV mass correlates with the severity of disease.[49] Hypertension, mitral valve prolapse, and heart failure are common clinical presentations. Definitive diagnosis may require endomyocardial biopsy.

Pompe's Disease

Pompe's disease (glycogen storage type II) is due to an inherited (autosomal recessive) metabolic abnormality due to acid maltase deficiency that causes massive amounts of glycogen deposition in the heart and skeletal muscles. A hypertrophied, hypokinetic LV in an infant with muscle hypotonia, hyperreflexia, and failure to thrive are characteristic findings. The echocardiographic manifestations may be indistinguishable from hypertrophic obstructive cardiomyopathy. The diagnosis can be made by absence of α-1,4-glucosidase activity on skeletal muscle biopsy.

Adults with glycogen storage type III disease (debranching enzyme deficiency) may have marked LVH on echocardiography.[50]

Endomyocardial Diseases

OBLITERATIVE ENDOMYOCARDIAL DISEASES

Endomyocardial Fibrosis and Hypereosinophilic Syndrome

Endomyocardial diseases that cause restrictive obliterative cardiomyopathies include endomyocardial fibrosis (EMF) and hypereosinophilic (Loeffler's) syndrome. The former accounts for 10 to 20 percent of deaths due to heart disease in equatorial Africa but is seen throughout the world. In contrast, Loeffler's endocarditis is seen mainly in countries with a temperate climate. Although it shares similar pathological features with EMF, it affects mainly men; is usually related to parasitic infections, leukemia, and immunologic reactions; and is characterized by intense eosinophila and thromboembolic phenomena.[51] The two conditions may represent different forms of the same disease (Loeffler's endocarditis representing an early and EMF an advanced stage), but considerable differences exist. Moreover, the endemic variety EMF may be related to high levels of cerium and low levels of magnesium; it may be pathophysiologically distinct from Loeffler's.[52]

HYPEREOSINOPHILIC SYNDROME

Cardiac involvement occurs in the majority of patients with the hypereosinophilic syndrome (unexplained eosinophilia exceeding 1500 eosinophils/mm^3 for at least 6 months and symptoms of organ involvement) and often has a biventricular distribution. Cardiotoxic eosinophils (abnormal cells containing vacuoles and having fewer than the normal number of granules) are central to the pathogenesis. The cardiac pathology consists of an acute eosinophilic myocarditis, fibrinoid vasculitis of the intramural coronary arteries, mural thrombosis (often with eosinophils), fibrotic endocardial thickening, and ventricular obliteration. In addition to symptoms due to cardiac involvement, patients have skin rash and constitutional symptoms. The disease is aggressive and rapidly progressive. Electrocardiographic abnormalities (especially involving the T wave) are common but nonspecific. Hemodynamic findings are typical of restrictive cardiomyopathy.

ENDOMYOCARDIAL FIBROSIS

In contrast to Loeffler's, EMF has a more insidious onset, has no gender predilection, and most often affects children and young adults. The disease is more indolent than Loeffler's, and biventricular involvement occurs in only about half the cases. LV involvement produces symptoms due to pulmonary congestion, whereas the less common isolated RV involvement (about 10 percent) may simulate constrictive pericarditis. Atrioventricular valve regurgitation and embolic episodes are frequent complications, and atrial fibrillation is common.

ECHOCARDIOGRAPHIC FEATURES

Endomyocardial disease is characterized by endocardial fibrosis of the apex and subvalvular regions of one or both ventricles, resulting in restriction to inflow to the affected ventricle.Although their clinical presentations differ, the pathology, and therefore the cardiac imaging studies, are generally similar in the endomyocardial diseases. M-mode echo findings are nonspecific and digitized M-mode studies reveal a decreased peak filling rate and a decreased duration of the peak filling.[53] On two-dimensional echo, apical obliteration of the right and/or left ventricle, apical thrombus, preservation of ventricular systolic function with thickening of the posterior atrioventricular valve apparatus and posterobasilar LV wall, echo densities in the endocardium, and small ventricular and large atrial cavities are noted (Fig. 68-10).[54] Involvement of the posterior mitral and tricuspid valve leaflets results in mitral and tricuspid regurgitation; less commonly, restricted motion may produce stenosis. Sparing of the outflow tracts is characteristic. Doppler interrogation yields typical patterns of restriction (increased E/A, decreased IVRT, decreased deceleration time), mitral and tricuspid regurgitation, and, less often, stenosis. Not surprisingly, the location, extent, and severity of involvement determine the clinical picture.

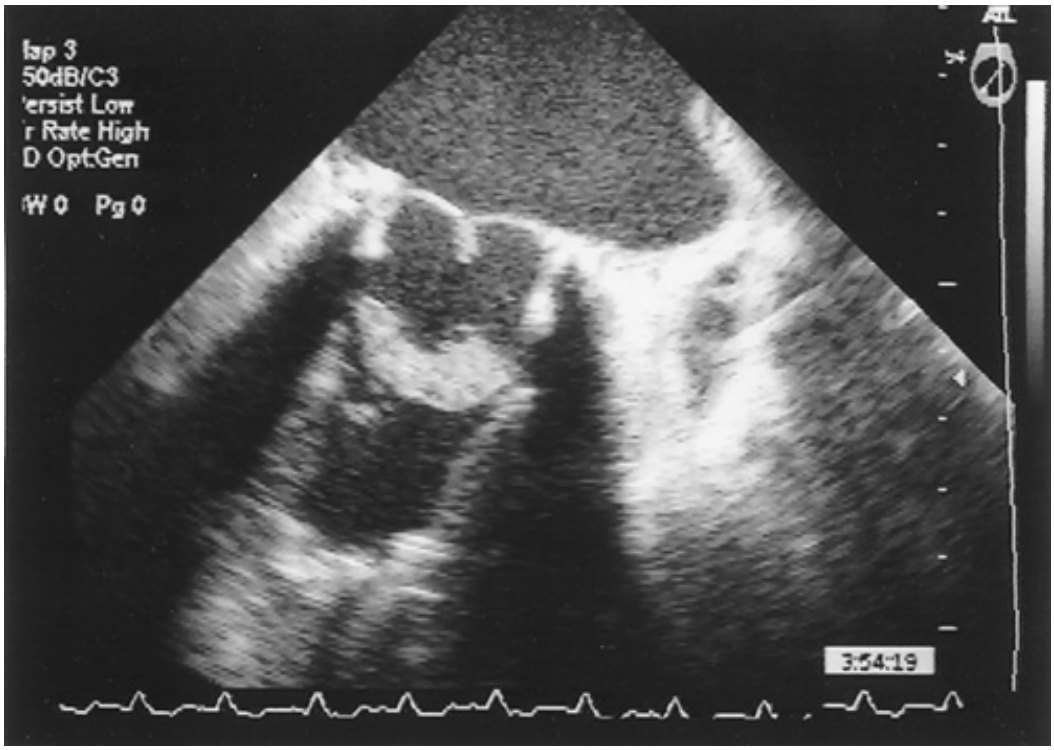

Figure 68-10: Transesophageal echocardiogram from a patient with eosinophilic endocarditis and prosthetic mitral valve replacement. Thrombus is noted below the valve struts, which at the the time of surgery was found to be adherent to the posterior LV wall. Note the apical obliteration and the apical endocardial thickening and calcification.

TREATMENT OF THE OBLITERATIVE RESTRICTIVE CARDIOMYOPATHIES

Medical therapy of Loeffler's is often ineffective and frustrating. Treatment consists of symptomatic relief, anticoagulants, corticosteroids, and hydroxyurea for myocarditis (interferon α has had some success[55]), and palliative surgery in the late, fibrotic stage. Surgical excision of fibrotic endocardium and valve replacement may offer symptomatic improvement, but at the expense of high (15 to 25 percent) operative mortality. The prognosis of advanced disease is grim (50 percent 2-year mortality), but it is considerably better in those with milder disease.

NONOBLITERATIVE ENDOMYOCARDIAL DISEASES

Carcinoid Syndrome

Carcinoid syndrome results from metastatic carcinoid tumors (most commonly arising in the small bowel and appendix, but also the bronchus and other sites) and consists of cutaneous flushing, diarrhea, and bronchoconstriction; involvement of the heart occurs as a late complication of carcinoid syndrome in approximately 50 percent of patients. (see also Chaps. 59 and 77). Hepatic metastases produce serotonin, bradykinin, and other substances that affect right heart structures but are inactivated in the lungs. Thus, LV involvement is distinctly uncommon and its presence suggests a right-to-left intracardiac shunt.[56] Fibrous endocardial plaques comprising smooth muscle cells in a stroma of collagen and acid mucopolysaccharide on the tricuspid and pulmonic valves and right heart endocardium are characteristic. Although tricuspid and pulmonic stenosis and regurgitation dominate the clinical picture, restrictive cardiomyopathy may occur.

The chest radiograph is often normal, but cardiomegaly, pleural effusions, and nodules may be evident; unlike the case with congenital pulmonic stenosis, poststenotic dilatation of the pulmonary artery trunk does not occur.[57] Electrocardiographic abnormalities are common, but nonspecific. Two-dimensional echocardiography reveals thickened, retracted tricuspid and pulmonic valves and right atrial and ventricular enlargement; right atrial wall thickening may be seen on transesophageal echo. Low-velocity tricuspid and pulmonic regurgitation on Doppler indicates normal pulmonary arterial pressures, which is typical of carcinoid heart disease. In one series, echocardiographic findings were detected in two-thirds of patients with carcinoid.[58] In another study, cardiac involvement was associated with a reduced 3-year survival as compared with those without cardiac involvement.[57] Catheterization findings are usually those of tricuspid regurgitation and/or pulmonic stenosis. Therapy is symptomatic, and valvular replacement (mechanical) or repair is warranted in patients with severe valve dysfunction.

Malignant Infiltration

Infiltrating tumors of the heart are generally metastatic (lung, breast, melanoma, lymphoma, leukemia) and rarely produce restriction to ventricular filling unless the pericardium is involved (see Chap. 77). Infiltration on echocardiography is suggested by a localized increase in wall thickness, often associated with abnormal wall motion and pericardial effusion. CT and MRI scans are also useful.

Iatrogenic Disease

Pericardial disease frequently complicates radiation therapy to the chest and may produce constrictive pericarditis; however, endo- and myocardial involvement may produce restrictive cardiomyopathy, at times presenting years after radiation therapy has been completed.[59] Anthracyclines and methysergide can cause endomyocardial fibrosis. Oils containing L-tryptophan were withdrawn from the market when they were implicated in the genesis of the eosinophilia-myalgia syndrome; this syndrome was associated with restrictive cardiomyopathy.[60] Finally, a restrictive pattern of LV filling is common soon after orthotopic cardiac transplantation and may persist for at least 1 year in as many as 15 percent.[61]

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Figure 68-7: Amyloidosis. *Top left:* M-mode echocardiogram showing increased thickness of the left ventricular myocardium (calibration mark = 1 cm). *Top right:* Doppler tracing of mitral inflow velocity. Note that the atrial contribution to mitral blood flow velocity is markedly reduced (calibration mark = 20 cm/s). *Bottom left:* electromicrograph showing extensive replacement of myocardium by amyloid. *Bottom right:* Right ventricular pressure tracing. A diastolic dip-plateau pattern is absent because of tachycardia. (From Shabetai R. Restrictive, obliterative, and infiltrative cardiomyopathies. In: Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2083. Reproduced with permission.)

Figure 68-8: M-mode and two-dimensional echocardiogram from a patient with biopsy-proven amyloidosis causing hemodynamic restriction. The left ventricular systolic function is mildly impaired, and there is biatrial enlargement and vena cava plethora. Left ventricular hypertrophy is best seen in the M-mode study. PLA, parasternal long axis; 4C, four chamber view; RV, right ventricle; LV, left ventricle; LA, left atrium; RA, right atrium; IVC, inferior vena cava. (From Hoit BD. Restrictive cardiomyopathy. In: Pohost G, O'Rourke R, Shah P, Berman D, eds. *Imaging in Cardiovascular Disease*. New York: Lippincott Williams & Wilkins; in press. Reproduced with permission.)

Figure 68-9: Chest radiograph of a patient with cardiac hemochromatosis before (*top right*) and after (*top left*) several months of treatment with phlebotomy. *Bottom:* Endomyocardial biopsy that established the diagnosis. (From Shabetai R. Restrictive, obliterative, and infiltrative cardiomyopathies. In: Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2084. Reproduced with permission.)

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Part 11: CARDIOMYOPATHY AND SPECIFIC HEART MUSCLE DISEASES
Chapter 69:

MYOCARDITIS AND SPECIFIC CARDIOMYOPATHIES-ENDOCRINE DISEASE AND ALCOHOL

Authors: Donna M. Mancini, Ainat Beniaminovitz

The diagnosis of cardiomyopathy encompasses a wide spectrum of diseases with widely divergent pathogenic mechanisms, that have as their final common pathway the syndrome of congestive heart failure. These heart muscle diseases may be primary or secondary-i.e., resulting from specific cardiac or systemic disorders. A list of etiologies associated with the development of cardiomyopathy is presented in Fig. 69-1.

Coronary artery disease, hypertension, valvular heart disease, and cardiomyopathy are the most common causes of heart failure for both sexes. Comparison of the Framingham[1] and SOLVD[2] (Study of Left Ventricular Dysfunction) registries demonstrates a shift in the predominant etiology of heart failure from hypertension to ischemic heart disease. This probably reflects recent intensified efforts to control high blood pressure.

Inflammatory cardiomyopathies, particularly viral myocarditis, have served as a model to understand the development of heart failure. More than 70 different specific cardiomyopathies associated with general systemic disease, neuromuscular disorders, sensitivity and toxic reactions, and the peripartum state have been described. When considered as a group, these disorders are infrequent; when considered individually, they are rare.

This chapter reviews the inflammatory cardiomyopathies and specific cardiomyopathies with an emphasis on endocrine and infiltrative disorders. Cardiac disorders caused by pulmonary hypertension and congenital cardiac anomalies are not addressed.

ISCHEMIC

Ischemic cardiomyopathy is defined as a dilated cardiomyopathy in a patient with known coronary disease, specifically a patient with a prior history of infarct or a greater than 70 percent narrowing of a major epicardial artery.

Compensatory mechanisms to improve stroke volume result in myocyte hypertrophy, ventricular dilatation, and activation of the sympathetic nervous system. Remodeling of the left ventricle and a decrease in ejection fraction occur in 15 to 40 percent of patients within 12 to 24 months following an anterior wall infarct[3] and in a smaller percentage following an inferior infarction.[4] In the Framingham study, 14 percent of men developed *congestive heart failure* (CHF) within 5 years of a first myocardial infarction[4] and half were dead within 5 years.[5] Prognosis in ischemic heart failure is known to be worse than in other forms of cardiomyopathy,[6,7] presumably due to the superimposed risk of ongoing ischemic events. Aggressive coronary revascularization in instances of significant heart failure may be justified and may achieve a survival benefit without necessarily affecting functional improvement[8] (see also Chaps. 40 and 48).

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Chapter 69: MYOCARDITIS AND SPECIFIC CARDIOMYOPATHIES-ENDOCRINE DISEASE AND ALCOHOL

HYPERTENSIVE

Cardiac hypertrophy due to long-standing arterial hypertension is associated with a high incidence of heart failure.[9] Initially, myocyte hypertrophy occurs to reduce wall stress and to accommodate the increased pressure load imposed on the heart.[10] This increase in myocyte wall thickness is accompanied by biochemical and molecular changes, such as a shift to fetal phenotype gene expression[11] and alterations in the intracellular handling of calcium.[12] Alterations in the nonmyocyte compartment-such as excessive myocardial fibrosis-also ensue.[13] In concert these changes lead to an altered contractile performance of the heart.[14]

Although the precise mechanisms that accelerate the progression from compensated hypertrophy to failure are not known, activation of the renin-angiotensin system has been postulated to play a major role.[15] In vivo, angiotensin II has been shown to increase left ventricular mass[16] and contributes to cardiac phenotype modulation independently from its effect on arterial pressure.[17] In vitro, studies have demonstrated that angiotensin II causes myocyte hypertrophy and promotes interstitial fibrosis.[18] A current clinical trial with the angiotensin-converting enzyme (ACE) inhibitor ramapril has demonstrated that blockade of the renin-angiotensin system in patients with normal left ventricular function but at high risk for cardiovascular events leads to a decrease in the combined end point of death from cardiovascular causes, myocardial infarction, and stroke.[19] This clinical prevention trial further confirms the deleterious effects of the renin-angiotensin axis on cardiac function.

The patient with hypertensive cardiomyopathy typically presents with left ventricular hypertrophy in association with features of dilated or restrictive cardiomyopathy. The prognosis is generally better than that of other forms of cardiomyopathy[20]; however, the prognosis is significantly worsened by the presence of comorbid conditions such as diabetes mellitus, coronary artery disease, and persistent hypertension[21] (see also Chap. 58).

Hypertensive cardiomyopathies are common in the elderly and may be related to an increased prevalence of hypertension due to central arterial stiffness and inherent myocardial changes that occur with normal aging. Recent advances in molecular biology and in echocardiographic and Doppler techniques have led to an improved understanding of the various distinct causes of hypertrophic heart disease in the elderly[22] and the realization that the process is not solely due to the changes associated with aging. Hypertrophic obstructive cardiomyopathy, once thought to be a familial disorder affecting primarily younger individ uals, has been diagnosed in older individuals with increasing frequency.[23,24] As shown in Table 69-1, the clinical syndrome, prognosis, and echocardiographic/electrocardiographic findings are somewhat different in the elderly form of the disease.[25]

Table 69-1: Differences between Old and Young Patients with Hypertrophic Cardiomyopathy

Findings	Old	Young
Echocardiographic	Ovoid ventricle	Crescentic ventricle
	Large left atrium	Small left atrium
	LVH diffuse	LVH anterior septum
	Proximal septal bulge	No septal bulge
Mutations	Gene for cardiac myosin-binding protein C	β-myosin heavy chain and cardiac troponin genes
Etiology	Sporadic, 40%	Primarily inherited
Symptoms	More severe	Less severe
Progression	Slower	Rapid
Prognosis	Better	Worse
Sudden death	Uncommon	Common

Similarly, hypertensive hypertrophic cardiomyopathy is another significantly unappreciated cause of hypertensive cardiomyopathy in the elderly.[26] In contrast to the hypertrophic obstructive form, there is a higher female predominance,[26] which is thought to be due to gender-specific differences in the degree of myocyte hypertrophy to intraventricular pressure-overload previously described in women with aortic stenosis.[27] There is no apparent familial component, and patients give a long history of isolated systolic hypertension. In comparison to the prevalence of hypertension in patients over age 65, which varies from 50 to 70 percent, hypertensive hypertrophic cardiomyopathy remains relatively rare, suggesting a unique and currently poorly understood pathophysiology.[28] Many postulate that in hypertensive hypertrophic cardiomyopathy, as in the hypertrophic obstructive form, the development of senescent hypertension may act influentially on an already genetically altered substrate to lead to the respective phenotypes.[29]

PREVIOUS | NEXT

Chapter 69: MYOCARDITIS AND SPECIFIC CARDIOMYOPATHIES-ENDOCRINE DISEASE AND ALCOHOL

VALVULAR

Valvular cardiomyopathy is defined as systolic dysfunction out of proportion to the wall stress imposed by the initial valvular lesion.[30] It occurs most commonly with left-sided regurgitant (mitral and aortic insufficiency) rather than stenotic lesions (aortic and mitral stenosis). The prognosis depends on the nature and extent of the valvular abnormality but more importantly on the degree of left ventricular dysfunction at the time of the proposed surgical repair. Generally even severe left ventricular dysfunction due purely to aortic stenosis will have a favorable prognosis after surgical repair. This is in marked contrast to a surgical approach for similar degrees of left ventricular dysfunction due to mitral[31] or aortic regurgitation. Owing to high surgical risks, medical therapy with afterload reduction-and, if indicated, cardiac transplantation-are acceptable modes of therapy in these instances. Cardiac reduction surgery with valve repair has become an increasingly popular modality for treatment of these high-risk patients. No large-center randomized trial is currently available to evaluate the efficacy and safety of this approach.

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Chapter 69: MYOCARDITIS AND SPECIFIC CARDIOMYOPATHIES-ENDOCRINE DISEASE AND ALCOHOL

MYOCARDITIS

Infective

VIRAL

As early as 1806, a relationship between infection and chronic heart disease (diphtheria) was postulated, but it was not until the 1970s, with the advent of endomyocardial biopsies, that diagnosis of myocarditis could be established during life. Multiple infectious etiologies (Table 69-2)[32] have been implicated as the cause of myocarditis, with the most common being viral, specifically, Coxsackie B.[33] In the majority of patients, active myocarditis remains unsuspected because the cardiac dysfunction is subclinical, asymptomatic, and self-limited. Histologic evidence of myocarditis following traumatic death is identified in 1 to 3 percent of autopsies,[34,35] suggesting that the frequency of myocarditis is underestimated by analyzing data only from symptomatic patients.

Table 69-2: Causes of Myocarditis

Infectious
Viruses
Coxsackievirus, echovirus, HIV, Epstein-Barr virus, influenza, cytomegalovirus, adenovirus, hepatitis (A and B), mumps, poliovirus, rabies, respiratory synctial virus, rubella, vaccinia, varicella zoster, arbovirus
Bacteria
Cornyebacterium diptheriae, Streptococcus pyogenes, Staphylococcus aureus, Haemophilus pneumoniae, Salmonella spp., *Neisseria gonorrhoeae, Leptospira, Borrelia burgdorferi, Treponema pallidum, Brucella, Mycobacterium tuberculosis,* Actinomyces, *Chlamydia* spp., *Coxiella burnetti, Mycoplasma pneumoniae, Rickettsia* spp.
Fungi
Candida spp., *Aspergillus* spp., *Histoplasma, Blastomyces, Cryptococcus, Coccidioidomyces*
Parasites
Trypanosoma cruzii, Toxoplasma, Schistosoma, Trichina
Noninfectious
Drugs causing hypersensitivity reactions

Antibiotics: sulfonamides, penicillins, chloramphenicol, amphotericin B, tetracycline, streptomycin
Antituberculous: isoniazid, para-aminosalicylic acid
Anticonvulsants: phenindione, phenytoin, carbemazepine
Anti-inflammatories: indomethacin, phenylbutazone
Diuretics: acetazolamide, chlorthalidone, hydrochlorothiazide, spironolactone
Others: amitriptyline, methyldopa, sulfonylureas
Drugs not causing hypersensitivity reactions
Cocaine, cyclophosphamide, lithium, interferon alpha
Nondrug causes
Radiation, giant-cell myocarditis

Pathogenesis

Infection by cardiotropic viruses prompted the initial hypothesis that the viral infection was responsible for myocardial injury. However, several investigators noted that cardiac dysfunction increased after the eradication of the infective agent and speculated that the pathogenesis may be due to the immunologic responses initiated by the virus (Fig. 69-2). Support for this theory comes initially from the work of Woodruff, who noted that the histologic evidence of cardiac injury in Coxsackie B infection occurred only after the virus was no longer detectable in the myocardium.[36] Subsequently, demonstration of T-lymphocyte and macrophage infiltration,[37] perforin granules,[38] and a variety of cytokines known to depress myocardial contractility[39] in endomyocardial biopsies of patients with active carditis strengthened the concept of immune-mediated injury. Furthermore, immunosuppressive therapy in animal models attenuated inflammation-with improved survival, less cellular infiltrate, and less necrosis.

The specific immune responses that lead to the myocardial injury are incompletely defined. A murine model of myocarditis induced by coxsackie B3 has provided some insight into immunologic sequence of events. Following infection with coxsackie B3 virus, macrophages are present in the infiltrate until day 8.[40] After macrophage activity decreases, both effector (CD8) and helper (CD4) T cells are identified within myocardial lesions. At peak infiltration, some murine strains showed a predominance of CD8-positive cells while in others CD4 cells predominate, suggesting participation of both humoral- and cell-mediated immune responses.[41] In human subjects, T-lymphocyte and macrophage infiltration characterizes the immunohistochemical picture, whereas B lymphocytes and natural killer cells are absent.[37] T-lymphocyte subset analysis of human serum does not demonstrate consistency in dominance of CD4 or CD8 cells.

The mechanisms of injury when lymphocytes infiltrate the myocardium are unknown. In the murine model, messenger ribonucleic acid (m-RNA) of perforin, the pore-forming protein mediating cytotoxicity, was identified in cytoplasmic granules of infiltrating cells by in situ hybridization.[42] Similarly, biopsy samples from patients with active myocarditis contain perforin granules in infiltrating cells,[38] implying that direct cytotoxicity can occur. Alternatively, release of cytokines such as interleukin-1, interleukin-6, interleukin-8, and tumor necrosis factor alpha may

cause reversible depression of myocardial contractility without resulting in cell death.[39] Therefore, the effect of T cell-mediated immune injury may be either irreversible as a result of cell death through cytotoxicity (perforin) or reversible as a result of injury mediated by cytokines. A marked reduction in myocardial cell damage is noted in T cell-depleted mice inoculated with encephalomyocarditis virus.

Antiheart antibodies in the serum of patients with myocarditis have been reported but may reflect nonspecific myocardial damage.[43] When serum from patients with myocarditis was screened for autoantibodies, high-titer immunoglobulin G (IgG) with cardiac specificity was detected in 59 percent of patients with myocarditis and in none of the normal samples.[44] Antibodies with specificity for contractile and energy-transport proteins have been identified. In sera from patients with active myocarditis, Western immunoblotting demonstrated reactivity of a fraction that includes antibody to the heavy chain of cardiac myosin.[44] In a murine myocarditis model, cardiac myosin antibodies are observed following coxsackie B virus infection.[45] Moreover, injection of cardiac antimyosin antibodies without infection results in myocarditis that is histologically similar to that seen following coxsackie B3 virus infection.[46,47]

The role of viral infection has been deemphasized following the popularization of the immune injury hypothesis. Viral infection is the trigger for the immune response that is deleterious. Attempts to culture virus from human myocardial tissue generally have been unsuccessful. Only a single case report of Coxsackievirus identified in a myocardial biopsy specimen in an adult has been described.[48] However, identification of viral genomic fragments in myocardial samples by in situ hybridization and polymerase chain reaction from patients with myocarditis and dilated cardiomyopathy have been reported.[49-66] These genomic fragments may not be capable of replicating as intact cardiotropic virus but probably serve as a persistent source of antigen to drive the deleterious immune responses.[67]

In addition to the tropism of the virus, host immune responses play an important role in determining the severity of the clinical disease. When quantitative peripheral T- and B-lymphocyte populations were analyzed in patients with dilated cardiomyopathy and myocarditis, no consistent changes were detected.[68,69] However, immunologic assays demonstrate a reduction in the function of natural killer cells, antibody-dependent cellular cytotoxic cells, and suppressor cells and an increase in circulating levels of interleukin-1 and tumor necrosis factor alpha.[69-72] These immunoregulatory defects may predispose the host with a high antigenic load to develop immune responses that are not modulated by the natural inhibitory immunoregulatory mechanisms.

In addition to chronic inflammatory immune mechanism or persistent viral infection, apoptotic cell death may be another mechanism by which myocarditis can result in cardiomyopathy. Several different viruses have been reported to be triggers for apoptosis.

The association between acute myocarditis and dilated cardiomyopathy has been recognized for the past two centuries. However, the link between these two diseases remains circumstantial. Autoreactive antibodies and interleukin-2 receptors are identified commonly in both patients with myocarditis and those with dilated cardiomyopathy. Serologic titers to cardiotropic viruses are more common in patients with cardiomyopathy than in normal subjects. Viral genomic material can be detected more frequently by polymerase chain reaction (PCR) in patients with dilated cardiomyopathy versus other cardiac diseases. Animal models of myocarditis can progress to dilated cardiomyopathy, as can patients with clinically suspected or biopsy-proven myocarditis. However, the percentage of patients with idiopathic dilated cardiomyopathy that represent the end stage of an active myocarditis is unknown.

Clinical Presentation

The clinical manifestations of myocarditis are variable. Most patients have a self-limited disease, whereas others present in profound cardiogenic shock. The most obvious symptom suggesting myocarditis is an antecedent viral syndrome. Flu-like symptoms occur in approximately 60 percent of patients.[73] Chest pain may occur in up to 35 percent of patients and may be typically ischemic, somewhat atypical, or pericardial in character. Occasionally patients will present with a clinical syndrome identical to an acute myocardial infarction, with left ventricular asynergy, electrocardiographic evidence of injury or Q waves, and ischemic cardiac pain[74] (Fig. 69-3). In this syndrome, at autopsy, the coronary arteries are widely patent, although viral coronary arteritis has been reported.[75,76] Coronary vasospasm has also been associated with acute myocarditis.[77]

Patients may present with syncope or palpitations with atrioventricular (AV) block or ventricular arrhythmia. Complete AV block is common with some patients presenting with Stokes-Adams attacks. The complete heart block is generally transient and rarely requires a permanent pacemaker.[78] Sudden cardiac death can be the initial presentation of myocarditis in some patients, presumably from complete heart block or ventricular tachycardia. In a 20-year review of sudden death among Air Force recruits, 20 percent had myocarditis documented at autopsy.[79] In some patients with refractory ventricular arrhythmias, endomyocardial biopsy or autopsy has revealed myocarditis. Systemic or pulmonary thromboembolic disease is also associated with myocarditis.[80,81]

A familial tendency for the development of myocarditis may be present. In one report, a suppressor cell defect was detected, predisposing to development of active myocarditis.[82] Patients with peripartum cardiomyopathy have a high frequency of myocarditis on endomyocardial biopsy.[83] The immunoregulatory changes during and following pregnancy may heighten susceptibility to viral myocarditis, and exposure to trophoblastic antigens may predispose to immune-mediated myocardial injury.

Patients with new-onset left ventricular dysfunction given the diagnosis of idiopathic dilated cardiomyopathy may actually have active myocarditis despite the absence of clinical signs and symptoms of acute infection.[84]

Diagnosis

Laboratory findings are generally not diagnostic. Sixty percent of patients will have an elevated erythrocyte sedimentation rate and 25 percent an elevated white blood cell count.[73] Elevated titers to cardiotropic viruses may be present. However, a fourfold rise in IgG titer over a 4- to 6-week period is required to document acute infection. Elevated IgM antibody titer may denote an acute infection more specifically than a rise in IgG antibody titer. Unfortunately, a rise in antibody titer documents only the response to a recent viral infection and does not indicate active myocarditis.

Abnormalities in peripheral T- and B-lymphocyte counts have been reported, but these findings have not been consistent and cannot be used as diagnostic adjuncts.

Increase in the MB band of CPK is observed in approximately 12 percent of patients.[73] Troponin levels may also increase. In the Myocarditis Treatment Trial, elevated troponin levels were found in 32 percent of the patients and were predictive of inflammatory involvement.

The electrocardiogram most frequently shows sinus tachycardia. Diffuse ST-T-wave changes, prolongation of the QTc interval, low voltage, and even an acute myocardial infarct pattern has been noted in some patients with myocarditis. Conduction delay is common,[85] with left bundle branch block identified in 20 percent of patients. Cardiac arrhythmias are frequently observed in patients with myocarditis, including complete heart block, supraventricular arrhythmias-especially

in the presence of congestive heart failure or pericardial inflammation, and ventricular arrhythmias.[86]

Echocardiography can reveal left ventricular systolic dysfunction in patients with a normal-sized left ventricular cavity. Segmental wall motion abnormalities may be observed.[87] Wall thickness may be increased, particularly early in the course of the disease, when inflammation is fulminant.[88] Ventricular thrombi are detected in 15 percent of those studies.[89] Echocardiographic findings in active myocarditis can mimic restrictive, hypertrophic, or dilated cardiomyopathy.

Endomyocardial biopsy is the critical test to confirm the diagnosis. Endomyocardial biopsy techniques enable the repetitive sampling of the human myocardium with minimal discomfort and minor morbidity.[84,90,91] Right ventricular myocardial specimens can be obtained by accessing the right internal jugular or femoral vein. Intravascular biopsy of the left ventricle is infrequently performed due to the higher morbidity associated with this approach. The right ventricular bioptome is positioned under fluoroscopy or echocardiography to sample the interventricular septum.[90] As the myocarditis can be focal, a minimum of four to six fragments are obtained. Sampling error is reduced by less than 5 percent. Using the Stanford bioptome, typical samples are 2 to 3 mm in maximal diameter and 5 mg in wet weight. Samples are processed, paraffin-imbedded, sectioned, and stained with hematoxylin-eosin and trichrome. Special stains are employed if other diagnoses are considered. Diagnoses that can be made or confirmed by endomyocardial biopsy are listed in Table 69-3.

Table 69-3: Diagnoses That Can Be Made byEndomyocardial Biopsy

1. Myocarditis
   - Giant cell
   - Cytomegalovirus
   - Toxoplasmosis
   - Chagas
   - Rheumatic
   - Lyme
2. Infiltrative
   - Amyloid
   - Sarcoid
   - Hemochromatosis
   - Carcinoid
   - Hypereosinophilic
   - Glycogen storage
   - Cardiac tumors
3. Toxins
   - Doxorubicin
   - Chloroquine
   - Radiation injury
4. Genetic
   - Fabry
   - Kearns-Sayre syndrome
   - Right ventricular dysplasia

Several investigators have performed endomyocardial biopsies in patients with unexplained

congestive heart failure and/or ventricular arrhythmia.[84,92-122] The percentage of patients with biopsies interpreted as myocarditis varied widely, primarily owing to the different diagnostic criteria for active myocarditis used by the investigators. This variability of endomyocardial biopsy criteria prompted a meeting of cardiac pathologists to reach a consensus on the pathologic definition of myocarditis, now known as "the Dallas criteria." Active myocarditis was defined as "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease."[123] Examination of a minimum of four to six fragments from each patient is required for interpretation. The term *borderline* myocarditis is applied when the inflammatory infiltrate is too sparse or myocyte injury is not demonstrated. Repeat biopsy is then suggested. A high frequency of active myocarditis is confirmed by repeat biopsy in patients whose initial histologic samples demonstrated borderline myocarditis.[124] When right ventricular endomyocardial biopsy has failed to establish the diagnosis, sampling the left ventricle may improve diagnostic yield (Fig. 69-4).

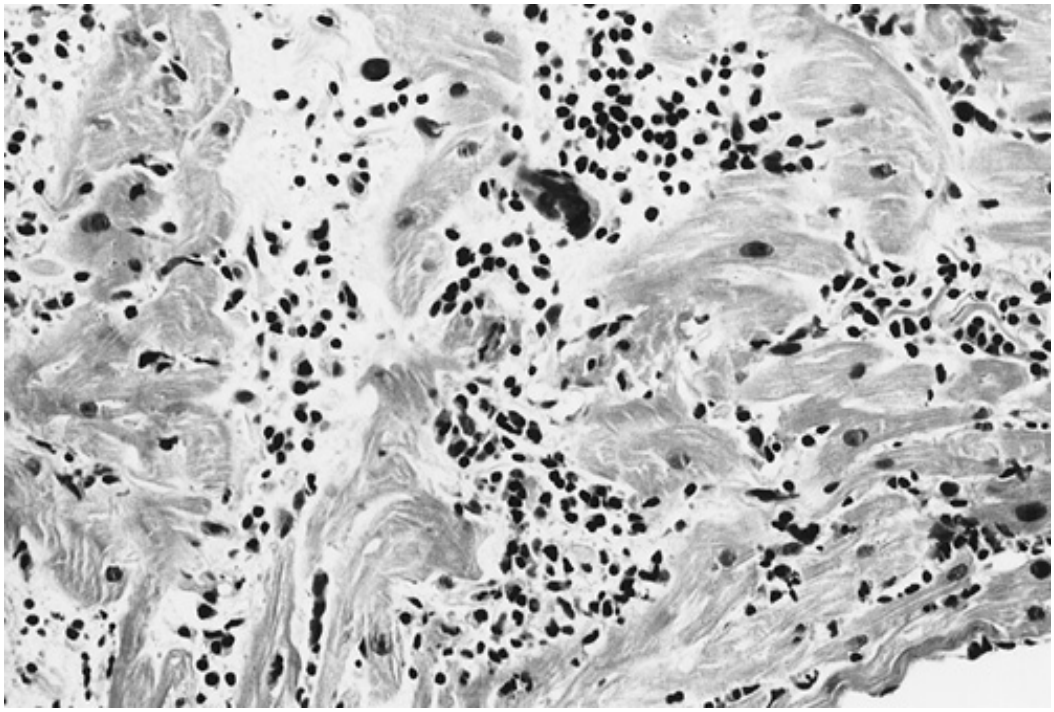

Figure 69-4: Photomicrograph showing extensive interstitial infiltrates of lymphocytes and myocytes with focal myocyte necrosis. (H&E, ×40.)

Endomyocardial biopsy must be applied as quickly as possible to maximize the diagnostic yield. Biopsies in patients with peripartum cardiomyopathy have the highest yield when performed early after onset of symptoms.[83] Resolution of active myocarditis has been documented within 4 days of initial biopsy, with progressive clearing over several weeks on serial biopsy.[125] Progression of active myocarditis to dilated cardiomyopathy has been documented when serial biopsies are performed.[126]

Newer molecular biology techniques are being applied to the analysis of endomyocardial tissue for the detection of viral nucleic acid. The usefulness of PCR amplification of viral genomic material from endomyocardial tissue in children with suspected myocarditis was shown in a study that found PCR amplified viral product in 67 percent of the children studied.

Noninvasive Studies

Although technetium-99m-pyrophosphate scintigraphy has proved useful in the detection of myocarditis in a murine model, it has not been effective in diagnosing myocarditis in humans. Imaging with gallium 67, an inflammation-avid radioisotope, has shown promise as a screening method for active myocarditis, with a specificity and sensitivity of 83 percent and a negative predictive value of 98 percent in biopsy-proven myocarditis.[100] Indium 111-labeled antimyosin antibody scans can be used to detect myocyte necrosis. Application of this technique in patients with myocarditis has demonstrated a sensitivity of 83 percent, a specificity of 53 percent, and a positive predictive value of a normal scan of 92 percent.[124] In those patients who were antimyosin antibody-positive and biopsy-negative, the possibility of inflammation undetected by biopsy has been considered. Antimyosin imaging, however, detects myocyte injury independent of etiology, and noninflammatory causes of heart muscle injury in young patients may cause false-positive scans. The usefulness of scintigraphy in diagnosing myocarditis is limited by low specificiy, radiation exposure, and expense (see also Chap. 16).

Tissue alterations associated with myocarditis may be identifiable using magnetic resonance imaging (MRI).[127] Preliminary results suggest that myocardial inflammation may induce abnormal signal intensity of the myocardial walls. Use of T2-weighted images to visualize tissue edema has been described in several case reports of patients with active myocarditis. More recently, contrast media-enhanced MRI has been used to characterize myocardial changes in myocarditis. The MRI imaging contrast agent gadopentetate dimeglumine accumulates in inflammatory lesions (see Chap. 18A). It is a hydrophilic agent that accumulates in the extracellular space of water-containing tissues. Gadolinium increases the signal of T1-weighted images. A total of 19 patients with clinically suspected myocarditis and 18 normal subjects underwent contrast-enhanced MRI. Global relative enhancement was higher in patients than controls. Contrast MRI also visualized the area of inflammation and the extent of inflammation and may prove to be a valuable technique in both the diagnosis and monitoring of disease activity.

Despite the promise of noninvasive techniques, endomyocardial biopsy remains the diagnostic standard.

Treatment

The immune injury hypothesis generated application of potential therapies, including immunosuppression. Anecdotal success with immunosuppression in active viral myocarditis[101,106] led to the large Multicenter Myocarditis Treatment Trial.[128] In this study, 111 patients with biopsy-proven myocarditis were randomized between conventional medical therapy versus steroid/azathioprine or steroid/cyclosporine immunosuppression. The primary end point of the study was change in ejection fraction over 28 weeks. For all patients, the average increase in ejection fraction over baseline was 9 percent. Treatment assignment was not predictive of improvement in left ventricular ejection fraction, attenuation of clinical disease, or mortality[129] (Fig. 69-5).

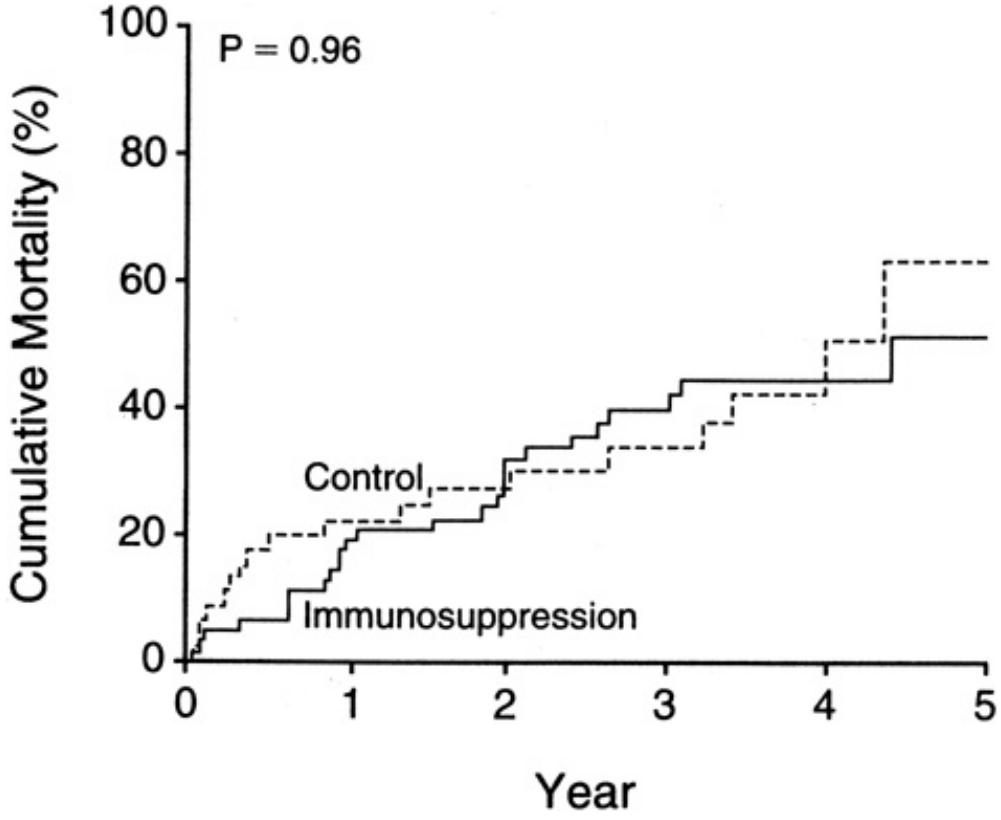

Figure 69-5: Actuarial mortality curves from the Myocarditis Treatment Trial illustrating no difference in survival between the treatment groups. (From Mason et al.,[129] with permission.)

Recently, immune modulatory therapy with immune globulin has been shown to be an effective treatment for Kawasaki's disease and new-onset cardiomyopathy in pediatric patients.[130] Subsequently, a small open-label study was performed in 10 adult patients with new-onset heart failure.[131] Significant improvement in left ventricular function was observed in 9 of 10 patients. These findings formed the basis for a multicenter study investigating the use of this treatment modality. The IMAC trial (Intervention in Myocarditis and Acute Cardiomyopathy with immune globulin) used a single infusion of high-dose immunoglobulin (2 g/kg) to treat presumed inflammatory cardiomyopathies. In this placebo-controlled 6-month trial, the improvement in left ventricular ejection fraction and symptoms was similar in both groups. Thus no benefit of immunomodulation could be demonstrated.

Despite the experimental data supporting the immune injury hypothesis, no randomized study has yet demonstrated the efficacy of immunosuppressive therapy in myocarditis. Immunosuppressive therapy is therefore not routinely recommended for infective myocarditis. Standard heart failure treatment remains the mainstay of therapy.

Prognosis

About one-third of those who present with clinical carditis and recover will be left with some cardiac abnormality ranging from mild changes on electrocardiography (ECG) to significant heart failure. The multicenter myocarditis trial provided insight into the natural history of myocarditis with current treatment. The degree of left ventricular dysfunction at initial presentation was most predictive of recovery. Approximately 40 percent of patients fully recovered.[104] Other predictors of recovery included shorter duration of disease and less intensive conventional drug therapy. One-year survival in this study was 80 percent, with a 4-year survival of only 44 percent.

The prognosis of myocarditis depends to some extent on the causative agent, but if clinical heart

failure develops, 5-year mortality rates are in the 50 to 60 percent range, comparable with figures seen in idiopathic cardiomyopathy.[132] Chronic inflammation, viral persistence, or both may affect disease progression and prognosis. Future therapies will need to identify the predominant factor to target treatment and hopefully improve survival.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is increasingly recognized as a cause of dilated cardiomyopathy. In some inner-city hospitals, it may represent a very common diagnosis. The relatively recent emergence of this virus in the early 1980s has provided a unique opportunity to prospectively monitor the development of heart failure to chronic viral infection. The etiology of this cardiomyopathy may be from infection of myocardial cells with HIV or coinfection with other cardiotropic viruses, postviral autoimmune response, or cardiotoxicity from illicit drugs or drug therapy. Barbaro et al.[133] recently studied the development of dilated cardiomyopathy in 952 asymptomatic HIV-positive patients. Patients with a history of illicit drug use, prior cardiac disease, previous treatment with antiretroviral or immunomodulating drugs, or with an ejection fraction less than 50 percent were excluded from prospective study. In the 60 months of follow up, 8 percent of the patients developed cardiomyopathy, with annualized incidence rate of 16 cases per 1000 patients. A predisposing factor to cardiomyopathy development was a CD4 cell count below 400/mL. In 83 percent of the patients, a histologic diagnosis of myocarditis was made. In 92 percent of these positive biopsies, HIV nucleic acid sequences were detected by in situ hybridization. Coexistent infection with coxsackie virus group B, cytomegalovirus and Epstein-Barr virus was detected in a small segment of this cohort. Other studies suggest that disease duration and illicit drug use as factors contributing to the development of this disease.[134]

As the symptoms of heart failure and HIV can be very similar (i.e., fatigue, wasting, etc.), careful cardiologic follow-up of these patients is probably indicated to detect early development of left ventricular dysfunction. Conventional heart failure management can then be instituted to alleviate cardiac-related symptoms.

Cytomegalovirus

Cytomegalovirus may lead to myocarditis in the general population, but ordinarily the myocarditis is self-limited and asymptomatic. In the cardiac transplant recipient, however, cytomegalovirus myocarditis may become a more serious disease resulting in cardiac dysfunction.[135] The treatment of cytomegalovirus myocarditis is intravenous ganciclovir, which effectively eradicates the virus. Early cytomegalovirus infection correlates with the development of allograft coronary artery disease, the major cause of death beyond the first year after cardiac transplantation. It is proposed that infection of either subintimal fibroblasts or endothelial cells results in immunologic injury that predisposes to this potentially fatal condition.

NONVIRAL

Chagas' Disease

American trypanosomiasis, or Chagas' disease, is the most common cause of congestive heart failure in the world.[136] This condition results from the bite of the reduviid bug, leading to infection with *Trypanosoma cruzi,* and is endemic to rural South and Central America.

Pathogenesis

The pathogenesis of chronic, chagasic cardiomyopathy is controversial because the parasite is rarely present in the myocardium. As in the viral cardiomyopathy model, the cardiac injury is thus

thought to be immunologically mediated.[137] Both cellular and humoral immune responses have been implemented in the myocardial injury.[137] Myocardial biopsies demonstrate that the inflammatory infiltrate in chronic Chagas' disease consists mainly of CD8+ T cells, with a low number of CD4+ T cells.[138-140] This suggests some degree of immunologic depression in the host, since the activation of T-helper cells is known to be the most effective mechanism of defense against the parasites.[141] Some have postulated that the diminished expression of CD4+ T cells during acute *T. cruzi* infection may be related to a mechanism of tolerance induced by the parasite. Evidence for this comes from studies that have shown that the addition of interleukin-1 (IL-1) in vitro restores helper T-cell function, thus implementing a macrophage defect in this process.[142] Furthermore, IL-2 and the IL-2 receptor are absent or scarce in the inflammatory infiltrate,[143] attesting to the attenuated role of the T-helper subset in this disease.

Clinical Presentation

This parasitic disease has an acute phase, where hematogenous spread of the parasite leads to invasion of various tissues and organ systems. The invasion is accompanied by an intense inflammatory reaction with mononuclear cells and is characterized by fever, sweating, myalgias, myocarditis, hepatosplenomegaly, and a case fatality rate of about 5 percent. Most patients recover from the acute illness and enter an asymptomatic latent phase, but 20 to 30 percent will develop a chronic form of the disease up to 20 years after the initial infection.

The chronic stage is a result of gradual tissue destruction. The gastrointestinal tract and the heart are the most common sites of involvement, with the primary cause of death being cardiac failure. In the gut, the destruction of the myenteric plexus is responsible for the development of megaesophagus and megacolon. In the heart, the myofibrils and the Purkinje fibers are replaced by fibrous tissue, leading to cardiomegaly, congestive heart failure, heart block, and arrhythmia. The microscopic findings are those of extensive fibrosis, but a chronic cellular infiltrate composed of lymphocytes, plasma cells, and macrophages is often present and parasites are found in about a quarter of the patients.

The diagnosis of the acute disease depends on the discovery of trypomastigotes in the blood of the infected individual. In chronic infection, direct diagnosis is less useful due to less circulating trypomastigotes. Xenodiagnosis (where the patient is bitten by reduviid bugs bred in the laboratory and subsequent identification of the parasites in the intestine of the insect) is the most useful test, which will detect infection in about half the patients. The complement-fixation test (MachadoGuerreiro test) also has high sensitivity and specificity for identification of chronic Chagas' disease. In the other lab tests, it is necessary to rely on positive serologic tests (such as the indirect immunofluorescent antibody, the enzyme-linked immunosorbent assay, and the hemagglutination tests) together with symptoms and signs compatible with Chagas' disease.

Endomyocardial biopsy may show active myocarditis using the Dallas criteria.[144] Noninvasive assessment commonly shows segmental wall motion abnormalities, specifically apical aneurysms. Electrocardiographic findings include complete heart block, atrioventricular block, or right bundle branch block with or without fascicular block in 11 percent of infected individuals.[145] Ventricular arrhythmias may require antiarrhythmic drugs, including amiodarone.[146]

The treatment of chronic Chagas' disease is symptomatic and includes a pacemaker for complete heart block, an implantable cardioverter-defibrillator for recurrent ventricular arrhythmia, and standard therapy for congestive heart failure as outlined for other forms of myocarditis. Antiparasitic agents such as Nifurtimox and benzimidazole eradicate parasitemia during the acute phase and are typically curative. They should be administered if the disease has not previously been treated and may be used as prophylaxis if there is a high likelihood of recurrence, such as following immunosuppressive therapy. The role of immunosuppression therapy for chagasic myocarditis is controversial, and heart transplantation is effective for end-stage refractory cardiac

disease.

Lyme Carditis

Lyme disease may result from infection with the spirochete *Borrelia burgdorferi*, introduced by a tick bite. The initial presenting symptom in patients with the disease who progress to cardiac involvement is frequently complete heart block. Left ventricular dysfunction may be seen but is unusual.[147] Endomyocardial biopsy may show active myocarditis. Rarely are spirochetes seen on biopsy. Corticosteroid administration is helpful in treating Lyme carditis following therapy with tetracycline.[148]

Among other infectious etiologies is *Toxoplasma gondii*, which is curable by pyrimethamine and sulfadiazine[149] and occurs most commonly in the immune-deficient host. Leptospirosis is yet another common cause in fatal cases of myocarditis. Fifty percent of cases have ST- and T-wave changes on electrocardiography.

Rheumatic Carditis

One form of myocarditis that has declined dramatically in the latter half of the twentieth century is rheumatic carditis.[150] The availability of antibiotics and changes in the virulence and serotypes of group A streptococcus may explain the decreasing frequency of this disease.[151]

Acute rheumatic fever can occur in children and young adults. It generally follows a group A streptococcal pharyngitis, but only indirect evidence linking the two has been found. Rheumatic carditis may result from a direct toxic effect of some streptococcal product versus an immunologic mechanism.[152-154] Group A streptococci have a number of structural components similar to those of human tissue. Antibodies to streptococci cross-react with the glycoproteins of heart valves. The serum of patients with rheumatic fever contains autoantibodies to myosin and sarcolemma. The Aschoff body, pathognomic for this disorder, represents persistent focal inflammatory lesions in the myocardium. These nodules can persist for years after an acute attack. Macrophages containing myosin have been identified in these nodules.

Clinical diagnosis is made using the Jones criteria[155] (see also Chap. 55). The major manifestations are carditis, polyarthritis, chorea, erythema marginatum, subcutaneous nodules, and evidence of preceding streptococcal infection (i.e., positive throat culture, history of scarlet fever, elevated antistreptolysin titers). Minor criteria are nonspecific findings such as fever, arthralgia, previous rheumatic fever or rheumatic heart disease, elevated ESR or reactive protein, and prolonged PR interval. Diagnosis is made by the presence of two major criteria or one major and two minor criteria. Debate into whether the Jones criteria should be modified to incorporate Doppler-Echo indices are ongoing.[156,157]

Two-thirds of patients present with an antecedent pharyngitis, followed by the symptoms of rheumatic fever in 1 to 5 weeks, with a mean presentation of 18.6 days. Severe carditis resulting in death can occur but is unusual. CHF is observed in only 5 to 10 percent of cases. Usually the carditis is mild, with the predominant effect being scarring of the heart valves. Physical exam is notable for fever and heart murmurs reflecting the acute valvulitis. The mitral valve is involved three times as frequently as the aortic valve; therefore mitral murmurs are more common. Mitral regurgitation is the most common finding. A mid diastolic murmur over the apical area can frequently be heard. This is called the Carey Coombs murmur, and its presence almost certainly confirms mitral valvulitis. Aortic insufficiency can be auscultated with aortic valvulitis.

There are no characteristic ECG findings through PR prolongation, and nonspecific ST-T-wave changes are frequently described. Endomyocardial biopsy demonstrates the Aschoff nodules as

well as a diffuse cellular interstitial infiltrate including lymphocytes, polymorphonuclear cells, histiocytes, and eosinophils.

Laboratory tests suggestive of rheumatic fever include antibodies to antistreptolysin O and anti-DNAase B, an elevated sedimentation rate, and elevated C-reactive protein. Extracardiac manifestations generally predominant with an acute migratory polyarthritis of the large joints. Aspirin and penicillin are the mainstays of therapy. Corticosteroids can also provide symptomatic relief. Once rheumatic fever is diagnosed, antibiotic prophylaxis is required to prevent recurrent episodes. The most effective method is a single monthly intramuscular injection of 1.2 million units of benzathine Penicillin G until age 21.

Noninfective

HYPERSENSITIVITY

Hypersensitivity myocarditis is an example of the early phase of eosinophilic myocarditis and is thought to be due to an allergic reaction to a variety drugs (Table 69-4). Methyldopa, the penicillins, sulfonamides, tetracycline, and the antituberculous drugs are the pharmaceuticals most commonly associated with this entity. It is characterized by peripheral eosinophilia and infiltration into the myocardium by eosinophils, multinucleated giant cells, and leukocytes (Fig. 69-6).[158] The major basic protein of the eosinophil granule may be detected in the presence of acute necrotizing myocarditis, suggesting toxicity of the granule contents.[159] Good success has been reported with stopping the offending agent and treatment with corticosteroids.[160] Unfortunately, the presence of this condition often goes unnoticed and the first manifestation of cardiac involvement is sudden death due to arrhythmia.

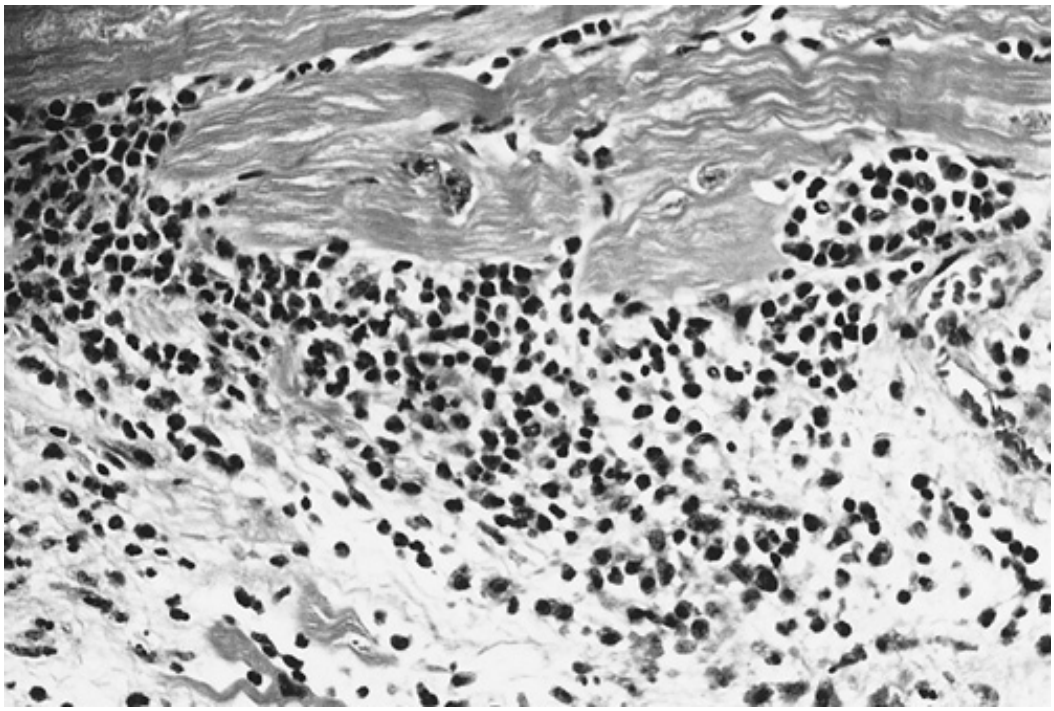

Figure 69-6: Photomicrograph showing interstitial infiltrates rich in eosinophils. (H&E, ×40.)

Table 69-4: Drug Causes of Eosinophilic Myocarditis

Drug	
Acetazolamide	Oxyphenylbutazone
Amitriptyline	Para-aminosalicylic acid
Amphotericin B	Penicillin
Ampicillin	Phenindione
Carbamazepine	Phenobarbital
Cefaclor	Phenylbutazone
Chloramphenicol	Phenytoin
Chlorthalidone	Spironolactone
Desipramine	Streptomycin
Hydrochlorothiazide	Sulfadiazine
Indomethacin	Sulfisoxazole
Interleukin-4	Sulfononylureas
Isoniazid	Tetanus toxoid
Methyldopa	Tetracycline

GIANT-CELL MYOCARDITIS

Giant-cell myocarditis is an extremely rare but aggressive form of myocarditis, typically progressive and unresponsive to medical therapy.[161] This disease is most prevalent in young adults, with a mean age at onset of 42 years (and a range of 16 to 69 years). Association with other autoimmune disorders is reported in approximately 20 percent of cases. Diagnosis is made by endomyocardial biopsy. Widespread or multifocal necrosis with a mixed inflammatory infiltrate including lymphocytes and histiocytes is required for histologic diagnosis. Eosinophils are frequently noted, as are multinucleated giant cells in the absence of granuloma (Fig. 69-7). Immunophenotyping of the cellular infiltrate has shown lymphocyte populations composed of T-helper or in some cases T-suppressor cells.

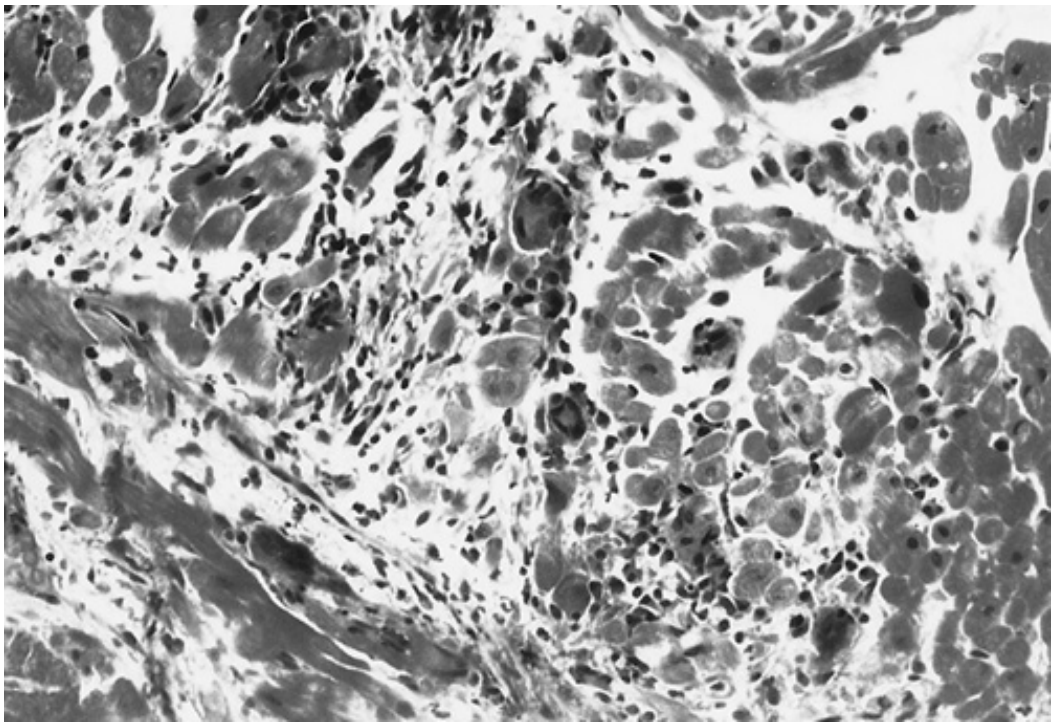

Figure 69-7: Photomicrograph showing extensive myocyte damage and infiltrates of mononuclear cells and numerous multinucleated giant cells. (H&E, ×60.)

The clinical course is usually characterized by progressive CHF and is frequently associated with refractory ventricular arrhythmia.[162] It is almost uniformly and rapidly fatal. Comparison of survival of patients with giant-cell myocarditis with that of patients with lymphocytic myocarditis demonstrates significantly worse survival in those patients with giant-cell disease (Fig. 69-8). There have been rare reports of response to aggressive immunosuppressive regimens that include cyclosporine and azathioprine in addition to corticosteroids.[162,163] Use of immunosuppressive therapy in these patients appears to prolong survival. Cardiac transplantation represents the best treatment option, though most patients expire prior to identification of a suitable donor. Giant-cell myocarditis may recur following cardiac transplantation, but the frequency of recurrence is unknown. Giant cells can be detected on routine surveillance biopsies up to 9 years posttransplant. This cellular infiltrate may respond to an increase in immunosuppressive therapy.

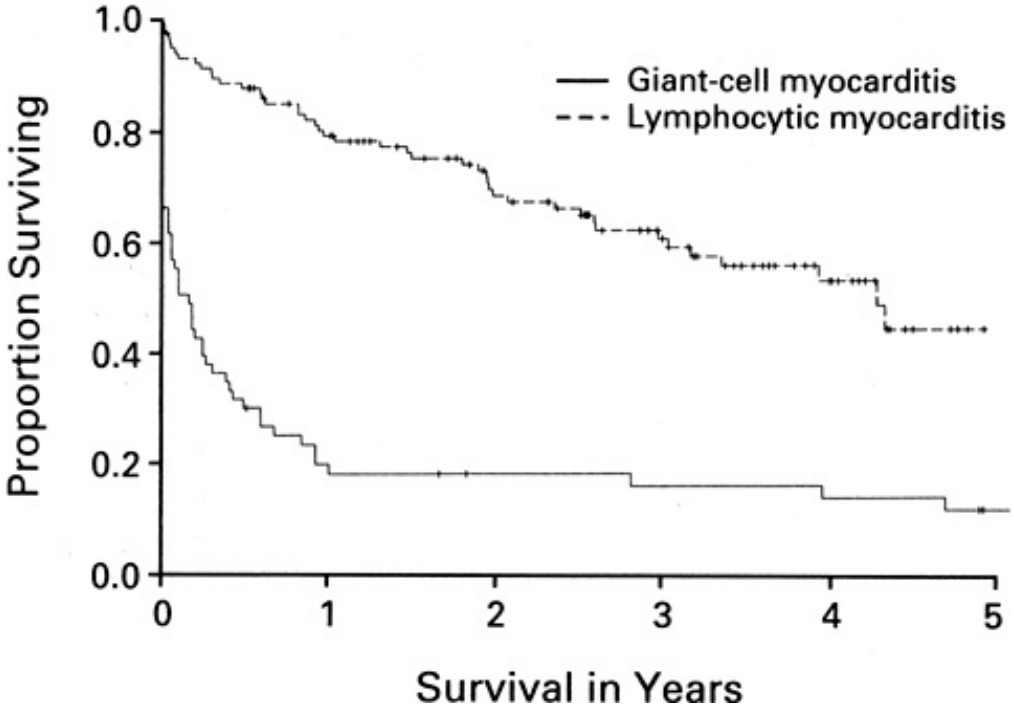

Figure 69-8: Kaplan Meier survival curves for patients with giant-cell myocarditis versus lymphocytic myocarditis. (From Cooper et al.,[161] with permission.)

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PERIPARTUM

Peripartum cardiomyopathy is an uncommon form of CHF first described by Virchow in 1870.[164] Estimates of its incidence vary from 1 to 1300 to 1 in 15,000 pregnancies.[165] The disease occurs more commonly in obese multiparous black females over age 30.[166] Cesarean delivery, multiple gestations, preeclampsia, and chronic hypertension are other predisposing factors. Patients present with heart failure in the last trimester of pregnancy or in the first 5 months postpartum. Absence of a demonstrable cause of heart failure and structural heart disease is required to make the diagnosis. Indeed, the hemodynamic stress of pregnancy can frequently unmask previously unknown cardiac disease (see also Chap. 82).

PATHOGENESIS

The etiology of this disorder is unclear. Proposed mechanisms include nutritional deficiencies, genetic disorders, viral or autoimmune etiologies, hormonal problems, volume overload, alcohol, physiologic stress of pregnancy, or unmasking of latent idiopathic dilated cardiomyopathy. Several lines of evidence suggest that peripartum cardiomyopathy may be the result of myocarditis due to a viral illness or an autoimmune etiology.[167-172] Given the relatively immunosuppressed state of pregnancy, susceptibility to cardiotropic viruses is higher,[167] as is the viral load during infection.[168] Furthermore, studies have demonstrated that when cardiac output rises, as is the case in pregnancy, myocardial viral lesions worsen.[169] Additionally, several studies have demonstrated histologic evidence of myocarditis on endomyocardial biopsy samples obtained from patients with peripartum cardiomyopathy.[170-172] Other investigators have postulated an autoimmune etiology to peripartum cardiomyopathy, specifically immunologic responses to fetal and endometrial antigens that cross-react with the patient's myocytes. In one case report, a patient with peripartum cardiomyopathy had antibodies to smooth muscle and actin produced in response to actin and myosin released during uterine degeneration after delivery. These antibodies later cross-reacted with the myocardium and induced cardiomyopathy.[173]

CLINICAL PRESENTATION

The presentation is that of heart failure. Presenting symptoms include shortness of breath, dyspnea on exertion, edema, palpitations, syncope, sudden death, and thromboembolic phenomena. The incidence of thromboembolism is high due to the hypercoagulability of pregnancy. Physical findings are notable for S3, S4, tricuspid or mitral insufficiency murmurs, edema, rales, ascites, hepatomegaly, jugular venous distension. The ECG frequently shows left ventricular hypertrophy. Echocardiographic findings can range from single-chamber left ventricular enlargement to four-chamber dilatation. In a small percentage of patients, endomyocardial biopsy may reveal myocarditis, but generally the findings are nonspecific.

PROGNOSIS AND TREATMENT

Too few patients with peripartum cardiomyopathy have been studied to fully analyze the natural history of the disease. In a small series of 27 patients, left ventricular size was analyzed at 6 months; 14 patients (50 percent) had normal dimensions. None of these patients died of CHF-

compared with 85 percent of those patients with persistent cardiomegaly, who died from CHF within 5 years.[174] The authors concluded, therefore, that if the congestive cardiomyopathy persists for more than 6 months, it is likely to be irreversible and to be associated with a worse prognosis. Similar findings were published in another series by O'Connell et al.[83] These authors also noted that those patients with higher ejection fractions and smaller ventricular diastolic dimensions at the time of diagnosis have a better long-term prognosis. Other prognostic studies suggest that those patients with persistent symptoms more than 2 weeks postpartum have a worse prognosis, raising the question as to whether this disorder has different etiologies.[175] The role of corticosteroids in the treatment of this disorder is controversial.[170,171] The incidence of thromboembolism is high due to the hypercoagulabilty of pregnancy; therefore anticoagulation is recommended.[175]

Patients with refractory heart failure referred for transplant have a survival posttransplant comparable with that of patients with idiopathic dilated cardiomyopathy, though higher early rejection rates are noted.

In patients with stable heart failure or recovery of left ventricular function, the possibility of subsequent pregnancy must be addressed. There are several case reports of patients with this diagnosis who went on to subsequent pregnancies. The outcomes of these patients are variable, with a few having uneventful pregnancies and others developing an exacerbation or recurrence of fulminant heart failure. Subsequent pregnancy should be viewed as high risk and all patients with this disorder should be counseled on birth control and even sterilization.

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HYPERTROPHIC AND FAMILIAL

Hypertrophic cardiomyopathy is characterized by disproportionate hypertrophy primarily of the left ventricle (Fig. 69-9) and occasionally the right ventricle. It most typically involves the septum but can also be concentric[176] and occurs in the absence of a recognizable stimulus to hypertrophy. This has led many to postulate and subsequently demonstrate a genetic basis to this disease.[177] Inheritance is of an autosomal dominant pattern; however, the phenotypic expression of this disease as measured by echocardiography is highly variable and reflects the different genetic mutations and incomplete penetrance.[178-180] The identification of certain well-characterized genetic abnormalities offers some measure of prognostication. Several familial hypertrophic cardiomyopathy-causing mutations have been characterized in the genes encoding sarcomeric contractile proteins-namely, the beta-myosin heavy chain,[181] cardiac troponin T,[178] alpha tropomyosin,[178] and cardiac myosin-binding protein C.[182,183] Previous theories suggested that variations resulting in a change in charge of the substituted amino acid were associated with a poor survival index.[184,185] However, the genotypic-phenotypic correlation is not always preserved. For example, a cytosine-for-guanine mutation hot spot responsible for familial hypertrophic cardiomyopathy has also been described in the beta-myosin heavy chain. In both mutations, a basic residue is replaced by an uncharged one. However, in one mutation, where glutamine replaces arginine, the mutation has a malignant phenotype; in the other, where tryptophan replaces arginine, the phenotype is that of mild hypertrophy with no sudden death.[186,187]

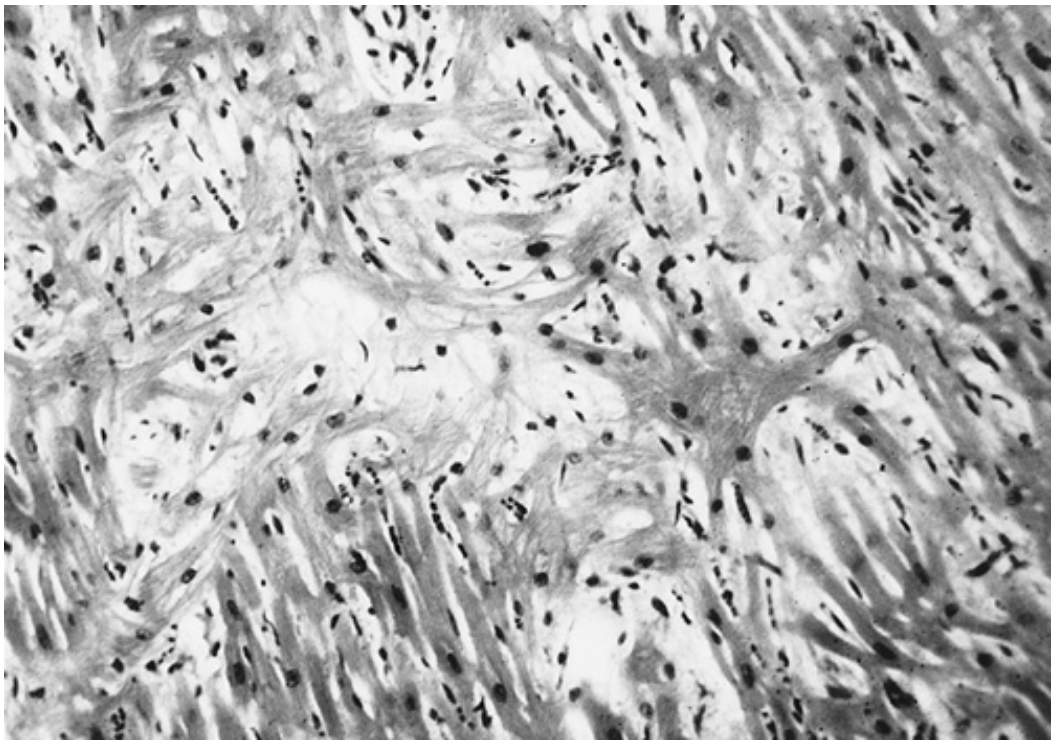

Figure 69-9: Photomicrograph showing significant myocyte disarray in hypertrophic cardiomyopathy. (H&E, ×40.)

Predicting the clinical course and outcome for individual patients with HCM has thus proved difficult.[188,189] In unselected populations, premature mortality is estimated at about 1 percent.[186] Sudden death is most common in the 12- to 35-year age group[190] and typically occurs in those who have previously been asymptomatic.[189] Most patients die while sedentary or during mild exertion; a substantial proportion collapse during or just after vigorous physical activity,[190] which forms the rationale for prohibiting sports participation for those afflicted with hypertrophic cardiomyopathy.

The mechanism of sudden death in hypertrophic cardiomyopathy is complex and probably multifactorial.[191] Recurrent syncope is the only symptom that has been shown to be reliably associated with subsequent sudden death.[192] Other proposed risk factors include prior cardiac arrest, sustained ventricular tachycardia, massive left ventricular hypertrophy, a malignant genotype or a previous family history of sudden premature death, repetitive salvos of nonsustained ventricular tachycardia on Holter monitoring, and early onset of symptoms in childhood.[193-196] The main forms of therapy have been primarily beta blockade, calcium channel blockers, amiodarone, and implantable cardioverter-defibrillators, with conflicting data on their impact on mortality.[197] Cardiac transplantation is pursued when significant symptomatic systolic dysfunction develops.[198]

As in the case of the myosin mutations noted in the hypertrophic cardiomyopathies, single genetic defects are presumed to underlie the dilated cardiomyopathies that have been described in several large families. There has been recent evidence that dilated cardiomyopathy is more frequently familial than generally realized.[199] In a single-center study of 96 patients with a diagnosis of idiopathic cardiomyopathy, approximately 20 percent had a familial basis.[200] Other studies have estimated a familial role in up to 50 percent of cases when firstdegree relatives are carefully screened.[201] The influence of a preceding viral infection,[202] alcohol use,[203] or pregnancy[204] on the clinical manifestation of cardiomyopathy in familial situations remain unclear.

Neuromuscular Diseases

Several heritable neuromuscular dystrophies may be associated with cardiomyopathy. Included in this category are diseases such as Beckel's, Duchenne's, and X-linked cardioskeletal myopathy, myotonic dystrophy (Stingert's disease), congenital myotonic dystrophy, limb-girdle muscular dystrophy (Erb's disease), familial centronuclear myopathy, Dugelberg-Welander syndrome, Friedreich's ataxia and Barth's syndrome. The myocardial involvement, natural history, and prognosis of each of these disorders are variable.

Duchenne's dystrophy is an X-linked disease with proximal muscle weakness and cardiomyopathy. A dystrophin gene mutation is responsible. Death usually results from respiratory and/or cardiorespiratory failure. Patients with myotonic dystrophy present between age 20 and 50 years, usually with arrhythmias.

Several mitochondrial myopathies have also been described.[177,205] Mitochondria are essential cellular organelles that convert oxygen to biochemically useful energy. Additionally, mitochondria function as calcium storage sites and modulators of cellular pH. As such, mitochondrial function affects muscle and ventricular function. Mitochondria are unique organelles with their own maternally inherited DNA, which encodes several respiratory chain proteins. Genetic defects in the mitochondrial respiratory chain enzymes-specifically complexes I, III, and IV-have been recognized as the cause in some cardiomyopathies. The presentation in mitochondrial myopathies is extremely heterogeneous, as each cell will contain a mixture of

normal and mutant DNAs. Deletion mutations in DNA can occur and are frequently observed in these myopathies.

Mitochondrial myopathies include such disorders as Kearns-Sayre syndrome, chronic ophthalmoplegia, myoclonic epilepsy, ragged-red-fiber disease, and mitochondrial encephalomyopathy. The MELAS syndrome-mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes-is associated with cardiomyopathy and generalized microangiopathy. Kearns-Sayre syndrome results from a deletion mutation in mitochondrial DNA. This ocular myopathic disease is associated with dilated or hypertrophic cardiomyopathy with cardiac conduction defects.

Defects in transport of molecules from the cytoplasm into the mitochondria have also been associated with cardiac and skeletal myopathy. One example is that of carnitine deficiency, discussed later in this chapter.

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INFILTRATIVE

The infiltrative cardiomyopathies comprise several acquired and heritable conditions; these include amyloidosis, hemochromatosis, carcinoid, sarcoidosis, glycogen storage disease, endocardial fibroelastosis, and endomyocardial fibrosis due to hypereosinophilic syndromes or other collagen vascular disorders such as scleroderma or Churg-Strauss syndrome.

Amyloid

CLASSIFICATION AND PATHOGENESIS

The most commonly encountered of the infiltrative cardiomyopathies is amyloidosis, leading to an overproduction of a monoclonal immunoglobulin protein that is deposited throughout the body. Secondary amyloidosis results from the deposition of a protein other than immunoglobulin. Whereas primary amyloid has no associated systemic diseases, other chronic diseases are present in the secondary form. Secondary amyloidosis may result from familial, senile, or chronic inflammatory processes (rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, tuberculous paraplegia associated with decubitus ulcers, cystic fibrosis, and heroin use with chronically infected cutaneous injection sites). Familial Mediterranean fever is an autosomal recessive inherited disease of Sephardic Jews, Armenians, and other Mediterranean peoples associated with amyloid deposition. In the familial diseases, more than 40 different genetic mutations of the plasma protein transthyretin (prealbumin) have been associated with amyloid deposition. Inheritance is autosomal dominant, with the genetic defect being confined to a single amino acid substitution in the mature protein.[206,207]

The frequency of cardiac involvement varies with the different etiologies. Of patients with primary amyloid, one-third to one-half have cardiac involvement and more than one-fourth have symptomatic heart failure. Cardiac involvement in patients with secondary amyloidosis is much less frequent. Indeed, in amyloid due to chronic inflammatory processes, amyloid protein deposition is usually limited to the intima and media of arterioles and not the heart. Familial amyloidosis is the rarest form of systemic amyloidosis, affecting only about 4 percent of cases; however, cardiomyopathy is present in 68 percent of those affected. Familial amyloidosis can manifest initially with progressive neuropathy, cardiomyopathy, or renal involvement. In some of the families, cardiac amyloidosis is not even symptomatic, while in others cardiac symptoms predominate. Senile cardiac amyloidosis is common in the elderly but often does not lead to a clinical cardiac syndrome and is only detected postmortem.[208]

CLINICAL PRESENTATION

Amyloid fibrils are rigid and as such lead primarily to relaxation abnormalities and diastolic dysfunction; however, when myocardial replacement occurs, systolic dysfunction becomes a prominent feature.[209] The cardiomyopathy may be restrictive or congestive in nature. Systolic left ventricular function deteriorates late in the disease process only after marked amyloid deposition.[210-217] The clinical presentation is that of congestive heart failure, with a more frequent occurrence of right-sided symptoms. Sudden death and myocardial infarction may result from vascular involvement. Atrial arrhythmias, from infiltration of atrial tissue with amyloid, are not

uncommon.

DIAGNOSIS

Diagnosis is made by characteristic echocardiographic features and endomyocardial biopsy.[218] Echocardiography can demonstrate symmetric thickening of the left ventricular wall with a diffuse hyper-refractile, granular sparkling appearance of the myocardium (Fig. 69-10*A*) (see also Chap. 13). Abnormal left ventricular diastolic filling manifested by reduction in the rate, in the volume of rapid diastolic filling with enhanced atrial contraction can be seen very early in cardiac amyloidosis.[219] The ECG typically demonstrates low voltage despite marked hypertrophy on echo (Fig. 69-10*B*). A pseudoinfarct or postinfarct anterior wall pattern is often present.[220] Cardiac involvement is generally present when mean left ventricular wall thickness on echocardiogram is greater than 11 mm in the absence of a history of hypertension or valvular heart disease, with unexplained low voltage (<0.5 mV) on the ECG. The majority of patients presenting with cardiac involvement have a monoclonal protein spike in the serum or urine reflecting the primary nature of the disease.[210]

Amyloid is detected easily in endomyocardial biopsy specimens using Congo red staining and is seen in the interstitium in a pericellular or nodular pattern, in the endocardium, or in myocardial blood vessels. Sulfated alcian blue, methyl violet, and thioflavine T are other histochemical stains used to detect cardiac amyloid (Fig. 69-10*C*). Immunoperoxidase stains for kappa and lambda light chains and for prealbumin may categorize the type of cardiac amyloid. Electron microscopic examination of biopsy specimens is likely the most sensitive method of recognizing amyloidosis (Fig. 69-10*D*).

Radionuclide imaging using technetium-99m pyrophosphate and indium-111 antimyosin showing increased diffuse uptake can also be used to diagnose cardiac amyloidosis.

TREATMENT

Prognosis is typically poor and treatment ineffective.[221] Increased myocardial concentrations of digoxin may occur from binding of the drug to amyloid fibrils, thus increasing the propensity for digoxin toxicity. Digoxin should therefore be used with caution in these patients. Prognosis depends on the extent of myocardial involvement, but once heart failure is present, the prognosis is poor, with a 5-year survival less than 5 percent. Indeed, patients with primary amyloidosis who fall into New York Heart Association (NYHA) class 3 or have recurrent cardiac syncope rarely survive for more than 6 months. Echocardiography with Doppler assessment can provide prognostic information. A shortened deceleration time and an increased ratio of early diastolic filling velocity to the atrial filling velocity were more powerful predictors of mortality from cardiac causes than left ventricular wall thickness or fractional shortening.[222-224]

A recent clinical trial comparing colchicine to the combination of melphalan, prednisone, and colchicine failed to demonstrate any survival benefit in cases of cardiac amyloid. Stem-cell transplant as treatment for primary amyloidosis is now being investigated.

Because of recurrence in the transplanted heart, results following heart transplantation have proved disappointing.[225] The immediate and early postoperative outcomes are similar to those in patients undergoing transplantation for other cardiac diseases; however, late survival is reduced (39 percent at 48 months) owing to recurrence of the disease in the transplanted organ and progressive disease in other organ systems. With the continuing donor shortage, the outcome associated with primary amyloidosis is unacceptable to the majority of cardiac transplant centers. In the future, combined cardiac and bone marrow transplant may provide successful treatment.

Sarcoidosis

PATHOGENESIS

Sarcoidosis is a systemic granulomatous disease of unknown etiology characterized by enhanced cellular immune responses. The pathologic hallmark of this disease is the noncaseating granuloma (Fig. 69-11). The initial lesion is an inflammatory infiltrate consisting of activated helper-inducer T lymphocytes and abundant macrophages that secrete cytokines. The macrophages aggregate and differentiate into epithelioid and multinucleated giant cells. Fibroblasts, mast cells, collagen fibers, and proteoglycans encase the inflammatory cells into a ball-like cluster. The fibrotic response results in end-organ damage.

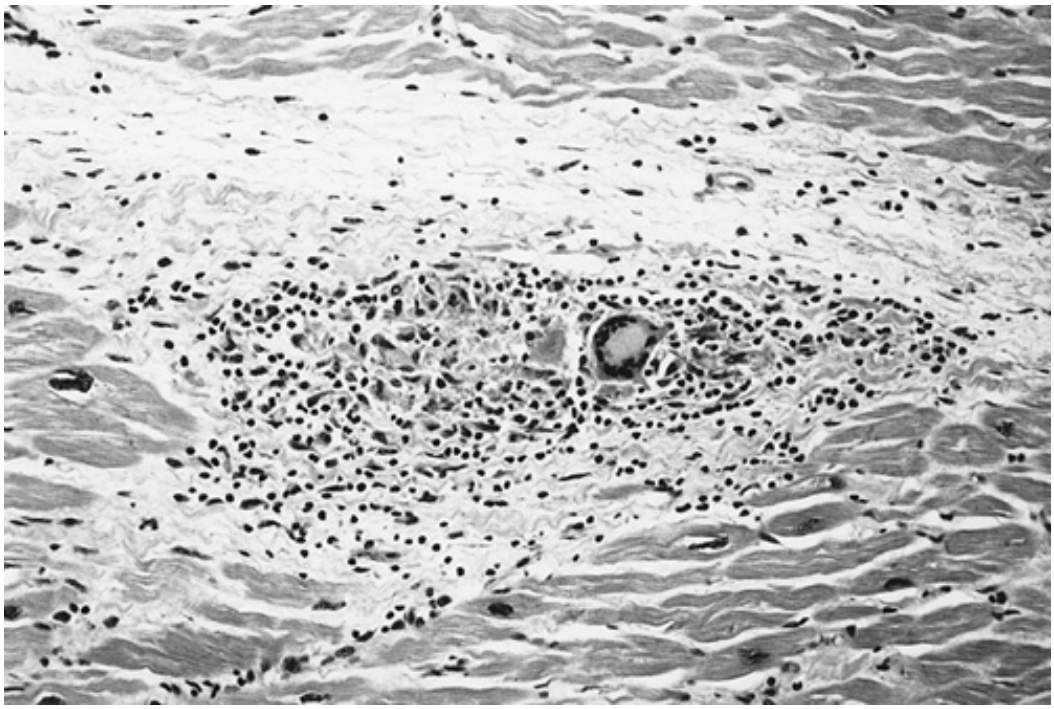

Figure 69-11: Photomicrograph showing interstitial noncaseating granulomas with a multinucleated giant cell. (H&E, ×40.)

Clusters of cases have been observed, suggesting spread by person-to-person exposure or environmental agents/pathogens. Genetic factors may also play a role in the development of the disease, as an exaggerated cellular immune response and the formation of granulomas may develop in genetically predisposed hosts after exposure to the offending antigen.

CLINICAL PRESENTATION

The clinical manifestations of sarcoidosis are protean. The disease may be widespread or limited to a single organ. Virtually any organ except the adrenal gland may be involved. The lymphoid, pulmonary, cardiovascular, hepatobiliary, and hematologic systems are the most commonly involved, with the lungs being affected in over 90 percent of patients.[226-228]

Cardiac sarcoid is more common than previously recognized. In a recent autopsy study of 38 patients with sarcoidosis, 76 percent had cardiac involvement, accounting for 50 percent of the deaths. In other series, sarcoidosis affected the heart in 25 to 50 percent of autopsy cases with fatality in 50 percent of the cases with cardiac involvement.[229] Cardiac sarcoid is more likely fatal

and less likely to be diagnosed antemortem than pulmonary sarcoid. Frequently the initial presentation is that of sudden death. Myocardial involvement peaks between the third and sixth decades of life. Less than 10 percent of patients with sarcoid have symptoms referable to the cardiovascular system.

In myocardial sarcoid, portions of the myocardial wall are replaced by sarcoid granulomas, which preferentially involve the cephalad portion of the ventricular septum or the left ventricular papillary muscles.[230] Myocardial involvement is much more common than pericardial involvement.[226231-234] Cor pulmonale due to extensive pulmonary sarcoidosis with interstitial fibrosis may occur.

Because of the varied extent and location of the myocardial granulomas, presenting signs and symptoms range from first-degree heart block to fulminant heart failure.[235] First-degree AV block, bundle-branch block, complete heart block, ventricular arrhythmias, sudden death, and heart failure occur with a frequency of 10 to 20 percent.[235] Heart failure can present as a cardiomyopathy with restrictive hemodynamics or systolic dysfunction. Some 25 percent of the deaths due to cardiac sarcoid are from heart failure, while sudden death accounts for one-third to one-half of the deaths.

DIAGNOSIS

In diagnosing cardiac sarcoid, evidence of other organ system involvement including lymphadenopathy, hepatomegaly, splenomegaly, or pulmonary findings should be sought. In cases where the heart is involved to a much greater degree than are other organs, little or no evidence of extracardiac sarcoidosis may be found. Chest x-ray, ECG, and echocardiography findings will depend on the extent and location of involvement. Due to the scattered nature of the granulomas, endomyocardial biopsy lacks sensitivity and seldom makes the diagnosis despite high specificity. Magnetic resonance imaging has been useful in diagnosing scars or lesions in the myocardium due to sarcoid.[236]

TREATMENT

Although no controlled trials have been performed, high-dose corticosteroids are usually given in the hope that the course of disease may be altered. Administration of corticosteroids can improve cardiac symptoms and reverse ECG changes in over half of the treated patients.[237] Antiarrhythmic drugs should be used as necessary, although drug therapy of ventricular tachycardia in patients with sarcoidosis, even when guided with programmed ventricular stimulation, is associated with a high rate of arrhythmia recurrence or sudden death.[238] Automatic internal cardioverter-defibrillators have been advocated. Prognosis after the diagnosis of cardiac sarcoid is variable but can be poor.[227] In one series of 247 patients, survival was 41 percent at 5 years and 15 percent at 10 years.[226,239] Transplantation is also a successful treatment, as the recurrence of sarcoid in the allograft is low, possibly due to posttransplant steroid therapy.[240]

Hemachromatosis

Primary hemachromatosis is an inborn error of metabolism leading to iron deposition in a variety of organs, including the heart, and resultant secondary myocardial fibrosis. Both restrictive and dilated presentations can occur.[241,242] In contrast to amyloidosis, treatment with phlebotomy[243] is highly effective. In the secondary forms of hemachromatosis due to multiple blood transfusions for blood dyscrasias, chelation therapy is highly effective. Diagnosis is made by symptom constellation in the presence of an elevated serum iron and ferritin. Endomyocardial biopsy is diagnostic (Fig. 69-12).

Carcinoid

Carcinoid heart disease typically leads to a restrictive pattern and often has asymmetrical involvement due to the predilection of the carcinoid for the tricuspid valve apparatus.[244,245] Diagnosis is generally made with right-sided heart findings in the setting of systemic features of carcinoid syndrome. Cardiac involvement responds favorably to control of the primary tumor with chemotherapy or catheter embolization.[244] Tricuspid valve replacement and/or pulmonary valvulotomy and outflow tract enlargement have been recommended when hemodynamically indicated.[244] Alternatively, balloon valvuloplasty for tricuspid or pulmonary stenoses has been used successfully[246] (see also Chaps. 59 and 77).

There are other heritable lesions leading to infiltrative cardiomyopathy. Pseudoxanthoma elasticum (also known as endocardial fibroelastosis) is an inherited disorder of elastic tissue metabolism that leads to a thickening and calcification of the endocardium.[247] Similarly, a number of metabolic inherited disorders cause massive infiltration of the myocardium in infancy and childhood. The best known is Pompe's disease, which is an autosomal recessive disorder caused by a deficiency of the enzyme α-glucosidase, leading to massive glycogen deposition in the cardiac and skeletal musculature. Interestingly, the pathophysiology resembles that of hypertrophic rather than restrictive cardiomyopathy.[248] Prognosis is poor, with no known therapy. Death typically ensues within the first year of life.

Eosinophilic Heart Disease

Eosinophilic heart disease was originally described several decades ago by Löffler,[249] who reported the observation of endocardial lesions, termed "endocarditis parietalis fibroplastica," in association with blood eosinophilia. Although initially thought to represent an isolated disease, Löffler's syndrome is now recognized to be only one manifestation of a spectrum of hypereosinophilic syndromes. Recently cases of isolated eosinophilic myocarditis without signs of endocardial involvement, with or without vasculitis, have been described.[250] Hypereosinophilic syndromes are characterized by peripheral eosinophilia and endocardial disease consisting of eosinophilic infiltration, fibrosis, and eventual occlusion of the ventricular cavity by scar and thrombus.[251] This leads to a very severe form of restrictive myocardial disease referred to as *obliterative myocardial disease*.[252]

PATHOGENESIS

Löffler's endomyocardial disease is considered to be an immunologic disorder caused by clones of abnormal eosinophils infiltrating both sides of the heart. This group of diseases may begin with myocarditis due to the direct toxic effects of the eosinophils and their granules.[253] Indeed, hypersensitivity myocarditis, discussed earlier in this chapter, may be an early variant of this disease. Chronic disease culminates in endomyocardial fibrosis after the disappearance of the initial eosinophilia.[254] The eosinophilic endocardial disease has since been well described[255,256] and is characterized by intense endocardial fibrotic thickening of the apex and subvalvular regions of one or both ventricles. These changes lead to inflow obstruction and restrictive physiology.

CLINICAL PRESENTATION

Löffler's syndrome was initially described primarily in men from temperate climates in their fourth decade of life with a hypereosinophilic syndrome. Diffuse organ involvement may be observed (lungs, bone marrow, brain), with cardiac involvement in more than 75 percent of patients. The typical clinical presentation includes weight loss, fever, cough, skin rash, and congestive heart failure. Overt cardiac dysfunction occurs in about half the patients and is the leading cause of death. Chest x-ray reveals cardiomegaly. ECG findings most commonly include

nonspecific ST- and T-wave changes, atrial fibrillation, and right bundle-branch block. Echocardiography commonly demonstrates localized thickening of the left ventricle with valvular leaflet abnormalities[257] and atrial enlargement due to atrioventricular valvular regurgitation and restrictive physiology. In cases of advanced endomyocardial fibrosis, there may be apical obliteration by thrombus[253] but normal systolic function.

Diagnosis is easily established in the acute phase by endomyocardial biopsy and typical ECG images.[252] Variable degrees of acute inflammatory eosinophilic myocarditis are observed. Marked changes can be seen histologically in the coronary vessels, including inflammatory, fibrotic, and thrombotic changes typically containing eosinophils. Fibrotic thickening of up to several millimeters[253] can be observed. Mural thrombosis is common.

Medical therapy with corticosteroids and cytotoxic drugs[159,257,258] in the early stages of disease may substantially improve survival. Routine therapy for heart failure with digitalis, diuretics, afterload reduction, and anticoagulation are adjuncts in the management of these patients. Surgical therapy offers palliation once the later fibrotic stages have been reached.[259]

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CARDIOMYOPATHY DUE TO PERSISTENT TACHYCARDIA

Incessant supraventricular or ventricular tachycardia can lead to severe dilated cardiomyopathy in both animals and humans.[260] Successful medical or surgical treatment of the tachyarrhythmia can lead to resolution of the myopathy. The mechanism between the sustained tachycardia and the development of cardiomyopathy is unknown but may be related to depletion of high-energy substrates.

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CARDIOMYOPATHY DUE TO RIGHT VENTRICULAR DYSPLASIA

Right ventricular dysplasia is a cardiomyopathy predominantly of the right ventricle. Left ventricle involvement is usually of a lesser and variable degree. Several anomalies may be included under this general heading: Uhl's anomaly,[261] arrhythmogenic right ventricular dysplasia,[262] and right ventricular cardiomyopathy.[263] It is currently recognized as an important inherited cardiomyopathy and a cause of sudden death, especially in youth.[264] Its cause is unknown, although an autosomal dominant pattern with variable expression and penetrance has been suggested, since many cases show a strong familial tendency.[265]

Clinically patients typically present with recurrent ventricular tachycardia of left-bundle-branch-block morphology and, less commonly, CHF. Standard electrocardiography discloses incomplete or complete right-bundle-branch block in most patients or T-wave inversions in leads V_1-V_3 (Fig. 69-13*A*). These conduction or repolarization abnormalities are thought to be due to adipose infiltration of the myocardium. Clinical diagnosis is based on detection of predominantly right ventricular morphologic changes on imaging studies. Echocardiography is an effective tool to demonstrate the characteristic abnormal structure[266] of the right ventricle, including hypokinesis, massive dilatation, and a "parchment-thin" wall[267] (Fig. 69-13*B*). In addition, tricuspid regurgitation and paradoxic ventricular septal wall motion are common. Pathologically, there is variable infiltration or replacement of the right ventricular myocardium by adipose and fibrous tissue.[268]

The importance of right ventricular dysplasia is its association with sudden death, with an incidence of up to 20 percent in some series.[264] Therapy therefore is focused on the prevention of sudden death with implantation of automatic internal cardioverter-defibrillators.

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CARDIOMYOPATHY DUE TO ENDOCRINE DISORDERS

Thyroid

Thyroid hormone has long been recognized to affect the heart and the peripheral vasculature.[269] Changes in cardiac function are mediated by T3 regulation of cardiac-specific genes.[270] Thyroid hormone metabolism is frequently abnormal in patients with CHF. In a study of 84 patients with advanced heart failure, T3 levels were found to be low.[271] Furthermore, a low T3/reverse T3 ratio was the only independent predictor of prognosis when a multivariate regression analysis was performed with known predictors of poor outcome such as ejection fraction, serum sodium, or hemodynamic variables. The low conversion to T3 was postulated to be an adaptive mechanism to decreased catabolism. In a subsequent study, Hamilton et al. studied the effects of intravenous T3 infusion to patients with class III or IV heart failure.[272] Cardiac output increased without a change in left ventricular ejection fraction or filling pressures. This was thought to be secondary to the effects of T3, causing vascular smooth muscle dilatation and therefore peripheral vasodilation. In another study of thyroid hormone replacement in heart failure, 20 patients with class II and III idiopathic dilated cardiomyopathy were given L-thyroxine orally.[273] Cardiac output improved, peripheral vascular resistance decreased, and exercise performance increased. The improved exercise performance was explained by a higher oxygen consumption at peak exercise due to improved oxygen uptake by skeletal muscle, increased perfusion of the musculature, or improved muscle metabolism by local action of L-thyroxine occurring during training. Similar results were obtained in a study by Moruzzi and colleagues.[274] In this series of 20 patients, ejection fraction, cardiac output, and left ventricular diastolic dimensions all increased. Functional capacity and peak exercise cardiac output also improved. The beneficial effects were sustained with the longer therapy regimen.

Like thyroid deficiency, thyroid toxicity can lead to the development of both high-output and low-output cardiac failure. A prolonged tachycardia and high-output state caused by thyrotoxicosis is thought eventually to produce left ventricular dilatation. A consequent progressive decline in systolic function leads to low-output heart failure. This process can often be reversed by reduction of excess hormone levels. In a study of 7 patients with a dilated cardiomyopathy and hyperthyroidism, Umpierrez et al. demonstrated echocardiographic normalization of left ventricular function after treatment with propylthiouracil or methimazole.[275]

Pheochromocytoma

Hypertension and its sequelae are the major cardiovascular manifestations of pheochromocytoma. However, there have been reports of a specific catecholamine-induced myocarditis[276] and/or cardiomyopathy.[277-279] Degenerative and fibrotic myocardial changes have been described in autopsy specimens of patients dying of suprarenal tumors.[276] Although progression to cardiac involvement is unusual, when the presentation of the tumor is aggressive, pheochromocytoma patients typically die of cardiovascular causes, most commonly congestive heart failure or malignant ventricular arrhythmias.[276,277] In the largest series, 15 of the 26 patients with proven pheochromocytomas had a pathologic diagnosis of myocarditis at autopsy.[276] Hemodynamic stabilization is generally obtained with alpha and beta blockers, and prompt adrenalectomy is required to eliminate catecholamine-induced cardiotoxicity. The cardiac abnormalities can be

reversed with tumor resection[280,281] (see also Chap. 51).

Acromegaly

It is not clear whether acromegalic cardiomyopathy is a specific entity or is secondary to the hypertension or atherosclerosis associated with this condition. However, 10 to 20 percent of patients with acromegaly develop congestive heart failure.[282] The congestive heart failure that develops in these patients is particularly resistant to conventional therapy[283] owing to higher collagen content in the acromegalic heart.[282] Histopathologically, the myocytes display cellular hypertrophy, patchy fibrosis, and myofibrillar degeneration. Inflammatory and degenerative damage to the sinoatrial and AV nodes can lead to sudden death.[283] Surgery and irradiation remain the mainstays of therapy, but often the cardiopathic manifestations persist despite a fall in growth hormone levels.[284]

Diabetes

Analysis of the Framingham data showed that the risk of developing heart failure was substantially increased among diabetic patients. Even after exclusion of patients with prior coronary or rheumatic disease and controlling for age, hypertension, obesity, and hypercholesterolemia, the diabetic patients have a fivefold increased risk of developing congestive heart failure.[285] This increased incidence suggested that the metabolic abnormalities associated with diabetes may contribute to myocyte dysfunction and produce a diabetes-induced cardiomyopathy. Histologically, this cardiomyopathy shows no evidence of epicardial atherosclerotic disease or abnormalities in myocardial capillary basal lamina.[286,287] Typically, interstitial fibrosis and arteriolar hyalinization are present. Clinically both systolic and diastolic dysfunction can occur, and the severity of the dysfunction is related to the degree of metabolic control.[288]

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OBESITY

Heart failure in the markedly obese is usually chronic. It often occurs due to reduction in left ventricular compliance due to the increases in left ventricular mass and resultant elevations of filling pressures. The chronic increases in cardiac work due to an increased myocardial output and arterial hypertension ultimately lead to systolic dysfunction. With exercise and weight reduction, left ventricular mass decreases[289] and function improves.[290] The improvement in function, however, seems limited to those patients whose obesity was of relatively short duration.[291]

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TOXINS

Alcohol

Congestive cardiomyopathy as a result of chronic alcohol abuse accounts for up to 45 percent of all dilated cardiomyopathies.[292] The untoward effects of alcohol on cardiac function were initially described more than 100 years ago. As an estimated 10 percent of the adult population are heavy alcohol users, cardiac toxicity from alcohol is a major problem.

PATHOGENESIS

The cardiodepressant effects of alcohol have been demonstrated following acute and chronic ingestion in animal models and in normal and alcoholic human subjects. Chronic excessive alcohol use can result in congestive heart failure, hypertension, and arrhythmias. Cardiac damage results from direct toxic effects of alcohol or one of its metabolites. Nutritional deficiencies, toxic cofactors, sympathetic stimulation, or coexistent hypertension may also contribute to disease development.[293]

Orally ingested alcohol is converted in the liver to acetaldehyde by the alcohol dehydrogenase enzyme system. Acetaldehyde is then converted into acetic acid by oxidation via acetaldehyde dehydrogenase. The activity of these enzyme systems varies greatly between individuals and in particular between races. Thus, depending on individual enzyme system activity, there are varying levels of alcohol and acetaldehyde concentrations after ingestion of an alcoholic beverage. Alcohol and acetaldehyde are both potent vasodilators. Additionally, acetaldehyde results in marked catecholamine release. Both alcohol and acetaldehyde interfere with a variety of cellular metabolic functions, including calcium transport and binding, lipid metabolism and fatty acid composition of the sarcolemma, protein synthesis, myofibrillar ATPase, and mitochondrial respiration.[292,294] Though ethanol can interfere with a number of myocardial metabolic steps, no predominant factor has been identified. Recently a nonoxidative pathway for the metabolism of alcohol in several organ systems including the heart has been described.[295] Nonesterified fatty acids are esterified with ethanol to produce fatty acid ethyl esters (FAEE). These molecules can accumulate in mitochondria and impair cellular function. Fatty acid ethyl esters are synthesized at high rates in the heart owing to the lack of oxidative ethanol metabolism in this organ. Other studies have demonstrated interference with lipid metabolism leading to triglyceride accumulation and alteration of the fatty acid composition of the sarcolemma.[292] Increased levels of acyl-CoA from enhanced glycerol acyltransferase activity may lead to triglyceride accumulation. The cellular membrane shows reduced changes results in decreased calcium uptake by the sarcolemma. Alcohol also is found to be an inhibitor of the sodium-potassium ATPase.

For many years, alcoholic cardiomyopathy was believed to be due to nutritional deficiencies. The stereotypical malnourished skid-row derelict could have a variety of nutritional deficiencies. Indeed, those subjects with heavy beer consumption could develop thiamine deficiency. As beer contains no thiamine, the consumption of this high-calorie, high-carbohydrate beverage can exhaust existing thiamine stores, particularly in the presence of a deficient diet. Thus, a small percentage of patients with alcohol cardiomyopathy may have coexistent thiamine deficiency. However, the majority of patients develop this disease despite adequate diets.[293]

Contamination of alcoholic beverages with heavy metals has resulted in heart failure. In the nineteenth century, an epidemic of heart failure occurred in Manchester, England, following accidental contamination of the beer with arsenic. More recently, in the 1960s, a new variant of alcoholic cardiomyopathy was described.[296] Patients presented with massive pericardial effusion, low cardiac output, elevated venous pressure, and polycythemia. After considerable medical detective work, the syndrome was linked to cobaltous chloride that was added to the beer as a foaming agent to increase and stabilize the beer head. Removal of the additive resulted in the resolution of this miniepidemic.

CLINICAL PRESENTATION

Although approximately 10 percent of the adult population are heavy drinkers, the prevalence of cardiac disease in this group is low-significantly lower than the prevalence of liver disease in the same population. Although patients with alcoholic cirrhosis may have evidence of asymptomatic myocardial disease, the simultaneous presentation of overt alcoholic liver and cardiac disease is extremely rare.[297]

The disease is observed most frequently in males age 30 to 55 years with a greater than 10-year history of heavy alcohol use. The disease is extremely rare in premenopausal women. The amount and duration of alcohol use is frequently difficult to establish. Criteria used to define heavy chronic alcohol use have included such estimates as the use of 125 mL/day of alcohol and/or 30 to 50 percent of daily calories derived from alcohol for a minimum of 10 years. In a study of 50 asymptomatic alcoholic men, Rubin et al. demonstrated that cardiomyopathy, as well as abnormalities of skeletal muscle, are common among persons with chronic alcoholism, and that alcohol is toxic to striated muscle in a dose-dependent manner.[203]

Presenting symptoms include dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, weakness, arrhythmias, or embolic phenomena. Atrial fibrillation is extremely common, followed by atrial flutter and ventricular premature contractions. Sudden death can be the initial presentation. ECG findings include first-degree heart block, left ventricular hypertrophy, nonspecific interventricular conduction defects, bundle-branch blocks and prolongation of the QT interval. The echocardiogram frequently shows left ventricular hypertrophy, single- to four-chamber enlargement, and mural thrombi.

In animal studies, left ventricular biopsies from dogs that developed alcoholic cardiomyopathy showed an accumulation of glucoprotein-like material in the interstitium on light microscopy as well as a dilatation of the intercalated discs on electron microscopic evaluation. These studies also demonstrated abnormalities of the sarcoplasmic reticulum and swelling of subsarcolemma regions.[298,299] The severity of these changes related to the duration and extent of alcohol use. Several histologic changes have been described on endomyocardial biopsies in alcoholic cardiomyopathy, but none of these changes are pathognomonic. Changes include myocyte loss, increased fibrosis, loss of sarcolemmal integrity, myofibrillar degeneration, mitochondrial swelling, intercellular edema and accumulation of fatty acids in particular triglycerides, and diminished levels of arachidonate in the cellular membrane.[300] Electron microscopy shows mitochondrial swelling with dense intramitochondrial inclusions, swollen vesiculated sarcoplasmic reticulum, and myofibrillar disruption.

TREATMENT

The mainstay of treatment is abstinence from alcohol. Alcohol withdrawal may have a remarkable impact on disease manifestation and progression, especially in the milder forms of the disease.[301-303] In animal models, following cessation of alcohol use, the hearts recover. In humans, the duration and extent of abuse is correlated with outcome.[304] Prognosis is extremely poor in those

patients who continue to drink compared with patients who become abstinent. Ninety-one percent of patients who abstain from alcohol after the initial diagnosis are alive at 42 months, versus 43 percent of those who continue to drink.

Although early in the disease process abstinence can result in recovery, there is a point at which cessation of alcohol is no longer effective,[305] and this correlates with the development of structural histologic abnormalities.[301] Survival of patients with alcoholic dilated cardiomyopathy who are abstinent appears to be significantly better than the long-term survival of patients with a comparable class of CHF due to idiopathic cardiomyopathy.[301,306] In a series of 75 patients with CHF, 23 had alcoholic cardiomyopathy compared with 52 with an idiopathic etiology.[306] Mean left ventricular ejection fraction, diastolic volumes, and NYHA class were similar. Overall survival was measured at 1, 5, and 10 years, and was 100, 81, and 81 percent for patients with alcoholic cardiomyopathy, and 89, 48, and 30 percent for patients with idiopathic cardiomyopathy, respectively. In another series however, no mortality difference was found,[307] but this may be due to persistent alcohol use in that cohort despite the onset of CHF.

Cocaine

Myocardial ischemia, infarction, coronary spasm, cardiac arrhythmias, sudden death, myocarditis, and dilated cardiomyopathy are all reported cardiovascular complications of cocaine abuse.[308] Clinical and experimental evidence suggests a variety of theories for the cardiotoxic effects of cocaine (see also Chap. 71).

The pharmacologic effects of cocaine on the heart partly explain its toxic effects.[309] By blocking the reuptake of norepinephrine, cocaine induces tachycardia, vasoconstriction, hypertension, cardiomyopathy, and ventricular arrhythmias. Cardiomyopathy may then result from secondary changes in the heart due to tachycardia or sustained increased ventricular afterload.

Cocaine has also been shown to exert a direct toxic effect on the heart. In vitro studies with isolated rabbit ventricular tissue[310] or isolated blood-perfused dog preparations[311] showed that high-dose cocaine depressed myocardial contractile force. Acute ventricular dilatation and reversible systolic dysfunction after intravenous cocaine administration have been documented in vivo in dogs.[312]

The risks and manifestations of toxic effects of cocaine in any given individual are unpredictable. The duration or amount of cocaine use is not predictable of disease. For example, among Andean Indians, heart failure rarely occurs from the chewing of coca even though plasma levels of cocaine are comparable to those of intranasal cocaine abusers.[313] This raises the possibility of a genetic susceptibility or that a metabolite or contaminant and not cocaine itself may be the inciting factor for development of cardiac damage.

Dilated cardiomyopathy in the absence of coronary abnormalities and myocarditis has been reported.[314,315] In these cases, myocardial depression is global and is generally reversible; it is attributed to a direct myocardial depressant effect of cocaine.[316]

There are no clinical or histologic features specific for cocaine-induced myocardial damage. Endomyocardial biopsy[308] and autopsy studies[317] confirm the presence of myocyte necrosis and a diffuse inflammatory cellular infiltrate in cocaine users. "Contraction-band necrosis" has been seen in a patient presenting with a clinical course similar to that of catecholamine cardiomyopathy,[318] but this is not characteristic. Although eosinophilic infiltrates can be seen, cocaine is not included in the list of typical drugs associated with a hypersensitivity syndrome. Thus the diagnosis is usually presumptive and is one of exclusion. The treatment of cocaine-related myocarditis and cardiomyopathy is nonspecific and focuses on abstinence and heart failure

therapy.

Chemotherapeutic Agents

Several chemotherapeutic agents can cause an acute and/or chronic cardiomyopathy. Among them, the anthracycline group (doxorubicin) and cyclophosphamide are the most common agents associated with heart failure.

Doxorubicin has been used as single or combination therapy for treatment of many different tumors including breast and esophageal tumors as well as sarcomas and lymphomas from the late 1960s. Its use is limited by its cardiotoxicity. The cause of the cardiotoxicity is unknown, but it is suspected to be due to increased oxidative stress from the generation of free radicals by doxorubicin. Moreover, endogenous antioxidants are reduced by treatment with doxorubicin. Increased oxidative stress results in the loss of myofibrils and cellular vacuolization, similar to what is observed with doxorubicin administration.[319]

Doxorubicin can be associated with early or late cardiotoxicity. Risk factors for the development of doxorubicin cardiomyopathy include age greater than 70 years, combination chemotherapy, mediastinal irradiation, prior cardiac disease, hypertension and liver disease. The early or acute cardiotoxicity manifests as a pericarditis-myocarditis syndrome[320] and is not dose-related. Left ventricular dysfunction is rarely seen, but arrhythmias, abnormalities of conduction, decreased QRS voltage, and nonspecific ST-segment and T-wave abnormalities are observed in up to 40 percent of patients.[321] The prognosis is good, with quick resolution of the abnormalities upon discontinuation of therapy.

In contrast, the late or chronic cardiotoxicity is due to the development of a dose-dependent degenerative cardiomyopathy[322] (Fig. 69-14). This syndrome generally occurs at doses above 550 mg/m^2. Serial assessment of nuclear ejection fractions is used clinically to monitor for adverse effects. However, histopathologic grading is most useful in delineating the safety of continued doxorubicin administration.[323] Cardiotoxicity may occur during therapy within a year of the last dose of anthracycline or as late as 6 to 10 years after its cessation. Therefore a course of this chemotherapy commits patients to prolonged cardiac surveillance.

Figure 69-14: Loss of myofibrils and vacuolization of cytoplasm (toluidine blue stain, ×40) in a patient with doxorubicin cardiotoxicity. (From Singal et al.,[319] with permission.)

Prognosis depends to some extent on the severity at time of presentation, but the incidence of death even in milder forms remains high.[324] The best management of anthracycline cardiotoxicity is prevention by limiting dosage. Lowering the peak blood levels of the drug by giving a continuous rather than bolus infusion also appears to significantly decrease drug-related damage.[325] Coadministration of doxorubicin with agents that would block free radical formation and not decrease its antineoplastic effects has been studied. Dexrazoxane, an iron chelating agent, has been used in clinical trials of patients with breast cancer or small-cell lung cancer to limit the cardiotoxicity of doxorubicin. The incidence of heart failure and the decrease in ejection fraction is less in those patients receiving combined therapy. Unfortunately, dexrazoxane is a potent myelosuppressive agent potentiating the effects of doxorubicin. It also may interfere with cancer therapy.

Heart failure due to doxorubicin has been very difficult to treat and is typically refractory to conventional therapy. In children with doxorubicin-induced cardiomyopathy, recent reports have described diminished symptoms and improved left ventricular function after treatment with beta blockers. Further studies on the use of these agents are needed.

In contrast to the anthracyclines, cyclophosphamide leads to an acute cardiotoxicity that is not related to cumulative dose.[326] Pericarditis, systolic dysfunction, arrhythmias, and myocardial edema make up the spectrum of cardiac abnormalities. Prior left ventricular dysfunction is a risk

factor for development of significant cardiomyopathy with cyclophosphamide. Although mortality is not trivial, survivors exhibit no residual cardiac abnormalities.[327]

Chemical Toxins

A variety of compounds can lead to a spectrum of cardiotoxicity, including cardiomyopathy. They include interferon alpha,[328] IL-2,[329] phenothiazines,[330] emetine,[331] methysergide,[332] chloroquine,[333] lithium,[334] hydrocarbons,[335] lead,[336] and carbon monoxide.[337] A summary of the cardiotoxicity seen with each compound is outlined in Table 69-5.

Table 69-5: Major Cardiovascular Complications ofChemical Toxins

Agent	Cardiac Toxicity
Cobalt	Congestive heart failure
Cocaine	Coronary abnormalities, arrhythmias, myocarditis, myocardial depression
Interferon alpha	Arrhythmias, dilated cardiomyopathy, congestive heart failure
Interleukin-2	Myocardial ischemia/infarct, arrhythmias, eosinophilic myocarditis
Phenothiazines	Electrocardiographic, arrhythmias, sudden death
Emetine	Mononuclear and histiocyte infiltration, electrocardiographic abnormalities
Methysergide	Left-sided valvular lesions, fibrotic endocardial and pericardial lesions, restriction and constriction
Chloroquine	Arrhythmias, cardiac dysfunction
Lithium	Arrhythmias, cardiac dilatation with myofibrillar degeneration
Hydrocarbons	Electrocardiographic changes, arrhythmias, and cardiomegaly
Lead	Electrocardiographic changes, arrhythmias, and congestive heart failure
Carbon monoxide	Arrhythmias and transient biventricular dysfunction

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CARDIOMYOPATHIES ASSOCIATED WITH NUTRITIONAL DEFICIENCIES

Vitamins

Thiamine deficiency, or beriberi, causes a high-output state, which leads to left ventricular dilatation and an elevated pulmonary capillary wedge pressure.[338] Vitamin D deficiency, or rickets, and vitamin D excess are associated with cardiovascular morbidity and mortality as well. There are about 25 reported cases of hypocalcemic cardiomyopathy in the adult population caused mostly by idiopathic hypoparathyroidism.[339] Similarly in children, cardiomyopathy has been documented in cases of hypocalcemia caused by vitamin D deficiency rickets.[340] Excess doses of vitamin D in humans have been associated with calcium deposition in the heart and QT shortening but not frank cardiomyopathy. Similarly, vitamin A, vitamin B_6, vitamin C, and niacin deficiency are not directly associated with overt cardiac dysfunction in humans but can be associated with ECG abnormalities.

Selenium

Interest in the role of selenium deficiency in cardiovascular diseases originated from observations of cardiomyopathy and sudden cardiac death in animals with dietary selenium deficiency.[341] Cardiomyopathy associated with inadequate dietary intake of selenium, termed Keshan's disease, has also been described in humans. This syndrome was discovered in regions of China with a low soil content of selenium.[342] Whether the cardiomyopathy results from the actual selenium deficiency or the selenium deficiency increases suspectibility to cardiotropic viruses is unclear. Coxsackievirus B3 (CVB 3/20), which causes no pathology in hearts of selenium-adequate mice, induces extensive myocarditis in selenium-deficient mice.[343] Furthermore, Coxsackievirus B3 recovered from the hearts of selenium-deficient mice and inoculated into selenium-adequate mice induced significant heart damage, suggesting mutation of the virus to a virulent genotype.[344] These findings may underlie the seasonal variation characteristic of Keshan's disease.

This disease is typically seen in children and pregnant women. Both acute and chronic forms of Keshan's disease exist.[345] In the acute form, cardiogenic shock, severe arrhythmias, and pulmonary edema are the manifestations of the systolic impairment. The chronic type shows a moderate to severe heart enlargement with varying degrees of cardiac insufficiency; often patients are asymptomatic. Its incidence is dramatically reduced with supplementation of sodium selenite.

Other than Keshan's disease, circumstantial evidence supports an association between selenium deficiency and cardiomyopathy. Congestive cardiomyopathy with low selenium levels has been reported in patients receiving total parenteral nutrition.[346] Patients with congestive cardiomyopathy have significantly lower serum selenium concentrations than healthy control subjects. Left ventricular ejection fraction is positively correlated with the selenium concentration in patients with cardiomyopathies.[346]

Carnitine

L-Carnitine is an essential compound in the transport of long chain fatty acids into mitochondria,

where they undergo beta oxidation. Since the normal heart obtains approximately 60 percent of its total energy production from fatty acid oxidation, this function of carnitine is thought to be of major importance.[347] Because of this function of carnitine and numerous case reports that have shown that some patients with carnitine deficiency exhibit cardiomyopathy,[348-350] it is believed that adequate levels of carnitine are required for normal energy metabolism and contractile function of the heart.[351] Interestingly, not all patients with carnitine deficiency exhibit cardiomyopathy. This may be explained perhaps by the degree of carnitine deficiency or by how cardiac performance is assessed.[352]

Deficiencies of carnitine can be either primary or secondary. Primary deficiencies arise from several genetic disorders involving carnitine synthesis or handling. These rare conditions are severe and are associated with muscle and plasma carnitine levels as low as 10 percent of normal (Fig. 69-15). Several case reports have established that primary carnitine deficiency is associated with cardiomyopathy.[353-355] The cardiomyopathy that ensues presents within 3 to 4 years of birth[356] and is profound; clinically, however, it responds to carnitine supplementation.

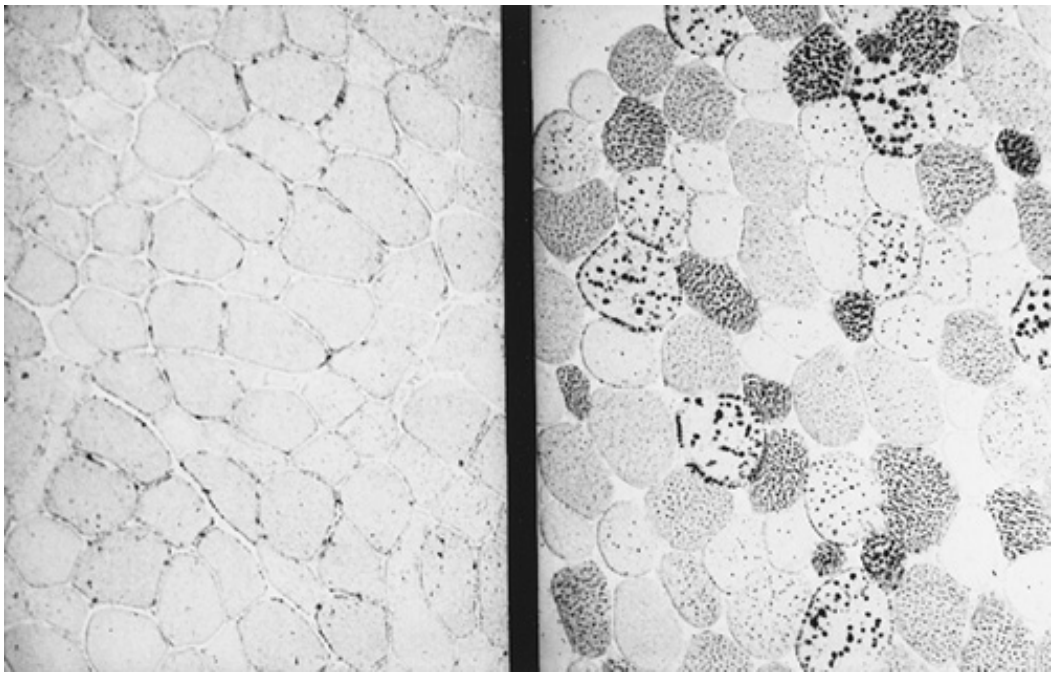

Figure 69-15: Photomicrograph of Oil red O stain demonstrating lipid deposits in type I and IIb fibers in normal (*right*) and carnitine-deficient (*left*) skeletal muscle.

Secondary carnitine deficiencies are much more common and arise from a large number of genetic diseases associated with defects in acyl-CoA metabolism.[357] In patients with long-chain or short-chain acyl-CoA dehydrogenase deficiency, carnitine levels are reduced to 25 to 50 percent of normal and a depression in cardiac contractile performance has been found.[357,358] Secondary carnitine deficiencies can also be acquired as a result of liver disease, renal disease[359,360] (Fanconi's syndrome, renal tubular acidosis), dietary insufficiencies[361] (chronic total parenteral nutrition, malabsorption), diabetes mellitus, and heart failure.[362] Many of these types of secondary carnitine deficiency are often associated with cardiomyopathy.[355,363] In cases of secondary carnitine deficiency, however, it has been difficult to determine whether the symptoms are due to carnitine deficiency or to the underlying genetic metabolic disorder. Based on this observation and the inconsistent reports of cardiomyopathy with these secondary deficiencies, it appears that a clear and strong association can only be made between cardiomyopathy and primary carnitine deficiency.

Coenzyme Q

Coenzyme Q (2,3-dimethoxy-5 methyl-6-decapreyl-1,4-benzoquinone) is another important factor involved in oxidative phosphorylation in mitochondria of the heart.[364] It has been postulated that its depletion, when found in myocardial biopsies of patients with cardiomyopathy,[365] may contribute to heart failure.[366] Several studies have claimed subjective and objective improvement in patients with heart failure after oral therapy with coenzyme Q.[367-369] These studies were small, unblinded, and uncontrolled trials. Recently a placebo-controlled double-blinded randomized crossover trial of coenzyme Q was performed in 30 patients with heart failure stabilized on conventional vasodilator therapy.[370] In this study, treatment with 3 months of oral coenzyme Q failed to improve resting left ventricular systolic function or quality of life despite an increase in plasma levels of coenzyme Q to more than twice basal values. Thus, given the lack of convincing and consistent data, coenzyme Q supplementation is not included in the basic repertoire of heart failure medications.

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CARDIOMYOPATHIES ASSOCIATED WITH ALTERED METABOLISM

Hyperoxaluria

Both primary and secondary oxalosis are characterized by excessive deposition of calcium oxalate crystals in various body tissues, including the heart.[371] Oxalate crystals are frequently deposited in the conduction system, leading to heart block and occasionally in the myocardium and the coronary arteries. On histology, variable degrees of cellular reaction-including fibrosis, necrosis, and mononuclear cell infiltration-can be seen, as well as foreign-body giant cells and myocardial granulomas. Cases of primary oxalosis can be treated with after combined kidney/liver transplantation.[372,373]

Hyperuricemia

Heart muscle disease associated with hyperuricemia is uncommon[374]; atherosclerosis and coronary artery disease are the most common cardiac manifestations associated with gout. Uric acid crystals can be found in the blood vessel walls, in the myocardial interstitium, along the valve surfaces, and in the pericardium and can lead to a granulomatous response with the formation of multinucleated giant cells.[373]

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IDIOPATHIC CARDIOMYOPATHY

Idiopathic cardiomyopathy (IDC) is the term used to describe a group of myocardial diseases of unknown cause. Idiopathic dilated cardiomyopathy probably represents the end result of a number of disease processes involving myocyte dysfunction, myocyte loss, myocyte hypertrophy and fibrosis. It is a diagnosis of exclusion. As discussed earlier in this chapter, an idiopathic dilated cardiomyopathy may be the end result of an infectious myocarditis. Endocardial biopsy in patients with dilated cardiomyopathy may reveal an inflammatory infiltrate. Surreptitious alcohol use as well as undiagnosed and untreated hypertension probably represent other etiologies of cardiomyopathy in many of these cases. Familial factors have generally been more predominant in hypertrophic cardiomyopathies than in dilated congestive cardiomyopathy. However more and more data are accumulating to suggest that genetic factors contribute to these cases as well. When one is making the diagnosis of idiopathic dilated cardiomyopathy, it is most important to exclude potentially reversible etiologies (Table 69-6).

Table 69-6: Potentially Reversible Dilated Cardiomyopathies

Ischemic with viable	Endocrine
myocardium	Hyperthyroidism
Valvular without surgi-	Pheochromocytoma
cally correctable lesion	Metabolic
Inflammatory	Hypocalcemia
CMV	Hypophatemia
Toxoplasmosis	Uremia
Mycoplasma	Carnitine
Lyme	Nutritional
Toxic	Selenium
Alcohol	Thiamine
Cocaine	Infiltrative
Cobalt	Hemachromatosis
	Sarcoidosis
	Hypersensitivity

The incidence of IDC has been estimated at 0.005 to 0.006 percent,[375] with the incidence increasing with age and males being more commonly afflicted.[376] A number of immune regulatory abnormalities have been characterized in IDC and include humoral and cellular autoimmune reactivity against myocytes,[377] decreased natural killer cell activity,[378] and abnormal suppressor cell activity.[70] Such findings suggest an immunologic etiology to IDC.

Several studies of the natural history of IDC have concluded that the prognosis is better than for ischemic cardiomyopathy[7]; without treatment, however, mortality approaches 50 percent at 5 years.[379] The risk of thromboembolic complications in IDC may be higher than for the ischemic group, but the clinical response to beta blockade as gauged by improvement in ventricular function is greater.[380] About 10 percent of patients with IDC will normalize their ejection fraction on beta blockade[381]; therefore, if tolerated, this therapy is warranted before consideration of cardiac transplantation.

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Part 11: CARDIOMYOPATHY AND SPECIFIC HEART MUSCLE DISEASES
Chapter 70:

AIDS AND THE CARDIOVASCULAR SYSTEM

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INTRODUCTION

The pandemic of acquired immunodeficiency syndrome (AIDS), after nearly 2 decades, has taken a tragic toll in lives in the United States and threatens a catastrophe in Africa and Southeast Asia. An estimated 10 million people worldwide are infected with the human immunodeficiency virus (HIV), and at least another 12 million have full-blown AIDS.[1] In the United States, over a million people are HIV positive, and about 2 million have been diagnosed with AIDS.[2,3]

In New York City, AIDS has become the most important cause of premature death among patients under age 65. In terms of years of potential life lost, AIDS advanced in rank order from the 8th leading cause of death in 1983 to the leading cause in 1994.[4]

AIDS is caused by infection with a virus of the family Retroviridae. This group of retroviruses comprises enveloped ribonucleic acid (RNA) viruses possessing an RNA-dependent deoxyribonucleic acid (DNA) polymerase (reverse transcriptase). There are two classes of AIDS viruses: HIV-1 and HIV-2.

The most specific definition of infection by HIV is by identification of the HIV organism in the host's tissues. Since isolation of the virus is not easily done and therefore lacks sensitivity, a patient with repeated positive screening test results for antibodies to HIV, as with an enzyme-linked immunosorbent assay (ELISA), confirmed by a supplemental test such as the Western blot immunofluorescence assay, should be considered to be infected by HIV.

The following classification system for the different stages of HIV infection as proposed by the United States Centers for Disease Control (CDC) is helpful[5]:

- *Group I:* Acute infection
- *Group II:* Asymptomatic infection
- *Group III:* Persistent generalized lymphadenopathy (PGL)
- *Group IV:* Chronic disease-AIDS with constitutional disease (such as unexplained diarrhea, weight loss, or fever over 1 month), neurologic disease, secondary infectious diseases, secondary cancers (Kaposi's sarcoma, non-Hodgkin's lymphoma, and primary lymphoma of the brain)

In January 1993, the CDC, together with other state and territorial health departments, broadened the surveillance definition for AIDS in adolescents and adults to add a measure of immunosuppression (a CD4+ T-lymphocyte count <200/μL or a CD4+ percentage <14), as well as three additional clinical conditions: pulmonary tuberculosis, recurrent pneumonia (two or more episodes within a year), or invasive cervical cancer.[6]

Patients with HIV infection have also been divided into three clinical categories. Category A includes asymptomatic patients, those with acute HIV infection or progressive lymphadenopathy. Category B includes symptomatic patients without AIDS-defining conditions. Category C includes patients with 25 AIDS-defining conditions, including opportunistic infections, tumors, central nervous system abnormalities, wasting syndrome, pulmonary tuberculosis, invasive cervical carcinoma, and recurrent pneumonia.[6]

The recognition of human infection by HIV in 1981 represented the startling development of a modern epidemic with many of the aspects of epidemics of the past, such as those of poliomyelitis and the black plague. This infection is due to a retrovirus that invades the nucleus of certain cells containing a specific receptor on their cell membranes and incorporates the DNA copy of HIV in the host's genetic material or genome. After an asymptomatic latent period from infection of 2 to 6 weeks, most patients experience a primary HIV-1 infection that is a self-limited viral syndrome not unlike infectious mononucleosis, characterized by fever, fatigue, pharangitis, lymphadenopathy, and maculopapular rash.[7] Over 95 percent of the patients seroconvert to a positive HIV serology within 6 months, most within 6 to 12 weeks.[8] After an apparent incubation (dormant) period of a mean of 8 to 10 years, the virus can eventually express itself by releasing into the cytoplasm double-stranded DNA copies of the virus, thus killing the cell and invading other immune cells, usually T-helper lymphocytes, to the point that the host's immune defense mechanisms are compromised.[9] Studies have demonstrated a high rate of viral replication in the lymph nodes during this quiescent period, indicating active progression of the disease, despite the low levels of infectious HIV in the plasma of some patients.[10]

A long-term prospective study showed the actuarial rate of progression from the time of infection to the appearance of AIDS to be 53 percent at 10 years and 68 percent at 14 years after infection, with an increasing progression after 5 years of infection.[11] About 30 percent of patients with PGL will progress to AIDS in 5 years.[12] A minority of patients have an accelerated course and develop full-blown AIDS in 1 or 2 years.[13] Small groups of patients have also been described who have had HIV infection for over 10 years without any symptoms.[14] At some point, there is a breakdown of the body's defense against certain neoplastic changes, resulting in the development of non-Hodgkin's lymphoma and Kaposi's sarcoma. These complications lead inevitably, at least in a very high percentage of cases, to death.

The average length of life after infection in the absence of treatment is approximately 10 years.[11] With the introduction of highly active antiviral therapy (HAART) including nucleocide reverse-transcriptase inhibitors and especially the protease-inhibitor drugs, elimination of the virus from the peripheral blood and prolongation of life have been demonstrated.[15] The impact of the new treatment with multiple drugs is seen in a fall in the rate of AIDS deaths by 12 percent in the United States in 1996 and by 47 percent in 1997.[16]

At the beginning of the epidemic in the United States, the HIV organism struck mainly at the male homosexual population. Later it was found to be transmitted not only through sexual intercourse but also through bloodborne contamination, soon affecting the population using intravenous drugs and other populations receiving blood products and blood transfusions, such as hemophiliacs. The disease is also transmitted perinatally, so that an increasing number of pediatric patients with AIDS are being seen. Although in the U.S. male-to-male sexual activity and intravenous drug users account for 75 percent of cases, in the developing world heterosexual transmission accounts for the majority of cases.[17]

From work with HIV-1, it has been found that the usual way in which the virus attacks cells is through interaction with a receptor on the surface membrane of the cell, the so-called CD4

receptor. This is present in T-helper lymphocytes. Macrophages, microglia, and Langerhans' cells may have specific receptors for HIV other than CD4. Other cells seem to lack an HIV receptor and therefore are much less often found to be sites of infection; the myocardial cell is one such cell.

From the beginning of the epidemic, it was recognized that the heart could be involved but that significant clinical involvement of the heart was unusual. Originally it was believed, through autopsy studies, that the heart was involved mainly because of pericarditis or metastatic Kaposi's sarcoma.[18,19] A few patients with nonbacterial thrombotic endocarditis (NBTE) were reported, but this could be nonspecific, since many of these patients have a wasting disease in which NBTE is not unusual.[20] On further review of autopsy series and clinical series and especially with the study of patients with AIDS who had echocardiography, it was apparent that abnormalities of the heart were seen frequently, even though clinical manifestations of heart disease still remained unusual.

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AUTOPSY FINDINGS

The incidence of cardiac involvement at autopsy varies, depending on the definition of cardiac disease. In 15 autopsy series, the incidence of cardiac involvement varies from none to 70 percent of the hearts, depending on whether lymphocytic infiltration with or without myocardial necrosis is included.[18-26] The presence of autopsy-proven cardiac involvement in patients who, during life, had clinically significant cardiac involvement is less impressive, especially if one includes the patients with localized, isolated collections of myocardial lymphocytes.

In evaluating autopsy reports, it is often difficult to discern how many patients had clinically significant abnormalities during life. In the large series of consecutive autopsies of AIDS patients, between 5 and 20 percent appear to have had cardiac lesions of potential clinical importance. These include patients with myocarditis with clinical manifestations, mainly with known pathogens-such as toxoplasmosis, clinically evident pericarditis, or nonbacterial endocarditis-which can cause systemic emboli.[27]

The largest recent autopsy series is by Barbero et al., where 440 AIDS patients had an autopsy. Cardiac involvement was documented in 18.6 percent and dilated cardiomyopathy in 2.7 percent.[28]

More important are the relatively few patients in whom cardiac abnormality was listed as the cause of death. The most common cause of death is respiratory failure and infection.[24,26,29,30] Neoplasm, lymphoma, and encephalopathy are also frequent causes of death.[31] Of 858 autopsied patients with AIDS from 15 series in the literature, only 9 (1 percent) had the cause of death listed as cardiac. If the cases with a recognized etiology for heart disease are removed, only 0.5 percent of deaths were possibly due to HIV "myocarditis."

Right ventricular hypertrophy and/or dilatation was reported in 12 of 71 patients (16.9 percent)[25] and in 18 of 115 patients (15.7 percent).[24] Pericarditis varied in frequency from 3 of 41 (7.3 percent)[20] to 3 of 101 (3 percent).[22]

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ECHOCARDIOGRAPHIC FINDINGS

Echocardiography in patients with either AIDS or PGL has been reported in a number of studies.[32-39] The prevalence of echocardiographic abnormalities varies from 15 to 60 percent and would be higher if the finding of mitral valve prolapse, an echocardiographic abnormality that may be related to cachexia, is included. The prevalence of left ventricular hypokinesis also varies from 12.5 to 41 percent in three large series.[33,34,36] In one series,[33] four of the eight patients had congestive heart failure; one died and at autopsy had a dilated cardiomyopathy without evidence of inflammatory myocarditis or cardiac opportunistic infections. Only in this study[33] was clinical congestive heart failure mentioned. Dilated cardiomyopathy was seen only in the hospitalized patients. In a large prospective echocardiographic study in 296 HIV-infected adults that was conducted over 4 years, Currie and colleagues found 13 (4 percent) with dilated cardiomyopathy.[37]

Cecchi and colleagues, from 1398 patients admitted for HIV infection, selected 127 (9 percent) with a clinical suspicion of cardiac disease and did echocardiograms on them: 92 (72 percent) had evidence of cardiac involvement, 6.5 percent of total HIV patients; 38 (2.7 percent) had pericardial effusion, and 20 (1.4 percent) had dilated cardiomyopathy.[38]

The finding of pericardial effusion was common, varying from 20 to 40 percent.[34,36,38] The incidence of tamponade varies: In one series[34] of 18 patients with pericardial effusion, 5 (28 percent) had tamponade. In this report of 300 patients with AIDS, 16 (5 percent) had clinically apparent heart disease, due in most cases to opportunistic infection or tumor.[34] Over a period of 3 years at the San Francisco General Hospital, Rapaport found that, of 1171 patients hospitalized with AIDS, an echocardiogram was ordered for 88 (7.5 percent) because of suspicion of cardiac disease (personal communication). Of these echocardiograms, 52 (59 percent) showed at least one abnormality. Of the 88 echocardiograms, 16 (18 percent) showed either left ventricular dilatation and/or left ventricular hypokinesis, and 26 (30 percent) showed pericardial effusion. There were no control subjects.

Steffen and colleagues[39] reported the prospectively collected results of echocardiography in 151 HIV-seropositive patients, 92 percent of whom were men with a median age of 37 years, and 73 percent were homosexual men. Of these, 13 percent were intravenous drug users, of whom 74 percent were in Walter Reed stages IV to VI, a classification using counts of T4 helper cells and clinical data.[40] A total of 107 patients (71 percent) had normal echocardiograms. Echocardiographic abnormalities attributed to HIV infection were present in 31 patients (20 percent). There was an association of abnormal echocardiographic findings with advanced clinical stages of the disease. The mortality during follow-up was the same for those with normal echocardiograms (35 of 102) as for those with abnormal echocardiograms (12 of 29) ($p = .48$). Even in those with the most advanced clinical disease, there was no independent prognostic significance of the echocardiographic cardiac involvement, with 44 percent of both echo-normal and echo-abnormal patients dying. This study shows a remarkably low incidence of HIV-associated echocardiographic abnormalities, most often asymptomatic pericardial effusion.

These studies suggest that the prevalence of echocardiographic abnormalities in HIV-positive patients depends on the stage of their clinical illness, with the sickest patients having the most

abnormalities.

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PERICARDIAL INVOLVEMENT

In general, pericardial effusion and pericarditis constitute the most commonly recognized cardiac involvement in AIDS. At autopsy, Kaposi's sarcoma involvement and lymphoma may be clinically silent, accompanied by asymptomatic pericardial effusion, or they may be clinically important because of pericardial tamponade.[41] Pericarditis due to specific organisms has frequently been reported. These organisms are most commonly *Mycobacterium tuberculosis*[34,42,43] or *Mycobacterium avium-intracellulare*.[35,42,44] One study[34] reported pericardial tamponade in five patients and large pericardial effusions in six. Of the patients with clinical heart disease in this study, 22 percent had echocardiographic evidence of tamponade, and another 33 percent had large pericardial effusions.

In a review of 15 autopsy and echocardiographic studies involving 1139 patients with HIV disease, the incidence of pericardial disease was 21 percent. Most cases were asymptomatic without an identifiable etiology. In those that were symptomatic, about two-thirds were caused by infection or neoplasm and one-third were of undetermined etiology. In the 66 published cases of pericardial tamponade, 26 percent were caused by *M. tuberculosis*.[42]

At San Francisco General Hospital, experience has been similar. In a consecutive series of 88 in-hospital AIDS patients who had echocardiograms, 36 (41 percent) had normal echocardiograms, whereas the most common abnormality, seen in 26 (30 percent), was pericardial effusion. We have recognized a total of 25 patients with AIDS or PGL who have pericardial disease. Ten of these patients had pericardiocentesis, of whom eight (32 percent) presented with tamponade, two had pericardial windows, and one died and was autopsied. Another two patients, who had neither pericardiocentesis nor pericardial windows, died and were autopsied. No etiology was found on examination of either fluid or tissue in any of the 12 patients.

In a prospective echocardiographic study among 231 patients recruited over a 5-year period, the prevalence of pericardial effusion for AIDS patients entering into the study was 5 percent. Over the follow-up time, the incidence of pericardial effusion increased as the stage of the HIV progressed from 0 percent per year in asymptomatic HIV-infected patients to 11 percent per year in patients with AIDS; 80 percent of these effusions were small and asymptomatic.[45] The survival of the AIDS patients who developed pericardial effusion was significantly shorter than the survival of those who did not, 36 percent versus 93 percent at 6 months. This shortened survival period remained significant even after adjustment for lead-time bias and was independent of CD4+ T-cell count.[45] Since death was not due directly to the pericardial effusion, the development of pericardial effusion in the setting of HIV infection probably suggests end-stage HIV disease.

Flum and colleagues also reported that AIDS-associated pericardial effusion was a grave prognostic sign. They reported 29 patients who had surgical windows for large effusions; only in 2 patients did this result in a change in clinical management. The mortality was 69 percent at 8 weeks after pericardial window.[46] They concluded that pericardial biopsy for diagnosis provided little practical therapeutic information and that surgical windows were justified only to relieve tamponade.

The etiology of pericardial effusion or pericarditis is not obvious; it may be HIV infection or other opportunistic viral infections with Coxsackie virus, cytomegalovirus, or neoplastic.[45] Occasionally, pericarditis has been reported to be caused by common organisms such as *Staphylococcus*,[46] *Cryptococcus neoformans*,[47] or herpes simplex virus.[48]

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MYOCARDIAL INVOLVEMENT

For a number of years, involvement of the pericardium and myocardium with both common and unusual opportunistic infections and neoplasms, such as Kaposi's sarcoma and lymphoma, has been recognized. At times, this involvement appears to be incidental and associated with the presence of organisms in many tissues, including the heart. Often, this involvement is not accompanied by signs of cell necrosis or even inflammation. At other times, the infection is accompanied by an intense myocarditis. Opportunistic infection has included viruses (herpes simplex, cytomegalovirus, and Coxsackie virus), bacteria, protozoa (*Toxoplasma gondii)*, and fungi (*Candida albicans, C. neoformans*, and *Aspergillus fumigatus*).[49-51] These specific infections have been diagnosed at autopsy but also during life with myocardial biopsy. The importance of identifying a specific organism as the cause of the myocarditis rests in the potential for treatment[42,52]; for instance, amphotericin B and flucytosine may be used to treat cryptococcosis. Grange and colleagues[53] reported a case of *T. gondii* myocarditis in a 58-year-old man with AIDS who was treated successfully with pyrimethamine and clindamycin. A similar case was reported by Albrecht and colleagues.[54]

The most common neoplasms are Kaposi's sarcoma and lymphoma of the non-Hodgkin's type.[18,19,24] With Kaposi's sarcoma, the tumor involvement of the myocardium or pericardium is most frequently an incidental finding. On occasion, myocardial involvement by lymphoma is diagnosed by needle biopsy of the myocardium.

One study reported a collection of 21 cases of lymphoma in AIDS patients-3 Hodgkin's and 18 non-Hodgkin's lymphoma of various histologic types-almost all of which were in the high-grade categories.[55] Unfortunately, these tend to be histologically aggressive tumors involving many organs, and they respond poorly to treatment. At times, the patient presents with pericardial tamponade or even superior vena cava syndrome.[56,58] Echocardiography revealing infiltration into the myocardium and/or myocardial or pericardial masses is most helpful in establishing a diagnosis.

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CARDIOMYOPATHY

In 1986, Cohen and colleagues reported three patients with AIDS who had clinical, echocardiographic, and morphologic findings of dilated cardiomyopathy.[59] All had a decreased ejection fraction, and two had congestive heart failure. All three died, and two had findings at autopsy compatible with myocarditis resulting in cardiomyopathy. Microscopic examination in both showed focal collections of inflammatory cells together with myofibrillar atrophy and myocardial necrosis. A subsequent report described 58 consecutively autopsied patients.[60] Seven (12 percent) had major clinical cardiovascular abnormalities, including four with congestive heart failure and others with ventricular tachycardia. All were late in the course of their disease. All patients with these major clinical cardiac abnormalities had focal myocarditis at autopsy. The etiology in these cases was not obvious but was believed to be viral myocarditis.

In another study of 71 patients with AIDS, 8 had left ventricular dilatation and decreased contractility and 4 had congestive heart failure.[33] In a similar echocardiographic study, none of 102 AIDS patients had congestive heart failure, although 41 percent had left ventricular hypokinesia.[36]

In autopsy studies reported in the literature, cardiac causes of death have been rare; clinically, the incidence of congestive heart failure has been extremely small, although microscopic focal myocarditis is frequently described. In 14 studies in the literature, 1009 patients with AIDS were reported. A total of eight died of cardiac involvement. One had cryptococcal myocarditis and one had toxoplasmic myocarditis; five came from one institution.[25]

Symptomatic cardiomyopathy in association with HIV-1 infection is uncommon; however, echocardiographic evidence of left ventricular dysfunction is more common, especially in patients who are the furthest along in the course of HIV disease. Individual reports of one to five cases of patients with either dilated left ventricle, hypokinetic left ventricle, or both have been frequent enough to require explanation.[59,61] Furthermore, the occurrence of cardiomyopathy in children, in whom a disease unrelated to HIV infection would be rare, further suggests a relationship between HIV disease and cardiomyopathy.[62]

Lipshultz and colleagues did a prospective study on 196 HIV-infected children, median age 2.1 years. Only two had congestive heart failure at enrollment. An echocardiogram done every 4 months revealed a 2-year accumulative incidence of cardiomyopathy of 4.7 percent (95 percent confidence interval, 1.5-7.9 percent).[63]

Prospective echocardiographic studies have been reported that show a high prevalence of myocardial dysfunction. DeCastro and colleagues did serial echocardiograms prospectively on 136 HIV-positive patients over a mean follow-up time of 415 ± 220 days. Seven AIDS patients developed clinical and echocardiographic findings of global left ventricular dysfunction. Of the six who died, five were autopsied: three had acute lymphocytic myocarditis, one had cryptococcal myocarditis, and one had myocardial fibrosis.[64]

Blanchard and colleagues did serial echocardiograms on 70 HIV-positive outpatients. Of the 50

patients with AIDS, 7 (14 percent) had echocardiographic evidence of left ventricular dysfunction. On repeat echocardiogram, three of the seven had improved left ventricular function, implying a transient problem that caused a transient decrease in left ventricular function.[65]

At San Francisco General Hospital, the cases of 74 AIDS outpatients were prospectively followed using serial quantitative Doppler echocardiography every 4 months. Control populations included HIV-positive patients without disease, HIV-positive patients with AIDS-related complex, and HIV-negative gay men. Over the follow-up period of 16.5 ± 12 months, no differences in left ventricular systolic or diastolic function were detected between the groups and no differences in mean values from the first to the last echocardiogram.[66]

The prospective study by Barbaro and colleagues reported 952 asymptomatic HIV-positive patients whose cases were followed clinically and by echocardiography for 60 ± 5.3 months.[67] By echocardiogram, dilated cardiomyopathy was diagnosed in 76 (8 percent) of patients-an incidence of 1.6 cases per 100 patients per year. A myocardial biopsy was done on all patients with cardiomyopathy, and a histologic diagnosis of myocarditis made in 83 percent. By in situ hybridization HIV nucleic acid sequences were found in 58 patients but only 36 (63 percent) had active myocarditis. Of these 36 patients, 25 percent had other cardiotropic virus infections with Coxsackie B virus in 6 (17 percent), cytomegalovirus in 2 (6 percent), and Epstein-Barr virus in 1 (3 percent). The authors concluded that dilated cardiomyopathy may be related either to direct HIV infection or to an autoimmune process induced by HIV, possibly in association with other cardiotropic viruses.

Possible Reasons for Cardiomyopathy

There are many theories on the etiology of congestive heart failure with a dilated, poorly contracting left ventricle found in the occasional patient. These explanations may well be related also to the more frequently observed echocardiographic reduction in left ventricular function with or without left ventricular dilatation. The most frequently mentioned etiology is that of myocarditis or postmyocarditis cardiomyopathy. There are occasional reports of virus being grown from cardiac muscle. In 1987, Calabrese and colleagues[68] were the first to report the culturing of HIV from a right ventricular myocardial biopsy from a patient with a hypokinetic right ventricle and a normal left ventricle.

There is some evidence that HIV itself invades the myocardial cell. The myocyte has no CD4+ receptors, which are the major way by which the virus enters the cell. Although there are other ways and possibly other receptors by which the virus could invade the cell, no one has convincingly shown the virus or a portion of the viral DNA or RNA within the genome of the myocardial cell.[69] One study reported detecting HIV nucleic acid sequences by in situ hybridization in cardiac tissue sections from 6 of 22 patients examined who had died of AIDS.[61] The hybridization target was thought to be myocytes, but this could not be proved by this technique. Furthermore, the myocardial cells showing the positive hybridization signal were sparse, comprising only one or a few cells per section; the myocardium was normal by light microscopy; and none of the patients had clinical evidence of cardiac disease. Still, the most compelling evidence for the ability of HIV virus to enter the myocardial cell comes from the previously mentioned study by Barbaro and colleagues.[67]

Other Theories for the Development of Cardiomyopathy

OPPORTUNISTIC INFECTIONS

Patients with AIDS are exposed to and susceptible to multiple bacterial, viral, mycotic, and

protozoal infections. Epstein-Barr virus and cytomegalovirus are both known to cause myocarditis in AIDS patients.[67,70] *Cryptococcus neoformans* and *T. Gondii* myocarditis have been well described.[29,52,53,71] Myocarditis due to *M. avium-intracellulare* has been reported.[20] *Aspergillus* endocarditis and myocarditis have been reported.[72]

DILATED CARDIOMYOPATHY AS A POSTVIRAL DISORDER

The study of patients with myocarditis without AIDS has shown that the myocarditis can be precipitated by viral infection and that the inflammatory reaction can progress when the virus is no longer recoverable from either the heart or even the patient. The viral infection precipitates an immune reaction either to viral antigen that cross-reacts with a myocardial protein or to altered myocardial protein, which acts as a foreign antigen, thus precipitating the immune reactions that continue the myocardial necrosis and inflammatory cell infiltration[73] (see also Chap. 69).

The evidence that congestive cardiomyopathy is precipitated by a previous viral myocarditis includes the biopsy finding of inflammatory infiltrate in some patients with dilated cardiomyopathy[74,75] and detection of increased elevated viral antibody titers and viral-specific RNA sequences in myocardial biopsies.[76] Thus, the cardiomyopathy can result from a previous infection with a number of organisms that are no longer recoverable from the myocardium.

Herskowitz and colleagues[77] reported the histologic and immunopathologic results of 37 endomyocardial biopsy samples from patients infected with HIV-1 who developed unexplained global left ventricular dysfunction. Twenty-eight patients had New York Heart Association (NYHA) class III and IV congestive heart failure. Four patients had myocarditis secondary to known etiologies. Of the remaining 33 patients, 17 (51 percent) had histologic evidence of idiopathic active or borderline myocarditis. Specific hybridization within myocytes was abnormal in five patients with HIV-1 antisense riboprobe and in 16 of the 33 with cytomegalovirus immediate early (IE-2) antisense riboprobe. This study is compatible with the possibility that cardiotropic virus infection and myocarditis may be important in the pathogenesis of HIV-associated cardiomyopathy.[77]

IMPAIRMENT OF THE IMMUNE MECHANISM LEADING TO CARDIOMYOPATHY

Humorally mediated autoimmune reactions involving antimyosin antibodies may also be implicated in the development of cardiomyopathy.[78] Circulating cardiac autoantibodies have been identified in four of six AIDS patients with cardiomyopathy and in none of the HIV-positive patients without cardiomyopathy. In situ hybridization with genomic probes failed to show evidence of HIV or any other viruses within the heart muscle. Results of ELISA showed a high titer of immunoglobulin G antibody to myosin and to cardiac mitochondrial adenine nucleotide transporter. In this study, it was concluded that the cardiomyopathy may be related not to HIV infection of the heart but rather to autoimmunity. Apparent improvement of left ventricular function in children with AIDS by using intravenously administered immunoglobulin is also suggestive of an immunologic etiology for the left ventricular dysfunction.[79]

ROLE OF CYTOKINES IN MYOCARDITIS

Ho and colleagues[80] proposed a primary role for neuroglial cell damage from the cytolytic effect of release of substances termed *cytokines* from HIV-infected monocytes, the "innocent bystander" destruction mechanism. Cytokines are biologically active mediators and are soluble proteins released by immune cells. Reversible myocardial depression is well documented in human and canine septic shock.[81,82] This was subsequently demonstrated to be due to a "myocardial depressant factor."[83] The exact nature of this myocardial depressant factor is not agreed upon, but

it could be related to a variety of mediators of sepsis such as endotoxin and the cytokine tumor necrosis factor (TNF) and interleukin 2.[84]

Other studies showed that the administration of endotoxin-released TNF caused depression of left ventricular function independent of left ventricular volume or loading conditions,[85] and elevated circulating levels of TNF have been noted in patients with severe chronic heart failure.[86] Increased circulating levels of TNF have been noted in patients with advanced HIV-1 infection.[87] This finding is consistent with a finding of increased production of the cytokine TNF by peripheral monocytes of patients with AIDS.[88]

Barbaro and colleagues[89] investigated the myocardial expression of TNF-α and inducible nitric oxide synthase (INOS) in endomyocardial biopsies in patients with HIV dilated cardiomyopathy and compared them with myocardium from patients with idiopathic dilated cardiomyopathy. The mean intensity of both TNF-α and INOS immunostaining was greater in the HIV patients compared with the idiopathic cardiomyopathy patients. The staining intensity of both TNF-α and INOS was inversely correlated with the CD4 count.

The increased levels of cytokines-including TNF, interleukins 1 and 2, and α-interferon-may lead to myocardial dysfunction either acting locally in a paracrine fashion on adjacent myocardium or systemically causing a decrease in myocardial function.[90,91]

CACHEXIA

Many patients with AIDS have marked weight loss and cachexia. In patients with anorexia nervosa, wall motion as assessed by two-dimensional echo Doppler was found to be abnormal in 8 of 14 patients but not in control subjects; also, lower stroke volume was found in patients compared with controls, possibly because of decreased heart size.[92] Starvation and refeeding studies in animals have demonstrated myofibrillar atrophy and cardiac interstitial edema that are accompanied by a decrease in left ventricular compliance and decreased peak systolic force.[93] These changes are thought to be due to protein-calorie malnutrition. Congestive heart failure may occur, especially during refeeding and recovery.[94]

VITAMIN- AND SELENIUM-DEFICIENCY STATES

Cachectic people can have vitamin-deficiency states; it is doubtful that many patients with cardiomyopathy have this as a prime etiology. Selenium deficiency has been described, together with reduced cardiac selenium levels in AIDS, similar to the Keshan's disease seen in Chinese with selenium deficiency. In one study, 10 patients with AIDS who had decreased left ventricular fractional shortening on echocardiography received sodium selenite for 23 days.[95] Six of eight showed a return toward normal of left ventricular fractional shortening within 21 days. Selenium deficiency has been reported to be common in malnourished pediatric patients with AIDS.[96]

DRUG-INDUCED CARDIOMYOPATHY

The effect of drugs, both recreational and therapeutic, on myocardial function is not well delineated in patients with AIDS. In most patients with AIDS and cardiomyopathy, however, drugs do not seem to be the cause[61,97]; nevertheless, in patients with AIDS, drugs such as doxorubicin, α_2-interferon, and interleukin 2 have been shown to produce cardiomyopathy that is sometimes reversible. Recombinant α_2-interferon-related cardiomyopathy in patients treated for primary renal cancer has been reported.[98] One report described three cases of reversible cardiac dysfunction associated with α-interferon therapy in AIDS patients with Kaposi's sarcoma.[99]

Cocaine use has been associated with myocarditis and dilated cardiomyopathy, which occasionally has been reported to be reversible.[100,101] Pentamidine has been reported to cause ventricular tachycardia.[102] The most common currently used drug in AIDS, zidovudine (AZT), a nucleoside analog, is a drug that inhibits replication of HIV in vitro, probably by inhibiting the reverse-transcriptase enzyme, which is essential to the replication of the retrovirus. No adverse cardiac effects have been reported in phase 1 clinical trials, and one study failed to show cardiotoxicity[103]; however, a toxic mitochondrial myopathy caused by long-term AZT after 12.8 months of therapy has been reported.[104] This myopathy is characterized by abnormal mitochondria with paracrystalloid inclusions. AZT-induced cardiomyopathy in rats has been shown to be related to oxidative damage and activated ADP-ribosylation reactions damaging mitochondrial energy production.[105] Whether this can occur in cardiac muscle in some patients is not clear. Foscarnet therapy for the treatment of cytomegalovirus infection has also been reported to produce a reversible cardiomyopathy.[106]

Conclusions

Clinical heart muscle disease and heart failure in AIDS are unusual. When this condition occurs, there may be explanations other than direct infection with HIV. The exact incidence of heart muscle disease in AIDS is as yet unknown but must be small, and the mechanisms that can cause failure are probably multiple.

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METABOLIC CARDIOVASCULAR COMPLICATIONS OF ANTIVIRAL DRUGS

With the introduction of protease inhibitors, a class of drugs that suppresses HIV replication, to the treatment of patients with HIV infection, metabolic abnormalities have been seen that have potential for development of cardiovascular disease. New-onset hyperglycemia similar to type II diabetes mellitus has been described, as well as worsening of preexisting diabetes in 1 to 6 percent of patients. This problem has been described with all of the protease inhibitors.[107] The cause of the hyperglycemia is not known, but it does respond to sulfonylureas, suggesting that the drug causes increased resistance to the peripheral effects of insulin although it is not possible to rule out a reduction in insulin secretion.[108] The treatment of hyperglycemia is similar to that of type II diabetes: diet and oral hypoglycemic drugs.

Lipid metabolic abnormalities have also been seen in patients taking protease inhibitors with extremely high triglyceride levels to over 1000 mg/dL,[109] which can occur within 2 weeks of starting therapy. In a study of ritonavir plus saquinavir, 11 percent of patients developed triglycerides above 1500 mg/dL. There were no instances of pancreatitis. There are also elevations in serum cholesterol.[110]

Although the mechanism by which this drug induces hyperlipidemia is unknown, there is a 60 percent homology of the catalytic region of the HIV-1 protease to which the drugs bind to two proteins regulating lipid metabolism: cytoplasmic retinoic acid-binding protein type I (CRABP-I) and low-density lipoprotein-receptor-related protein (LRP). Binding of the protease inhibitors to LRP would impair hepatic chylomicron uptake and triglyceride clearance.[108] The elevated triglycerides respond to gemfibrozil.

In 45 HIV-infected patients taking protease inhibitors who had abnormally elevated lipids, the National Cholesterol Education Program Guidelines were followed without disrupting the HIV therapy. Mean serum cholesterol prior to initiation of the protease inhibitors was 170 mg/dL. On the protease inhibitor, the mean cholesterol rose to 289 mg/dL, and triglycerides were 879 mg/dL. On diet, gemfibrozil alone, or with atorvastatin, the cholesterol fell to 201 mg/dL ($p = .01$) over a 10-month period.[111]

Finally, an abnormal redistribution of fat from the periphery centrally to the abdomen and thorax has been described. There is a loss of subcutaneous fat from the face and limbs (partial lipodystrophy), and the development of fat deposits in the abdomen ("protease pouch") and dorsocervical fat pad ("buffalo hump").[112-114] The abdominal fat may be either in the subcutaneous tissue or in the intraabdominal visceral fat.[112] The abnormal fat distribution appears to be associated with the use of ritonavir-saquinavir combinations rather than with indinavir and does not respond to dietary restriction or exercise. In patients with a buffalo hump, hypercortosolism has been ruled out as a cause, and half the patients with a buffalo hump had never been on protease inhibitors.[113] The relationship of these abnormalities to protease inhibitors is still not clear.

Since the protease inhibitors are such important drugs in the management of patients with HIV infection, every attempt must be made to control their metabolic side effects without stopping the drug. Diet and oral hypoglycemic drugs can control the hyperglycemia. Gemfibrozil and HMG-

CoA reductase inhibitors decrease the elevated triglycerides, cholesterol, and low-density lipoproteins, as noted. A potential problem is that protease inhibitors are metabolized by the hepatic cytochrome P450 CYP4-A system, and these drugs can both induce and/or inhibit the system. Therefore, other drugs metabolized by the cytochrome P450 system can have their plasma levels either decreased or increased when used together with the protease inhibitors, resulting in an extensive list of drug interactions and possibly drug toxicity. The importance of treating the metabolic abnormalities, however, is seen in the increasing number of reports of premature, extensive coronary artery disease in patients taking protease inhibitors.[115]

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CLINICAL WORKUP AND THERAPY

The workup of patients with AIDS and suspected cardiac involvement begins with the history and physical examination for symptoms and signs of cardiac disease. Since there is no therapeutic advantage to finding subclinical cardiovascular involvement, there is no justification for screening electrocardiograms or echocardiograms. If there are signs or symptoms suggesting cardiovascular disease-such as a friction rub, an S_3 gallop, or other evidence of congestive heart failure-an echocardiogram is useful in identifying pericardial effusion and in evaluating right and left ventricular function. Invasive diagnostic studies are rarely necessary.

If left ventricular dilatation and hypokinesis are found with or without clinical evidence of heart failure, consideration should be given to stopping all drugs that are not absolutely essential.[116] If, in a 2-week follow-up, echocardiography reveals improvement, the suspected drug should be eliminated.

The question of whether a myocardial biopsy is helpful is controversial. The finding of a treatable cause of biopsy-proved myocarditis is rare. Furthermore, there is no evidence that treating biopsy-proved focal myocarditis with steroids or antimetabolites is effective.[117] Therefore, by available evidence, myocardial biopsy is of little value.

The potential cardiotoxic roles of drugs for opportunistic infection as well as other known etiologies-such as hypertension, hypertrophic cardiomyopathy, and coronary artery disease-should be considered. The treatment of congestive heart failure is similar to that of the treatment of heart failure from other etiologies, e.g., diuretics, digoxin, and angiotensin-converting enzyme inhibitors (see Chap. 21).

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CARDIOVASCULAR SURGERY IN AIDS PATIENTS

There has been an increased interest in the danger to AIDS health care workers of becoming infected or of infecting patients and in the possibility of accelerating the disease through surgery. The problem is illustrated by the following questions:

1. Are we performing an expensive procedure that will cause prolonged hospitalization and probably not affect the outcome in AIDS patients?
2. What is the risk of accelerating the disease by surgery?
3. What is the risk of HIV infection to health care workers?
4. What is the risk of getting HIV infection during open-heart surgery?

In general, it is not wise to perform expensive procedures with some degree of morbidity and mortality that result in prolonged hospitalization of patients with a limited life span due to their underlying disease. For this reason, patients with AIDS should not be subjected to surgery that will most probably not significantly affect their survival. Before protease inhibitors were available, probably 70 percent of patients found to have AIDS would die within 3 to 4 years of the diagnosis.[118] Now, with newer drugs, life has been markedly prolonged. Therefore, if patients with AIDS have medically uncontrollable symptoms, invasive procedures that can ameliorate these symptoms are indicated.

With infective endocarditis, the vast majority of HIV-infected patients are intravenous drug users, and the most common valve involved is the tricuspid valve, which almost always can be treated medically. The most frequent problem in which the question of cardiovascular surgery arises in a relatively young subgroup involves the intravenous drug user with infective endocarditis on the aortic and/or mitral valve and congestive heart failure. The presence of HIV disease in these patients, who overall have a high mortality and poor results from surgery, would suggest that they be treated medically for as long as possible.[119] If failure persists, valvular replacement should be done.

HIV-positive patients and patients with PGL who have not had an opportunistic infection or cancer can have a prolonged course over many years and, in general, should be treated like patients without HIV disease. In fact, life span might be prolonged after HIV infection by using combinations of drugs, including reverse-transcriptase inhibitors and the new protease inhibitors. In this subgroup, cardiovascular surgery should be considered for the usual indications.

The question of whether progression of the HIV disease is accelerated by the immunologic challenge that occurs from cardiopulmonary bypass is largely unanswered. Instances of HIV-positive patients who developed AIDS shortly after open-heart surgery have been reported. It is known that cardiopulmonary bypass temporaily depresses phagocytic function and immune globulin production.[120] Cardiopulmonary bypass per se in HIV-negative patients causes prolonged abnormalities in the CD4+/CD8+ T-cell ratio up to 6 days postoperatively.[121] There is, therefore, a basis for concern that cardiopulmonary bypass surgery could accelerate the progression of HIV disease, and this must be taken into consideration.

Whether all patients undergoing cardiovascular surgery or other invasive procedures should have HIV testing is a matter of heated debate. Although the risk to health care personnel is small, HIV infection is usually tantamount to fatal infection; fear is great among both health care workers and the public. On the other hand, AIDS is an emotional subject, and patients who are known to be HIV positive may be subjected to prejudice and discrimination. At present, HIV testing of both health care workers and patients is voluntary; however, there are proposed recommendations requiring disclosure to patients that a health care worker is HIV positive and informed consent from patients before any invasive procedure is done. At present, there is only one instance of transmission of disease by a health care worker, that of an HIV-positive dentist who is believed to have infected five patients, probably from reuse of inadequately sterilized instruments. This matter is still under considerable debate.

Because of this risk, some cardiovascular surgeons and cardiologists are refusing to operate on or catheterize an HIV-positive person or a patient who will not allow an HIV test to be done. In 1989, a survey was done of the attitudes of cardiac surgeons in the United States concerning operating on HIV-positive patients.[122] More than half responded, and two-thirds of these were reportedly willing to perform open-heart surgery on HIV-positive patients no matter how the patients had acquired their HIV infection. One-quarter of the surgeons would not operate no matter how the HIV infection was acquired, and the rest were uncertain. Once the patient has gone from the HIV-carrier state to AIDS, two-thirds of the cardiac surgeons would not operate. Of those responding, 90 percent want to be able to test all their patients for HIV status. Whether these attitudes have changed in the last decade is unknown.

A physician's fear of becoming infected with HIV is understandable, but as in the case of other professions that involved personal dangers, the profession of the physician requires performance. Both the American College of Physicians and the American Medical Association currently have standards stating that physicians may not ethically refuse to treat patients solely because the patients are HIV positive.

As of 1995, the literature has reported 49 health care workers in the United States who had no other risk factors and were known to be HIV negative at exposure who have seroconverted after exposure.[123] The danger to health care personnel is greatest when there is exposure to blood and the chance of accidental needle or knife perforation or blood splash into the eyes or mouth. In one prospective study of 1307 consecutive procedures, accumulated exposure, parenteral or cutaneous, occurred in only 84 procedures (6.4 percent).[124] Parenteral exposure occurred in 1.7 percent. Knowledge of the patient's HIV status or awareness of the patient's high-risk status for such infection did not appear to influence the rate of exposure, suggesting that preoperative testing for HIV infection would not decrease the frequency of accidental exposure to blood.

In combined data from 20 prospective studies of the risk of HIV-1 transmission to health care workers, there were 6498 parenteral exposures among 1948 subjects.[125] The chance of seroconversion was 0.32 percent per exposure (95 percent confidence interval, 0.18 to 0.46 percent); in 2885 mucous membrane exposures, there was one seroconversion (0.03 percent per exposure). The risk of a health care worker developing HIV seroconversion from work-related activities was very low: approximately one infection in 300 documented exposures to HIV-positive blood.

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Part 11: CARDIOMYOPATHY AND SPECIFIC HEART MUSCLE DISEASES
Chapter 71:

EFFECT OF NONCARDIAC DRUGS, ELECTRICITY, POISONS, AND RADIATION ON THE HEART

Authors: Andrew L. Smith, Wendy M. Book

This chapter details many deleterious side effects of treatments and environmental agents on the heart. Toxic effects may occur acutely and require emergent intervention or may be chronic and not be manifest until days or years after exposure.

NONCARDIAC DRUGS

Chemotherapeutic Agents

The use of chemotherapeutic agents may result in acute or chronic cardiovascular toxicity. The heart, composed of nonproliferating myocytes, was traditionally thought to be protected from the effects of drugs on rapidly dividing cells. A variety of agents are now recognized to cause cardiovascular complications, including cardiomyopathy, myocarditis, pericarditis, myocardial ischemia, arrhythmias, and peripheral hypotension or vasospasm (see Table 71-1).[1]

Table 71-1: Chemotherapeutic Agents Commonly Associated with Cardiovascular Toxicity

Drug	Associated Toxicity
Anthracyclines	
Doxorubicin	Cardiomyopathy
Daunorubicin	
Epirubicin	
Idarubicin	
Mitoxantrone	
Alkylating agents	
Cyclophosphamide	Reversible systolic dysfunction, hemorrhagic myocarditis
Cisplatin	Raynaud's phenomenon
Antimetabolites	
5-Fluorouracil	Coronary vasospasm
Other	

Amsacrine	Arrhythmias
Paclitaxel	Arrhythmias
Interleukin 2	Hypotension, myocarditis
Interferon alpha	Hypotension, cardiomyopathy

Cardiovascular alterations in the patient receiving chemotherapy may be the result of a specific drug or combination of drugs or be related to tumor-associated factors such as hypercoagulability or release of myocardial depressant factors. Correlating a specific therapy with a particular adverse event may be difficult; however, knowledge of side effects of each agent should be considered when prescribing therapy.

ANTHRACYCLINES

The anthracycline antineoplastics-doxorubicin, daunorubicin, and epirubicine-are the leading cause of chemotherapy-related heart disease. These agents may cause cardiac problems during therapy, weeks after completion of therapy, or, unexpectedly, years later.[2] During acute therapy, electrocardiographic (ECG) changes occur in approximately 30 percent of patients and usually regress within weeks. Findings include ST-T changes, decreased QRS voltage, prolongation of the QT interval, and atrial and ventricular ectopy. Sustained atrial or ventricular arrhythmias are rare. The occurrence of early ECG abnormalities does not predict cardiomyopathy and is not an indication to discontinue therapy.[1] The development of persistent sinus tachycardia (although nonspecific) in an otherwise stable oncology patient, however, may raise the suspicion of ventricular dysfunction and impending congestive heart failure.

Congestive heart failure is related to the cumulative dose of the anthracycline administered. The incidences of heart failure at specific doses of doxorubicin include 0.4 percent at 400 mg/m^2 of body surface area, 7 percent at 550 mg/m^2, and 18 percent at 700 mg/m^2 (see Fig. 71-1). Traditionally, the cardiac limiting dose has been described as 550 mg/m^2 because of the acute rise in heart failure seen above this dose. There is great individual variability, however, with reports of heart failure occurring with doses less than 100 mg/m^2 and, conversely, with some patients tolerating greater than 1000 mg/m^2 without cardiac compromise.[3,4] Risk factors for anthracycline-induced cardiomyopathy are debated but include prior chest radiation, age greater than 70, and preexisting heart disease.[3] [5] Young women may be at particularly increased risk for late cardiac dysfunction.[5] Rapid infusion schedules associated with higher peak drug concentrations appear to result in greater cardiotoxicity. Combination therapy with cyclophosphamide is an additional risk factor.[1]

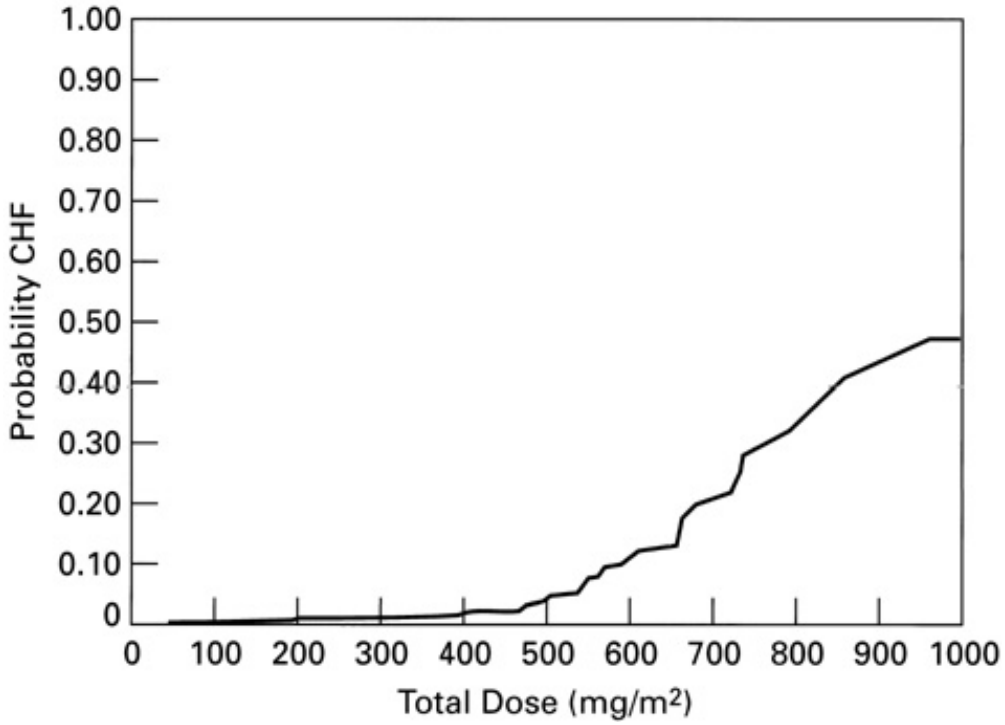

Figure 71-1: The development of doxorubicin-induced heart failure is related to cumulative dose. Toxicity may occur at any dose, but at 550 mg/m2 the probability increases significantly. (From Von Hoff et al.,[3] with permission.)

The pathogenesis of anthracycline-induced cardiotoxicity is not known. Theories generally implicate free-radical damage. One proposal is that enzymatic reduction of the anthracycline-quinone ring results in lipid peroxidation and cell membrane damage. Another theory involves the formation of an anthracycline-iron complex, which undergoes "redoxcycling" that results in oxygen radicals and degradation of microsomal, mitochondrial, and membrane lipids. Disturbances of calcium exchange have also been noted.[6]

The average time to clinical development of heart failure symptoms is 1 month from the end of therapy, but it may occur anytime within 1 year. Patient presentation is similar to that for other dilated cardiomyopathies (see Chap. 66). Biventricular systolic dysfunction occurs, and restrictive hemodynamics have been described.[7] The clinical course varies from fulminant heart failure to gradually progressive deterioration. Some patients have reversibility of systolic dysfunction. Therapy, in addition to withholding further anthracycline dosing or other myocardial toxins, is generally considered the same as recommended for patients with heart failure from dilated cardiomyopathy (Chap. 21).

Noninvasive assessment of left ventricular function has been utilized to guide anthracycline dosing and prevent cardiac toxicity. Serial echocardiography and/or radionuclide angiography (see Chaps. 13 and 16) are most commonly used.[8-10] Improved echocardiographic technologies are likely to increase the use of echocardiography in the adult population. The most commonly used parameter is resting left ventricular ejection fraction. Recognition that resting left ventricular ejection fraction is relatively insensitive for detecting early cardiotoxicity[2] has resulted in investigation of other variables (exercise or dobutamine echocardiography,[9] Doppler velocities, and systolic time intervals) in assessing this problem. These methods have generally been evaluated in small studies and have not gained widespread acceptance in current therapy guidelines. Adult guidelines for serial assessment have been developed. A drop in left ventricular ejection fraction greater than 10 percent (EF units) and to below a normal value of 50 percent is an indication to discontinue therapy. A baseline left ventricular ejection fraction less than 30 percent

has generally been considered a contraindication to initiating anthracycline therapy.[10]

Compared with the noninvasive methods, endomyocardial biopsy is considered more specific and provides earlier sensitivity in detection of anthracycline cardiotoxicity. The Billingham score, which quantifies cytoplasmic changes and the percent of myocytes damaged, has been utilized to assess the risk of congestive heart failure.[11] Clinical utility has been limited because of the invasive nature of this procedure and the special expertise required in obtaining and reading the specimens. Additionally, variability of histologic changes and the potential for sampling error have been noted.[12]

There is growing recognition of the occurrence of cardiac dysfunction years after completion of anthracycline therapy. This is particularly of concern in children. One study reported a 23 percent incidence of late cardiac abnormalities (decreased systolic function by noninvasive testing) in survivors of pediatric malignancies treated with anthracycline therapy.[13] The incidence of abnormalities was higher in the patients with the longer elapsed times since therapy, with a 38 percent incidence in patients with a follow-up period greater than 10 years. This study, as well as others,[14] suggests that subclinical myocardial damage may not become clinically evident until years after therapy. Although fewer than 5 percent of these patients had developed clinical heart failure, the potentially progressive nature of systolic dysfunction raises the issue of need for long-term clinical follow-up. There are presently no accepted guidelines, however, in either the pediatric or adult population for chronic monitoring. Early treatment of systolic dysfunction with angiotensin-converting enzyme inhibitors may be warranted in asymptomatic patients.[2] Additionally, patients presenting late after anthracycline therapy with exertional fatigue and normal resting ejection fractions have been noted to have abnormalities on dobutamine echocardiography. This observation suggests abnormalities in cardiac reserve that may lead to symptoms.

Clinical strategies for preventing anthracycline cardiotoxicity have had to balance the need for antineoplastic efficacy. Lower clinical toxicity has been noted with prolonged infusions of doxorubicin over 48 to 96 h in order to avoid high peak concentrations.[15] Several antioxidants have been evaluated, but with inconclusive results.[6,16] *Dexrazoxane*, [17] an iron-chelating agent, reduces free-radical generation by anthracyclines and is approved for use in women with breast cancer after a cumulative dose of doxorubicin of 300 mg/m^2. Studies demonstrate a decrease in cardiotoxicity and most but not all trials have suggested preserved efficacy of antitumor activity. New anthracyclines, including epirubicine and idarubicin, appear to have diminished cardiotoxic effects, although long-term results cannot presently be assessed.[2]

OTHER CHEMOTHERAPEUTIC AGENTS

Mitoxantrone, an anthracendione lacking the amino sugar of anthracyclines, causes cardiotoxicity with features similar to anthracycline-induced cardiomyopathy.[1] This drug appears to have less cardiotoxicity than doxorubicin at equal myelotoxic doses. Cumulative doses above 160 mg/m^2 are associated with an increasing incidence of congestive heart failure.[18]

High-dose *cyclophosphamide* (120 to 240 mg/kg over several days) used in bone marrow transplantation may cause acute cardiac toxicity.[1,19] Symptomatic systolic dysfunction, usually reversible with drug discontinuation, is associated with decreased QRS voltage on the ECG. Pericardial effusions have been noted, and a hemorrhagic myocarditis may result in death. Necropsy data demonstrate endothelial injury with resultant interstitial fibrin deposition and capillary microthrombosis. The cardiotoxicity of cyclophosphamide is likely due to damage from its biologically active metabolites. Rapid metabolizers of cyclophosphamide appear to be prone to cardiotoxicity. The metabolites cause the toxic endothelial damage leading to muscle damage.[19] Cyclophosphamide may also potentiate the cardiotoxic effects of the anthracyclines.[1]

5-*Fluorouracil* may occasionally cause angina, ECG changes, and rarely myocardial infarction.[1,20] The majority of episodes occur during the first cycle of therapy and resolve spontaneously after discontinuation. Arrhythmias and systolic dysfunction have been observed. The understanding of 5-fluorouracil toxicity is complicated because combination chemotherapy is generally utilized, patients may be systemically ill, and many receiving this medication have preexisting coronary artery disease.[20] The incidence of cardiac toxicity is uncertain but ranges from 1 to 8 percent.[21] Patients with known coronary artery disease are at higher risk for serious cardiotoxicity. The mechanism of toxicity remains unclear, although coronary vasospasm has been suspected. Coronary catheterization has generally failed to demonstrate vasomotor hyperreactivity with 5-fluorouracil on ergonovine challenge.

Amsacrine (AMSA) has been associated with prolongation of the QT interval. Malignant ventricular arrhythmias may occur in 1 percent of patients and are exacerbated by hypokalemia.[22]

Paclitaxel (taxol) is being used with increased frequency for breast and ovarian cancer. The most common cardiovascular effect is the development of transient asymptomatic bradycardia, occurring in up to 30 percent of patients. Bradycardia with adverse consequences occurs in only 0.1 percent of patients. A possible relationship of paclitaxel to heart failure has been questioned, but confirmatory data are lacking.[23]

Herceptin (recombinant humanized anti-HER2 antibody) is a relatively new treatment for breast cancer that appears to have favorable antitumor effects when added to standard chemotherapy in selected patients. Unfortunately, cardiac toxicity may limit the use of this drug. In a breast cancer treatment trial, 27 percent of patients receiving doxorubicin, paclitaxel, and Herceptin had cardiac dysfunction compared with 6 percent receiving doxorubicin and paclitaxel without Herceptin. Close cardiac monitoring is warranted.[24]

Immunomodulating Agents

The biological response modifiers *interleukin-2* (IL-2) and *interferon alpha* have been associated with cardiovascular toxicity predominantly secondary to peripheral vasodilatation. IL-2 causes tachycardia, hypotension, and a capillary leak syndrome. Myocarditis has been reported in patients who died soon after initiation of therapy. IL-2 therapy requires pretreatment assessment of cardiovascular risks and close monitoring during drug administration. Interferon alpha may cause supraventricular tachyarrhythmias. A reversible cardiomyopathy has been described.[1,19,25]

Psychotropic Agents

Psychiatric illness, particularly depression, is common in patients with cardiovascular disease[43] (see Chap. 80). Morbidity and mortality following cardiac events are increased in patients with depression, particularly if untreated.[26,27] A variety of psychotropic agents have conduction or vascular effects (see Table 80-11). A thorough understanding of these therapeutic but potentially toxic agents is necessary in the treatment of patients with preexisting cardiac disease. Intentional overdose with these drugs may result in serious cardiac manifestations.

TRICYCLIC ANTIDEPRESSANTS

The tricyclic antidepressants, including the tertiary (amitryptyline, clomipramine, doxepin, imipramine, trimipramine) and secondary (desipramine, nortriptyline, protriptyline) amines, have potentially serious cardiovascular effects. These effects include increased heart rate, orthostatic hypotension, ECG changes, and possible depression of ventricular function. These drugs have electrophysiologic properties similar to the type IA antiarrhythmics. There is the potential for late

proarrhythmia in patients with structural heart disease who are taking these agents.[28]

The tricyclic antidepressants have several properties that account for the majority of cardiovascular effects. These drugs inhibit uptake of both norepinephrine and serotonin, resulting in greater toxicity compared to the selective serotonin reuptake inhibitors (SSRIs). A hyperadrenergic state may result in tachycardia. Alpha blockade occurs at higher drug levels and may cause marked hypotension in the setting of overdose. The anticholinergic effects result in tachycardia, dry mouth, and constipation; in overdose they may delay gastrointestinal absorption of the drug. Sodium channel blockade, typical of the type IA antiarrhythmic compounds, results in conduction abnormalities[52] and the potential to suppress ventricular function.[29]

The most frequent side effect of tricyclic antidepressant treatment, orthostatic hypotension, is common in older patients and does not generally improve when doses are reduced to lower levels that will still maintain antidepressant effects. Orthostasis, mediated predominantly by alpha-1 adrenergic receptor blockade, may occur with all of these drugs but is less likely with nortriptyline.[29,30]

The most common ECG changes include nonspecific ST-T changes and prolongation of the QT interval, PR interval, and QRS duration. PR prolongation is due to prolonged infranodal conduction. Patients with preexisting conduction disease, particularly bundle branch block, are at increased risk of toxicity.[31] The type IA antiarrhythmic properties may potentially suppress ventricular ectopy. The results of recent antiarrhythmic studies, however, including those with type I agents, suggest the potential for a proarrhythmic effect for these drugs at therapeutic doses in patients with serious structural heart disease.[28,32] Tricyclic antidepressants are generally contraindicated in the recovery phase following myocardial infarction. Although tricyclic antidepressant therapy may be indicated in the treatment of severely depressed patients, the threshold for use should rise as the severity of heart disease increases or when there is QT prolongation.[28] These issues are discussed in detail in Chap. 80.

Tricyclic antidepressants may impair left ventricular function in patients with severe systolic dysfunction; however, decreases in left ventricular ejection fraction have generally not been noted in patients with moderately impaired function. Tricyclic antidepressant overdose carries a mortality of 2 to 3 percent, which is generally related to cardiac complications. Clinical status at initial presentation and serum drug levels are not predictive of prognosis. QRS prolongation is a sign of toxicity but may be absent in the patient with serious cardiac complications. Rightward deviation of the terminal 40 ms of the frontal plane QRS axis is a more sensitive marker. This finding, manifest by a terminal R wave in lead aV_R, has an 83 percent sensitivity and 63 percent specificity for toxicity.[33]

Aggressive support measures in tricyclic antidepressant overdose should be initiated immediately and include airway maintenance, gastric lavage, and repeated dosing of activated charcoal. Alkalinization with intravenous sodium bicarbonate decreases unbound drug and reverses cardiac and central nervous system conduction defects. Alkalinization is indicated in cardiac arrest, hypotension, arrhythmias, acidosis, and QRS prolongation. Hypotension refractory to volume loading and bicarbonate therapy should be treated with vasopressors, including norepinephrine and phenylephrine, and with vasopressor doses of dopamine. Type I antiarrhythmics (quinidine, procainamide, disopyramide) should not be used. Sodium bicarbonate is the initial therapy for ventricular dysrhythmias.[34]

The duration of monitoring after tricyclic overdose is controversial. Signs of major toxicity generally occur within 6 h of presentation in the emergency department. If clinical or ECG evidence of toxicity is absent and two doses of activated charcoal have been given, patients may not require admission for medical monitoring. Fluoxetine increases tricyclic antidepressant serum

levels, and additional monitoring is recommended in patients receiving this medication. Patients with cardiac disease or other serious medical problems may require a longer period of observation.[35]

OTHER ANTIDEPRESSANTS

Selective serotonin reuptake inhibitors (SSRIs) have not been extensively studied in patients with cardiac disease.[36] Case reports of cardiac toxicity are rare, despite the increasing popularity of these agents in the treatment of depression. These agents have rarely been associated with orthostatic hypotension and with bradycardia. Cardiac function does not appear to be depressed by these agents.[37] The SSRIs may affect the cytochrome P450 system and may therefore alter the metabolism of a variety of drugs, including agents used in cardiovascular disease such as antiarrhythmic medications, beta blockers, calcium channel blockers, and warfarin (see Chap. 80).

The monoamine oxidase inhibitors (MAOIs) have little effect on cardiac conduction or myocardial contractility. Orthostatic hypotension is common, particularly in elderly patients. The major concern with these agents is interaction with other drugs or tyramine-containing substances, resulting in hypertensive crisis.[38]

Lithium, used commonly in the treatment of bipolar disorder, is generally well tolerated in patients with cardiac disease. Suppression of sinus node automaticity, resulting in bradycardias, is the most common complication.[39] In patients free of known heart disease, clinically significant sinus node dysfunction occurs in fewer than 1 percent and is reversible with discontinuation of lithium therapy. Preexisting sinus node disease or concomitant therapy with drugs altering sinus node function, however, may result in sinus bradycardia. Lithium-induced hypothyroidism may be a contributing factor.[40] Pacemaker therapy may be required to allow continuation of lithium therapy.

Lithium therapy has been associated with ECG changes simulating hypokalemia. T-wave inversion, prominent U waves, and QT prolongation may occur. PR prolongation, bundle branch block, and complete heart block are rare.[39] Overdose with lithium may result in severe bradycardias requiring temporary pacemaker therapy. A low anion gap may suggest the presence of lithium toxicity.[41]

ANTIPSYCHOTIC AGENTS

The phenothiazine antipsychotic agents have potential cardiac toxicity similar to that of the tricyclic antidepressants. These drugs may cause sinus tachycardia, PR and QT prolongation, and disturbances of intraventricular conduction. Chlorpromazine and thioridazine[42] are the most commonly implicated phenothiazines as causes of torsades de pointes. The butyrophenone haloperidol is also associated with torsades de pointes at high doses given intravenously.[43]

Noncardiac Drugs and Toxic Antidepressants Causing Torsades de Pointes

As discussed above, the tricyclic phenothiazine and other psychotropic agents may prolong the QT interval and induce torsades de pointes. A variety of antiarrhythmic agents, particularly the type I agents, are most strongly associated with this potentially fatal arrhythmia. Other toxic causes of torsades de pointes[44] are listed in Table 71-2.

Table 71-2: Noncardiac Drugs and Toxins Known to Cause Torsades de Pointes

Psychotropic agents	Antihistamines
Tricyclic antidepressants	Terfenadine
Tetracyclic antidepressants	Astemizole
Phenothiazines	Other
Haloperidol	Cisapride
Chloral hydrate	Pentamidine
Antibiotics	Probucol
Erythromycin	Arsenic
Trimethoprim-sulfa-	Organophosphates
methoxazole	Liquid protein diets

The antibiotics erythromycin and trimethoprim-sulfamethoxazole[45,46] have only rarely been associated with torsades de pointes, the exception being the effect of erythromycin on the metabolism of terfenadine, astemizole, and cisapride. Liquid protein diets and starvation[47] may cause marked electrolyte and chemical disturbances, triggering QT prolongation. Probucol[48] may prolong the QT interval, resulting in torsades de pointes.

The QT prolongation and torsades de pointes reported with the antihistamines terfenadine and astemizole and with cisapride have been associated with high drug levels from excessive dosing or altered metabolism.[49,50] Prolongation of the QT interval induced by terfenadine, astemizole, and cisapride is due to the electrophysiologic activity of blocking HERG, the ion channel that is responsible for the rapid component of the delayed rectifier current for potassium(I_{kr}).[50] These drugs are metabolized by the cytochrome P450 3A isoenzyme.[51] A variety of agents inhibit this isoenzyme, including antifungals (ketoconazole, fluconazole, itraconazole), erythromycin or clarithromycin (not azithromycin), SSRIs (fluvoxamine, nefazodone, fluoxetine, sertaline), quinine, and grapefruit juice. Serious cardiac arrhythmias have been reported in patients taking terfenadine, astemizole, or cisapride with drugs that inhibit the cytochrome P450 3A isoenzyme. Patients with a history of prolonged QT interval or those with serious underlying cardiac disease are at higher risk for this problem. Some women appear to have slow metabolism of these drugs; thus female gender is a risk factor for drug-induced arrhythmias.[50]

Methylxanthines and Beta-Adrenergic Agonists

The methylxanthines caffeine and theophylline have pharmacologic actions of central nervous system stimulation, bronchial smooth muscle relaxation, and cardiac muscle stimulation and have diuretic effects on the kidneys. At therapeutic doses or those consumed in xanthine-containing beverages, these agents competitively inhibit adenosine receptors. At higher doses, they exhibit phosphodiesterase inhibition.[52] The effect of caffeine consumption on the cardiovascular system is variable and depends on chronicity of use, dose exposure, and individual responsiveness. Although elevations of catecholamines may occur with acute administration, this effect resolves with chronic usage. At higher concentrations, caffeine may cause tachycardia and dysrhythmias. Despite the concern that caffeine may be detrimental in patients predisposed to cardiac rhythm disturbances, it appears that moderate amounts of caffeine consumption may be well tolerated in patients with ventricular arrhythmias. The role of coffee, with or without caffeine, as a risk factor

for coronary artery disease has been debated. While heavy coffee drinking (>4 cups a day) has been suggested as a potential risk factor for cardiovascular mortality, the data are inconclusive.[53,54]

Theophylline has the potential to cause a slight increase in heart rate with minimal effects on blood pressure. Patients with obstructive lung disease commonly have atrial and ventricular arrhythmias, which can be exacerbated by theophylline therapy. Theophylline toxicity is associated with sinus tachycardia, atrial and ventricular arrhythmias, and hypotension.[55] Hypokalemia, hypercalcemia, hyperglycemia, hypophosphatemia, and metabolic acidosis may occur. Esmolol may be useful in the management of refractory arrhythmias. Dialysis may be helpful in patients with refractory arrhythmias or hypotension.[56,57]

The beta-adrenergic agonists terbutaline and albuterol are commonly used to treat asthma and premature labor. Although adverse reactions are uncommon with aerosol therapy, these agents may cause tachycardia and atrial and ventricular arrhythmias and, rarely, may worsen angina pectoris.[58] Use of oral $beta_2$ agonists has been associated with the development of heart failure.[59] Intravenous therapy may cause hypokalemia and acidosis. Controversy exists over the safety of long-term aerosol therapy with beta-adrenergic agonists in asthma. These concerns, however, relate predominantly to airway hyperresponsiveness and not to direct cardiac toxicity.[60]

Antimigraine Drugs

Ergotamine

The ergot alkaloids are commonly used in the treatment of migraine headaches. Ergotamine causes constriction of smooth muscle, and its effect on vascular smooth muscle may result in hypertension and increased peripheral vascular resistance.[61] Ergonovine maleate may be used in the catheterization laboratory to diagnose coronary artery spasm. Chronic use of ergotamine may result in variant angina or myocardial infarction.[61,62] Severe circulatory disturbances of the upper and lower extremities and abdominal arteries have been described.[62] Ergotamine and methysergide have similar chemical structures. Valvular heart disease has been reported with both agents. Either may cause pericardial, pleural, or peritoneal fibrosis or multivalvular heart disease. The occurrence of these side effects is less frequent with ergotamine.[63,64]

Methysergide

Methysergide, used in treating vascular headaches, can cause retroperitoneal, pulmonary, and cardiac fibrosis. Cardiac involvement most commonly affects the valves but may affect the endocardium, myocardium, and rarely the aorta. Regurgitant valvular lesions are most common, affecting the mitral and aortic valves more commonly than the tricuspid and pulmonary valves.[65] Patients receiving methysergide therapy should be monitored for the development of murmurs. Therapy should be discontinued if a new murmur is detected. Regression of valvular lesions may occur, although valve replacement is occasionally required. Patients with known valvular disease should not be given methysergide.

Sumatriptan

Sumatriptan, a selective serotonin type I agonist, may cause coronary artery vasospasm. Sumatriptan should not be taken within 24 h of treatment with ergotamine-like medications because of the risk of prolonged vasoconstriction.[66]

The antimigraine drugs ergotamine, methysergide, and sumatriptan are generally contraindicated in patients with obstructive coronary artery disease.[67]

Weight-Loss Medications

Dexfenfluramine and the combination of fenfluramine and phentermine may cause valvular heart disease (Chaps. 56, 57, and 59).[68-72] These agents had been prescribed for weight loss in obese patients, but dexfenfluramine and fenfluramine were withdrawn from the market in 1997 when up to 30 percent of users were reported to develop asymptomatic valve regurgitation.[69] Later reports suggested a lower incidence of problems, including reports of valvular regurgitation in approximately 7 percent of dexfenfluramine-treated patients versus 2 to 5 percent of controls.[70] The true incidence of valvular problems is uncertain and differences in reported cases may be secondary to differences in length of therapy, time from therapy to cardiac evaluation, and methods used to determine abnormalities. Mild aortic regurgitation is the most common finding. Abnormalities often improve with cessation of therapy.[71,72]

Histamine H_2-Receptor Antagonists

The histamine H_2-receptor antagonists have rarely been associated with cardiac effects. Episodes of severe bradycardia have been reported as well as hypotension, asystole, and ventricular arrhythmias. These complications have generally occurred with large doses given intravenously.[73] Electrophysiologic studies have not demonstrated any direct effect on sinus node function.[74]

Chloroquine

The antimalarial agent chloroquine is commonly used to treat collagen vascular and dermatologic disorders. Irreversible retinal damage is the primary concern with long-term or high-dose therapy. Skeletal myopathy and less commonly cardiomyopathy may occur. With cardiac involvement, features of restrictive cardiomyopathy are most common. Myocardial biopsy with analysis by electron microscopy showing curvilinear and myeloid bodies is diagnostic. These findings may be seen on skeletal muscle biopsy. The ECG may demonstrate T-wave changes and conduction abnormalities. Acute chloroquine poisoning results in hypotension, tachycardia, and prolongation of the QRS and is often fatal.[75,76]

Oral Contraceptive Agents

Epidemiologic studies prior to the 1980s demonstrated that women using oral contraceptives had an increased risk of cardiovascular disease, including venous thromboembolism, myocardial infarction, hypertension, and stroke.[128] Oral contraceptive formulations used in the 1960s and 1970s consisted of relatively high-dose estrogen. Although rare, the risk of myocardial infarction was increased approximately fourfold. Women smokers, particularly those older than age 35, had a dramatically increased risk of infarction. Coronary angiography done postinfarction not uncommonly demonstrated a discrete lesion in a single vessel or no obstructive lesions, suggesting acute thrombosis as a possible mechanism. The risk of venous thromboembolism was 4 to 10 times that of nonusers during this era.[77,80]

Recent formulations of oral contraceptives consist of less than 50 μg of ethinyl estradiol in combination with a low-dose progestin. Recent studies suggest that these second- and third-generation combined oral contraceptives are much safer in terms of cardiovascular complications.[77] The risks of venous thromboembolism and myocardial infarction are significantly reduced compared with the first-generation agents. Hypertension is rare, and the risk of stroke in otherwise healthy women is only minimally increased.[78]

Third-generation oral contraceptives that contain desogestrol or gestodene are reportedly associated with a 1.5 to 2.5 increased risk of venous thromboembolism compared with the second-

generation agents. The significance of this finding has generated controversy, but generally, the cardiovascular risk profile of these agents is considered favorable. However, smokers greater than 35 years of age should use a nonestrogen contraceptive.[77-80]

Anabolic Steroids

Illicit use of androgens has been identified as a problem in competitive athletes and body builders. It is estimated that 300,000 persons in the United States have had recent steroid use and over 1 million have had prior use.[81-83] Anabolic steroids, including testosterone, stanozolol, and nandrolone, are frequently used in combination and at high doses for intermittent periods of several weeks to months. Doses commonly exceed 100 times the doses used for medical purposes.[81] Animal data indicate that these agents can cause abnormal lipids, left ventricular hypertrophy, increased blood volume, and hypertension. Data on human toxicity are limited but suggest similar toxicity.[84] Stanozolol and nandrolone reduce total high-density lipoprotein levels by over 50 percent and increase low-density lipoprotein levels by over 30 percent.[85] Isolated reports of young men (<age 35) developing severe coronary atherosclerosis, myocardial infarctions, or stroke exist in the literature.[81,86] Because of the secrecy surrounding the use of these agents, the full clinical significance of abuse is not known.

Cocaine

Cocaine is a common drug of abuse associated with potentially lethal cardiac toxicity. It is estimated that over 30 million Americans have used cocaine at least once and that 5 million use it regularly.[87] Cocaine may be swallowed, inhaled nasally, smoked, or injected intravenously. Cardiovascular toxicity is broad, ranging from sudden death to chronic cardiomyopathy.[88] A summary of the cardiovascular syndrome associated with illicit cocaine use is shown in Table 71-3. Use of cocaine with other drugs such as ethanol[89] or tobacco[90] may have combined detrimental effects. Cardiovascular susceptibility in an individual is difficult to predict due to the lack of dose-response relationship and the high degree of variability in the individual response to cocaine.[91]

Table 71-3: Cardiovascular Complications of Cocaine

Sudden death
Acute myocardial infarction
Chest pain without myocardial infarction
Accelerated coronary atherosclerosis
Intimal hyperplasia of coronary vessels
Electrocardiographic abnormalities
Sinus tachycardia
Premature ventricular complexes
Ventricular tachycardia
Torsades de pointes
Ventricular fibrillation
Prolongation of QT interval

Early repolarization (ST-segment changes)
Acute reversible myocarditis
Dilated cardiomyopathy
Acute severe hypertension
Acute aortic dissection, rupture
Pneumopericardium
Stroke
Subarachnoid hemorrhage
Endocarditis (intravenous use)

Cocaine has a generalized sympathomimetic effect and has local anesthetic properties.[88] It blocks the reuptake of norepinephrine and dopamine on preganglionic sympathetic nerve terminals. This produces sympathetic stimulation both centrally and peripherally. These catecholamine effects acutely result in tachycardia, hypertension, increased myocardial contractility, and vascular constriction. The local anesthetic effect, occurring through blockade of the fast sodium channel, results in slowed conduction in myocardial tissues. This may result in ECG abnormalities, including prolongation of the PR, QRS, and QT intervals, similar to those seen with toxicity from type I antiarrhythmic agents. These effects increase the vulnerability to reentrant ventricular arrhythmias.[8788-92]

Use of cocaine may result in increased thrombogenicity.[88,90] Platelet aggregation is enhanced and endothelial function is altered,[94] resulting in the potential for development of coronary thrombosis in the absence of coronary atherosclerosis. Chronic use of cocaine is associated with premature coronary atherosclerosis.[88,93] Cocaine indirectly causes constriction of both diseased and nondiseased coronary artery segments, but its effect is more marked in diseased vessels. Ethanol use and tobacco smoking may worsen the potential for vasospasm.[89,90] In up to one-third of reported cases, patients with cocaine-induced myocardial infarctions have normal coronary arteries.[88] The combined cardiac effects-including early coronary atherosclerosis, coronary vasospasm, increased thrombogenicity, increased myocardial oxygen demands, and proarrhythmic effects-make this drug a lethal threat to users of all ages.

Cocaine may produce direct or indirect myocardial toxicity. Animal studies suggest a direct negative inotropic effect on the heart, possibly related to its local anesthetic properties. Chronic dosing has demonstrated myocardial contraction bands, myofibrillar disorganization, interstitial edema, and mitochondrial swelling. Mononuclear infiltrates have been noted. Myocardial changes may mimic those seen with catecholamine excess, as in pheochromocytoma. Clinical case reports have described transient toxic cardiomyopathy, acute myocarditis, and permanently dilated cardiomyopathy.[88]

Chest pain is the most common reason for cocaine users to seek medical attention. Over 64,000 patients are evaluated annually for cocaine-related chest pain, of whom over half are admitted to the hospital.[95] The evaluation of cocaine-related chest pain is difficult. Prospective studies demonstrate that approximately 6 percent of patients presenting to an emergency department with cocaine-related chest pain have myocardial infarction. These patients are often young men without other risk factors for coronary artery disease except for tobacco smoking. The duration and quality of discomfort does not readily distinguish those eventually noted to have enzyme documentation

of infarction. Many young patients have early repolarization patterns with ST elevation in leads V_1 to V_3, a normal variant that may be confused with acute infarction. Infarction has been noted in patients with normal or nonspecific ECGs. Because of the difficulty in excluding myocardial infarctions, patients are often monitored for a period of at least 12 h until enzymes have excluded infarction (Chaps. 40 and 42).[87]

Treatment strategies for cocaine-induced myocardial ischemia have been developed based on the known cardiac and nervous system toxicity of the drug.[87,92] Randomized prospective trials of therapy do not exist. Patients presenting with anxiety, tachycardia, or hypertension may respond well to benzodiazepines. Nitroglycerin may reverse coronary vasoconstriction induced by cocaine. Aspirin may prevent thrombus formation. Patients not responding to these measures may benefit from the alpha-adrenergic antagonist phentolamine or from calcium channel blocker therapy with verapamil.[87] Beta-adrenergic antagonists have been avoided because of the potential of enhanced coronary vasoconstriction and for unopposed alpha-mediated hypertensive crisis. Combined alpha and beta blockade with labetalol has been utilized to treat tachyarrhythmias but is not an accepted therapy for myocardial ischemia.[87] However, the bias against beta blockade is undergoing clinical reevaluation with recognition that beta blockers may block the hyperadrenergic effects that result in thrombosis and vasospasm.[96]

In documented myocardial infarction, thrombolytic therapy is highly effective; however, over 40 percent of patients without infarction will meet accepted ECG criteria for use of lytic therapy.[97] The early repolarization pattern common in young men makes diagnosis difficult, particularly when a prior ECG is not available. Thrombolytic therapy carries increased risk of hemorrhagic stroke in patients with recently uncontrolled hypertension. Therefore emergent coronary angiography may be necessary to document coronary occlusion as well as direct strategies such as primary angioplasty or thrombolysis[147] (see Chap. 42).

Management of supraventricular or ventricular tachyarrhythmias may be facilitated by administration of benzodiazepines. Rhythm disturbances may be exacerbated by acidosis or electrolyte disorders. Intravenous sodium bicarbonate and magnesium may be beneficial. Lidocaine should be used cautiously because of concerns of lowered seizure threshold and potential proarrhythmic effects following recent cocaine use.[92]

Patients with cocaine-associated chest pain not related to myocardial infarction have a favorable 1-year prognosis, particularly if cocaine use is discontinued. Urgent diagnostic cardiac evaluation is not generally recommended. Unfortunately, recurrent cocaine use after cocaine-associated chest pain occurs in over 60 percent of cases.[87]

Methamphetamines

The biologic effects of methamphetamines are similar to those of cocaine, but vasoconstriction is less. Cardiovascular toxicity is common and includes tachycardia, hypertension, and arrhythmias. Chest pain and myocardial infarction are less common than with cocaine.[98] Chronic use may result in a catecholamine-mediated dilated cardiomyopathy.

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Chapter 71: EFFECT OF NONCARDIAC DRUGS, ELECTRICITY, POISONS, AND RADIATION ON THE HEART

ELECTRICAL INJURY

Environmental Accidents

Accidental contact with electricity may occur in the home, where young children are particularly vulnerable.[100] Job-related electrical injuries are most common in construction and electrical workers but may also occur on any job in which electrical equipment is used, including the health care setting. Approximately 1200 deaths related to domestic electrical injury occur each year in the United States. There are two to three times as many serious injuries, including burns and neurologic complications.[101] Lightning kills at least 100 people per year in the United States, representing a 30 percent mortality rate in reported cases. Lightning injuries generally occur between May and September in the late afternoon hours, and affect predominantly young people involved in outdoor recreational activities.[102] Death following electrical shock is usually secondary to immediate cardiac rhythm disturbances, although later cardiac complications secondary to internal injury may occur.

PATHOPHYSIOLOGY

The degree of total body injury from electricity is determined by the amount of current delivered, tissue resistance, and duration of contact. Specific organs or tissues injured are in part determined by the path of the current. Electrical injuries are classified as high-voltage (>1000 V) or low-voltage (<1000 V). High-voltage electrical wires and household current (120 or 220 V) are alternating currents (AC) that may result in prolonged exposure due to tetatanic muscle contractions and inability of the victim to "let go." The frequencies of domestically generated AC (50 to 60 cycles per second) result in an increased risk for ventricular fibrillation even at household voltages.[101] Sources of domestic direct current (DC) are usually low-voltage (3 to 24 V), including batteries, appliance transformers, and portable emergency generators and are less likely to cause injury. Lightning is extremely high voltage direct current of brief duration.

Heat injury tissue necrosis is more severe with high-voltage AC. These burns are often internal and may mimic crush injuries. Tissue resistance to current flow is least in nervous and vascular tissues; therefore the heart and neurovascular bundles may serve as conduits for electrical current through the thorax. Arm-to-arm pathway of current is associated with greater risk for cardiac injury, followed by arm-to-leg pathways determined by entry and exit sites. A stride potential, leg to leg, is infrequently associated with cardiac effects.

CARDIOVASCULAR EFFECTS

Cardiac damage in electrical injury may occur as a result of contusion injury or myocardial necrosis or may be in part related to massive release of catecholamines. Typical symptoms or signs of myocardial damage may be absent. Lightning injuries result from brief, high-voltage direct current. Immediate death may be secondary to asystole or ventricular fibrillation or may result from apnea secondary to injury of the central respiratory centers. Lightning strikes may occur by a direct hit, side splash, or ground strike. Direct hits cause mechanical trauma to organs secondary to dissipated energy. Strikes to the chest can result in severe, often reversible global myocardial dysfunction or localized myocardial contusion. ECG abnormalities, including QT_c

prolongation and ST-T abnormalities, may be the result of cardiac or neurologic injury. ST elevation has been noted with direct strikes. Conduction abnormalities, including right bundle branch block and complete heart block, have been noted. Pericardial effusions may develop following direct strikes. Elevated levels of CK-MB are generally noted.[102] Splash strikes in which a tree or other object is hit prior to the victim's being hit are associated with CK-MB release in less than two-thirds of patients. Severe myocardial injury is unlikely unless there is a short distance between the directly hit object and the victim. Ground strikes generally do not cause a significant cardiac injury but may be associated with nonspecific ST-T abnormalities.

Domestic alternating current accidents may cause myocardial necrosis and conduction abnormalities. An injury pattern mimicking infarction may be seen on the ECG but is generally related to direct myocardial injury and not from coronary thrombosis.[165] Household voltages (120 to 220 V) may cause sudden death, particularly when they involve arm-to-arm pathways or low skin resistance in a wet victim. Serious myocardial damage is rare.[100]

Treatment for cardiac arrest should be initiated immediately after the patient is disconnected from the current source. Resuscitation efforts should be continued for a prolonged period. In lightning strikes involving multiple victims, attention should be directed first to those who are "apparently dead." This is because there is a higher resuscitation rate for these individuals than for those with medical cardiac arrest. Of note, lightning victims with vital signs generally survive without immediate medical attention.[103]

Patients surviving high-voltage injuries generally require admission, usually for attention to neurologic complications and internal or external burn injuries and less commonly for cardiac monitoring. An initially normal ECG carries a favorable cardiac prognosis, leading some authors to question the need for 24-h ECG monitoring. Patients with arm-to-arm or arm-to-leg passage of current may be at risk for postadmission rhythm disturbances; a higher index of suspicion is required in such patients. Adults and children presenting to the emergency department following low-voltage shocks of less than 240 V have a low incidence of myocardial injury and most do not require further monitoring.[100]

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is accepted for the treatment of a variety of psychiatric illnesses including depression resistant to pharmacologic therapy, severe suicidal ideation with vegetative signs, acute mania, and depression with intolerance to medication side effects secondary to cardiac problems[104] (see also Chap. 80). ECT involves a brief unilateral or bilateral electrical stimulus to the brain while the patient is under short-acting anesthesia with a hypnotic drug and a muscle depolarizing agent.[105] The shock produces brief, intense stimulation of the central nervous system. Cardiovascular complications may result from this stimulation or from the drugs used to modify the response.[106,107]

Initially, the ECT stimulus activates the vagus nerve and may produce bradycardia, hypotension, and rarely asystole. Sympathetic discharge occurs, which is amplified by a 15-fold rise in epinephrine and 3-fold rise in norepinephrine levels, resulting in tachycardia and hypertension. Transient atrial and ventricular tachyarrhythmias may occur in approximately 10 percent of patients with known or suspected cardiovascular disease. Transient ECG alterations-including ST-T-wave changes, QRS changes, QT prolongation, and peaked T waves-may occur.[104-108]

The mortality rate of ECT is less than 3 in 10,000, and the complication rate is approximately 0.3 percent. Patients with severe heart disease may successfully undergo ECT with acceptable risk. Prior to ECT, electrolyte abnormalities should be corrected and systemic hypertension should be controlled. Patients with pulmonary disease require special evaluation, because hypoxia and

respiratory acidosis may precipitate cardiovascular events.[104]

Following ECT, hypertension and tachycardia may be controlled with adrenergic blockade with intravenous labetalol[109] or esmolol.[107] Other antihypertensive agents such as clonidine or calcium channel blockers may be utilized. Sustained ventricular arrhythmias are treated with lidocaine, but pretreatment with lidocaine is not indicated.[104] Patients with cardiac pacemakers can safely undergo ECT.[110] Currently used pacemakers are not likely to be affected by ECT current. Although these newer devices have not been systematically studied, the 50 to 100 W delivered to the scalp during ECT are probably inadequate to reprogram current pacemakers.

Lithotripsy

Extracorporeal shock wave lithotripsy used to treat renal stones and gallstones has the potential to cause cardiac arrhythmias. Rhythm disturbances may be related to electrical stimulus from the shock wave or from enhanced vagal tone associated with the procedure. Electrocardiographic monitoring is recommended for patients with cardiac disease. Gating of the shock waves to the QRS cycle may be necessary in high-risk patients, although ungated lithotripsy with newer devices is reportedly safe in most patients.[111,112]

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Chapter 71: EFFECT OF NONCARDIAC DRUGS, ELECTRICITY, POISONS, AND RADIATION ON THE HEART

POISONS

Plants

A variety of plants contain active cardiac glycosides. Ingestion of these plants may result in a clinical presentation similar to that of digoxin toxicity, including gastrointestinal and visual disturbances as well as dysrhythmias. Plants with cardiac glycoside-like effects[113] are listed (Table 71-4).

Table 71-4: Plants with Cardiac Glycoside Effects

Foxglove (*Digitalis purpurea, D. Lanata*)
Oleander (*Nerium oleander*)
Lily-of-the-valley (*Convallaria majolis*)
Christmas rose (*Helleborus niger*)
Wallflower (*Cheirina cheiri*)
Milkweed (*Asclepias* sp.)

Herbal Therapies

The use of herbal treatments and nonprescription remedies is increasing among patients. In one study, 38 percent of congestive heart failure patients questioned were using herbal products.[114] Herbal medicines may contain varying doses and contaminants and are not subject to regulations governing safety and efficacy. Serious adverse effects and drug interactions may therefore occur. The cardiac effects of some herbal remedies are listed in Table 71-5.[115-117]

Snakes and Scorpions

Snake bites cause fewer than 15 deaths per year in the United States but over 40,000 deaths per year worldwide. The majority of lethal snake bites occur in Asia, South America, and Africa. Snake venoms contain a variety of enzymes and toxins that may affect the nervous system, blood vessels, coagulation systems, or heart. The majority of deaths are from the elapids (cobra, mamba, coral snake, taipan), the bites of which cause severe neuromuscular toxicity. Cardiotoxins are present in variable amounts in snake venom. Cobra venoms may cause augmentation of myocardial contraction at low concentration and asystole at high concentration. Rattlesnake venom may affect myocardial sodium channels and depress myocardial contractility. These venoms may cause pulmonary hypertension.[118]

Scorpion stings are a common medical problem in areas including India, Southeast Asia, the southwestern United States, Mexico, and Israel. Venoms from different families have different

toxicities. The *Buthidae* venoms, primarily neurotoxic, result in spontaneous sympathetic and parasympathetic depolarization. Massive catecholamine release may cause cardiac toxicity, including tachycardia, hypertension, arrhythmias, and myocardial impairment.[119,120]

Arthropods

Direct cardiac effects related to bee, hornet, and wasp stings are difficult to establish. Cardiac complications, including arrhythmias, are generally related to anaphylaxis or epinephrine administration. Animal studies of bee venom toxicity suggest direct cardiac effects.[121,122]

Marine Toxins

Exposure to marine toxins may have serious cardiovascular effects. The venom of scorpion fish can cause sympathetic and parasympathetic discharges. Rhythm disturbances and heart failure may result. Stingray venom contains phosphodiesterases and has rarely been associated with cardiac rhythm disturbances. Ingestion of sea cucumber, which contains holothurin, may result in cardiac glycoside toxicity. Ingestion of pufferfish, which contain tetrodotoxin, may result in vascular collapse and severe bradycardia.[118,123]

Halogenated Hydrocarbons

Halogenated hydrocarbons are used in fire extinguishers, solvents, and refrigerants and in the manufacture of pesticides and plastics. Heavy acute exposure to these compounds may result in cardiac arrhythmias and sudden death.[124] Direct cardiac effects include depression of myocardial contractility and sensitization to the arrhythmogenic effects of catecholamines. Indirect cardiotoxicity may result from hypoxia or central nervous system toxicity.[125]

Organophosphates

Organophosphates, used commercially in pesticides, are powerful inhibitors of acetylcholinesterase, and this inhibition can result in parasympathetic overstimulation. Suicide attempts account for the majority of fatalities associated with ingestion of large doses of organophosphates. Signs and symptoms of ingestion include respiratory depression, bronchospasm and secretion, and pulmonary edema. Deaths are generally related to respiratory failure. Cardiac toxicity is generally associated with QT prolongation. Torsades de pointes, atrioventricular conduction disturbances, and ST-T abnormalities have been noted. Cardiac arrhythmias have been noted up to 15 days after exposure. Direct myocardial toxicity has been postulated, in addition to cholinergic hyperactivity.[126] Treatment includes atropine administration at doses sufficient to dry mucous membranes and to increase heart rate to 100 beats per minute. Obidoxime therapy has also been studied in severe overdoses.[127]

Carbon Monoxide

Toxicity from carbon monoxide is related to tissue hypoxia. Carbon monoxide has a much higher affinity for hemoglobin than does oxygen, preventing adequate oxygen exchange. Carbon monoxide exposure worsens angina pectoris and increases the risk of myocardial infarction. Carbon monoxide poisoning results in ECG abnormalities, including sinus tachycardia, atrial fibrillation, atrioventricular block, and ST-T abnormalities. Cardiac enzyme elevation may occur. Severe exposure can result in myocardial necrosis and cardiomyopathy.[128] Transient evidence of cardiac toxicity, however, is not necessarily associated with long-term sequelae.[129]

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Chapter 71: EFFECT OF NONCARDIAC DRUGS, ELECTRICITY, POISONS, AND RADIATION ON THE HEART

RADIATION

Mediastinal radiation-commonly used to treat Hodgkin's disease, lung cancer, breast cancer, and seminoma-may result in acute or late cardiac sequelae. Prior to the 1960s, the heart was thought to be resistant to the effects of clinical radiation. It is now recognized that a variety of cardiac problems may result from radiation, including acute or chronic pericardial disease, coronary atherosclerosis, myocardial dysfunction, conduction defects, and, occasionally, valvular dysfunction (Table 71-6).[130,131]

Table 71-6: Radiation-induced Cardiac Disease

Pericardial
Acute pericarditis
Chronic pericarditis
Pericardial constriction
Coronary atherosclerosis
Restrictive cardiomyopathy
Dilated cardiomyopathy (concomitant anthracyclines)
Conduction disease
Valvular abnormalities

The incidence of radiation-induced heart disease is influenced by several factors, including total radiation dose, fraction size, volume of heart irradiated, concomitant anthracycline use, and presence of mediastinal tumor.[130] Improved radiation techniques have diminished the occurrence of acute or chronic cardiac toxicity.[132] Cardiac injury has generally been associated with doses above 40 Gy.[130] Increased toxicity is associated with radiation for Hodgkin's disease, where larger volumes of the heart are irradiated, compared to the small cardiac exposure given as adjuvant treatment for breast carcinoma. Large doses per fraction and anterior-weighted fields result in greater toxicity.[133]

Pericardial disease is the most common manifestation of radiation toxicity to the heart. With the current techniques of subcarinal shielding, equal weighting of anterior and posterior ports, and limiting the dose to less than 30 Gy, the incidence of clinical pericarditis is approximately 2.5 percent.[132] Anatomic changes of the pericardium occur in the majority of patients but are clinically silent. Clinically apparent pericarditis is most frequent 4 to 6 months after therapy. Acute pericarditis, asymptomatic pericardial effusion, or pericardial tamponade may occur. Other etiologies of pericarditis should be considered, particularly malignant involvement of the pericardium. Pericarditis occurring during treatment of a mediastinal mass contiguous to the heart

is generally secondary to tumor effects and does not correlate with late pericardial complications.[134,135]

Radiation may cause an exudative pericarditis. Cellular infiltrate is uncommon. Pericardial fibrosis may follow secondary to fibroblast proliferation and collagen deposition. The majority of patients with pericardial effusion recover spontaneously.[130] Constrictive pericarditis may occur months to years after pericardial effusion or may develop in patients without previously recognized pericardial disease.

The majority of patients with pericardial disease have a relatively benign course. Treatment is based on symptoms, including pericardiocentesis for tamponade and antipyretics for fever. Animal data suggest possible benefit from steroids.[130]

The surgical management of postirradiation constrictive pericarditis is difficult.[134] Extensive mediastinal and pericardial fibrosis make pericardiectomy technically challenging. Surgical morbidity and mortality are significant. Radiation-induced constriction is often associated with coronary atherosclerosis, myocardial dysfunction, or conduction and valvular abnormalities. Comorbid cardiac or general medical conditions should be considered when patients are selected for pericardiectomy.

Clinically important myocardial dysfunction related to radiation generally occurs in combination with pericardial disease. Asymptomatic patients may have varying degrees of myocardial fibrosis. The anterior right ventricle is most susceptible. Areas of fibrosis may be patchy or diffuse. Noninvasive techniques such as echocardiography may show mild impairment of systolic function; however, this is usually not clinically significant.[132] Diastolic abnormalities may occur due to fibrosis.

Restrictive cardiomyopathy has been reported but is rare.[130] Premature coronary artery disease may result from radiation therapy, particularly in patients who were irradiated in an era when cardioprotective techniques were not used. Several series have reported a significantly increased risk of coronary artery disease years following therapeutic radiation involving cardiac exposure.[135] The Stockholm Trial demonstrated increased mortality secondary to coronary artery disease in women receiving high-dose radiation to the heart as adjuvant therapy for carcinoma of the left breast.[135] A review of 635 patients at Stanford treated for Hodgkin's disease before age 21 between the years 1961 and 1991 showed a significantly increased risk for myocardial infarction.[136,137] It is not clear, however, whether present techniques of mediastinal radiation will result in a clinically significant increase in coronary events. Percutaneous angioplasty and coronary bypass surgery have been successful in selected patients. The commonly associated mediastinal and pericardial fibrosis, however, make surgical revascularization more difficult.[130]

Clinically significant valvular heart disease secondary to radiation is rare but, when present, usually involves the aortic or mitral valves.[130,131] Fibrous thickening of the cardiac valves has been noted at autopsy. This thickening often causes asymptomatic aortic or mitral regurgitation.[138] Coexisting pericardial disease is the rule. Symptoms related to valvular dysfunction have been noted to occur 15 to 40 years after radiation treatment. Surgical reports are rare and most commonly are for replacement of the aortic valve due to aortic stenosis.[131]

Radiation may result in fibrosis of the nodal and infranodal pathways. Complete atrioventricular block, right bundle branch block, and, less commonly, left bundle branch block may occur. Progression to complete heart block is rare.

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Part 12: PERICARDIAL DISEASES AND ENDOCARDITIS
Chapter 72:

DISEASES OF THE PERICARDIUM

Author: Brian D. Hoit

INTRODUCTION

Anatomy of the Pericardium

The pericardium is composed of visceral and parietal components. The visceral pericardium is a mesothelial monolayer that adheres firmly to the epicardium, reflects over the origin of the great vessels, and, together with a tough, fibrous coat, envelops the heart as the parietal pericardium (Fig. 72-1). The pericardial space is enclosed between these two serosal layers and normally contains up to 50 mL of a plasma ultrafiltrate, the pericardial fluid. Pericardial reflections around the great vessels tether the pericardium superiorly and result in the formation of two potential spaces: the oblique and transverse sinuses. The left atrium is anterior to the oblique sinus and is therefore largely an extrapericardial chamber; this relationship explains why effusions generally are not seen behind the left atrium. Superior and inferior pericardiosternal and diaphragmatic ligaments limit displacement of the pericardium and its contents within the chest and neutralize the effects of respiration and change of body position. The phrenic nerves are embedded in the parietal pericardium and, for this reason, are vulnerable to injury during pericardial resection.

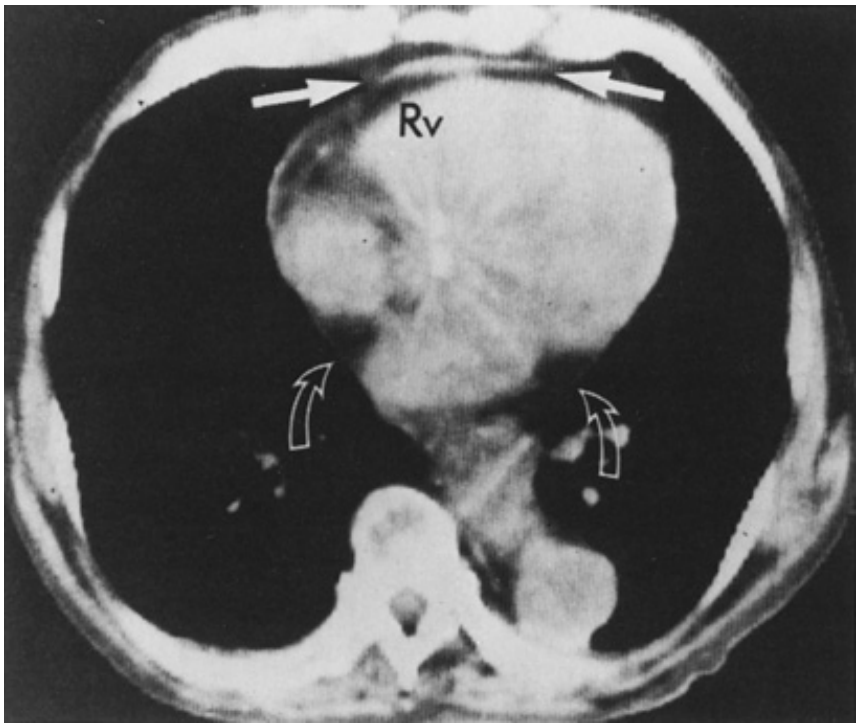

Figure 72-1: Computed tomographic (CT) scan shows the normal pericardium as a thin, curvilinear line (*open arrows*). The increased thickening over the anterior surface of the heart

(*solid arrows*) is probably an artifact from transmitted right ventricular pulsations. (From Moncada R, Baker M. In: Higgins CB, ed. *CT of the Heart and Great Vessels.* Mt. Kisco, NY: Futura; 1983:292. Reproduced with permission.)

Histologically, the pericardium is composed predominantly of compact collagen layers interspersed with elastin fibers. The abundance and orientation of the collagen fibers are responsible for the characteristic viscoelastic mechanical properties of the pericardium. For example, the pressure-volume relation of the pericardium is nonlinear; i.e., the relation is initially flat (producing little to no change in pressure for large changes in volume) and develops a "bend" or "knee" at a critical pressure, which terminates in a steep slope (producing large changes in pressure for small changes in volume) (Fig. 72-2). In addition, the pericardium is anisotropic; i.e., it stretches more in the short axis than in the long axis.

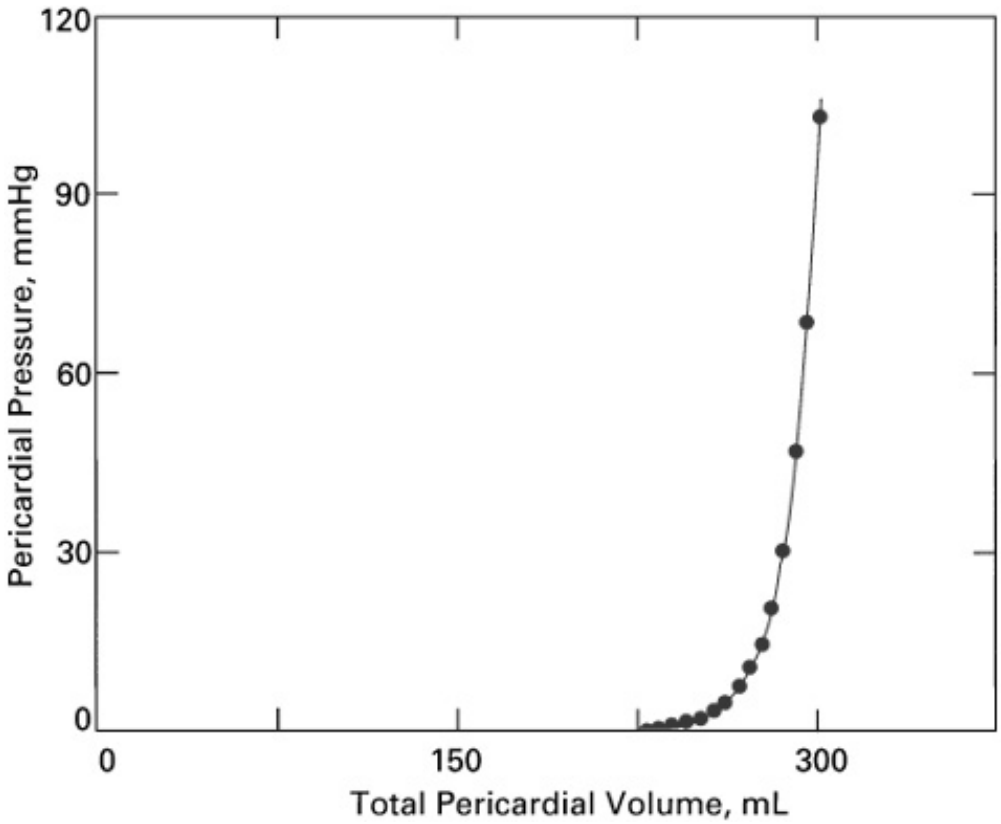

Figure 72-2: Pericardial pressure-volume relation in a dog. (From Holt JP. The normal pericardium. *Am J Cardiol* 1970; 26:455. Reproduced with permission.)

Physiology of the Pericardium

The pericardium is not essential for life; no adverse consequences follow congenital absence or surgical removal of the pericardium. However, the pericardium serves many important (although subtle) functions (Table 72-1). The pericardium limits distention of the cardiac chambers and facilitates interaction and coupling of the ventricles and atria.[1] Thus, changes in pressure and volume on one side of the heart can influence pressure and volume on the other side. Limitation of cardiac filling volumes by the pericardium also may limit cardiac output and oxygen delivery during exercise.[2] The pericardium also influences quantitative and qualitative aspects of ventricular filling[3]; the thin-walled right ventricle (RV) and atrium are more subject to the influence of the pericardium than is the more resistant, thick-walled left ventricle (LV).[4]

Table 72-1: Functions of the Pericardium

Mechanical
Effects on chambers
Limits short-term cardiac distention
Facilitates cardiac chamber coupling and interaction
Maintains pressure-volume relation of and output from cardiac chambers
Maintains geometry of left ventricle
Effects on whole heart
Lubricates, minimizes friction
Equalizes gravitation, inertial, hydrostatic forces
Mechanical barrier to infection
Immunologic
Vasomotor
Fibrinolytic
Modulation of myocyte structure, function, and gene expression
Vehicle for drug delivery and gene therapy

Although the magnitude and importance of pericardial restraint of ventricular filling at physiologic cardiac volumes remain controversial, there is general agreement that pericardial reserve volume (i.e., the difference between unstressed pericardial volume and cardiac volume) is relatively small and that pericardial influences become significant when the reserve volume is exceeded. This may occur with rapid increases in blood volume and in disease states characterized by rapid increases in heart size (e.g., acute mitral and tricuspid regurgitation, pulmonary embolism, RV infarction). In contrast, chronic stretching of the pericardium results in "stress relaxation"; this explains why large but slowly developing effusions do not produce tamponade. In addition, the pericardium adapts to cardiac growth by "creep" (i.e., an increase in volume with constant stretch) and cellular hypertrophy. Pericardial thickening, which is characterized by mesothelial cell and matrix rearrangments, and the absence of diastolic abnormalities on echocardiography are features of vibroacoustic disease.[5]

The pericardium serves a variety of other important functions. It prevents excessive torsion and displacement of the heart, minimizes friction with surrounding structures, and is an anatomic barrier to the spread of infection from contiguous structures. The thin layer of pericardial fluid reduces friction on the epicardium and is thought to equalize gravitational forces over the surface of the heart; transmural cardiac pressures therefore do not change during acceleration or differ regionally within cardiac chambers. In addition, pericardial fluid equalizes inertial and hydrostatic forces. The pericardium also has immunologic, vasomotor, and fibrinolytic activity.[6] Epicardial mesothelial cells may modulate myocyte structure and function and gene expression.[7] Finally, the pericardial space has been used as a vehicle for drug delivery in gene therapy; studies using radiolabeled growth factors indicate that substances more consistently and reproducibly gain

access to the coronary arteries via pericardial fluid than via endoluminal delivery.[8,9]

PERICARDIAL MICROPHYSIOLOGY

The pericardium is richly innervated; neuroreceptors in the epicardium and fibrosa, sympathetic afferents, stretch-sensitive mechanoreceptors, and phrenic afferents monitor dynamic changes in cardiac volume and tension.[10] Chemo- and mechanoreceptors with sympathetic afferents may be responsible for the transmission of pericardial pain.[11]

The mesothelium of the pericardium is metabolically active and produces prostaglandin E_2, eicosanoids, and prostacylin; these substances modulate sympathetic neurotransmission and myocardial contractility and may influence epicardial coronary arterial tone. The concentration of angiogenic growth factors bFGF and VEGF increases in unstable angina,[12] suggesting a role for these factors in response to ischemia and injury. The level of brain natriuretic peptide (BNP) in the pericardial fluid is a more sensitive and accurate indicator of ventricular volume and pressure than is either plasma BNP or atrial natriuretic factor and may play an autocrine/paracrine role in heart failure.[13] In addition, levels of pericardial 8-iso-PGF2α (a marker of oxidant stress) increase directly with increasing ventricular dilatation and severity of heart failure, suggesting a role of oxidant stress in ventricular remodeling and the development of heart failure.[14]

Pericardial Pressure

Pericardial pressure measured by a fluid-filled catheter in the pericardial space is subatmospheric and is essentially equal to pleural pressure throughout the respiratory cycle. Small fluctuations related to the events of the cardiac cycle (pericardial pressure is lowest during ventricular ejection) are superimposed on the larger fluctuations related to the events of the respiratory cycle. Although much of the understanding of pericardial physiology is based on fluid pressure, pericardial restraint is a contact force, defined as fluid pressure plus deformational force (much like the force at the knee joint that, although considerable, is negligible when measured with a needle in the joint space). Pericardial contact pressure measured with flat balloons is considerably higher than liquid pressure and varies regionally.[3]

Balloon pressure is similar to the theoretical pericardial pressure that is calculated as the difference in LV diastolic pressure before and after pericardiectomy. This theoretical pressure has important implications for understanding the role of the pericardium in states of altered ventricular loading, such as pulmonary hypertension, aortic stenosis, and congestive heart failure, but does not explain pericardial influences on transmural pressure, for example, during acceleration and deceleration. When liquid versus contact pressure is more relevant is controversial among physiologists but is far less relevant to clinicians, who measure pericardial pressure only when there is a pericardial effusion.

Pathology of the Pericardium

In view of its simple structure, clinicopathologic processes involving the pericardium are understandably few; indeed, pericardial heart disease includes only pericarditis (an acute, subacute, or chronic fibrinous, "noneffusive," or exudative process) and its complications, tamponade and constriction (an acute, subacute, or chronic adhesive, fibrocalcific response), and congenital lesions. However, despite a limited number of clinical syndromes, the pericardium is affected by virtually every category of disease, including infections, neoplastic, immune/inflammatory, metabolic, iatrogenic, traumatic, and congenital etiologies. Thus, the physician is likely to encounter patients with pericardial disease in a variety of settings, either as an isolated phenomenon or as a complication of a variety of systemic disorders, trauma, or certain drugs.

Pericardial disease often remains clinically silent and may be detected only during the evaluation of unrelated complaints by the electrocardiogram (ECG), chest radiography, or echocardiography. Despite exhaustive etiologic lists (Table 72-2), the cause of pericardial heart disease often is never identified. Recently, an increased prevalence of pericarditis, (owing largely to therapeutic advances such as cardiovascular surgery, hemodialysis, and radiation therapy), pericardial involvement in AIDS, and advances in the recognition, diagnosis, and therapy of pericarditis and its complications have resulted in a resurgence of interest in pericardial heart disease. The remainder of this chapter reviews pericarditis and its sequelae, pericardial effusions, cardiac tamponade and constrictive pericarditis, and congenital diseases of the pericardium.

Table 72-2: Causes of Pericardial Heart Disease

Idiopathic
Infectious
Bacterial (pneumococcus, streptococcus, staphlococcus, *Haemophilus influenzae*, gram-negative rods, *B. melitensis, F. tularensis, Legionella pneumophilia, P. gonorrhoeae, N. meningitidis*, Lyme disease, myocoplasma)
Viral (coxsackie virus, echovirus, adenovirus, varicella, influenza, cytomegalovirus, HIV, hepatitis B, mumps, infectious mononucleosis)
Mycobacterial (*M. tuberculosis, M. avium-intracellulare*)
Fungal (histoplasmosis, coccidioidomycosis, blastomycosis, *Candida albicans, Nocardia*, actinomycosis)
Protozoal (toxoplasmosis, echinococcosis, amebiasis)
AIDS-associated
Neoplastic
Primary (mesothelioma, fibrosarcoma)
Secondary (breast, lung, melanoma, lymphoma, leukemia)
Immune/inflammatory
Connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosis, scleroderma, acute rheumatic fever, dermatomyositis, mixed connective tissue disease, Wegener's granulomatosis)
Arteritis (temporal arteritis, polyarteritis nodosa, Takayasu's arteritis)
Acute myocardial infarction and post-MI (Dressler's syndrome)
Postcardiotomy
Posttraumatic
Metabolic
Nephrogenic

Aortic dissection
Myxedema
Amyloidosis
Iatrogenic
Radiation injury
Instrument/device trauma (implantable defibrillators, pacemakers, catheters)
Drugs (hydralazine, procainamide, daunorubicin, isoniazid, anticoagulants, cyclosporine, methysergide, phenytoin, dantrolene, mesalazine)
Cardiac resuscitation
Traumatic
Blunt
Penetrating
Surgical
Congenital
Pericardial cysts
Congenital absence of pericardium
Mulibrey nanism

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ACUTE PERICARDITIS

Acute fibrinous or dry pericarditis is a syndrome characterized by typical chest pain, a pathognomonic pericardial friction rub, and specific ECG changes. A variety of conditions are associated with acute pericarditis (Table 72-2). The following description refers to viral and idiopathic pericarditis without significant effusion. Specific forms of pericardial heart disease are reviewed later in the chapter.

History

Acute pericarditis typically produces sharp retrosternal pain that radiates to the trapezius ridge and is aggravated by lying down and relieved by sitting up; its onset frequently is heralded by a prodrome of fever, malaise, and myalgia (Fig. 72-3). The pain of pericarditis is often worse with inspiration and is difficult to distinguish from pleurisy; in some cases, the pain is indistinguishable from that of myocardial infarction. The quality, severity, and location of pain vary greatly, and chest pain may be absent in acute pericarditis, especially in early pericarditis complicating myocardial infarction or cardiac surgery and in uremic pericarditis.

Physical Findings

The hallmark of acute pericarditis is the pericardial friction rub; because of its superficial, creaky, or scratchy character, it often is likened to the sound of walking on dry snow or the squeak of a leather saddle (Fig. 72-3). Rubs are heard anywhere over the precordium but most often between the lower left sternal edge and the cardiac apex; they usually are heard best with the diaphragm of the stethoscope applied firmly and with respiration suspended. Most pericardial friction rubs are independent of the respiratory cycle, but on occasion they are louder during inspiration. The pericardial rub may be confined to ventricular systole but most often includes a component during atrial systole and occasionally during ventricular diastolic filling, resulting in biphasic and triphasic rubs, respectively. Biphasic rubs must be distinguished from murmurs of mixed aortic valve disease, and monophasic rubs often are mistaken for systolic murmurs. Frequent examinations are necessary to detect a rub because of its evanescent nature; pericardial fluid does not prevent a friction rub.

In uncomplicated pericarditis, the jugular venous pressure usually remains normal. Ventricular third and fourth heart sounds indicate coexisting myocardial disease. The history and physical examination are helpful also in recognizing complications and in identifying underlying diseases associated with pericarditis. Depending on the etiology, there may be fever and other signs of inflammation or systemic illness.

Electrocardiography

The ECG may either confirm the clinical suspicion of pericardial disease or first alert the clinician to the presence of pericarditis (Fig. 72-4). Serial tracings may be needed to distinguish the ST-segment elevations caused by acute pericarditis from those caused by acute myocardial infarction (MI) or normal early repolarization. The ST-T wave changes in acute pericarditis are diffuse and have characteristic evolutionary changes. In the first stage, ST-segment elevations (which differ from ischemic ST elevations by their upward concavity and seldom exceed 5 mm in

height) typically occur within a few hours of the onset of chest pain and persist for hours or days. Depression of the PR segment (except in lead aV_R) may be seen in this stage and may differentiate acute pericarditis from early repolarization variants.[15] In the second stage, the ST segments return to baseline; at this point, the T waves may appear normal or exhibit a loss of amplitude. In the third stage, tracings show inversion of T waves. T-wave inversions may persist indefinitely, particularly with tuberculous, uremic, or neoplastic pericarditis. The ECG normalizes in the variably present fourth stage. In a typical case of acute pericarditis, the approximate time frame for these ECG changes is 2 weeks. However, only about half of patients with acute pericarditis display all four ECG stages, and variations are very common. Atrial arrhythmias complicate 5 to 10 percent of cases of acute pericarditis.[16]

The ST-segment elevation seen in acute pericarditis usually can be distinguished from that of acute MI by the absence of Q waves, the upwardly concave ST segments, and the absence of associated T-wave inversions. The acute ST-segment elevation of Prinzmetal's variant of angina is more transitory and is associated with ischemic pain. Although the ST-segment elevation in the early repolarization variant (common in young individuals, especially blacks, athletes, and psychiatric patients) may simulate the ECG of acute pericarditis, the former is distinguished by the absence of PR-segment depression and evolutionary ST-T wave changes.

Imaging and Laboratory Studies

In uncomplicated acute pericarditis, the chest radiograph is generally normal. However, an enlarged cardiac silhouette may be evident because of a moderate or large pericardial effusion (Fig. 72-5). The chest radiograph may provide evidence of tuberculosis, fungal disease, pneumonia, or neoplasm.

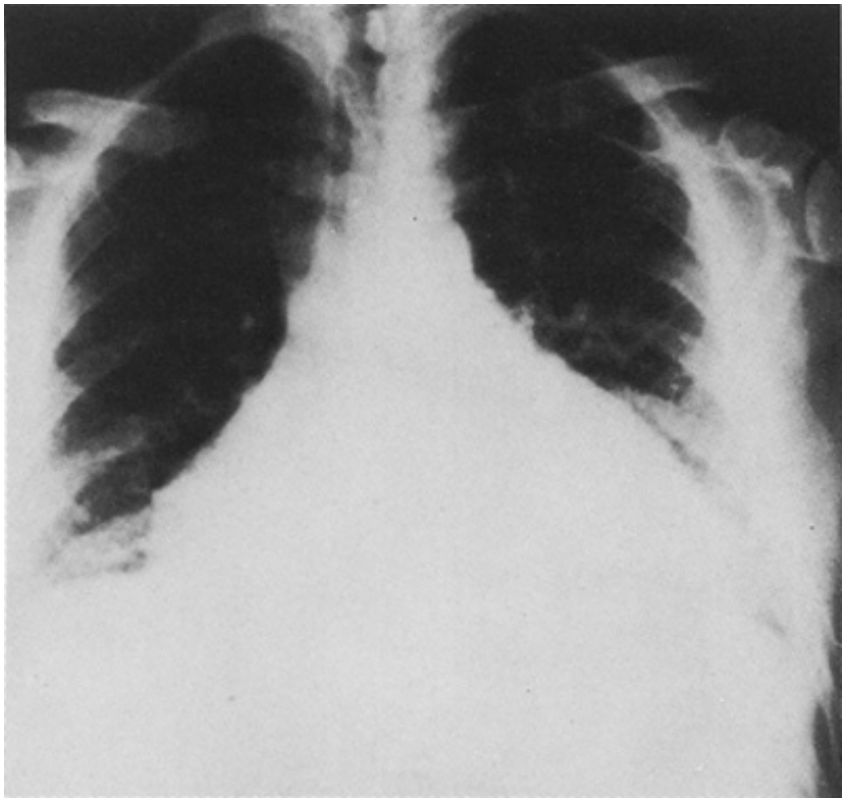
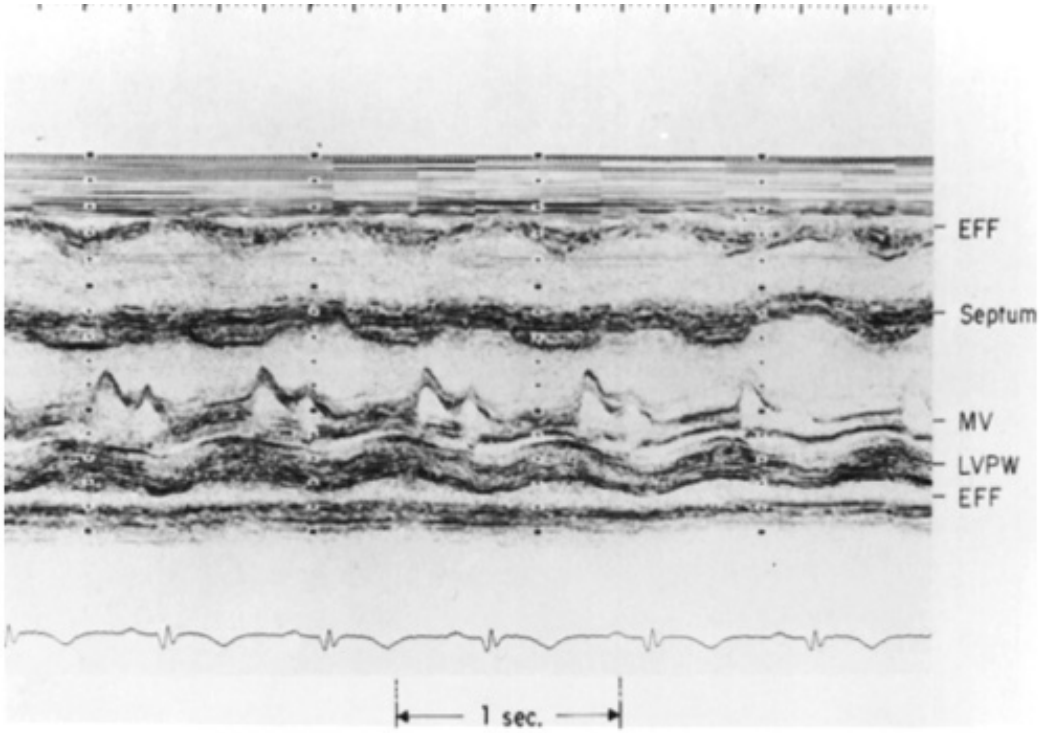


Figure 72-5: Chest radiograph from a patient with a large pericardial effusion. Note the "flask-shape" appearance of the cardiac silhouette. (From Hoit BD. Imaging the pericardium. *Cardiol*

Clin 1990; 8:588. Reproduced with permission.)

Echocardiographic identification of pericardial effusion confirms the clinical diagnosis of acute pericarditis (Fig. 72-6), but a patient with purely fibrinous acute pericarditis often has a normal echocardiogram. Echocardiography estimates the volume of pericardial fluid, identifies cardiac tamponade, suggests the basis of pericarditis, and documents associated acute myocarditis with congestive heart failure.



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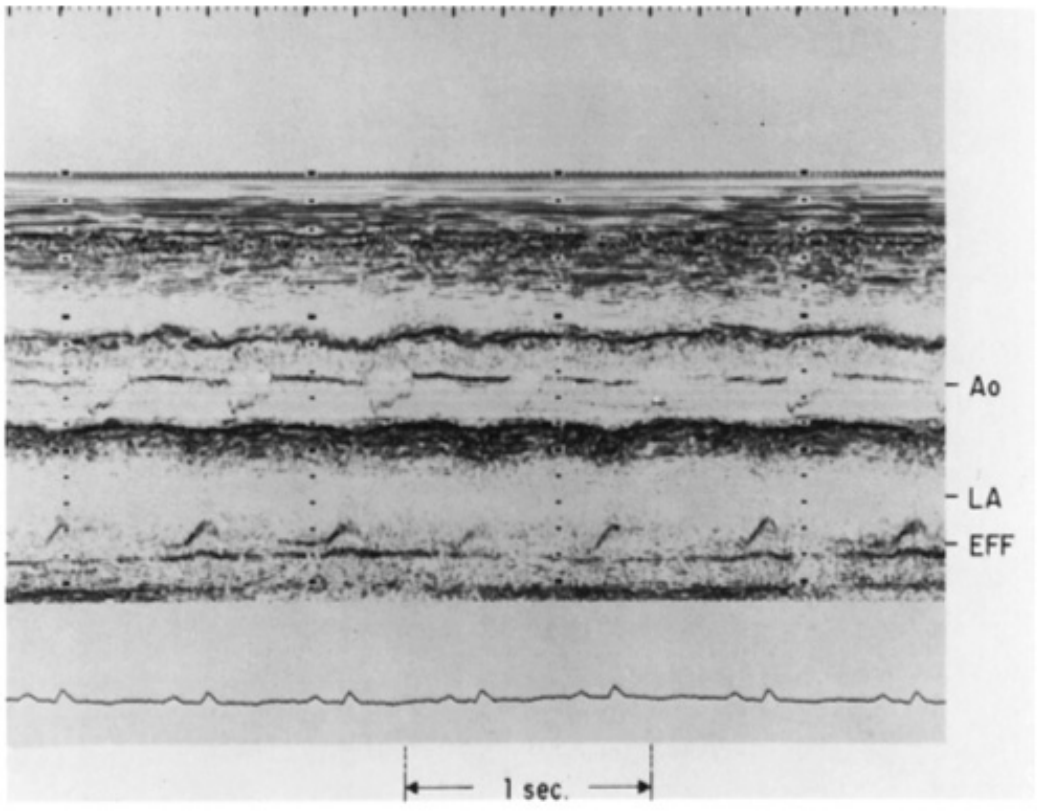

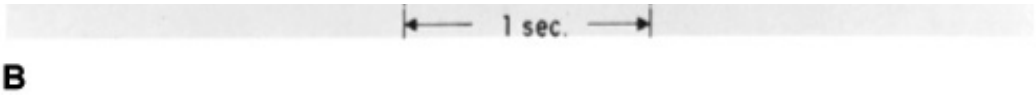

Figure 72-6: M-mode echocardiograms of pericardial effusion (EFF). *A.* The effusion appears as an echo-free space posteror to the left ventricular posterior wall (LVPW). Note that parietal pericardium has relatively flat motion throughout the cardiac cycle. MV = mitral valve. *B.* Pericardial effusion behind the left atrium (LA). Note the exaggerated motion of the posterior left atrial wall. (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:588. Reproduced with permission.)

Although ^{99}technetium pyrophosphate scans may be positive in patients with pericarditis associated with epicarditis and gallium scans have proved useful in displaying the characteristics of purulent pericarditis, these tests rarely are used to diagnose acute pericarditis.

Nonspecific blood markers of inflammation, such as the erythrocyte sedimentation rate and the white blood cell count, usually increase in cases of acute pericarditis. Patients with extensive epicarditis occasionally have increases in serum cardiac isoenzymes suggestive of acute MI.

Therapy for Acute Pericarditis

Hospitalization is warranted for most patients who present with an initial episode of acute pericarditis to determine the etiology and observe for cardiac tamponade. Establishing the exact cause of acute pericarditis is an important aspect of management, but considerable judgment must be exercised in deciding whether and how to investigate the possibility of concomitant systemic disease.

An extensive evaluation is generally unnecessary in a young, previously healthy adult who presents with a viral syndrome, typical pericardial chest pain, and a pericardial friction rub. Most cases of viral pericarditis are recognized long after the period of viral activity, making a specific etiologic diagnosis and antiviral chemotherapy unnecessary. Thus, differentiating viral from idiopathic pericarditis is difficult, expensive, and generally of little practical importance. Depending on the history and symptoms at presentation, trauma, myocarditis, systemic lupus erythematosus (SLE), and/or purulent pericarditis require consideration in younger patients. In older adults, myocardial infarction, tuberculosis, and neoplastic disease should be considered.

Acute pericarditis usually responds to oral nonsteroidal anti-inflammatory agents (e.g., ASA 650 mg q3-4h or ibuprofen 600 to 800 mg q6h). Indomethacin reduces coronary blood flow and theoretically should be avoided. Some data suggest that the addition of colchicine (1 mg/day) is effective for an acute episode and may prevent recurrences.[17] The intensity of therapy is dictated by the distress of the patient; narcotics may be required for severe pain. Some cases necessitate steroid therapy (prednisone 60 to 80 mg/day) for a week to control pain, with the dose tapered rapidly thereafter. Corticosteroids should be avoided unless there is a specific indication. They may enhance viral multiplication and produce recurrences when the dose is tapered; colchicine may be useful in this situation. Nevertheless, corticosteroids are useful in acute pericarditis associated with uremic pericarditis and connective tissue diseases. Importantly, tuberculous and pyogenic pericarditis should be excluded before steroid therapy is initiated.

Patients in whom pericarditis represents one manifestation of systemic illness (such as sepsis, uremia, connective tissue disease, or neoplasia) should, in addition to palliative and supportive treatment, receive therapy directed toward the primary disorder.

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RECURRENT PERICARDITIS

Recurrent or relapsing acute pericarditis is one of the most distressing disorders of the pericardium for both patient and physician; it may occur with or without pericardial effusion and occasionally is associated with pleural effusion or parenchymal pulmonary lesions. Recurrences occur with highly variable frequency over a course of many years. The reasons for relapse are unclear, but the phenomenon suggests that acute pericarditis itself may represent or generate an autoimmune process. Recurrences may be spontaneous but more commonly are associated with discontinuation or tapering doses of anti-inflammatory drugs. When associated with pericardial effusion, relapsing pericarditis can cause cardiac tamponade; however, this is unusual.

Painful recurrences of pericarditis may respond to nonsteroidal anti-inflammatory agents but commonly require corticosteroids. Once steroids are administered, dependency and the development of steroid-induced abnormalities are potential sequelae. Prednisone is begun at a high dose (60 to 80 mg/day), but rapid tapering should be initiated within a few days of clinical resolution. When necessary, the risks of long-term steroids should be minimized by using the lowest possible dose, alternate-day therapy, combinations with nonsteroidal drugs, or colchicine (1 to 2 mg/day).[18] In the most difficult cases, relapse occurs every time the dose of prednisone is reduced below 5 to 20 mg/day. When this occurs, the patient should be maintained for several weeks on the lowest suppressive dose before the next taper commences. Azathioprine (50 to 100 mg/day) also has been used to prevent recurrent episodes.[19] Although encouraging results have been reported in a series of patients who underwent pericardiectomy for recurrent pericarditis, pericardiectomy may simply abbreviate rather than terminate the painful recurrences. Thus, pericardiectomy should be considered only when repeated attempts at medical treatment have clearly failed.

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PERICARDIAL EFFUSION

Etiology

Accumulation of transudate, exudate, or blood in the pericardial sac is a common complication of pericardial disease and should be sought in all patients with acute pericarditis.

Pericardial effusions are reported to be associated with heart failure, valvular disease, and myocardial infarction in 14, 21, and 15 percent of cases, respectively.[20] Hydropericardium results from elevated right atrial pressure and limited venous and lymphatic drainage from the pericardium. Although this is the usual explanation for effusions associated with heart failure and LV hypertrophy, recurrent bloody effusions that can be attributed only to congestive heart failure may occur.

Pericardial effusions are very common after cardiac surgery. In 122 consecutive patients studied before and serially after cardiac surgery, effusions were present in 103 patients; the majority appeared by postoperative day 2, reached their maximum size by postoperative day 10, and usually resolved without sequelae within the first postoperative month.[21] Symptoms and physical findings of significant postoperative pericardial effusions are frequently nonspecific, and echo-detection and echo-guided pericardiocentesis, when necessary, are safe and effective; prolonged catheter drainage reduces the recurrence rate.[22] Pericardial effusions in cardiac transplant patients are associated with an increased incidence of acute rejection.[23] Chronic effusive pericarditis is an entity of unknown etiology that may be associated with large, asymptomatic effusions. Many conditions that cause pericarditis (e.g., uremia, tuberculosis, neoplasia, connective tissue disease) produce chronic pericardial effusions.

Nature of the Pericardial Fluid

Characteristics of the pericardial fluid other than culture and cytology are usually too nonspecific to be of diagnostic value. However, in one retrospective series, one-fifth of the patients had a specific etiologic diagnosis that had implications for management and prognosis.[24] Moreover, in certain situations it is mandatory to determine the nature of the pericardial fluid. For example, in patients with neoplastic disease, it is important to determine whether pericardial effusion indicates invasion of the pericardium or a complication of radiation therapy. Cytologic examination of the fluid is also important in cases in which the primary tumor has not been identified clearly. In cases of bacterial or other nonviral infections, it becomes necessary to discover whether the pericardial effusion is exudative and to culture pericardial fluid; this is particularly important when tuberculous or fungal pericarditis is suspected. Transudative effusions (hydropericardium) occur in heart failure and other states associated with chronic salt and water retention (including pregnancy), and exudative effusions occur in a large number of the infectious and inflammatory causes of pericarditis. Although frank hemorrhagic effusions suggest recent intrapericardial bleeding, sanguineous and serosanguineous effusions occur in many infectious and inflammatory disorders. In certain disorders, the nature of the pericardial fluid has greater diagnostic value. For example, chylous pericarditis implies injury or obstruction to the thoracic duct, and cholesterol pericarditis is either idiopathic or associated with hypothyroidism, rheumatoid arthritis, or tuberculosis.

Diagnostic Studies

Specific diagnoses are possible using visual, cytologic, and immunologic analysis of the pericardial effusion and pericardioscopic-guided biopsy of the epicardium and pericardium.[20,25] Observations using these techniques have suggested that (1) fibrin strands and neovascularization are common in inflammatory pericardial diseases, (2) the etiology of viral pericarditis can be established by using a variety of methods, such as in situ hybridization, microneutralization, and polymerase chain reaction, (3) combined analysis of the cytology in the effusion and epicardial biopsy are most important, and pericardial biopsy is often inconclusive, and (4) viral and autoreactive effusions are associated with high titers of antimyolemmal and antisarcolemmal antibodies and in vitro cardiocytolysis of isolated rat heart cells. However, the clinical utility of these diagnostic methods and observations remains to be determined.

There are clinical situations in which it is unnecessary to obtain pericardial fluid for analysis. For example, when pericardial effusion is found in a patient with typical viral or idiopathic pericarditis, pericardiocentesis should not be considered unless the effusion fails to respond to anti-inflammatory treatment or cardiac tamponade develops. Similarly, when a patient undergoing chronic hemodialysis develops pericardial effusion, examination of pericardial fluid is needed only when the clinical course suggests a different etiology or when hemodynamic embarrassment is suspected.

IMAGING STUDIES

Echocardiography is the procedure of choice for the diagnosis of pericardial effusion. Although flask-shaped enlargement of the cardiac silhouette on chest radiography occurs with a moderate or large pericardial effusion (Fig. 72-5), differentiation of large effusions from cardiac dilatation often is difficult or impossible. In contrast, the relative contributions of cardiac enlargement and pericardial effusion to overall cardiac enlargement and the relative roles of tamponade and myocardial dysfunction to altered hemodynamics can be evaluated with echocardiography. Attention to technical detail results in excellent sensitivity and specificity. The diagnostic feature on M-mode echocardiography is the persistence of an echo-free space between parietal and visceral pericardium throughout the cardiac cycle (Fig. 72-6). Separations that are observed only in systole represent clinically insignificant accumulations. Two-dimensional (2-D) echocardiography (Fig. 72-7) has superior spatial orientation and allows delineation of the size and distribution of pericardial effusion as well as detection of loculated fluid. As the amount of pericardial fluid increases, fluid distributes from the posterobasilar LV apically and anteriorly and then laterally and posteriorly to the left atrium. Fluid adjacent to the right atrium is an early sign of pericardial effusion. Frondlike, bandlike, or shaggy intrapericardial echoes should alert one to the possibility of a difficult and potentially less therapeutic pericardiocentesis (Fig. 72-8) but have little value in identifying the cause of the effusion.

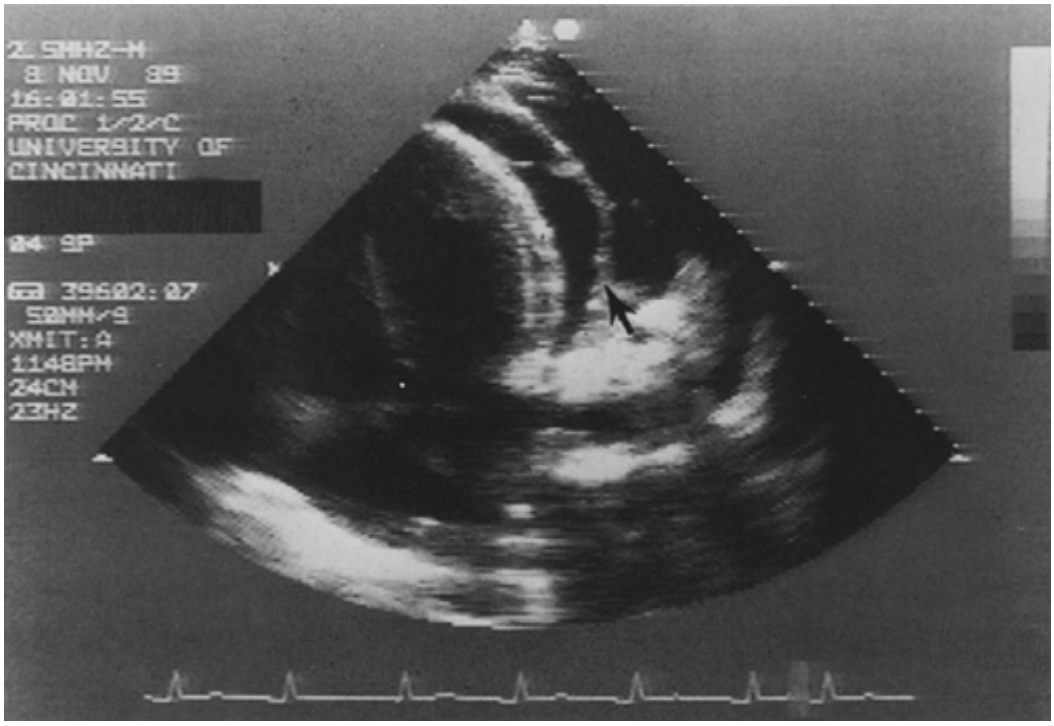

Figure 72-7: Two-dimensional echocardiogram from a patient with pleural and pericardial effusions. The thickness of the pericardium (*arrow*) can be appreciated in this patient. (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:596. Reproduced with permission.)

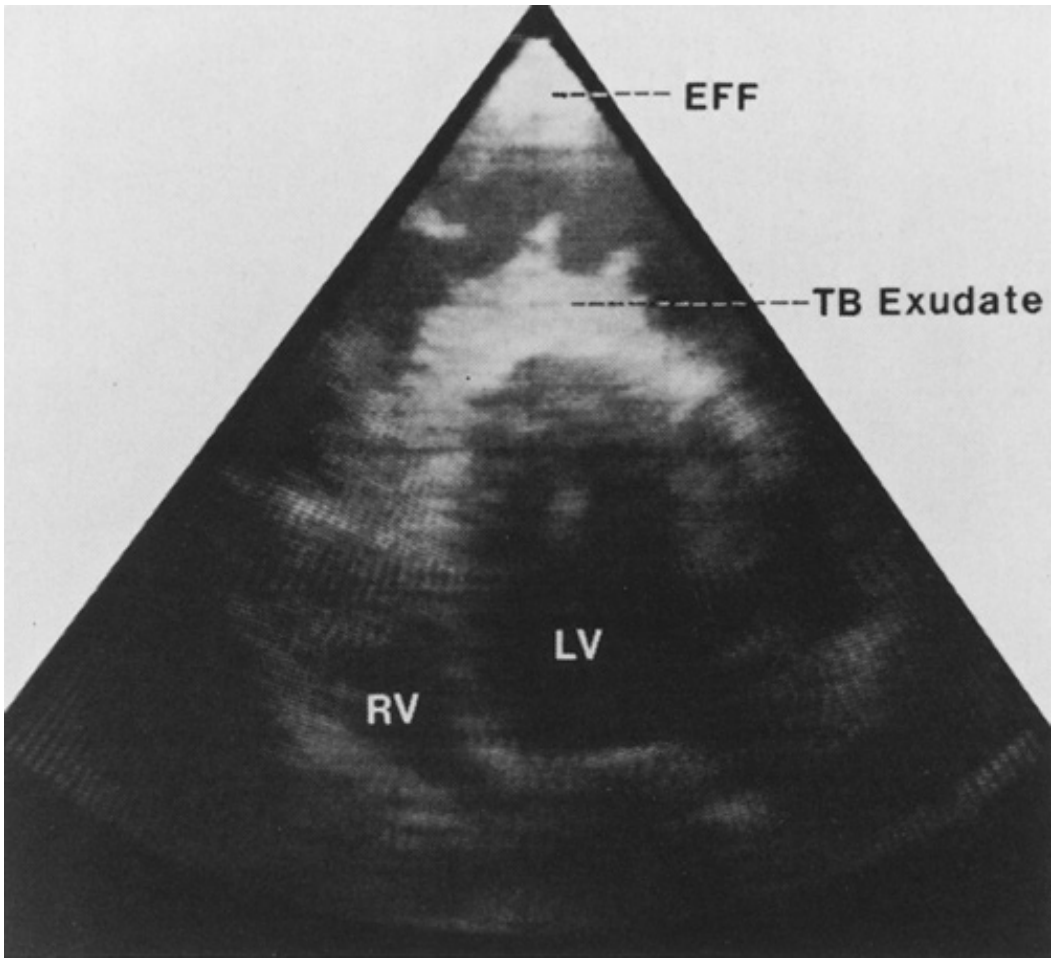

Figure 72-8: Two-dimensional echocardiogram from a patient with tuberculous pericarditis. Note the thickened pericardium with shaggy exudate that bridges a large pericardial effusion (EFF). (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:590. Reproduced with permission.)

Pericardial effusions are easily detected by computed tomography (Fig. 72-9). The size, geometry, and distribution of pericardial effusions can be obtained with this technique, and the attenuation coefficients for blood, exudate, chyle, and serous fluid are generally sufficiently characteristic to identify the nature of the effusion. Computed tomography may be useful in identifying loculated and atypically loculated pericardial effusions and in guiding pericardiocentesis. Loculated and recurrent pericardial effusions can be treated safely and effectively with video-assisted thoracoscopic pericardial fenestration.[26]

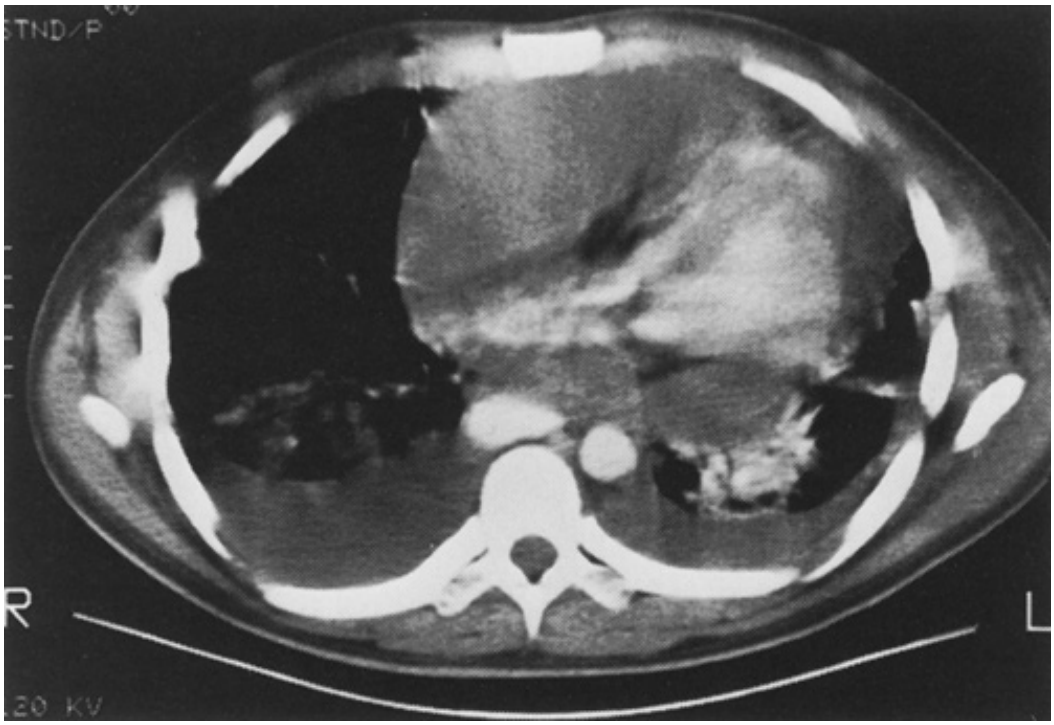

Figure 72-9: Computed tomographic scan from a patient with a large pericardial effusion. Note the compression of contrast-filled cardiac chambers. (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:590. Reproduced with permission.)

Magnetic resonance imaging (MRI) detects pericardial effusion with high sensitivity and provides an estimate of pericardial fluid volume; in addition, it effectively detects loculated pericardial effusion and pericardial thickening.[27] Inflamed pericardium and adhesions have a high signal intensity relative to pericardial fluid and myocardium, providing a potential means of identifying the nature of the effusion.

Treatment of Pericardial Effusion

Drainage of a pericardial effusion is usually unnecessary unless purulent pericarditis is suspected or cardiac tamponade supervenes, although on occasion, pericardiocentesis is needed to establish the etiology of a hemodynamically insignificant pericardial effusion. Persistent or progressive effusion, particularly when the cause is uncertain, also warrants pericardiocentesis. However, routine drainage of a large pericardial effusion without tamponade or suspected purulent

pericarditis has a low diagnostic yield and no clear therapeutic benefit.[28] Anticoagulants should be discontinued temporarily if possible to reduce the risk of cardiac tamponade. In patients on chronic oral anticoagulation, heparin should be used, since its effect can be reversed rapidly. Large effusions may respond to nonsteroidal anti-inflammatory drugs, corticosteroids, or colchicine.[17] Specific treatment for pericardial effusion is considered below.

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CARDIAC TAMPONADE

Cardiac tamponade is a hemodynamic condition characterized by equal elevation of atrial and pericardial pressures, an exaggerated inspiratory decrease in arterial systolic pressure (pulsus paradoxus), and arterial hypotension. Arterial hypotension is generally a late sign in chronic effusions, and occasionally, a heightened sympathoadrenal state produces systemic hypertension. As intrapericardial pressure rises, venous pressures increase to maintain cardiac filling and prevent collapse of the cardiac chambers. Although the absolute intracardiac pressures are elevated, the transmural pressures-i.e., cavitary diastolic pressure minus pericardial pressure-are practically zero or even negative. The greatly reduced preload is responsible for the fall in cardiac output, and when compensatory mechanisms are exhausted, arterial pressure decreases.

Clinical Features

Cardiac tamponade may be acute or chronic and should be viewed hemodynamically as a continuum ranging from mild (pericardial pressure lower than 10 mmHg) to severe (pericardial pressure higher than 15 to 20 mmHg). Mild cardiac tamponade is frequently asymptomatic, whereas moderate tamponade and especially severe tamponade produce precordial discomfort and dyspnea.

Tamponade may be so sudden that the patient does not complain of symptoms; in less drastic circumstances, patients with acute cardiac tamponade may complain of severe shortness of breath accompanied by chest tightness and dizziness. The venous pressure is greatly elevated, and the systemic arterial pressure is severely depressed. Pulsus paradoxus usually can be appreciated but may be absent when hypotension is extreme. In striking contrast to the elevation of venous pressure, arterial hypotension, and pulsus paradoxus, cardiac pulsations often are impalpable (Beck's triad). In the most severe cases, consciousness may be impaired, and except for the raised venous pressure, such patients appear to be in hypovolemic shock.

When cardiac tamponade complicates a diagnostic procedure, vague discomfort, generalized uneasiness, and precordial pain are common. Fluoroscopy shows an enlarged cardiac silhouette and diminished pulsations.

Cardiac tamponade should be suspected in a victim of recent chest trauma who appears to be in shock, especially when the venous pressure is elevated. When circumstances are deemed life-threatening, an immediate therapeutic trial of rapid infusion of fluid and diagnostic pericardiocentesis should be attempted. Otherwise, pericardiocentesis should be delayed until the presence of significant pericardial fluid can be demonstrated by prompt echocardiography. An exception to this rule is when tamponade occurs in the diagnostic laboratory; in this instance, when pressures are being monitored and fluoroscopy is available, the diagnosis can be established safely without echocardiographic confirmation.

Other causes of acute tamponade are cardiac rupture complicating acute MI and rupture of a dissecting hematoma of the proximal aorta. Although successful pericardiocentesis may relieve aortic tamponade and increase hemorrhage, a limited pericardiocentesis is reasonable if cardiac tamponade is severe enough to be considered a threat to survival. Finally, after cardiac surgery, dyspnea and fatigue should raise the suspicion of tamponade; in these instances, the effusion is

often loculated, and echocardiographic and hemodynamic findings may be unreliable.

A large number of diseases may be associated with more slowly developing cardiac tamponade. In these instances, symptoms may be due to the underlying illness, the culpable pericardial disease, and/or the tamponade itself. Many patients with inflammatory pericarditis give a history of prodromal fever, myalgia, and arthralgia, and patients with neoplastic disease may have symptoms associated with the neoplasm and its treatment. The symptoms of cardiac compression include rapidly progressive dyspnea accompanied by fullness or tightness in the chest, occasionally with dysphagia; pericardial pain is often absent. The course may be less rapid, allowing time for an increase in abdominal girth and the rapid onset and progression of edema.

Pathophysiology

Elevated intrapericardial pressure exerted on the heart throughout the cardiac cycle, with only slight momentary relief when intrapericardial pressure falls (owing to the decrease in cardiac volume during ventricular ejection), is responsible for the pathophysiologic findings of cardiac tamponade. To understand the relation between venous and pericardial pressures in cardiac tamponade, it is useful to review the normal biphasic pattern of venous return. A surge of venous return occurs at the onset of ventricular ejection and is accompanied by a small reduction in intrapericardial pressure. A second surge of venous return occurs in early diastole, when the tricuspid valve opens and atrial pressure decreases. In contrast, the venous return in cardiac tamponade is unimodal and is confined to ventricular systole, and in severe cardiac tamponade, venous return is halted in diastole, at a time when cardiac volume and intrapericardial pressure are maximal. Pericardial pressure and right atrial pressure are elevated above normal and are equal to each other (Fig. 72-10). The inspiratory fall in intrathoracic pressure is transmitted to the pericardial space and preserves the normal inspiratory increase in systemic venous return (Kussmaul's sign is absent).

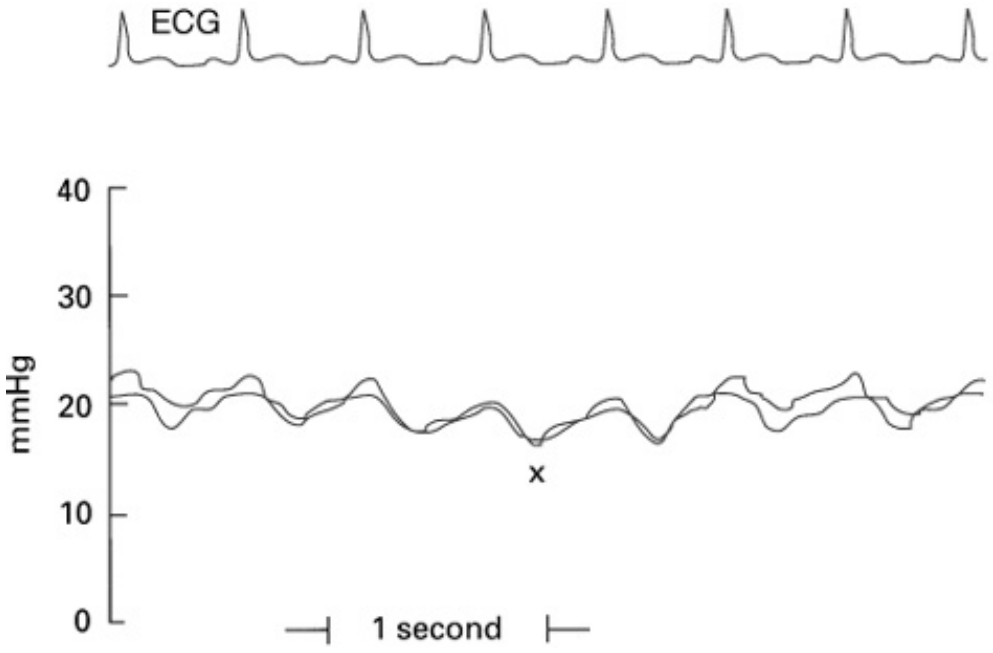


Figure 72-10: Simultaneous right atrial and pericardial pressures from a patient with severe cardiac tamponade. The pressures are elevated and equal to one another, and only the X descent on the right atrial tracing is present; the Y descent is absent. The pressures fall normally during inspiration. (From Shabetai R. Diseases of the pericardium. In: Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart,* 9th ed. New York: McGraw-Hill; 1998:2179. Reproduced with

permission.)

Although systolic ventricular function is often supranormal, unrelieved extreme tamponade becomes fatal when venous pressure cannot increase to equal the pericardial pressure and maintain circulation. In severe cases, diminution of myocardial perfusion is aggravated by direct compression of the epicardial coronary arteries, abnormal transmyocardial distribution of blood flow, and, as a result, impaired ventricular systolic function.

PULSUS PARADOXUS

In healthy individuals, systolic blood pressure may decline by as much as 10 mmHg during quiet inspiration. Pulsus paradoxus is an exaggeration of this normal physiologic response. A number of normal and abnormal mechanisms combine to create pulsus paradoxus in cardiac tamponade. Inspiratory augmentation of systemic venous return in cardiac tamponade increases the volume of the right side of the heart at the expense of the left side. The volume of the left side of the heart is decreased, in part by bulging of the intraventricular septum from right to left (changing the size, shape, and compliance of the LV) and in part by increased transmural pericardial pressure (decreasing pulmonary venous return). However, the inspiratory expansion of the volume of the right side of the heart and the transit time of the resulting augmented right heart stroke volume are important in the genesis of pulsus paradoxus. In addition, the negative thoracic pressure produced by inspiration is transmitted to the aorta, increasing LV afterload and reducing stroke volume. LV stroke volume falls more sharply than normal in response to decreased ventricular filling in cardiac tamponade because the small ventricle is operating on the steep ascending limb of the Starling curve. Finally, inspiratory traction by the diaphragm on the taut pericardium, reflex changes in vascular resistance and cardiac contractility, and increased respiratory effort owing to pulmonary congestion contribute to the genesis of pulsus paradoxus.

Pulsus paradoxus appears when both ventricles fill against a common resistance. Therefore, when LV diastolic pressure is elevated by coexisting LV disease, pulsus paradoxus does not develop in cardiac tamponade.[29] Similarly, atrial septal defects and aortic regurgitation prevent reciprocal inspiratory changes in the filling of the two sides of the heart; therefore, in these conditions, cardiac tamponade can occur without pulsus paradoxus.[30]

Physical Findings

Physical findings are dictated by both the severity of cardiac tamponade and the time course of its development. Careful inspection of the jugular venous pulse waveform is essential for the diagnosis, although the venous pressure may be normal in early tamponade, whereas extreme elevations of venous pressure may go unrecognized in a recumbent or semirecumbent patient. Compression of the heart by pericardial fluid results in a characteristic loss of the atrial Y descent, but because of the decrease in intrapericardial pressure that occurs during ventricular ejection, the systolic atrial filling wave and the X descent are maintained. Kussmaul's sign, a failure of venous pressure to decrease during inspiration, is a sign of constriction and generally is not seen in pure cardiac tamponade.

An inspiratory decline of systolic arterial pressure exceeding 10 mmHg (pulsus paradoxus) may be detected with palpation of an arterial pulse, such as the femoral or brachial artery, and quantified by using sphygmomanometry by subtracting the pressure at which Korotkoff's sounds are heard only during expiration from the pressure at which sounds are heard through the respiratory cycle. The origin of the paradoxical pulse is complex and multifactorial, and pulsus paradoxus is neither sensitive nor specific for cardiac tamponade.[30] Nevertheless, in the appropriate clinical setting, pulsus paradoxus is a key finding that signifies cardiac tamponade, and its presence should be sought diligently.

Diagnostic and Imaging Studies

Low voltage on the ECG and/or electrical alternans should suggest cardiac tamponade. However, electrical alternans is insensitive, occurring in only about 20 percent of instances.[31] When effusion is massive, the heart swings freely within the pericardial sac and acquires a pendular, rotary motion that is associated with electrical alternans. When tamponade is suspected, an echocardiogram should be obtained unless even a brief delay might prove life-threatening. During inspiration, a greater than normal increase in RV dimension and a decrease in LV dimension occur in many cases of tamponade. These respiratory changes also accompany other conditions associated with pulsus paradoxus, such as chronic obstructive lung disease and pulmonary embolism.[32] Diastolic collapse of the RV, which is recognized as an abnormal posterior motion of the anterior RV wall during diastole (Fig. 72-11), signifies that pericardial pressure exceeds early diastolic RV pressure, i.e., that transmural RV diastolic pressure is negative (see also Chap. 13). Although this sign is a relatively sensitive and specific marker for tamponade, RV diastolic collapse is sensitive to alterations in ventricular loading conditions and may not be seen in the presence of RV hypertrophy. In addition, right heart chamber collapse occurs with smaller collections of fluid and higher pericardial pressures when there is coexisting LV dysfunction.[29] Late diastolic right atrial collapse is virtually 100 percent sensitive for tamponade but is less specific (Fig. 72-12). A duration of right atrial collapse exceeding one-third of the cardiac cycle increases specificity without sacrificing sensitivity.[33] Posterior loculated effusions after cardiac surgery have been reported to produce left atrial and LV diastolic collapse.[34,35] The value of transesophageal echocardiography has been recognized in the detection and treatment of unusual cases of cardiac tamponade.[36] In patients with unexplained hypotension who are undergoing transesophageal echo, a diagnosis of a nonventricular limitation to cardiac output was associated with improved survival in the intensive care unit compared with a diagnosis of ventricular disease or hypovolemia/low systemic vascular resistance.[37]

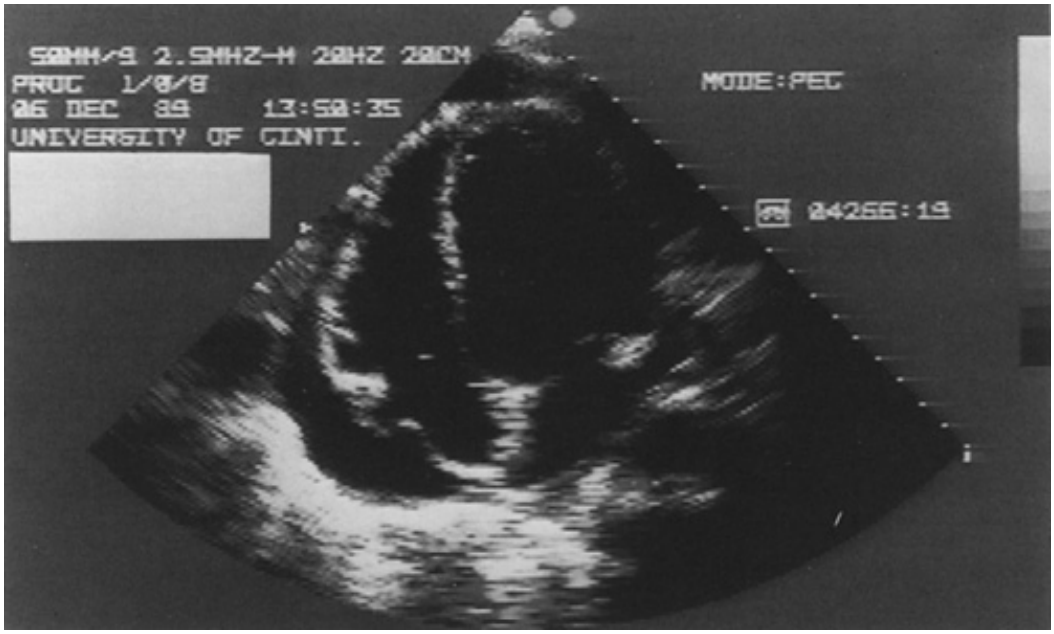


Figure 72-12: Two-dimensional echocardiogram in the apical four-chamber view. During late diastole, there is inversion of the lateral wall of the right atrium. (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:593. Reproduced with permission.)

During cardiac tamponade, tricuspid and pulmonary flow velocities measured by Doppler

echocardiography (Fig. 72-13) increase markedly with inspiration, and mitral and aortic valve flow velocities decrease significantly compared with normal control patients and patients with asymptomatic effusions.[38] Changes in the pattern of venous flow (reflecting the predominance of systolic flow) and exaggerated respiratory variations of venous flow velocities (Fig. 72-14) also are seen in cardiac tamponade.[39] Indeed, abnormal venous flow had a good correlation with clinical tamponade with greater sensitivity than RV diastolic collapse and greater specificity than right atrial collapse.[40]

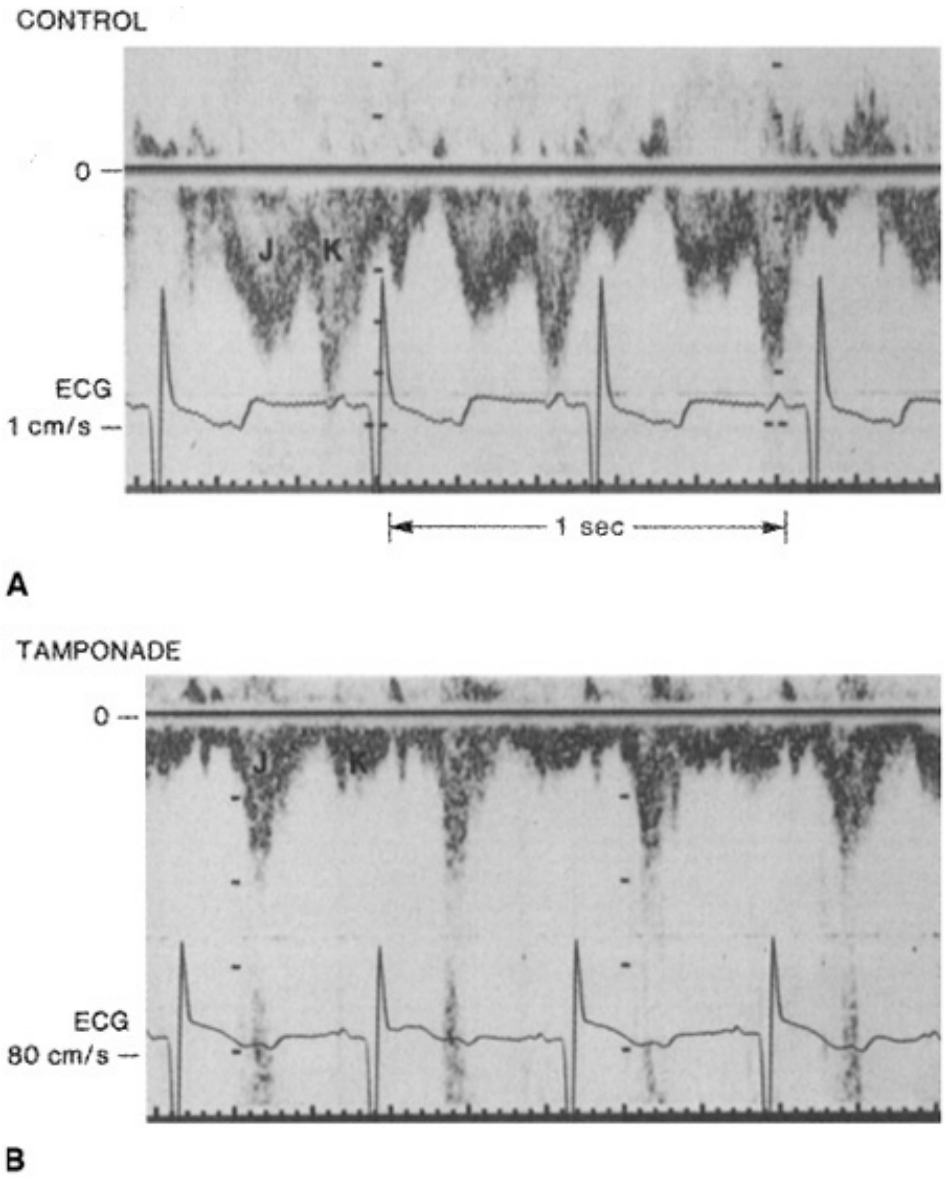


Figure 72-14: Doppler echocardiograms of pulmonary venous flow velocity from a dog before (*A*) and after (*B*) creation of cardiac tamponade. Note the predominance of systolic flow after tamponade. J = systolic flow; K = diastolic flow. (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:595. Reproduced with permission.)

Cardiac Catheterization

The diagnosis of cardiac tamponade is confirmed by right heart catheterization. The right atrial, pulmonary capillary wedge, and pulmonary artery diastolic pressures are elevated, usually between 10 and 30 mmHg, and are equal within 4 to 5 mmHg (Fig. 72-15). Pericardial pressure is

elevated and is equal to right atrial pressure; the degree of elevation is related to both the severity of tamponade and the patient's intravascular volume status (Fig. 72-16). The right atrial and wedge pressure tracings reveal an attenuated or absent Y descent. Cardiac output is reduced, and systemic vascular resistance is elevated. Equal elevation of diastolic pressures also may be seen with dilated cardiomyopathy and with RV infarction. Neither Kussmaul's sign nor the early ventricular diastolic dip and plateau (i.e., the "square root" sign) characteristic of pericardial constriction is seen in tamponade.

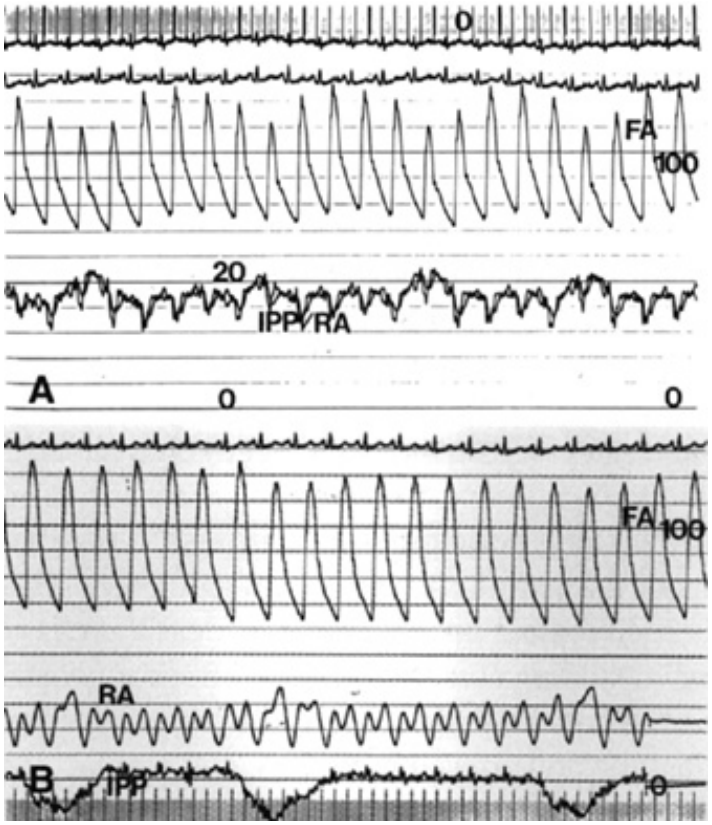
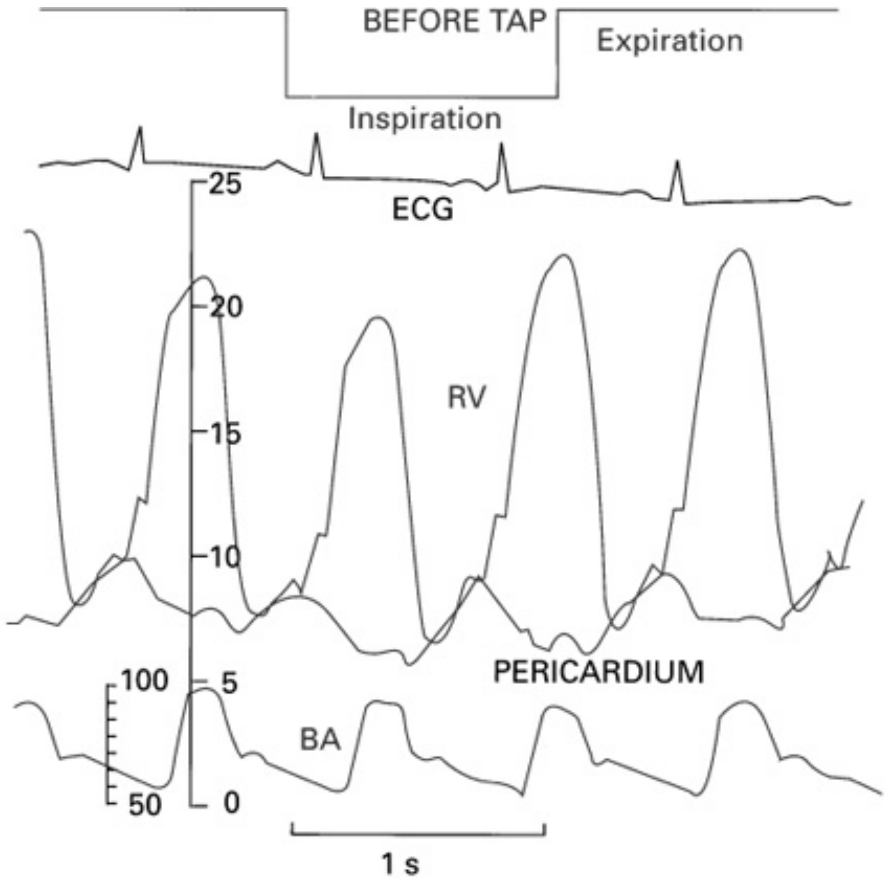
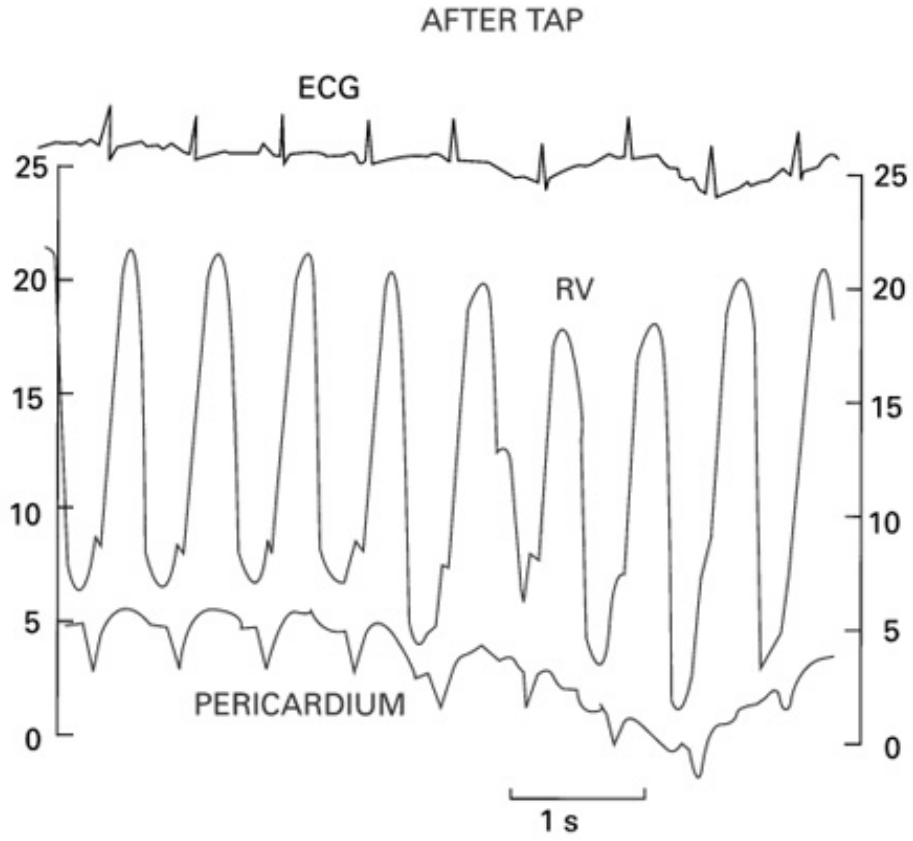


Figure 72-15: Hemodynamic record from a patient with cardiac tamponade before (*A*) and after (*B*) pericardiocentesis. *A*. Pulsus paradoxus is evident from the femoral artery (FA) pressure tracing. Note the absent Y descent on the right atrial (RA) tracing and the equal and elevated RA and pericardial (IPP) pressures. *B.* After removal of pericardial fluid, pericardial and right atrial pressures decrease and the pulsus paradoxus disappears. (Courtesy of Noble O Fowler, MD. From Hoit BD. Pericardial disease and pericardial heart disease. In: O'Rourke RA, ed. *Stein's Internal Medicine*, 5th ed. Mosby-Year Book;1998:273. Reproduced with permission.)



A



B

Figure 72-16: *A.* Low-pressure cardiac tamponade. Right ventricular (RV) diastolic pressure is

only slightly elevated but is equal to pericardial pressure. Hypotension and pulsus paradoxus are absent. *B.* After pericardiocentesis, pericardial pressure is consistently lower than ventricular diastolic pressure. (From Shabetai R. Diseases of the pericardium. In Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart,* 9th ed. New York: McGraw-Hill; 1998:2185. Reproduced with permission.)

Management of Cardiac Tamponade

Removal of small amounts of pericardial fluid (~50 mL) produces considerable symptomatic and hemodynamic improvement because of the steep pericardial pressure-volume relation. Unless there is concomitant cardiac disease or coexisting constriction (i.e., effusive-constrictive pericarditis), removal of all the pericardial fluid normalizes pericardial, atrial, ventricular diastolic, and arterial pressures and cardiac output.

Unless the situation is immediately life-threatening, pericardiocentesis should be performed by experienced staff in a facility equipped for hemodynamic monitoring. The advantages of needle pericardiocentesis include the ability to perform careful hemodynamic measurements and relatively simple logistic and personnel requirements. The safety of the procedure has been improved by using 2-D echo guidance.[41] A catheter can be advanced over a guidewire into the pericardial space and remain there for several days; sclerosing agents, steroids, urokinase, and specific chemotherapeutic agents may be given through the catheter.[42,43] In a pilot study, intrapericardial instillation of cisplatin for 24 hours prevented recurrence of a hemodynamically significant pericardial effusion after 6 to 12 months in 14 out of 15 patients with a neoplastic effusion; in 12 out of 14 patients with autoreactive pericarditis, recurrence was prevented with intrapericardial triamcinolone.[25] Although pericardiocentesis may provide effective relief, percutaneous balloon pericardiotomy, subxiphoid pericardiotomy, or the surgical creation of a pleuropericardial or peritoneal-pericardial window[44,45] may be required. Nevertheless, in one retrospective review, pericardiocentesis with intrapericardial sclerotherapy was as effective as an open surgical drainage procedure in patients with malignant pericardial effusion.[46] The feasibility and accuracy of three-dimensional computer-assisted pericardiocentesis was recently described in the experimental laboratory.[47]

Open surgical drainage offers several advantages, including complete drainage, access to pericardial tissue for histopathologic and microbiologic diagnoses, the ability to drain loculated effusions, and the absence of traumatic injury resulting from blind placement of a needle into the pericardial sac. The choice between needle pericardiocentesis and surgical drainage depends on institutional resources and physician experience, the etiology of the effusion, the need for diagnostic tissue samples, and the prognosis of the patient. Needle pericardiocentesis is often the best option when the etiology is known and/or the diagnoses of tamponade is in question, and surgical drainage is optimal when the presence of tamponade is certain but the etiology is unclear. It should be recognized that surgical approaches (subxiphoid pericardiotomy and thoracoscopic drainage) can be performed using local anesthesia with little attendant morbidity. Irrespective of the method of retrieval, pericardial fluid should be sent for smear, culture, and cytology.

Fluids should be given to patients with cardiac tamponade who are awaiting pericardial drainage in an effort to expand the intravascular volume. Dobutamine or nitroprusside may be used to increase cardiac output after the blood volume has been expanded, but only as a temporizing measure. Vagal reflexes complicating tamponade and pericardiocentesis are treated with atropine. Positive-pressure breathing should be avoided, and if present, metabolic acidosis should be corrected.

Recurrent effusions may be treated by repeat pericardiocentesis, sclerotherapy with tetracycline, surgical creation of a pericardial window, or pericardiectomy. A pericardial window usually is performed in patients with malignant effusions, and pericardiectomy may be required for recurrent

effusions in dialysis patients. In critically ill patients, a pericardial window may be created percutaneously with a balloon catheter.[48,49]

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Chapter 72: DISEASES OF THE PERICARDIUM

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis is a condition in which a thickened, scarred, and often calcified pericardium limits diastolic filling of the ventricles. Although acute pericarditis from most causes may eventuate in constrictive pericarditis, the most common antecedents are idiopathic conditions, cardiac trauma and surgery, tuberculosis and other infectious diseases, neoplasms (particularly lung and breast), radiation therapy, renal failure, and connective tissue diseases. Rare causes include Dressler's syndrome, sarcoidosis, Whipple's disease, amyloidosis, and dermatomyositis. Mulibrey nanism is a hereditary form of constrictive pericarditis that is associated with abnormalities of the *mu*scle, *li*ver, *br*ain, and *ey*es (see Chap. 10).

Clinical Features

Constrictive pericarditis resembles the congestive states caused by myocardial disease and chronic liver disease. Patients generally complain of fatigue, dyspnea, weight gain, abdominal discomfort, nausea, increased abdominal girth, and edema. Although symptoms usually develop over years, they progress over a period of months in patients with subacute constrictive pericarditis after trauma, cardiac surgery, and mediastinal irradiation and may develop acutely and resolve spontaneously during the course of pericarditis.[50]

Physical Findings

Physical findings include ascites, hepatosplenomegaly, edema, and, in long-standing cases, severe wasting. This general appearance often leads to an erroneous diagnosis of hepatic cirrhosis. However, misdiagnosis is avoided through a careful examination of the neck veins. In constrictive pericarditis, the venous pressure is elevated and displays deep Y and often deep X descents. The venous pressure fails to decrease with inspiration (Kussmaul's sign), but frank inspiratory swelling of the neck veins is uncommon. Kussmaul's sign lacks specificity, as it is seen also in cases of restrictive cardiomyopathy, RV failure and infarction, and tricuspid stenosis.[51] The heart is often normal-sized, and when it is not, enlargement is modest. A pericardial knock that is similar in timing to the third heart sound is pathognomonic but occurs infrequently.[51,52] Pulsus paradoxus may occur with associated pericardial effusion (effusive-constrictive pericarditis). Except in severe cases, the arterial blood pressure is normal.

Diagnostic and Imaging Studies

Low QRS voltage, nonspecific T-wave changes, and P mitrale are common, but the ECG findings are nonspecific (Fig. 72-17). Atrial fibrillation is seen in approximately one-third of cases, and atrial flutter is seen less often, although the exact percentage of atrial arrhythmias depends on the duration of constriction.

The cardiac silhouette may be normal or enlarged. Pericardial calcification is present in less than half the cases seen in the United States and Europe. Pericardial calcification may be seen with chronic adhesive pericarditis in the absence of constriction, but then it is usually less dense and has a more patchy distribution (Fig. 72-18).

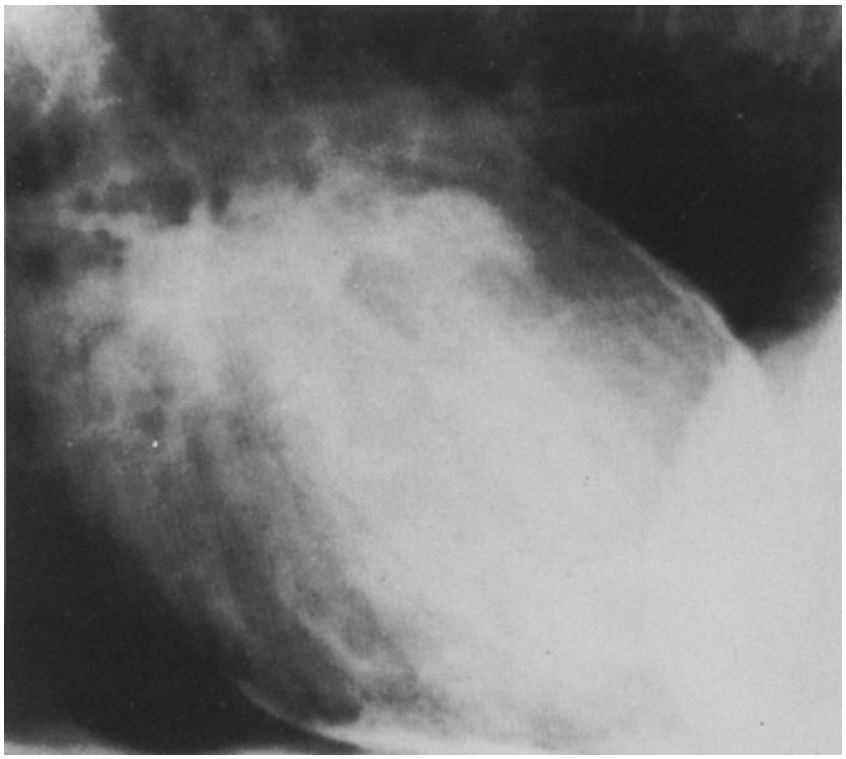

Figure 72-18: Calcification of the pericardium seen on a lateral chest radiograph in a patient with chronic constrictive pericarditis. (Courtesy of Ralph Shabetai, MD. From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:595. Reproduced with permission.)

Pericardial thickening and calcification and abnormal ventricular filling produce characteristic changes on the M-mode echocardiogram.[53] Increased pericardial thickness is suggested by parallel motion of the epicardium and parietal pericardium, which are separated by a relatively echo-free space at least 1 mm thick. Echocardiographic correlates of the hemodynamic abnormalities of constrictive pericarditis include flattening of the LV posterior wall endocardium, abnormal septal motion, and occasionally premature opening of the pulmonary valve (Fig. 72-19). These findings, which reflect abnormal filling of the ventricles, are insensitive and subtle and lack the specificity to be clinically useful. Although no sign or combination of signs on M-mode echocardiography is diagnostic of constrictive pericarditis, a normal study virtually rules out the diagnosis.[53]

Computed tomography (CT) is a highly accurate method of evaluating pericardial thickness and therefore plays an essential role in the diagnosis and management of constrictive disease (Fig. 72-20).[54] The normal pericardium is identified as a 1- to 2-mm curvilinear line of soft tissue density, whereas in constrictive pericarditis, the parietal pericardium is 4 to 20 mm thick. Failure to visualize the posterolateral LV wall on dynamic CT suggests myocardial fibrosis or atrophy and is associated with a poor surgical outcome.[55] Because of the close physiologic similarities of constrictive pericarditis and restrictive cardiomyopathy, increased pericardial thickness detected by tomographic scanning is the most reliable means of distinguishing between the two disorders, as normal pericardial thickness excludes most cases of constrictive pericarditis. CT also is useful in planning pericardiectomy because of its ability to define the distribution of pericardial thickening.[56]

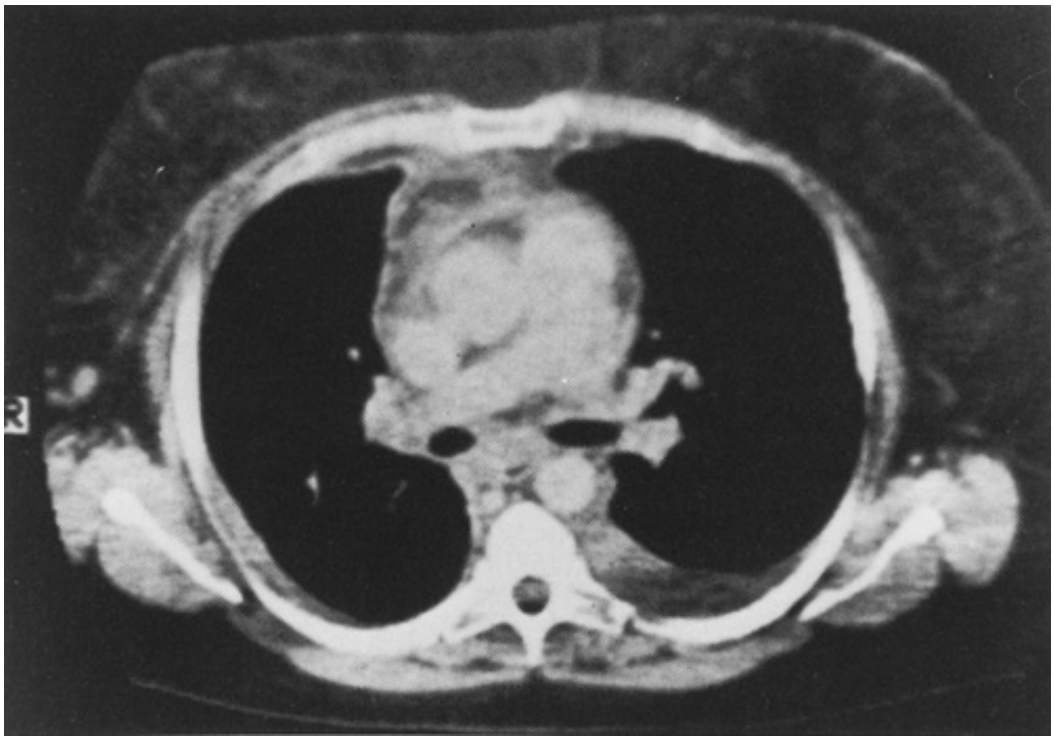

Figure 72-20: Computed tomogram from a patient with constrictive pericarditis. The diffusely thickened pericardium is bordered by low-intensity epicardial and mediastinal fat. (Courtesy of Dr. N. O. Fowler. From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:597. Reproduced with permission.)

Accurate definition of pericardial thickness and its distribution also is possible with MRI (Fig. 72-21).[27,57] Unlike CT, ECG gating is necessary for adequate visualization, resolution is not quite as good, and calcification is difficult to distinguish from fibrosis. However, excellent diagnostic accuracy in identifying surgically confirmed constrictive pericarditis has been reported.[58] Preliminary studies suggest that phase velocity mapping techniques may provide additional diagnostic information, analogous to Doppler echo.

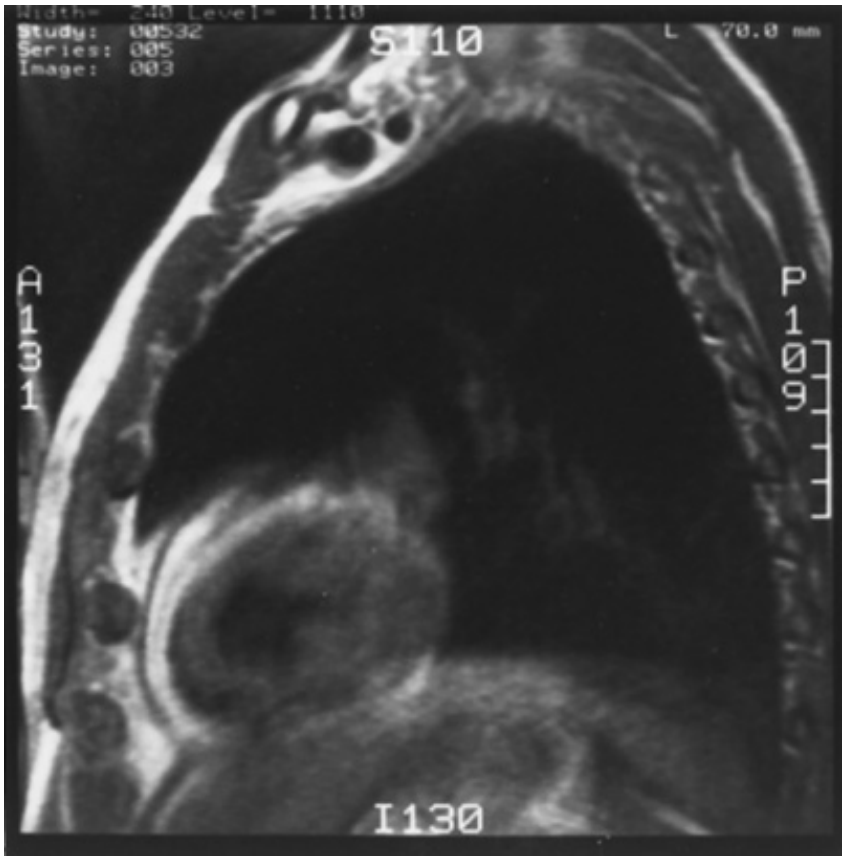

Figure 72-21: MRI scan (spin-echo image) from a patient with constrictive pericarditis. The pericardium is viewed as a line of low signal intensity (black) sandwiched between higher-intensity epicardial and pericardial fat (white). Note the regional variation of pericardial thickness, which is normally 1 to 2 mm. (From Hoit BD. Pericardial disease and pericardial heart disease. In: O'Rourke RA, ed. *Stein's Internal Medicine*, 5th ed. St. Louis, Missouri: Mosby-Year Book;1998:273. Reproduced with permission.)

Cardiac Catheterization

Cardiac catheterization is used to confirm the clinical suspicion of pericardial disease, uncover occult constriction, diagnose effusive-constrictive disease, and identify associated coronary, myocardial, and valvular disease. Endomyocardial biopsy is sometimes necessary to exclude restrictive cardiomyopathy, which shares many hemodynamic abnormalities with constrictive pericarditis.

Differences between Constrictive Pericarditis and Cardiac Tamponade

The waveform of venous pressure in constrictive pericarditis differs from that in cardiac tamponade. In constrictive pericarditis, cardiac volume is determined by the thickened, rigid pericardium, and the heart is unable to exceed this volume, which is attained near the end of the first third of diastole. During ejection, venous return commences unimpeded, and therefore, the normal systolic surge of venous return is preserved. Cardiac compression remains insignificant at end systole (unlike cardiac tamponade), so that when the tricuspid valve opens, blood fills the ventricles at a supranormal rate. Thus, in constrictive pericarditis, the venous return is biphasic, but with a diastolic component greater than or equal to the systolic component.

Unlike cardiac tamponade, the intrapericardial space is obliterated in constrictive pericarditis. As a result, during inspiration, the decreased intrathoracic pressure is not transmitted to the heart, venous pressure does not fall, and systemic venous return fails to increase. Another important

distinction from cardiac tamponade is that early diastolic filling is faster than normal in constrictive pericarditis, and consequently, the ventricular diastolic pressure is characterized by a dip in early diastole (Fig. 72-22). By the end of the rapid filling phase, the ventricles are completely filled and the ventricular diastolic pressure remains unchanged and elevated for the remainder of diastole. The resultant pattern of ventricular diastolic pressure in constrictive pericarditis is referred to as the "dip-and-plateau pattern" or the "square-root sign."

In contrast to cardiac tamponade, early diastolic filling in constrictive pericarditis is unrestrained, and only at the end of the first third of diastole does the stiff pericardium abruptly restrict ventricular filling. As a result, ventricular pressure falls rapidly in early diastole and subsequently rises abruptly to an elevated level, where it remains until the next ventricular systole. End-diastolic ventricular pressures and mean atrial pressures are elevated and nearly equal (within 5 mmHg), and end-diastolic volumes and, consequently, stroke volume and cardiac output are reduced. These pathophysiologic changes are responsible for the hemodynamic and physical findings that characterize constrictive pericarditis.[51]

Pulsus paradoxus is much less common in constrictive pericarditis than it is in cardiac tamponade because in constrictive pericarditis, inspiratory increases in venous return and in the volume of the right side of the heart seldom occur, and the position of the ventricular septum relative to the two ventricles is not as dramatically altered.

Systolic LV function is usually unimpaired in both constrictive pericarditis and cardiac tamponade. Long-standing calcific constrictive pericarditis may invade the myocardium and coronary vessels, leading to conduction disturbances and impaired ventricular function.

Syndromes of Constrictive Pericarditis

Classic *chronic constrictive pericarditis* is encountered less frequently than it was in the past, whereas *subacute constrictive pericarditis* is becoming more common. In the latter syndrome, pericardial calcification is uncommon and the course may span a matter of weeks to a few years. *Postoperative constrictive pericarditis* is an important cause of constriction, with a reported incidence of 0.2 percent[59]; this incidence is surprisingly low considering that in these operations the pericardium is subject to cellular injury and is exposed to proinflammatory substances such as blood and local hypothermia.

Occult constrictive pericarditis requires a fluid challenge for detection.[60] In the first series reported, the patients complained of nondescript chest pain, for which they underwent cardiac catheterization and coronary arteriography. Although hemodynamic studies revealed normal basal atrial and ventricular pressures, the right atrial pressure waveform assumed the characteristics of constrictive pericarditis and the diastolic pressures in the two ventricles became equal after a rapid infusion (10 min) of approximately 1 L of saline solution. Histologic examination confirmed the surgical findings of a thickened and fibrosed pericardium. Rapid, large fluid challenges at cardiac catheterization should be administered with caution; furthermore, the induction of hemodynamic changes suggesting constrictive pericarditis by this technique should seldom, if ever, be taken alone as an indication for pericardiectomy.

Localized constrictive pericarditis is rare, but occasionally a localized band constricts the inflow or outflow region of one or more of the cardiac chambers. The clinical picture then simulates valve disease or venous obstruction. Evidence of *transient* (*acute*)*constriction* may occur in ~15 percent of patients with acute effusive pericarditis.[61] Therefore, before one proceeds with pericardiectomy, the possibility that pericardial constriction may be reversible and amenable to medical therapy should be considered.

Management of Constrictive Pericarditis

Pericardiectomy is the definitive treatment for constrictive pericarditis but is unwarranted either in very early constriction or in severe, advanced disease (functional class IV), when the risk of surgery is excessive (30 to 40 percent mortality) and the benefits are diminished.[62] Involvement of the visceral pericardium also increases the surgical risk. Symptomatic relief and normalization of cardiac pressures may take several months after pericardiectomy; they occur sooner when the operation is carried out before the disease is too chronic and when the pericardiectomy is almost complete. Complete or extensive pericardial resection is desirable, although data suggest that in some instances, subtotal pericardiectomy may be preferred.[63]

Pericardiectomy is commonly carried out via a median sternotomy, although some surgeons prefer a thoracotomy. Despite a decline in the risk of mortality, it remains 5 to 15 percent. The risk is increased by heavy calcification and involvement of the visceral pericardium. LV systolic dysfunction may occur after decortication of a severely constricted heart. Although this condition may require treatment for several months, it usually resolves completely.

Medical therapy of constrictive pericarditis plays a small but important role. In some patients, constrictive pericarditis resolves either spontaneously or in response to various combinations of nonsteroidal anti-inflammatory agents, steroids, and antibiotics.[50] Antibiotic therapy should be initiated before surgery and continued afterward. Diuretics and digoxin (in the presence of atrial fibrillation) are useful in patients who are not candidates for pericardiectomy because of their high surgical risk.

Prevention consists of appropriate therapy for acute pericarditis and adequate pericardial drainage. Although urokinase instillation is promising, corticosteroids are often ineffective.

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Chapter 72: DISEASES OF THE PERICARDIUM

EFFUSIVE-CONSTRICTIVE PERICARDITIS

Effusive-constrictive pericarditis occurs when pericardial fluid accumulates between the thickened, fibrotic parietal pericardium and visceral pericardium. Neoplasia, chest irradiation, infection, idiopathic pericarditis, and connective tissue diseases are common antecedents. Transient effusive-constrictive pericarditis may complicate chemotherapy.[64] The hemodynamic features are those of cardiac tamponade before, and constrictive pericarditis after, pericardiocentesis. Thus, removal of pericardial fluid fails to lower atrial and ventricular diastolic pressures, but the previously attenuated or absent atrial Y descent becomes prominent (Fig. 72-23).

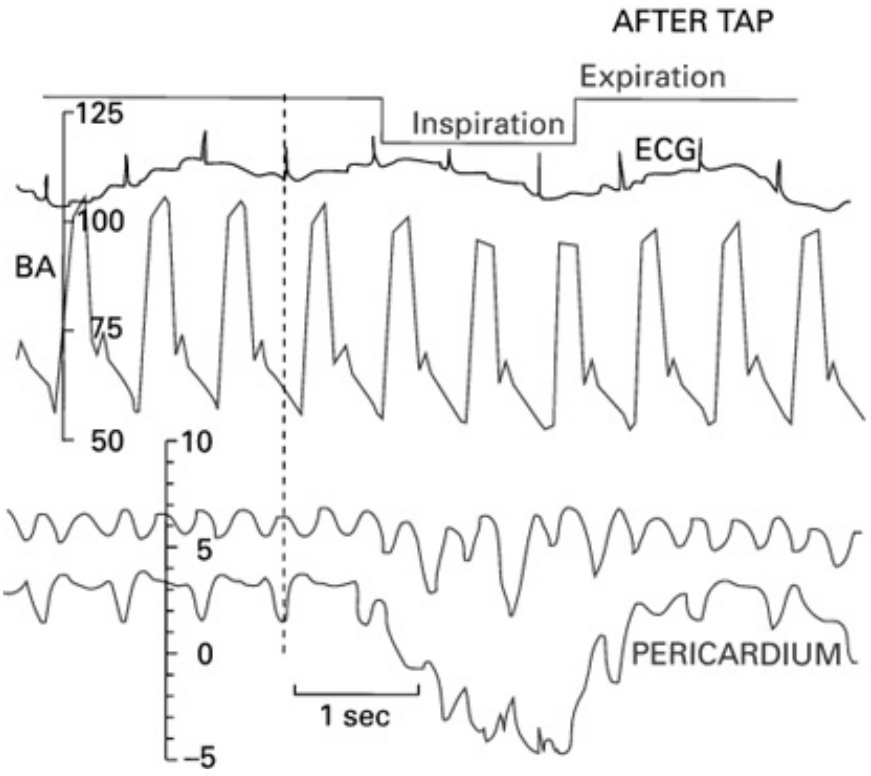

Figure 72-23: Recording from a patient with effusive-constrictive pericarditis caused by lung cancer. The tracings were obtained during the pericardiocentesis; right atrial pressure elevation persists, and there are prominent X and Y descents without respiratory variation. (From Shabetai R. *The Pericardium*. New York: Grune & Stratton; 1981:273. Reproduced with permission.)

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Chapter 72: DISEASES OF THE PERICARDIUM

SPECIFIC FORMS OF PERICARDIAL HEART DISEASE

Idiopathic Pericarditis

Acute pericarditis is most often idiopathic and is typically a self-limited disease lasting 2 to 6 weeks.[65] Recurrence occurs in 25 percent of cases and occasionally proves resistant to therapy. Small pericardial effusions occur commonly, but cardiac tamponade is unusual. Heart failure caused by associated myocarditis and constrictive pericarditis are uncommon. These complications usually can be detected by clinical and echocardiographic evaluation. The clinical course and prognosis of individuals with pericarditis are otherwise determined largely by the presence and nature of any underlying disease.

Infectious Pericarditis

VIRAL PERICARDITIS

Viral pericarditis is the most common infectious type, although a definitive diagnosis from acute and convalescent (3 weeks) viral neutralizing antibodies is generally not helpful in a sporadic case of pericarditis. Viral isolation from pericardial fluid and in situ hybridization techniques have been used to identify a specific etiology.[20,66] However, viral infection often is presumed rather than proved, and many cases are classified as idiopathic. Epicardial biopsy via a pericardioscope is a promising investigative technique for establishing the etiology of acute pericarditis. Common viral infections causing acute pericarditis are those resulting from echovirus and coxsackie virus; however, a great many different viruses may cause pericarditis (Table 72-2).

BACTERIAL PERICARDITIS

Bacterial (purulent) pericarditis most often is caused by streptococci, staphylococci, and gram-negative rods; *Haemophilus influenzae* is an important cause in children.[67] The increasing frequency of cardiac surgery and instrumentation, selection-induced changes in the flora responsible for hospital-acquired infections, and the prolonged survival of immunocompromised hosts (HIV, steroids) have changed the incidence and bacterial spectrum of purulent pericarditis. Pericardial involvement often is unrecognized when it complicates systemic infection; unusually high fever and white blood cell counts are clues to the presence of pericarditis. Children and immunosuppressed patients of all ages are most vulnerable, and the characteristic features of acute pericarditis are frequently absent. The course of bacterial pericarditis is fulminant, often presenting with cardiac tamponade; adhesive and constrictive pericarditis are common sequelae in survivors and may develop suddenly and early.[67,68] However, pericarditis complicating systemic infection and sepsis may go unrecognized and misdiagnosed.[69] Many patients lack the typical findings of pericarditis, and the diagnosis of purulent pericarditis often is made either at autopsy or after cardiac tamponade develops; empyema is a common antecedent.[67] Purulent pericarditis rarely is caused by anaerobic bacteria, and the few reported cases resulted from contiguous infection or hematogenous seeding.[70] Bacterial pericarditis is treated with surgical exploration and drainage and appropriate systemic antibiotics. Fibrinolytics may be used to lyse fibrous adhesions and prevent constrictive pericarditis.[71-73]

Legionella infections account for ~10 percent of community-acquired pneumonias and may be

associated with pericarditis more often than previously was appreciated. Studies suggest that patients with pericardial involvement tend to be younger and healthier than are those without it.[74] Recurrent pericarditis, effusion, and chronic constriction occur in about 20 percent of cases.[75] Pericarditis is an early complication of Lyme disease.[76]

MYOCBACTERIAL AND FUNGAL PERICARDITIS

Tuberculosis is a major cause of pericarditis in nonindustrialized countries but is an uncommon cause in the United States. Nevertheless, its incidence is increasing because of HIV infection; therefore, tuberculosis should be considered in the differential diagnosis of pericardial heart disease.[77] Tuberculous pericarditis results from hematogenous spread of primary tuberculosis or from the breakdown of infected mediastinal lymph nodes; therefore, affected individuals generally lack the typical symptoms and signs of pulmonary tuberculosis. Fever, weight loss, and night sweats occur early; pericardial pain and friction rubs are often absent. Patients may present with tamponade or constriction, which may be subacute. A fibrinous pericarditis with caseating necrosis and mononuclear infiltrate gives rise to an effusive phase, which is often voluminous and hemodynamically significant. An adhesive phase follows resolution of the effusion and eventuates in dense, calcific adhesions with clinical constriction in nearly 50 percent of patients.

Mycobacteria are difficult to culture from pericardial fluid, which is diagnostic in only one-third of cases; polymerase chain reaction (rtPCR) recently was used to amplify and identify *Mycobacterium tuberculosis.*[78] A presumptive diagnosis generally requires a history of contact and/or purified protein derivative conversion (although the latter lacks sensitivity and specificity). Gadolinium-enhanced MRI may be useful in early diagnosis.[79] Increased adenosine deaminase activity in pericardial fluid is supportive. However, the diagnosis of tuberculous pericarditis is based on (1) histologic identification, (2) culture of *M. tuberculosis,* (3) pericarditis with proven extracardiac tuberculosis, or (4) pericardial effusion responsive to antituberculosis therapy.

Early pericardiectomy has been recommended by some researchers in all cases of tuberculosis pericarditis, but the long-term (16 years) prognosis of patients without cardiac compression during the acute illness who are treated with medical therapy alone is excellent.[80] Multiple-drug therapy and corticosteroids are effective in tuberculous pericarditis, whereas atypical mycobacterial infections (especially *M. avium-intracellulare*) may be resistant to treatment. Patients with tuberculous pericarditis should receive triple-drug therapy (isoniazid, rifampin, and streptomycin or ethambutol) for a minimum of 9 months. Corticosteroids may be useful if pericardial effusion persists or recurs during therapy; pericardiectomy may be necessary for recurrent cardiac tamponade. Patients should be observed for constriction; up to half these patients will require pericardiectomy.[81] In contrast, pericarditis complicating deep fungal infection (histoplasmosis, coccidioidomyocosis) may be immunologic, resolve spontaneously, and not require specific therapy. Surgical decompression and specific antifungal therapy may be necessary for disseminated infection with *Candida, Aspergillus, Actinomycetes,* and *Nocardia.*

AIDS PERICARDITIS

Acquired immunodeficiency syndrome (AIDS) is an important cause of pericardial heart disease. Typically, pericardial effusions are small and asymptomatic in outpatients, but large effusions and tamponade are common in hospitalized patients with AIDS. Indeed, in one study, a moderate or large effusion was present in more patients with symptomatic than asymptomatic HIV infection (17 percent versus 2 percent), and most of these cases were clinically unsuspected.[82] The incidence and prevalence of pericardial effusion in a prospective, 5-year follow-up study of AIDS patients were high (11 percent/year and 5 percent, respectively).[83] A literature review of echocardiographic and autopsy series found an average incidence of pericardial disease of 21 percent.[84]

Pericardial involvement may be due to associated malignancies (e.g., lymphoma and Kaposi's sarcoma), viruses (including HIV) and opportunistic infections (e.g., mycobacteria, cytomegalovirus, *Nocardia*, and cryptococci) and, irrespective of its cause, predicts a poor prognosis in patients with HIV infection.[85] Large, symptomatic pericardial effusion in patients with HIV infection should be aggressively investigated, as two-thirds of these cases have an identifiable cause.[84] Tamponade in patients with HIV is mycobacterial (*M. tuberculosis* or *avium-intracellulare*) in origin in approximately one-third of patients.[84]

In 68 patients with HIV infection prospectively admitted to the intensive care unit, only 5 had evidence of cardiac disease, but 35 had echocardiographic abnormalities (20 effusions, 2 with tamponade, 15 cases of left ventricular dysfunction, and 4 valvular abnormalities).[86] The presence of an effusion was associated with greater 6-month mortality in patients with AIDS (96 percent versus 36 percent); interestingly, an asymptomatic pericardial effusion may signal end-stage HIV disease, independent of the CD4 count and albumin level.[83]

Neoplastic Pericarditis

Metastatic neoplasia remains the leading cause of pericardial disease in hospitalized patients, most often in patients with lung or breast cancer, melanoma, lymphoma, and acute leukemia. Many cases are asymptomatic and are found only incidentally at autopsy, but others cause symptoms and may progress to cardiac tamponade. Primary cardiac tumors may invade the pericardium directly.

Primary mesothelioma of the pericardium is a rare and highly lethal tumor.[87] Signs and symptoms are nonspecific, and chest radiography and echocardiography are insensitive for its detection; CT and MRI are the most promising diagnostic tests. Other primary tumors of the pericardium are quite rare.

In patients with elevated jugular pressure and an intrathoracic mass, an important inclusion in the differential diagnosis is the superior vena cava syndrome. In this disorder, the characteristic pulsations of the jugular veins are not observed and pulsus paradoxus is not present. However, in a patient with respiratory distress, pulsus alternans, arrhythmia, and/or tachycardia, pulsus paradoxus may be obscured.

The pericardium may be thickened and cause constriction; less commonly, effusive-constrictive pericarditis occurs. Echocardiography rapidly and accurately detects pericardial effusion, identifies metastatic lesions, and provides evidence for cardiac compression. MRI is particularly useful in evaluating pericardial mass lesions. Neoplastic cells can be recovered from the pericardial fluid, which is usually bloody, in many cases. However, it is important to remember that more than half of pericardial effusions in cancer patients are due to causes other than metastatic disease, such as infections, radiation, and drug therapy; thus, the presence of pericarditis in cancer patients does not imply imminent death.[88]

Postmyocardial Infarction Pericarditis

Pericarditis is common in the first few days after an MI, occurring in as many as 28 to 43 percent of fatal infarctions, but is clinically apparent in as few as 7 percent of cases.[89] When friction rub is required for diagnosis, there is an underestimation of the incidence of postinfarction pericarditis. On average, pericarditis was diagnosed by rub alone in 14 percent compared with 25 percent when classic symptoms, a rub, or both were used as diagnostic criteria.[90] The detection of atypical T-wave evolution on ECG (i.e., either persistent positivity or temporally late positivity) may be a more sensitive and objective means of diagnosing postinfarction pericarditis.[91]

Pericardial involvement is related to infarct size and is associated with a poor prognosis.[92] An important clinical problem is the extent to which acute pericarditis in myocardial infarction influences management with anticoagulants. A pericardial friction rub occurring in the first 2 or 3 days without an associated pericardial effusion should not influence clinical decisions, but pericarditis occurring later in the course or accompanied by pericardial effusion or tamponade is a contraindication to anticoagulant therapy.

In a prospective, consecutive series of 174 patients with acute myocardial infarction, pericarditis occurred in 24 percent and was associated with anterior infarct location, heparin therapy, and pericardial effusion.[93] Cardiac tamponade seldom occurs, except in patients who receive systemic anticoagulants or have cardiac rupture.

Thrombolytic therapy almost invariably precedes the development of pericarditis; therefore, clinical decision making usually is not affected. Surprisingly, thrombolytic therapy reduces the incidence of postinfarction pericarditis by approximately one-half.[94] However, when acute pericarditis is mistaken for acute myocardial infarction, thrombolytic therapy can have calamitous consequences. In patients treated mistakenly for myopericarditis with thrombolytics, the outcome was favorable.[95]

Dressler's syndrome (postmyocardial infarction syndrome) consists of pleuropericardial chest pain, friction rub, fever, leukocytosis, and pulmonary infiltrates. It usually occurs weeks or months (>10 days to 2 weeks) after the causative infarction. Dressler's syndrome may be caused by a combination of viral activation and myocardial antibodies and is clinically and pathogenetically similar to the postpericardiotomy syndrome. Cardiac tamponade of and late constriction may occur. For reasons that are not entirely clear, thrombolytic therapy has helped render post-myocardial infarction pericarditis nearly extinct.[96]

Radiation-Induced Pericardial Disease

Radiation injury to the pericardium is said to occur after exposure in excess of 4000 rads; the incidence also is dependent on the use of subcarinal blocks, the nature of the radiation source, and the duration and fractionation of the radiation regimen. For example, approximately 20 percent of Hodgkin's disease patients receiving ^{60}Co radiation with anterior weighting of the beam develop pericarditis, whereas the incidence of pericarditis after high-dose radiation for breast cancer (which includes less of the heart in the radiation field) is less than 5 percent.

Acute pericarditis occurring early during therapy is uncommon and most likely is a result of the radiation-induced effects on the tumor rather than a direct toxic effect of the radiation on the pericardium.[97] In this instance, therapy should not be disrupted, although a reduction in dose may be necessary. A delayed (usually less than 1 year but highly variable) form of pericardial injury may present as acute pericarditis or effusion (often with some degree of cardiac compression). The reaction of the pericardium to radiation is fibrinous inflammation,[98] often with an effusion. Although the acute lesion usually subsides within 2 years without sequelae, constrictive and effusive-constrictive pericarditis may become manifest only after many years.

The pathophysiology of radiation pericarditis is poorly understood but may involve extensive damage to the pericardial microcirculation and pericardial lymphatics with resultant ischemic injury. The incidence increases when anteriorly weighted field techniques are employed and is more common in patients who also have received adjunctive chemotherapy.

In the effusive stage, the differential diagnosis includes recurrence of the neoplasm, and examination of pericardial fluid is then helpful, as the fluid is positive in about 30 percent of cases.[99] Effusion may be due to the hypothyroid state induced by radiation therapy. Cytology is

reliable in breast and lung cancer but less so in lymphoma and leukemia, where pericardial biopsy may be needed. Acute radiation-induced pericarditis can be managed symptomatically as acute idiopathic pericarditis. Hemodynamically insignificant pericardial effusion also can be managed conservatively, as spontaneous resolution is the rule; however, pericardiectomy should be offered to symptomatic patients with large, recurrent pericardial effusions. Constrictive pericarditis requires pericardiectomy unless the biopsy reveals significant endomyocardial fibrosis.

Traumatic Pericardial Disease

Blunt trauma and penetrating trauma are important causes of pericarditis, particularly among young men.[100] Chronic constrictive pericarditis, recurrent pericardial effusion, and recurrent acute pericarditis are well-recognized complications. Traumatic pericarditis may be life-threatening. The application of echocardiography in the trauma unit rapidly and accurately diagnoses hemopericardium in patients with potentially penetrating cardiac wounds.[101] Failure to repair the injury responsible for tamponade is associated with a poor clinical outcome.[102] Constrictive pericarditis occasionally occurs and may be delayed, presenting weeks or years after the injury.[103] Chylous pericardial effusions generally follow traumatic or surgical injury to the thoracic duct but may result from neoplastic obstruction of the thoracic duct or may be idiopathic.

Nephrogenic Pericardial Disease

Pericarditis complicates both uremia and dialytic therapy (hemo- and peritoneal dialysis) and may be clinically silent. The clinical manifestation of nephrogenic pericardial disease may be acute fibrinous pericarditis, pericardial effusion, or cardiac tamponade; classic constrictive pericarditis is rare.

The pathogenesis remains unknown. The etiology of pericarditis in dialyzed patients may be different from that in end-stage renal disease. The theory that uremic pericarditis is a chemical response to retained products of metabolism fails to account for a poor relationship between the blood urea nitrogen (BUN) or other nitrogenous metabolites and the frequency of pericarditis. Since pericarditis is less common in patients undergoing peritoneal dialysis than in those receiving hemodialysis, there is a possible role for "middle molecules." Moreover, the hemorrhagic diathesis seen in the uremic syndrome may predispose to pericarditis; the resultant pericarditis is highly vascular, and consequently, the uremia or dialysis-related pericardial effusion is generally bloody. Renal insufficiency is associated with increased susceptibility to infection, and therefore, the possibility of viral, tuberculous, or even bacterial pericarditis must be considered. Immunologic abnormalities also have been implicated as a cause of pericardial disease in this setting. A presumptive diagnosis of dialysis-related pericarditis should be made only after other causes of pericardial heart disease (such as neoplasia and post-MI) that are common in this patient population have been excluded.

The clinical manifestations of cardiac tamponade may be atypical and difficult to distinguish from cardiovascular deterioration in patients undergoing hemodialysis. Cardiac tamponade remains one of the principal causes of hemodialysis-associated morbidity and terminates fatally in 20 percent of cases.

Although intensification of dialysis is an accepted treatment modality for hemodynamically insignificant disease, considerable controversy exists regarding the optimal management of large, persistent, or recurrent pericardial effusion and tamponade. Severe tamponade is an indication for pericardial drainage, but a conservative approach-intensification of dialysis and nonsteroidal anti-inflammatory agents-may suffice in less severe cases. The instillation of nonabsorbable steroids directly into the pericardial space has been advocated.[42] Dialysis-associated effusive pericarditis usually responds to an intensification of dialysis and regional heparinization or to a change to peritoneal dialysis. Pericardiectomy may be necessary for intractable effusions.

Myxedema Pericardial Disease

Pericarditis with effusion (sometimes containing cholesterol) occurs in about one-third of patients with myxedema. Effusions develop slowly and may reach a prodigious size; slow resolution usually follows the institution of thyroid replacement therapy. A case of hypothyroidism and viral pericarditis in a patient presenting to the emergency room with abdominal pain and shock was reported recently.[104]

Connective Tissue Disease-Related Pericardial Disease

Pericarditis may accompany virtually any connective tissue disease and may present as either acute or chronic pericarditis with or without an effusion.[105] Although tamponade, effusive-constrictive disease, and constrictive pericarditis are recognized complications, most cases are subclinical and in many instances are recognized only at autopsy.[106]

Rheumatoid pericardial disease is more common in middle-aged men in whom the onset of arthritis is acute. Serologic tests for rheumatoid disease are usually positive, and typical rheumatoid nodules are common. Rheumatoid arthritis is one of the causes of cholesterol pericarditis. Constrictive pericarditis is usually subacute and seldom is calcific. Pericardiectomy may be required within months of the first diagnosis of acute pericarditis and is almost always required within 5 years.[107,108]

Effusions are common in patients with SLE, and recurrent pericarditis, adhesion, and constriction may eventuate[109]; indeed, pericardial disease develops in nearly all patients with SLE when life is prolonged by steroid treatment. The pericardial fluid usually has a high protein content and a normal or slightly reduced glucose content; LE cells may be found. As in rheumatoid arthritis, the complement level is low.

Pericardial involvement may be found in systemic sclerosis (scleroderma), often in association with cardiomyopathy and diffuse scleroderma.[110] Dermatomyositis is not infrequently associated with pericardial involvement, including tamponade. Pericarditis is a rare complication in a wide variety of connective tissue disorders and arteritides (Table 72-2).

Iatrogenic Pericardial Disease

Iatrogenic pericardial disease results from both the calculated complications and the unanticipated misadventures of diagnostic and therapeutic procedures. Radiation pericarditis is one type of iatrogenic pericardial disease and was discussed earlier.

Postcardiotomy syndrome, which complicates 5 to 30 percent of cardiac operations, usually appears in the second or third week to 2 months after cardiac surgery; affected patients frequently have high titers of antiheart and antiviral antibodies and may develop cardiac tamponade.

Cardiac perforation complicating diagnostic cardiac catheterization and pacemaker insertion, complications of endoscopic sclerotherapy of esophageal varices, and automatic defibrillator electrode placement are other causes of iatrogenic pericardial disease. Pericardial abnormalities may develop in response to a number of drugs, of which the more important are hydralazine, procainamide, and daunorubicin, although these abnormalities have been reported with a number of agents (Table 72-2). Cardiac tamponade after thrombolysis with rtPA given for stroke has been reported.[111]

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Chapter 72: DISEASES OF THE PERICARDIUM

CONGENITAL PERICARDIAL HEART DISEASE

Absence and Partial Absence of the Pericardium

Congenital absence of the pericardium is an uncommon anomaly, usually involving a portion or the whole of the left parietal pericardium. Its presence usually is suspected from the chest radiogram, which shows a leftward shift of the cardiac silhouette, elongation of the left heart border, and radiolucencies between the aortic knob and the pulmonary artery and between the left hemidiaphragm and the base of the heart (Fig. 72-24). This anomaly may be associated with congenital malformations of the heart and lungs.[112]

Although most of these patients are asymptomatic, chest pain may result from torsion of the great vessels, and recurrent pulmonary infections may be a significant feature. Physical findings are not often helpful, but a conspicuous LV heave may be found when the deficiency is substantial. Systolic and diastolic murmurs have been described.

The ECG in patients with complete absence of the left side of the pericardium usually shows an incomplete right bundle branch block. Echocardiographic changes consist of RV enlargement and paradoxical septal motion. Contrast-enhanced CT and MRI detect lesions missed by chest radiography and echocardiography and reliably establish the anatomy of the defect.[113]

Total and very small defects are not associated with pathophysiologic changes, whereas medium-size defects may allow herniation of the left atrium. Strangulation requires surgical closure or enlargement of the defect to reduce the herniation; this may be accomplished with a thoracoscope.

Pericardial Cysts

Pericardial cysts are rare remnants of defective embryologic development of the pericardium. Cysts usually present as a prominent round, sharply demarcated opacity seen on chest radiography in an asymptomatic patient. They vary greatly in size and most commonly are found in the right cardiophrenic angle, although hilar and mediastinal locations are observed occasionaly. Cysts are benign and produce no local or general symptoms; their importance lies in differentiation from neoplasm. Although they can be demonstrated on echocardiography, the nature of the lesion usually is confirmed by CT. A case of video-assisted surgical excision of a recurrent pericardial cyst has been reported.[114]

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Figure 72-12: Two-dimensional echocardiogram in the apical four-chamber view. During late diastole, there is inversion of the lateral wall of the right atrium. (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:593. Reproduced with permission.)

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Figure 72-14: Doppler echocardiograms of pulmonary venous flow velocity from a dog before (*A*) and after (*B*) creation of cardiac tamponade. Note the predominance of systolic flow after tamponade. J = systolic flow; K = diastolic flow. (From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:595. Reproduced with permission.)

Figure 72-15: Hemodynamic record from a patient with cardiac tamponade before (*A*) and after (*B*) pericardiocentesis. *A.* Pulsus paradoxus is evident from the femoral artery (FA) pressure tracing. Note the absent Y descent on the right atrial (RA) tracing and the equal and elevated RA and pericardial (IPP) pressures. *B.* After removal of pericardial fluid, pericardial and right atrial pressures decrease and the pulsus paradoxus disappears. (Courtesy of Noble O Fowler, MD. From Hoit BD. Pericardial disease and pericardial heart disease. In: O'Rourke RA, ed. *Stein's Internal Medicine*, 5th ed. Mosby-Year Book;1998:273. Reproduced with permission.)

Figure 72-16: *A.* Low-pressure cardiac tamponade. Right ventricular (RV) diastolic pressure is only slightly elevated but is equal to pericardial pressure. Hypotension and pulsus paradoxus are absent. *B.* After pericardiocentesis, pericardial pressure is consistently lower than ventricular diastolic pressure. (From Shabetai R. Diseases of the pericardium. In Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2185. Reproduced with permission.)

Figure 72-17: Electrocardiogram of a patient with tuberculous constrictive pericarditis showing widespread inversed polarity of the T waves. Leads are mounted in the conventional sequence. (From Shabetai R. Diseases of the pericardium. In Alexander WA, Schlant R, Fuster V, et al., eds. *Hurst's The Heart*, 9th ed. New York: McGraw-Hill; 1998:2188. Reproduced with permission.)

Figure 72-18: Calcification of the pericardium seen on a lateral chest radiograph in a patient with chronic constrictive pericarditis. (Courtesy of Ralph Shabetai, MD. From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:595. Reproduced with permission.)

Figure 72-19: M-mode echocardiogram from a patient with constrictive pericarditis. An abrupt posterior motion of the septum begins after the onset of atrial systole. This atrial systolic notch is not seen on premature or paced beats. Note also the thickened pericardium and flat posterior wall in middle and late diastole. (From Tei C, Child JS, Tanaka H, et al. Atrial systolic notch on the interventricular septum echogram: An echocardiographic sign of constrictive pericarditis. *J Am Coll Cardiol* 1983; 1:908. Reproduced with permission.)

Figure 72-20: Computed tomogram from a patient with constrictive pericarditis. The diffusely thickened pericardium is bordered by low-intensity epicardial and mediastinal fat. (Courtesy of Dr. N. O. Fowler. From Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:597. Reproduced with permission.)

Figure 72-21: MRI scan (spin-echo image) from a patient with constrictive pericarditis. The pericardium is viewed as a line of low signal intensity (black) sandwiched between higher-intensity epicardial and pericardial fat (white). Note the regional variation of pericardial thickness, which is normally 1 to 2 mm. (From Hoit BD. Pericardial disease and pericardial heart disease. In: O'Rourke RA, ed. *Stein's Internal Medicine*, 5th ed. St. Louis, Missouri: Mosby-Year Book;1998:273. Reproduced with permission.)

Figure 72-22: Hemodynamic record of a patient with surgically proven constrictive pericarditis. *Top.* Slow paper speed recording of high-gain left ventricular (LV) pressure and simultaneous right heart pullback from pulmonary capillary wedge (PCW) to pulmonary artery (PA), right ventricle (RV), and right atrium (RA). *Bottom.* Fast paper speed recording of LV and simultaneous RV and RA pressure tracings. Note the increased and equal atrial and diastolic pressures, the prominent X and Y descents on the RA tracing, and the dip and plateau on the RV and LV tracings during longer diastoles. (Courtesy of Peter J. Engel, MD. From Hoit BD. Pericardial disease and pericardial heart disease. In: O'Rourke RA, ed. *Stein's Internal Medicine*, 5th ed. St. Louis, Missouri: Mosby-Year Book; 1998:273. Reproduced with permission.)

Figure 72-23: Recording from a patient with effusive-constrictive pericarditis caused by lung cancer. The tracings were obtained during the pericardiocentesis; right atrial pressure elevation persists, and there are prominent X and Y descents without respiratory variation. (From Shabetai R. *The Pericardium*. New York: Grune & Stratton; 1981:273. Reproduced with permission.)

Figure 72-24: *A.* Posteroanterior chest radiogram of a patient with congenital absence of the pericardium. *B.* Computed tomography scan of the same patient. (Reproduced with permission from Hoit BD. Imaging the pericardium. *Cardiol Clin* 1990; 8:598.)

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Part 12: PERICARDIAL DISEASES AND ENDOCARDITIS
Chapter 73:

INFECTIVE ENDOCARDITIS

Author: Jeff Anderson

Infective endocarditis is the disease caused by microbial infection of the endothelial lining of the heart. Its characteristic lesion is a *vegetation*, which usually develops on a heart valve but occasionally appears elsewhere on the endocardium. Sometimes a nidus of infection develops on the lining of a large artery, causing *infective endarteritis;* this variant can produce clinical findings that resemble those of infective endocarditis.

DEFINITIONS AND TERMINOLOGY

The following abbreviations for various forms of endocarditis will be used in this chapter:

- IE: Infective endocarditis
- SBE: Subacute bacterial endocarditis
- ABE: Acute bacterial endocarditis
- NVE: Native valve endocarditis
- PVE: Prosthetic valve endocarditis
- NBTE: Nonbacterial thrombotic endocarditis

The terms *subacute* and *acute bacterial endocarditis* (SBE and ABE) have descriptive value when accurately applied. SBE progresses over a period of weeks to months and is usually caused by organisms of low virulence such as viridans streptococci, which possess limited ability to infect other tissues.[1-4]

In contrast, ABE evolves over a period of days to 1 or 2 weeks; the clinical progress is rapidly changing, complications develop earlier, and the diagnosis is usually made in less than 2 weeks.[4-6] ABE is most often caused by primary pathogens such as *Staphylococcus aureus*, which are capable of causing invasive infection at many other sites in the body.

Infection of a heart valve that was either previously normal or damaged by congenital or acquired disease is termed *native valve endocarditis* (NVE). Infection of an artificial heart valve is termed *prosthetic valve endocarditis* (PVE). This infection was first arbitrarily defined as early PVE, when onset is within the first 2 months after surgery, and as late PVE thereafter.[6-11] Some authors have defined infections occurring between 2 months and 1 year of valve replacement as intermediate PVE,[11] while others consider any prosthetic valve infection beginning before 1 year as early PVE.

Sterile vegetations sometimes develop within the heart. The term *noninfective endocarditis* is a misnomer, because the lesions are primarily thrombotic rather than inflammatory.[12] Thus the term *nonbacterial thrombotic endocarditis* (NBTE) is used broadly to describe any sterile vegetation. This category includes a spectrum of lesions ranging from microscopic aggregates of platelets to the large vegetations of marantic endocarditis, which sometimes develop in patients with terminal malignancy or other chronic diseases.[13-15]

Infective endocarditis is designated best by naming the infecting organism, for example, "*Staph. aureus* endocarditis" or "*Candida albicans* PVE." This terminology is specific and informative, allowing useful inferences about the likely natural history, prognosis, and treatment of the case in question.

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Chapter 73: INFECTIVE ENDOCARDITIS

EARLY STUDIES

Riviere, Lancisi, and Morgagni each described patients who died with endocarditis in the seventeenth and eighteenth centuries.[16] Jean-Baptiste Bouillaud introduced the terms *endocardium* and *endocarditis* between 1824 and 1835. By 1846, Virchow recognized valvular vegetations at autopsy, but the microbial etiology of infective endocarditis was not fully appreciated until Virchow et al. independently demonstrated bacteria in vegetations between 1869 and 1872.[16]

William Osler studied the disease extensively, choosing infective endocarditis as the subject for his Goulstonian lectures of 1885.[17,18] Further major contributions to the knowledge of the natural history, pathogenesis, and pathology of the disease were made by Lenharz, Harbitz, and Schottmuller[16] in Germany; by Horder[19] in England; and by Blumer,[1] Thayer,[2] Allen,[20] Libman and Friedberg,[21] and Beeson et al.[22] in the United States. The technique of blood culture was introduced in Europe and the United States between 1890 and 1910.[3] In 1955, Kerr published a classic monograph summarizing the state of knowledge on subacute bacterial endocarditis to that date.[3]

Attempts to cure endocarditis before the advent of antimicrobial drugs were unsuccessful. In 1939, one patient with infective endarteritis involving a patent ductus arteriosus was cured by surgical closure of the ductus.[23] The first successes in the treatment of endocarditis are closely linked to the history of penicillin.[24] The first patient to receive parenteral penicillin was a young man with streptococcal endocarditis who was treated in 1940 at Columbia University in New York.[25] Although the patient did not receive enough penicillin to effect a cure, his treatment antedated the first administration of penicillin to a patient by Florey's team (Abraham et al.) in Oxford[26] by several months. After initial failures, by 1944 it had been established that penicillin,[27] unlike sulfonamides,[28] could cure most cases of streptococcal endocarditis. Subsequently, the antibiotic treatment of endocarditis was clearly established.[29-33] After antibiotics, the next great advance was cardiac valve replacement for treatment of endocarditis in 1965,[34] which provided an essential intervention to improve survival rates in selected patients.

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Chapter 73: INFECTIVE ENDOCARDITIS

EPIDEMIOLOGY

Incidence

The incidence of infective endocarditis can only be estimated, because it is not a reportable disease. Various studies in developed countries have estimated the incidence to be 1.6 to 6.0 cases per 100,000 person-years.[35-39] In the United States, this would result in 4000 to 15,000 new cases per year. In a study from the Delaware Valley, where the population includes a large number of intravenous drug users (IDU), the estimated rate was much higher: 11.6 cases per 100,000 per year.[40]

Evolution of the Clinical Syndrome

IE today is a different disease from that seen in the preantibiotic era, when its salient clinical features were exhaustively reported.[1-3] Since 1961, many authors have described the "changing face" of "modern endocarditis,"[41-47] identifying the following trends:

- Increased median age of patients
- Increased ratio of males to females
- Increased proportion of acute cases
- Reduced incidence of some of the classic physical signs of advanced SBE, such as Osler's nodes, finger clubbing, splenomegaly, or Roth's spots
- Decreased proportion of cases due to streptococci, with an increased incidence of staphylococci
- Lengthened list of etiologic organisms, with more reports of cases caused by gram-negative bacilli, fungi, and miscellaneous rare or unusual microbes
- Increased number of cases in IDU
- Increased number of prosthetic valve infections
- Increased incidence of concomitant human immunodeficiency virus (HIV) infection and endocarditis

Susceptible Populations

These striking changes in the clinical features and epidemiology of IE are due to changes in susceptible populations, to earlier diagnosis and treatment of patients with subacute disease and to the impact of antibiotic therapy.[45,48] The prevalence of rheumatic valvular disease, formerly the most common substrate for endocarditis, has steadily decreased; meanwhile, the number of children surviving with congenital heart disease has increased. The number of individuals using illicit drugs intravenously has increased markedly in the United States and Europe since the 1960s, and HIV has spread widely throughout this group as well.[49]

Effect of Antibiotics

Although the advent of antibiotics revolutionized treatment of endocarditis, the overall incidence of the disease has not changed strikingly. The availability of rapidly effective treatments for pneumococcal pneumonia and gonorrhea has probably been responsible for the striking decrease in the incidence of endocarditis caused by *Streptococcus pneumoniae* and *Neisseria gonorrhoeaea* since 1944, while the incidence of reported cases caused by miscellaneous unusual antibiotic-resistant organisms has increased during the antibiotic era.[48,50-53] Apart from these special cases, the widespread use of antimicrobial agents seems to have exerted considerably less influence than have alterations in the populations at risk on the changing epidemiology of endocarditis.[45] Prophylactic use of antibiotics before medical procedures that cause bacteremia has not reduced the incidence of endocarditis significantly; this is not surprising considering that only a small proportion of all cases can be attributed to such procedures.[54-56] Also,

startling studies question the effectiveness of prophylactic antibiotics during dental procedures to prevent endocarditis.[56,57]

Preexisting Heart Disease

Some patients develop endocarditis even though they have no known heart disease. This is most common in cases of ABE,[57] in children less than 2 years of age,[58-64] and in IDUs.[65-70] Most patients who develop IE, however, have a preexisting cardiac condition. Approximate figures for the frequency of the main predisposing factors in children, adults, and IDUs are given in Table 73-1.

Table 73-1: Approximate Frequency of Major Preexisting Cardiac Lesions in Patients with Infective Endocarditis in the United States

Lesion	Children under 2 years, %	Children 2-15 Years, %	Adults 15-50 Years, %	Adults >50 Years, %	Adults Who Are IV Drug Abusers, %
○ Prosthetic heart valves ○ Previous infective endocarditis ○ Cyanotic congenital heart disease ○ Aortic valve disease ○ Mitral regurgitation ○ Mitral regurgitation and stenosis ○ Patent ductus arteriosus ○ Ventricular septal defect ○ Coarctation of the aorta					
○ Mitral valve prolapse with regurgitation ○ Pure mitral stenosis ○ Tricuspid valve disease ○ Pulmonary valve disease ○ Asymmetric septal hypertrophy ○ Hyperalimentation or pressure-monitoring lines that reach the right atrium ○ Nonvalvular intracardiac prosthetic implants ○ Degenerative valvular disease in elderly patients					
○ Mitral valve prolapse without regurgitation ○ Trivial valvular regurgitation by echocardiography without structural abnormality ○ Atrial septal defects, secundum type ○ Arteriosclerotic plaques ○ Coronary artery disease ○ Syphilitic aortitis ○ Cardiac pacemakers ○ Surgically corrected cardiac lesions (without prosthetic implants, more than 6 months after operation)					

Includes mitral valve prolapse.
SOURCE: Adapted from Refs. [35-5158-7081,202].

The relative propensity of various cardiac lesions to become infected can be estimated by noting their frequency in published series of cases of IE, even though there is wide variation among individual studies (Table 73-2).

Table 73-2: Estimates of the Relative Risk of Infective Endocarditis Posed by Various Cardiac Lesions

Relatively High Risk	Intermediate Risk	Very Low or Negligible Risk
Prosthetic heart valves	Mitral valve prolapse with regurgitation	Mitral valve prolapse without regurgitation
Previous infective endocarditis	Pure mitral stenosis	
Cyanotic congenital heart disease	Tricuspid valve disease	Trivial valvular regurgitation by echocardiography without structural abnormality
Aortic valve disease	Pulmonary valve disease	
Mitral regurgitation	Asymmetric septal hypertrophy	
Mitral regurgitation and stenosis	Hyperalimentation or pressure-monitoring lines that reach the right atrium	Atrial septal defects, secundum type
Patent ductus arteriosus		Arteriosclerotic plaques
Ventricular septal defect	Nonvalvular intracardiac prosthetic implants	Coronary artery disease
Coarctation of the aorta		Syphilitic aortitis
	Degenerative valvular disease in elderly patients	Cardiac pacemakers
		Surgically corrected cardiac lesions (without prosthetic implants, more than 6 months after operation)

SOURCE: Adapted from Refs. [36,38,39,43,50,51,71-81,86,116,370].

Mitral valve prolapse (MVP) can predispose to endocarditis.[71-78] (see Chap. 58). MVP underlies 15 to 30 percent or more of cases.[35,72,75,76,80] However, MVP is common and represents a broad spectrum of valvular and clinical disease. The annual percentage of patients with MVP that develop complications (including IE) is small, and the need for IE prophylaxis is controversial. Hence, American Heart Association recommendations include an algorithm to more clearly define when prophylaxis is recommended in MVP.[79] The risk of IE is primarily increased (five- to eightfold) when MVP is associated with regurgitation.[72,73,78] The use of prophylactic antibiotics is supported by cost-benefit analysis in those with auscultatory or Doppler evidence for mitral insufficiency.[79] In contrast, endocarditis risk is not

increased in the absence of regurgitation and prophylaxis is not recommended[2,8,9,79] (see Chap. 58).[72,73] However, this remains controversial. Although commonly used to confirm diagnoses, routine use of echocardiography does not appear to be cost effective.[74]

Children

IE occurs at all ages but is relatively uncommon during childhood and rare during infancy,[58-64,81,82] although the incidence is increasing among smaller infants with cyanotic disease.[83] Males predominate-65 percent in one series.[84] Endocardial infection in children with no predisposing heart disease develops most often in association with infection elsewhere, often in infants and very young children.[85] Endocarditis in these settings is likely to be caused by invasive pathogens and follow an acute course. IE can occur as a rare complication of septicemia caused by staphylococci or group B streptococci or of pneumonia, other respiratory tract infections, osteomyelitis, and severe burns.[58,62] Nosocomial cases associated with intravenous catheters are important.[85] Endocarditis complicating congenital or other preexisting heart lesions is more likely to occur in older children and present as a subacute disease without an obvious portal of entry.[85] Children with a systemic pulmonary shunt constructed surgically are most likely to have endocarditis caused by viridans streptococci.[84] *Haemophilus influenzae* type B endocarditis is very rare, even though this organism was a common cause of bacteremia in children prior to the introduction of conjugate vaccines.

The leading underlying cardiac lesions in children are tetralogy of Fallot and other forms of cyanotic congenital heart disease, ventricular septal defects, aortic stenosis, patent ductus arteriosus, pulmonary stenosis, and coarctation of the aorta. A high proportion of cases (77 percent of those with chronic heart disease) occur in children who have undergone palliative or corrective surgery for congenital cardiac defects.[62,84,86] Atrial septal defects of the ostium secundum type very rarely become infected (Chap. 64). Successful repair of ventricular septal defects and closure of patent ductus arteriosus appears to have greatly reduced the risk of endocarditis. In developed countries, preexisting rheumatic heart disease is now much less common than congenital disease. No underlying cardiac disease is found in about 15 percent of children with endocarditis, but the proportion is higher in those less than 2 years of age (Table 73-1).

A firm diagnosis of IE is more difficult to make in infants and small children than it is in adults. Signs and symptoms, however, are similar: fever occurs in 99 percent of pediatric cases, fatigue in 60 percent, arthralgias in 17 percent, petechiae in 21 percent, changing murmur in 21 percent, splenomegaly in 21 percent, and congenative heart failure in 9 percent. Blood cultures are positive in over 90 percent of the cases, which is also similar to adults. Viridans streptococci account for 38 percent of cases, *Staph. aureus* for 32 percent, enterococci for 7 percent, and a mixture of gram-positive cocci and gram-negative organisms for the rest.[84] Once the diagnosis is suspected, improved diagnostic criteria can help determine whether the child has endocarditis.[85] The clinical manifestations of acute rheumatic fever may mimic endocarditis (and vice versa), but fortunately the two conditions rarely coexist.

The choice of antibiotic treatment for children should be governed by the same principles as for adults, with appropriate dose adjustment for age. As in adults, valve replacement or other potentially curative surgical treatment should not be delayed if the child has heart failure that does not respond well to medical therapy.[87] Children with *Staph. aureus* endocarditis are most likely to have persistent fever bactermia, and complications, require surgery, and have a higher mortality rate than those who do not have *Staph. aureus*.[84,88]

The Elderly

With the increase in elderly people, endocarditis in this group has become more common.[89-92] The median age of patients with endocarditis has risen steadily for three decades, from about 30 to about 50 years. At present, approximately one-fourth of all patients are over age 60.[35,93] The annual risk for endocarditis is strongly age-related, being about 5 times higher in patients over age 80.[39] Male patients now outnumber females by approximately 1.5 to 1 overall, but by as much as 8 to 1 among patients over age 60.[33,94] Elderly patients are more likely to have underlying degenerative or calcific valve lesions.[90] Older patients (>70 years) had a higher proportion of bacteria from a gastrointestinal source (group D streptococci and

enterococci accounted for 50 percent of cases in one series).[92] There is a higher mortality rate (28 versus 13 percent) for patients who are <70 years.[92]

Intravenous Drug Users

Illicit intravenous drug use poses a high risk for IE.[65-70,95] IDUs are 300 times more likely to die suddenly with IE than are nonusers.[96] Bacteremias related to parenteral drug abuse are common and arise either from direct intravenous injection of bacteria or from the skin flora and local infections at injection sites, including cellulitis, abscesses, or suppurative thrombophlebitis. Addicts seldom use sterile injection techniques, sometimes even taking water from toilet bowls to dissolve their drugs. Nevertheless, the organisms that cause drug-related endocarditis most frequently originate from the addict's skin and mucosal bacterial flora.[97] Strains of *Staph. aureus* cause more than 60 percent of cases of endocarditis among parenteral drug abusers, more than all other species combined.[50,70] Infections with gram-negative bacilli, especially *Pseudomonas* species[98,99] or yeasts and other fungi,[100] are notably more common than in nonaddicts (Table 73-3). *Candida parapsilosis* and other *Candida* species are the most common fungi causing drug-related endocarditis, but occasional infections with a wide range of other fungal species have been recorded.[100,101] Polymicrobial and culture-negative cases of endocarditis occur occasionally in IDUs, but together account for less than 5 percent of cases.[65,67,70,102]

Table 73-3: Frequency of Various Organisms Causing Infective Endocarditis[a]

Organism	NVE, %	IV Drug Abusers, %	Early PVE, %	Late PVE, %
Streptococci	60	15-25	5	35
Viridans, alpha-hemolytic	35	5-10	<5	25
0x002003 *Streptococcus bovis*	10	<5	<5	<5
0x002003 *Enterococcus faecalis*	10	10	<5	<5
Other streptococci	<5	<5	<5	<5
Staphylococci	25	50	50	30
Coagulase-positive	23	50	20	10
Coagulase-negative	<5	<5	30	20
Gram-negative aerobic bacilli	<5	5	20	10
Fungi	<5	<5	10	5
Miscellaneous bacteria	<5	5	5	5
Diphtheroids, propionibacteria	<1	<5	5	<5
Other anaerobes	<1	<1	<1	<1
Rickettsiae	<1	<1	<1	<1
Chlamydiae	<1	<1	<1	<1
Polymicrobial infection	<1	1-5	5	5
Culture-negative endocarditis	5-10	<5	<5	<5

[a]These are representative figures collated from the literature; wide local variations in frequency are to be expected. NVE = native valve endocarditis; PVE = prosthetic valve endocarditis; IV = intravenous.

SOURCE: Adapted from Refs. [43,51,65-70,100-110,115,159].

Endocarditis in addicts frequently follows an acute course,[5,65,66,101] reflecting the high frequency of *Staph. aureus* infection. This finding partly explains the overall modest increase in the proportion of acute to subacute cases that has been observed over the past 25 years.[45]

The outstanding clinical feature of endocarditis in IDUs is the unusually high incidence of right-sided valvular infection. In various series, the tricuspid valve is involved in 60 to 70 percent of cases.[50,61,103] The aortic and/or mitral valves are involved in 30 to 40 percent.[50,103] More than one valve on either side of the heart may be infected simultaneously. Pulmonary valve infection is unusual even among IDUs, occurring in only some 2 percent of cases.

Tricuspid vegetations commonly embolize to the lungs, causing septic pulmonary infarcts, which result in multiple focal opacities on chest x-ray, sometimes with cavitation. In a drug addict with fever, this radiologic finding is a highly characteristic sign of acute right-sided endocarditis.[5,70] Mortality rates are much lower (4 percent) with endocarditis in IDUs than in other patient populations, even though the most common cause is *Staph. aureus.* This most likely reflects the benign nature of tricuspid valve involvement compared to left-sided disease.

Patients Infected with Human Immunodeficiency Virus

The primary risk factor for IE in HIV-infected people is the continued use of intravenous drugs, although IE is independently associated with HIV infection. Prior endocarditis, female sex, and skin abscesses are independent risk factors.[104] In one study, the adjusted odds ratio for HIV-infected IDUs with CD4 cell levels > 350 who developed endocarditis was 2.31 versus non-HIV-infected IDUs, but increased to an odds ratio of 8.31 when the CD4 cell count fell to < 350.[107] Several cases of *Bartonella* endocarditis have been reported in patients with acquired immunodeficiency syndrome (AIDS);[105] this appears to be a rare instance of true opportunistic infection of the endocardium. Patients in the earlier stages of HIV infection respond well to standard treatment for endocarditis, but mortality due to IE is high after the CD4+ T-cell count falls below 200 cells per cubic millimeter [49,106] (see also Chap. 70).

Post-Cardiac Surgery Patients

Intracardiac operations, especially valve replacements, have created a whole new population at risk for IE. In the 1950s, surgeons first noted that *Staph. epidermidis* endocarditis occurred fairly frequently after mitral valvotomy.[108] Subsequently, *Staph. epidermidis*, which rarely infects native valves, has become a common cause of both early and late PVE (Table 73-3).[8-11,95] Contamination of blood circulating through pump oxygenators with *Staph. epidermidis* or other organisms or from the operating room air can initiate infection at the time of operation, resulting in early PVE. In late PVE, the causative organisms usually originate from the normal flora of the skin or gastrointestinal tract, but their portal of entry largely remains unknown. Gram-negative bacilli and fungi infect prosthetic valves much more frequently than native valves, especially in early postoperative cases.[11,95,109] The spectrum of organisms causing late PVE more nearly resembles that of subacute native valve infection (Table 73-3).

Figure 73-1 shows the curve for incidence of PVE per month after valve replacement. The peak time of onset is 3 to 9 weeks after operation, with the risk falling quickly thereafter.[9] This important time relationship emphasizes that *Staph. epidermidis* and certain other organisms are often inoculated during or immediately after surgery, while streptococci infect the prosthesis during bacteremias that may occur at any time, unrelated to surgery.

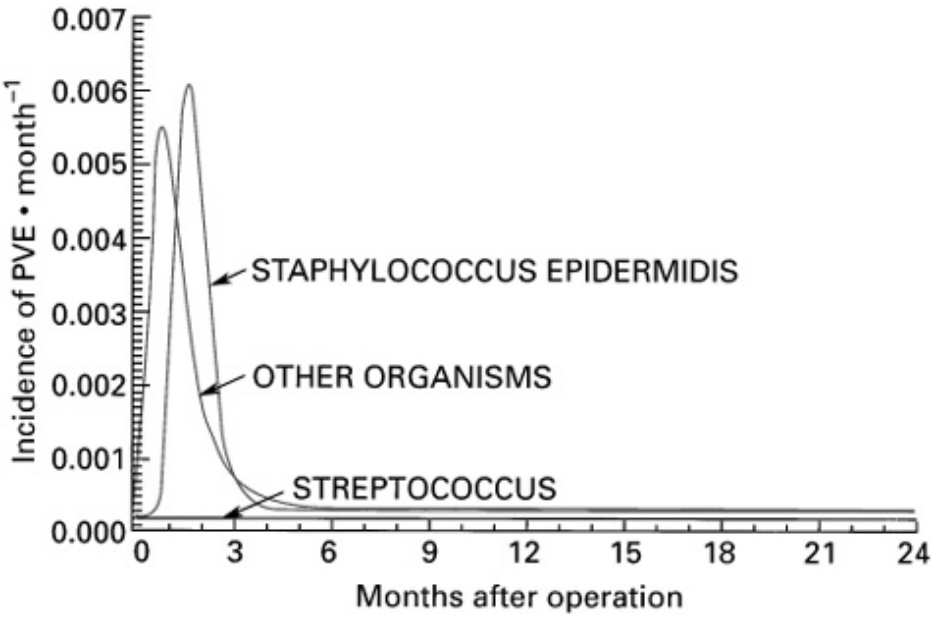

Figure 73-1: Incidence of prosthetic valve endocarditis (PVE) over 24 months after valve replacement. The hazard function has been stratified according to the infecting organisms. (From Ivert TSA, Dismukes WE, Cobbs CG, et al. Prosthetic valve endocarditis. *Circulation* 1984; 69:223. Reproduced with permission.)

The total number of cases of postsurgical endocarditis has increased along with the number of operations, even though the incidence per patient has decreased. This decrease reflects improved operative techniques and possibly the use of prophylactic antibiotics. Currently the rate is about 0.5 percent for early PVE, with a range of 0.3 to 1.2 percent.[8-11]

Patients with prosthetic valves now routinely survive for many years and remain at higher risk for late IE for the rest of their lives.[11,95,109,110] Late PVE occurs at a rate of about 0.3 to 0.5 percent per year.

Obstetric and Gynecologic Patients

Endocarditis occurring as a complication of pregnancy is most likely to develop at the time of delivery or in the puerperium.[111] Normal delivery presents a low risk of endocarditis, even in the presence of preexisting valvular disease,[112] but bacteremias associated with perinatal infective complications such as endometritis, parametritis, septic thrombophlebitis in pelvic veins, or urinary tract infection can seed the mother's endocardium.[111] Septic abortion or pelvic infection related to intrauterine contraceptive devices also can provide the portal of entry for bacteremia resulting in endocarditis.[113] The organisms most often involved are *Enterococcus faecalis*, group B streptococci, *Staph. aureus*, and occasionally gram-negative enteric bacilli or anaerobes.

Nosocomial Endocarditis

Hospital-acquired IE can involve either prosthetic or native valves.[114,115] This serious complication is not rare; one study[116] reported no fewer than 35 examples of probable nosocomial endocarditis among 125 cases (28 percent), and the rate may be rising.[114] Intensive medical care predisposes to endocarditis in several ways. Endocardial damage can be produced by surgery, by intracardiac catheters, and by intravascular devices such as hyperalimentation catheters and cerebrospinal fluid shunts if they reach into the right atrium. Portals of entry for microorganisms are provided by wounds, biopsy sites, pacemakers, intravenous and arterial catheters,[117] urinary catheters, and intratracheal airways. In one study, 75 percent of the suspected sources of infection were vascular access sites.[118] Nosocomial bacteremias arising from local infections are common in seriously ill patients. Up to two-thirds of patients with nosocomial endocarditis had no known predisposing cardiac abnormalities.[118]

Many of the previously mentioned factors coexist in *severely burned* patients. In one study, either NBTE or IE was found at autopsy in all of 6 burned patients who sustained repeated episodes of bacteremia while a pressure-monitoring catheter was maintained in the right side of the heart before death.[119] This observation has been confirmed in another autopsy study of patients with flow-directed pulmonary artery catheters.[120] Of 55 patients, 29 had one or more right-sided endocardial lesions, including 13 with thrombi and 4 with infective endocarditis. *S. aureus* and gram-negative bacilli are the most common organisms isolated. Since persistent bacteremia and fever usually are the only consistent findings, an echocardiogram may be of diagnostic value in this setting.[121] Another group at high risk are patients with *prosthetic valves* who develop nosocomial bacteremias, especially if the organism is a staphylococcus.[115] The portal of entry in these cases is most often an intravascular line or device, and PVE can develop later even if the patient received a course of appropriate antibiotics for the nosocomial infection. In comparison, catheterization of the right side of the heart for brief periods in patients without bacteremia, as in a coronary care unit, presents a very low risk for IE. IE is rare in patients with leukemia but has been observed in other immunocompromised patients-for example, after bone marrow transplantation[122] and heart transplantation.[123] In a report of 46 cases after solid organ transplantation, *Aspergillus fumigatus* and *Staph. aureus* were causative in 50 percent, whereas viridans streptococci were isolated in only 4 percent. Six of 10 cases that occurred within 30 days of transplantation were fungal. No predisposing cardiac abnormality was known to be present in 80 percent. Infected venous access devices and wounds were suspected portals of entry in three-fourths of the cases. The mortality rate was 57 percent, and most infections were not diagnosed prior to death.[124]

Overall, the leading organisms causing nosocomial endocarditis are staphylococci, enterococci, *Candida* species, and gram-negative bacilli. *Staph. aureus* is especially associated with wound infections, cellulitis, and cannula infections; *Staph. epidermidis* with ventriculoatrial shunts; and *C. albicans* with parenteral alimentation.

The prognosis for nosocomial native valve endocarditis is worse than for other forms of native valve infection (up to 50 percent mortality).[114,118] These patients often have serious underlying disease that may delay diagnosis of endocarditis by obscuring the symptoms and signs, while the organisms most commonly involved (staphylococci and enterococci) are more difficult to eradicate than viridans streptococci.

Hemodialysis

Creation of arteriovenous shunts for hemodialysis predisposes patients to develop IE by providing a ready portal of entry for bacteremias. Another possible factor is increased cardiac output. Dogs with high cardiac output due to surgically created arteriovenous fistulas are predisposed to develop not only infective endarteritis at the site of the shunt but endocarditis as well.[125] Therefore, it is not surprising that endocarditis has been reported in 2 to 6 percent of patients on long-term hemodialysis employing either arteriovenous fistulas or cannulas. *Staph. aureus* and *Staph. epidermidis* have been the most common etiologic organisms, followed by viridans streptococci and *E. faecalis*.[126] The diagnosis of endocarditis is difficult in these patients, partly because coexisting intravascular infection at the shunt site often confuses the clinical picture. Mortality is high (53 percent), and a high index of suspicion and use of an echocardiography followed by aggressive treatment of both shunt infections and endocarditis in dialysis patients are necessary to improve outcome.[126] In one study of 20 cases of IE in hemodialysis patients, vegetations were found in 50 percent by transthoracic echocardiogram (TTE) and 81 percent by transesophageal echocardiogram (TEE).[127] In 65 hemodialysis patients with *Staph. aureus* bacteremia, 8 (12 percent) were found to have IE by TEE (6 of whom had normal TTEs).[128]

Pacemaker Infective Endocarditis

The placement of permanent pacemaker leads into the right ventricle may result in endocardial lead infection in 0.2 to 7 percent of patients. These may occur early (6 weeks to 3 months after placement) and are caused by *Staph. epidermidis* in 90 percent, or late, when *Staph. epidermidis* or *Staph. aureus* each account for nearly 50 percent, with gram-negative bacilli causing the remaining few. The definitive diagnosis usually requires TEE, which will detect vegetations in or around the leads in >90 percent of cases. The chest x-ray is predictive in one-third for pulmonary emboli. Cure requires removal of the

pacemaker generator and leads, and treatment with antibiotics.[129-132]

Infective Endarteritis

Focal intravascular infection located outside the heart itself can mimic most of the clinical manifestations of endocarditis, including vascular and immunologic phenomena.[50] In the past, about one-quarter of all patients with an uncorrected patent ductus arteriosus developed bacterial endarteritis.[3] Coarctations of the aorta also presented a significant risk, but endocarditis located on an associated bicuspid aortic valve was 3 times more common than was endarteritis with vegetations located in the coarctation. Endarteritis occasionally complicates traumatic arteriovenous fistulas, but arteriosclerotic aneurysms rarely become infected.[50] When bacterial endarteritis does occur within an aneurysm, the organisms usually grow in a multilayered thrombus in the lumen of the aneurysm rather than in vegetations.

The spectrum of organisms causing infective endarteritis is similar to that found in endocarditis except that there is a higher frequency of infection with salmonellae in arteriosclerotic abdominal aneurysms.[50,133] The pattern of embolization observed differs according to the site of infection. Thus, petechiae may occur on the skin of the lower extremities in a patient with an infected abdominal aneurysm, and infarctions may appear in the lungs of a patient with an infected dialysis fistula in the forearm.

Because many of the congenital and acquired vascular lesions that predispose to infective endarteritis can be corrected by modern surgery, endarteritis-except in arteriovenous shunts constructed for the purpose of hemodialysis-is uncommon today in developed countries.

PREVIOUS | NEXT

Chapter 73: INFECTIVE ENDOCARDITIS

ETIOLOGIC ORGANISMS

The range of microbial species that can cause infective endocarditis is extraordinarily wide, yet only a few species account for the great majority of cases. On native valves, streptococci and staphylococci together cause more than 80 percent of infections.[38,43,51,116] By comparison, NVE caused by *Staph. epidermidis*, enteric bacilli, and fungi are uncommon. Among IDUs and patients with prosthetic valves, the incidence of infection due to these organisms is higher. Table 73-3 offers representative data from the literature on the relative frequency of the major etiologic organisms on native valves, in drug addicts, and on prosthetic valves. It should be emphasized that the relative frequency with which various organisms cause endocarditis can vary widely between countries and between medical centers.

Streptococci

Streptococci cause more cases of endocarditis than any other group of organisms.[38,51,134-136] The alpha-hemolytic or viridans streptococci account for the majority of these cases, but have decreased in frequency when compared with others during the last 30 years. Viridans streptococci are ubiquitous (although outnumbered by anaerobes) in the oropharyngeal and gastrointestinal flora. They are usually low-grade pathogens (except for *Strep. milleri*), often recovered from clinical specimens in mixed culture with other organisms but seldom themselves causing disease. Their strong association with SBE is therefore determined by the frequency with which they enter the bloodstream and by their ability to adhere to endocardium rather than by their innate virulence.

The nomenclature of these organisms is complex and has been subject to repeated revisions.[134,137,138] The following species frequently cause SBE: *Strep. sanguis*, *Strep. mitis*, *Strep. oralis*, and *Strep. gordonii*. Many other species occasionally cause SBE; for example, the *Strep. milleri* group: *Strep. anginosus*, *Strep. intermedius*, and *Strep. constellatus*.[134,136,137] A few cases are caused by strains that require media supplemented with L-cysteine or pyridoxine for growth.[139-142] These strains are more difficult to isolate from blood and seem to be more difficult to eradicate with antibiotic treatment than the other viridans streptococci.

Group D streptococci are next in frequency among the streptococci as a cause of endocarditis.[94,143,144] The nonenterococcal group D species, *Strep. bovis*, accounts for about one-fifth of streptococcal cases. IE caused by *Strep. bovis* tends to occur in older patients, affect multiple valves, and require surgery more commonly than IE caused by other organisms.[145] Gastrointestinal lesions, especially colonic polyps and cancers, are present in > 50 percent of patients who develop *Strep. bovis* bacteremia and/or endocarditis.[146,147] Hence, recovery of this species from blood cultures should prompt investigation for colonic disease, whether or not the patient has gastrointestinal symptoms.

Strains of *E. faecalis* (enterococci) cause about 10 percent of streptococcal cases. In the past it was said that this species caused endocarditis "in young women and old men," because it was found in association with infections of the genital and urinary tract in women of childbearing age and of the urinary tract in old men with prostatic disease. Today, enterococcal endocarditis is also likely to be found in drug addicts, in patients with nosocomial endocarditis, and in those with chronic renal failure.[94] Enterococci commonly cause urinary tract, wound, and intravenous line infections,

which often give rise to nosocomial bacteremias.[148,149] Fewer than 2 percent of such patients have endocarditis, but if enterococcal bacteremia is community-acquired without a primary focus of infection, about one-third will have IE.[148] Antibiotic resistance, especially in strains of *E. faecium*, presents major difficulties in treatment of enterococcal endocarditis.[94,150-152]

Many other species and strains of streptococci occasionally cause endocarditis, but they are rare compared with the viridans and group D organisms. *Strep. pneumoniae* endocarditis has become uncommon since the advent of antibiotics. This species causes acute endocarditis,[153] affects primarily the aortic valve in patients without underlying valvular disease (15 of 16 in one series), and often requires immediate valve replacement for aortic insufficiency and cardiac failure (7 of 16).[154,155] In debilitated alcoholics, bacteremic pneumococcal pneumonia is occasionally complicated by the development of pneumococcal endocarditis and meningitis. This triad of simultaneous pneumococcal infections carries an extremely poor prognosis.[153] Beta-hemolytic streptococci rarely cause IE, but in a report of 31 cases, one-third had underlying diabetes mellitis, three-fourths had significant complications, and one-half required cardiac surgery.[156] In children, group A streptococcus may complicate varicella.[157] Group B streptococcal endocarditis is also rare, but may complicate obstetric or other surgical procedures (abortions) or injection drug use, and may involve the tricuspid valve.[158]

Staphylococci

Staph. aureus is the leading cause of acute bacterial endocarditis. Median duration of illness prior to hospitalization was 3 days in one series.[160] It is the predominant etiologic organism in IDUs with endocarditis[70] and frequently causes PVE.[95] *Staph. aureus* endocarditis is also a complication of diabetes mellitis (13 percent in one study), corticosteroid therapy (11 percent), cirrhosis (5 percent), malignancy (4 percent), and chronic renal failure (4 percent).[160] In nosocomial cases, infected intravascular devices were the most common portal of entry. Because it is an invasive primary pathogen, patients with staphylococcal ABE often develop disseminated disease with metastatic infections in skin and soft tissue, bone, joints, eye, or brain.[159-162] More than one-third of patients with *Staph. aureus* endocarditis will have central nervous system involvement.[160]

Only a minority of all patients with *Staph. aureus* bacteremia have endocarditis (6 to 15 percent), and it is often difficult to identify this subgroup clinically. However, use of TEE in this setting is highly effective in establishing the diagnosis of IE. Factors that increase the probability that such a patient has endocarditis are (1) community-acquired bacteremia, (2) absence of a primary focus of infection, and (3) presence of metastatic foci of staphylococcal infection. Up to two-thirds of patients with all 3 of these characteristics have endocarditis.[162] *Staph. epidermidis* is a rare cause of native valve infection (<5 percent), usually associated with an indolent subacute or chronic course.[163] However, serious complications, including systemic embolization, congestive heart failure, myocardial abscess, and valve destruction are common and mortality is high (up to 36 percent).[164] *Staph. lugdunensis*, a recently described species of coagulase negative staphylococcus, appears to be especially virulent and more likely to infect native cardiac valves than *Staph. epidermidis*.[165] In striking contrast, *Staph. epidermidis* is a common cause of PVE (40 to 50 percent), which may follow either an acute or subacute clinical course.[163,166]

Gram-Negative Bacteria

Although most of the species of gram-negative bacteria that colonize and/or infect humans have been reported to cause IE, they account for only a small proportion of cases of native valve infection. A significant subgroup of cases are caused by a group of nutritionally fastidious gram-negative bacilli: *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. These are often referred to by the acronym

HACEK, which is derived from their initials,[167,168] and cause approximately 3 percent of cases of IE. In one report, most patients had symptoms between 2 weeks and 3 months and presented with fever, a new or changing murmur, splenomegaly, and emboli.[169] Blood cultures usually took 3 to 4 days to turn positive.[169] Prognosis with medical therapy and surgery, when necessary (one-fourth of patients), was good, with 87 percent overall survival.

Cases caused by *Haemophilus* predominate in this group. Endocarditis caused by this genus is usually due to *H. parainfluenza* (62 percent), *H. aphrophilus* (21 percent), *H. paraphrophilus* (10 percent), and only rarely to *H. influenzae*. *Haemophilus* endocarditis is characterized by large vegetations and arterial emboli (35 to 60 percent).[170]

The common aerobic enteric gram-negative bacilli seldom cause endocarditis. For example, cases of endocarditis caused by *Escherichia coli* and *Klebsiella* are notably rare,[99] even though these species frequently cause gram-negative bacteremia. The reasons for this striking disparity are probably multiple, including low adhesiveness of gram-negative enteric bacilli to heart valves[171] and fibrin[172] and susceptibility of many strains to complement-mediated bacteriolysis.[173] Despite these factors, two special populations are at increased risk of gram-negative endocarditis: IDUs and patients with prosthetic valves. Gram-negative bacilli account for about 5 percent of endocarditis in IDUs,[65,68-70] with *Pseudomonas* species, *Serratia,* and *Enterobacter* species predominating. Gram-negative bacilli cause 15 to 20 percent of early PVE and about 10 percent of late PVE.[11,95] Strains of gram-negative bacilli such as *Stenotrophomonas* (*Xanthomonas*) *multophilia,* which are resistant to most antibiotics, are becoming more common. They typically cause nosocomial IE (50 percent), occur on prosthetic heart valves (50 percent), and are associated with IDUs or indwelling vascular catheters (18.8 percent).[174]

Interesting but unusual cases caused by species of *Salmonella, Brucella, Acinetobacter,* and other gram-negative bacilli have been reported.[99] *Brucella* endocarditis is well known in the Mediterranean basin[175-177] but is rare in most other regions. Endocarditis caused by anaerobic bacteria is rare (1 percent or less of cases),[178,179] possibly because the oxygen tension in heart blood is too high to favor growth of these species on the endocardium.

N. gonorrhoeaea causes an acute form of the disease,[2] often involving the right side of the heart. Like the pneumococcus, *N. gonorrhoeaea* has become uncommon as a cause of endocarditis since the introduction of penicillin.[51,52]

Yeasts and Dimorphic Fungi

Although many species of yeasts and other fungi can infect the endocardium, only two genera account for the great majority: *Candida* and *Aspergillus*.[100,101,180,181] *Candida* causes native valve infections in IDUs and in patients receiving parenteral alimentation, while *Aspergillus* species often involve prosthetic valves. Fungal infection of native valves in nonaddicts is rare (Table 73-3).

Miscellaneous Organisms

Many less common organisms occasionally cause endocarditis; for example, *Coxiella burnetii* (Q fever) and *Chlamydia*. Q-fever endocarditis is a chronic, febrile systemic illness with prominent hepatic as well as cardiac valvular involvement.[182-188] Most cases have been reported from Europe, Canada, and Australia and occur in approximately 7 percent of cases of Q fever. Patients typically present with intermittent fever for months to years (91 percent) or with congestive heart failure (77 percent), and almost all have underlying valvular heart disease (97 percent). Diagnosis is difficult and usually based on serology or identification of the organism in cardiac tissue.[183]

One report indicates that *Bartonella* may cause up to 3 percent of cases of IE[189]; in the past, most of these cases were listed as culture-negative, while some were misdiagnosed as chlamydial due to false-positive cross-reacting serologic tests.[189] When suspected on clinical and epidemiological grounds (homeless patient: *Bartonella quintana;* close association with cats: *Bartonella henselae*), PCR (polymerase chain reaction)-based genomic detection or antibody determination are considerably more sensitive than culture in identification of the organism.[190] Chlamydial endocarditis is rare; a few cases have been reported in bird fanciers.[191,192] In such cases, the etiologic diagnosis can be established only by specialized culture techniques, serologic studies, or examination of vegetations using immunofluorescent antibodies. More than 50 cases of *Listeria monocytogenes* endocarditis in both native and prosthetic valves have been reported with a high mortality rate (37 percent).[193] Many other unusual species occasionally infect prosthetic valves, including *Mycoplasma hominis*,[194] *Legionella* species,[53] and mycobacteria.[195] Some examples of rare or unusual organisms that have caused one or more cases of endocarditis are listed in Table 73-4.

Table 73-4: Some Unusual or Rare Causes of Infective Endocarditis

Bacteria	Fungi
❍ *Bacillus cereus* ❍ *Bartonella elizabethae* ❍ *Bartonella henselae* ❍ *Corynebacterium diphtheriae* biotype *gravis* ❍ *Corynebacterium jeikeium* ❍ *Corynebacterium pseudodiphtheriticum* ❍ *Erysipelothrix rhusiopathiae* ❍ *Haemophilus influenzae* type b ❍ *Lactobacillus* species ❍ *Legionella* species ❍ *Mycoplasma hominis* ❍ *Rothia dentocariosa* ❍ *Streptobacillus moniliformis*	❍ *Blastoschizomyces capitatus* ❍ *Conidiobolus* sp. ❍ *Curvularia lunata* ❍ *Engyodontium album* ❍ *Fusarium oxysporum* ❍ *Histoplasma capsulatum* ❍ *Neosartorya fischeri* ❍ *Phialophora richardsiae* ❍ *Pseudallescheria boydii* ❍ *Scedosporium inflatum* ❍ *Scedosporium apio-spermum* ❍ *Thermomyces lanuginosus tsiklinsky* ❍ *Trichosporon beigelii*

Culture-Negative Endocarditis

The term, *culture-negative endocarditis*, refers to the active IE whose repeated blood cultures are

all negative.[196-198] This syndrome was occasionally observed in the preantibiotic era,[199] usually in subacute cases of long duration (*Endocarditis lenta*). Today, most (but not all) culture-negative cases are caused by antibiotic treatment that is sufficient to suppress the bacteremia but not to sterilize the vegetation. In most such cases, organisms will eventually reappear in the blood after antibiotics are discontinued, usually within a few days. The blood cultures from a few patients with active endocarditis remain persistently culture-negative after antibiotics are stopped.[116]

Negative blood culture results should be expected from about one-fifth of patients with NVE or PVE caused by *Candida* or other yeasts,[101] and from four-fifths of patients with endocarditis caused by *Aspergillus* or other molds.[101,180,200,201]

The reported incidence of culture-negative endocarditis varies widely. Among large unselected series of cases collected from several hospitals, as much as 15 to 20 percent may be culture-negative.[51,196-198] Smaller series of patients studied by a single clinical and laboratory team that is experienced in evaluation of endocarditis usually show only about 5 percent culture-negative cases.[202,203] Thus, in a patient with suspected IE, other diagnoses should be meticulously excluded before a diagnosis of culture-negative endocarditis is accepted. When a patient appears to have IE but blood cultures are negative, the following checklist of possibilities should be considered:

- The patient has received some antibiotic therapy, commonly an oral drug such as ampicillin that was taken at home.
- The etiologic organism is slow-growing, requiring longer incubation of the blood culture for isolation, e.g., some nutritionally variant streptococci, some HACEK species, or mycobacteria.
- The etiologic organism is nutritionally fastidious, requiring special procedures or supplemented media for isolation, e.g., nutritionally variant streptococci, *C. burnetii* (Q fever), *Chlamydia*, *Mycoplasma*, *Bartonella*, and *Legionella*.
- The etiologic organism is a strict anaerobe, requiring anaerobic culture conditions.
- The etiologic organism is *Aspergillus* or another mold; these are rarely recovered from blood during the course of endocarditis (although they may be recovered from an arterial embolus removed at surgery).
- The etiologic organism is nonculturable, which is usually diagnosed by PCR on cardiac tissue during surgery for valve insufficiency. Few clinical cases are present as these patients may not have gastrointestinal symptoms, although most will have arthralgias.
- The patient has an alternative diagnosis that simulates IE-e.g., rheumatic fever, tuberculosis, brucellosis, etc.
- The patient has NBTE or marantic endocarditis, associated with a major underlying disease such as malignancy or tuberculosis.
- The patient has Libman-Sacks endocarditis (a variant of NBTE), associated with antiphospholipid antibody syndrome and/or systemic lupus erythematosus.

In some cases, a working diagnosis of endocarditis based on clinical manifestations can be supported by the progress of the disease and good response to empiric antibiotic treatment. If blood culture results always remain negative, a definitive etiologic diagnosis can be made only by detecting organisms in an infected embolus or in vegetations excised during surgery or at autopsy.

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Chapter 73: INFECTIVE ENDOCARDITIS

PATHOGENESIS AND PATHOLOGY

A general concept of the pathogenesis of NBTE and SBE is presented in Fig. 73-2.

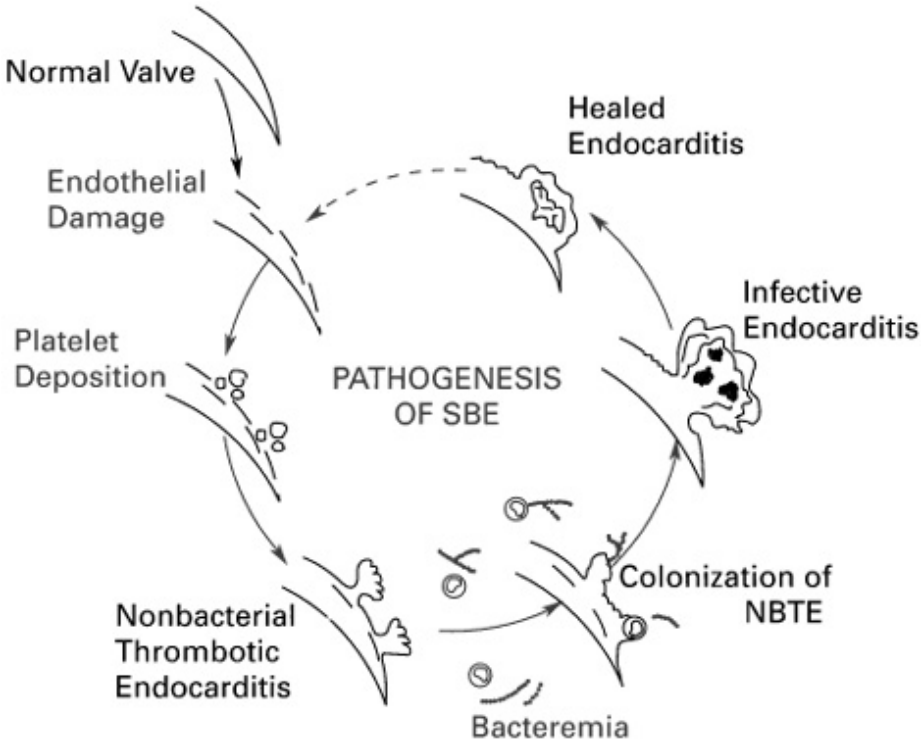

Figure 73-2: The main events in the pathogenesis of nonbacterial thrombotic endocarditis (NBTE) and subacute bacterial endocarditis (SBE).

Noninfective Endocarditis

Sterile thrombotic lesions may develop on heart valves in a variety of clinical conditions.[204] Small aggregates of platelets can occasionally be found on normal valves, but they occur frequently on the surfaces of valves damaged by congenital, rheumatic, or granlomatous disease[205] or by IE. These could be considered as incipient vegetations or microvegetations.

The common factor leading to platelet deposition is endothelial damage. This exposes subendothelial connective tissue containing collagen, which activates platelets to adhere and aggregate at the site. These microscopic platelet thrombi may embolize away harmlessly, or they may be stabilized and grow by deposition of fibrin and more platelets to form vegetations of NBTE. This process can be duplicated experimentally by catheter-induced endothelial damage in animals.[206] In humans, intracardiac pressure-monitoring catheters may produce identical lesions.[119,120] Both experimental[207] and human[119,122,204] NBTE can be colonized by circulating bacteria, resulting in IE.

The vegetations of marantic endocarditis occur most often in patients with advanced malignancy[13-15] but may also complicate other chronic wasting diseases, such as tuberculosis or uremia.

Sterile vegetations (termed *Libman-Sacks endocarditis*-see Chap. 76) sometimes develop in patients with systemic lupus erythematosus and/or antiphospholipid antibodies.[208] Typically, Libman-Sacks vegetations are small, sessile masses located on the ventricular surfaces of the mitral valve leaflets.

The vegetations of NBTE are friable white or tan masses, usually situated along the lines of valve closure (Fig. 73-3, Plate 101). These vary greatly in size; from tiny to large and exuberant, with a corresponding tendency to embolize to arteries supplying the myocardium, spleen, kidney, brain, mesentery, or extremities and causing infection. Since there is little inflammatory reaction at the site of attachment, fresh vegetations can dislodge and embolize frequently.[204] Histologically, the vegetations of NBTE consist of degenerating platelets interwoven with strands of fibrin, forming a bland, eosinophilic mass, featureless except for a few trapped leukocytes.[204,206]

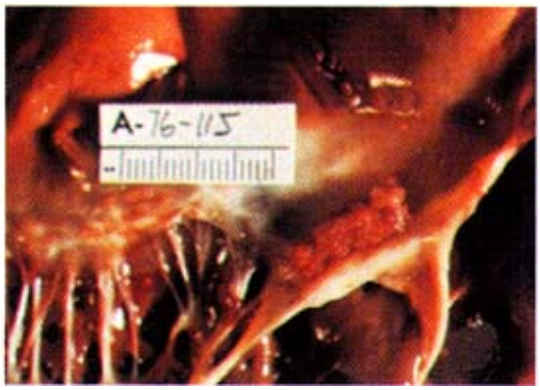

Figure 73-3: (Plate 101) Typical vegetation of nonbacterial thrombotic endocarditis found at necropsy in a cachectic patient who died with disseminated lung cancer.

Pathogenesis of Infective Endocarditis

For IE to develop, two events are essential. First, microbes must attach to an endocardial surface. Second, the microbes must persist and multiply locally, eluding host defense mechanisms. In the case of SBE, which usually develops on previously abnormal valves, bacteria circulating in the bloodstream probably colonize preexisting platelet aggregates or NBTE.[204] It is not known whether ABE, which often affects apparently normal valves, develops in a like manner by colonization of microscopic sterile vegetations, or by direct microbial invasion of normal endothelium.

A critical initial step in the pathogenesis of IE is the attachment or adherence of the circulating microorganism to the disrupted cardiac valve endothelium that has deposits of fibrin and platelets (NBTE). The characteristic that gives the microbe selective adherence advantage to this surface are virulence factors for the development of IE. Early studies identified dextran production in viridans streptococci as an important adherence factor (it had been previously shown to be important in adherence to teeth and production of dental caries).[172] A host of other microbial factors have been described. These include a fibrinectin-binding protein,[377] enterococcal aggregation substance, and enterococcal binding substances (proteins that also mediate formation of mating aggregate between bacteria that cause horizontal transfer of plasmids encoding such things as antibiotic resistance[210] and FimA, a surface-associated protein found on oral streptoccoci and enterococci, that, when used as an antigen (similar to other surface proteins of the Lral family) produce an antibody that reduces adherence to valve surfaces and reduces development of endocarditis in animal model.[209-212] Since FimA is found in 80 percent of streptococci and enterococci strains that produce endocarditis, a protective vaccine strategy is an intriguing probability. Binding to fibronectin appears to be an important property shared by many but not all of the bacterial species that commonly cause endocarditis.[50,209] Clumping factor produced by coagulase-positive staphylococci favors attachment to fibrinogen, adherence to platelet-fibrin clots, and ability to cause endocarditis in rats.[213] Extracellular slime production by coagulase-negative staphylococci may favor localization on prosthetic valves.[214] *Thus, microbial adherence, which can be mediated by a variety of different surface components*

and receptors, is a key virulance factor for colonization of the endocardium.[50,209]

The role of the platelet in this postadherance event has been elucidated. First, adherence of *Staph. aureus* to platelets is an important virulance factor for development of experimental IE.[219-225] In addition, acetylsallicylic acid treatment reduces *Staph. aureus*-induced platelet aggregation and adherence to fibrin (with or without platelets) matrices in vitro and reduced vegetation size and embolic events in vivo.[224,225] When *Staph. aureus* (or enterococci) adhere to damaged valves in vivo, tissue thromboplastin is generated, which locally activates the clotting cascade, generating thrombin.[205,220] A vegetation is formed that provides a protected environment for unrestricted bacterial growth. However, thrombin also elicits the secretion from platelets of a low-molecular-weight cationic protein with potent antimicrobial properties (against *Staph. aureus, Staph. epidermidis,* viridans streptococci and *Candida*) termed *thrombin-induced platelet microbiocidal protein* (tPMP).[221] Strains of *Staph. aureus* that are resistant to tPMP are more likely to cause endocarditis in animals and humans.[222] In addition, strains that hypersecrete alpha toxin (a toxin known to lyse platelets and release tPMP) produced a less virulent form of IE, likely due to the antimicrobial action of tPMP.[223]

Therefore, once lodged on NBTE, bacteria must elude local defenses, including platelet microbicidal proteins[215] and leukocytes, if they are to survive. Microbes that cannot do this may die out quickly after adhering to the endocardium.[216] Those that can survive antimicrobial defense mechanisms multiply rapidly in the vegetation, soon reaching high numbers and then entering a stationary growth phase.[207] The vegetation provides an ideal supporting stroma for the growth of microbial colonies, into which essential nutrients can diffuse from the blood. The presence of bacteria is a powerful stimulus for further thrombosis,[217,218] which may be mediated by thromboplastin generated by leukocytes when they are exposed to fibrin.[218] New layers of fibrin are deposited around growing bacteria, causing the vegetations to enlarge.[206] Inflammatory cytokines are produced by monocytes[226] (and presumably other leukocytes) in response to endocardial infection and likely cause some of the patient's symptoms.

The location of vegetations is relevant to understanding and managing endocarditis. Approximate incidence of vegetations at various locations is given in Table 73-5. The frequency of involvement of each valve is directly proportional to the mean blood pressure upon it;[227] thus, the left side of the heart is involved much more often than the right. This rule does not hold true for acute endocarditis in IDUs, in whom tricuspid infection by *Staph. aureus* predominates (Table 73-5).

Table 73-5: Approximate Frequency of Anatomic Location of Vegetations in SBE, ABE, and Endocarditis Associated with IV Drug Abuse[a]

Location	SBE, %	ABE, %	Endocarditis in IV Drug Abusers, %
Left-sided valves	85	65	40
Aortic	15-26	18-25	15-20
Mitral	38-45	30-35	15-20
Aortic and mitral	23-30	15-20	13-20
Right-sided valves	5	20	50-70
Tricuspid	1-5	15	45-65
Pulmonary	1	Rare	2
Tricuspid and pulmonary	Rare	Rare	3

Left- and right-sided sites	Rare	5-10	5-10
Other sites (patent ductus, ventricular septal defect, coarctation, jet lesions)	10	5	5

[a]SBE = subacute bacterial endocarditis; ABE = acute bacterial endocarditis.
SOURCE: Adapted from Refs. [51,65-70,86,116,159,227,230].

Vegetations are usually located on the downstream side of anatomic abnormalities in the heart or great vessels. Rodbard[228] developed the unifying concept that vegetations usually arise at a site where blood flows from a high-pressure source (e.g., the left ventricle) through a narrow orifice (e.g., a stenotic aortic valve) into a low-pressure sink (e.g., the aorta). Illustrative examples from human disease include aortic stenosis, ventricular septal defect, coarctation, and mitral regurgitation. Experimentally, Rodbard showed that bacteria carried in an aerosol flowing through a constricted tube into an area of low pressure were deposited on the walls of the tube immediately beyond the constriction due to Venturi pressure effects and turbulence.[228] These observations fit well with the actual location of vegetations found at autopsy in cases of endocarditis (Fig. 73-4). Vegetations also may develop on jet lesions, which are areas of endothelial roughening and reactive fibrosis at sites where a swift, turbulent regurgitant stream of blood strikes the endothelium.[229] *MacCallum's patch,* on the wall of the left atrium in some patients with mitral regurgitation, is an example of a jet lesion; an infected vegetation occasionally develops at this site (Fig. 73-4).

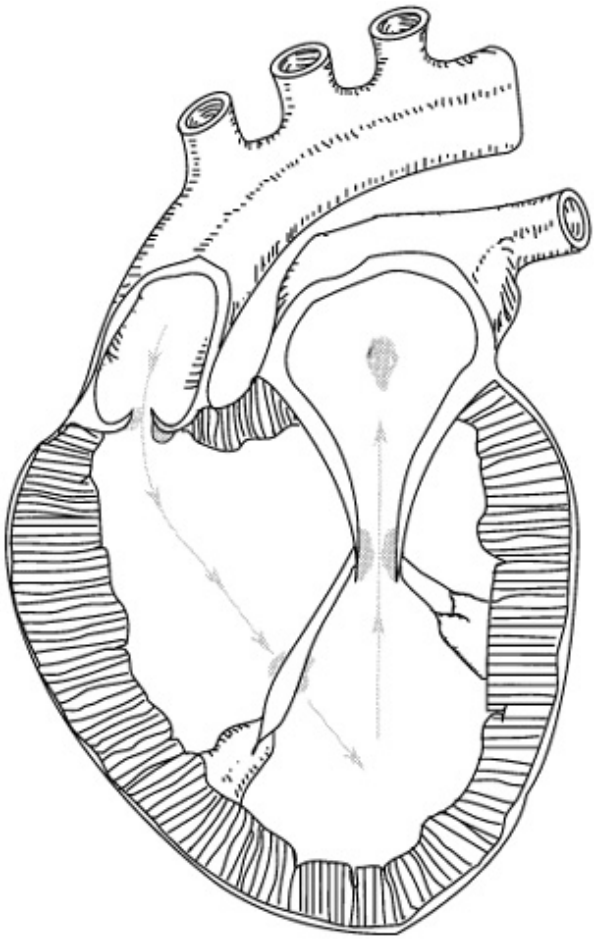

Figure 73-4: The sites where endocarditis occurs in aortic and mitral regurgitation. The arrows on the left

indicate a high-velocity regurgitant stream passing through the orifice of an incompetent aortic valve into a low-pressure sink (left ventricle in diastole). Vegetations appear on the ventricular surface of the aortic valve. The regurgitant stream may cause a jet lesion on the chordae tendineae of the anterior leaflet of the mitral valve. The arrow on the right shows regurgitation from the high-pressure source of the left ventricle during systole into the left atrium, with vegetations developing on the atrial surface of the mitral valve. Vegetations also can occur on the jet lesion where the regurgitant stream through the mitral valve strikes the atrial endocardium, an area known as *MacCallum's patch*. (From Rodbard S. Blood velocity and endocarditis. *Circulation* 1963; 27:8. Reproduced with permission.)

Vegetations of infective endocarditis vary greatly in size and morphology, from small (<1 mm), warty nodules to large (several centimeters), cauliflower-like polypoid masses. That may cause functional stenosis of valve orifices (Fig. 73-5, Plate 102). Fungal vegetations are often larger than bacterial ones, but otherwise the etiologic species does not correlate reliably with vegetation size. Their color also varies widely, from white to tan to greenish-gray.[67,230] Histologically, colonies of microorganisms are found embedded in a fibrin-platelet matrix.[206,207,231,232] The vegetation characteristically contain relatively few leukocytes that are prevented from reaching bacteria by layers of fibrin, which form protective barriers around colonies (Fig. 73-6).

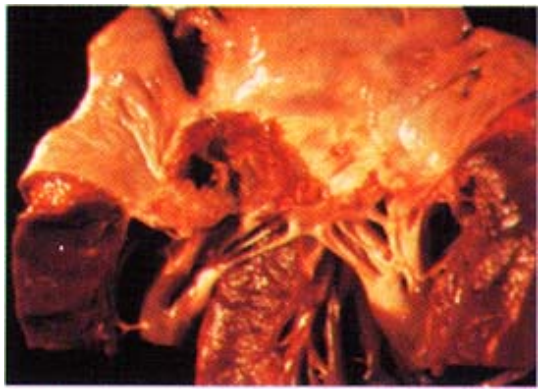

Figure 73-5: (Plate 102) Typical vegetation of bacterial endocarditis, complicated by perforation of the anterior mitral valve leaflet. Note that the valve shows preexisting chronic rheumatic disease, with thickening, deformity, and fusion of chordae tendineae.

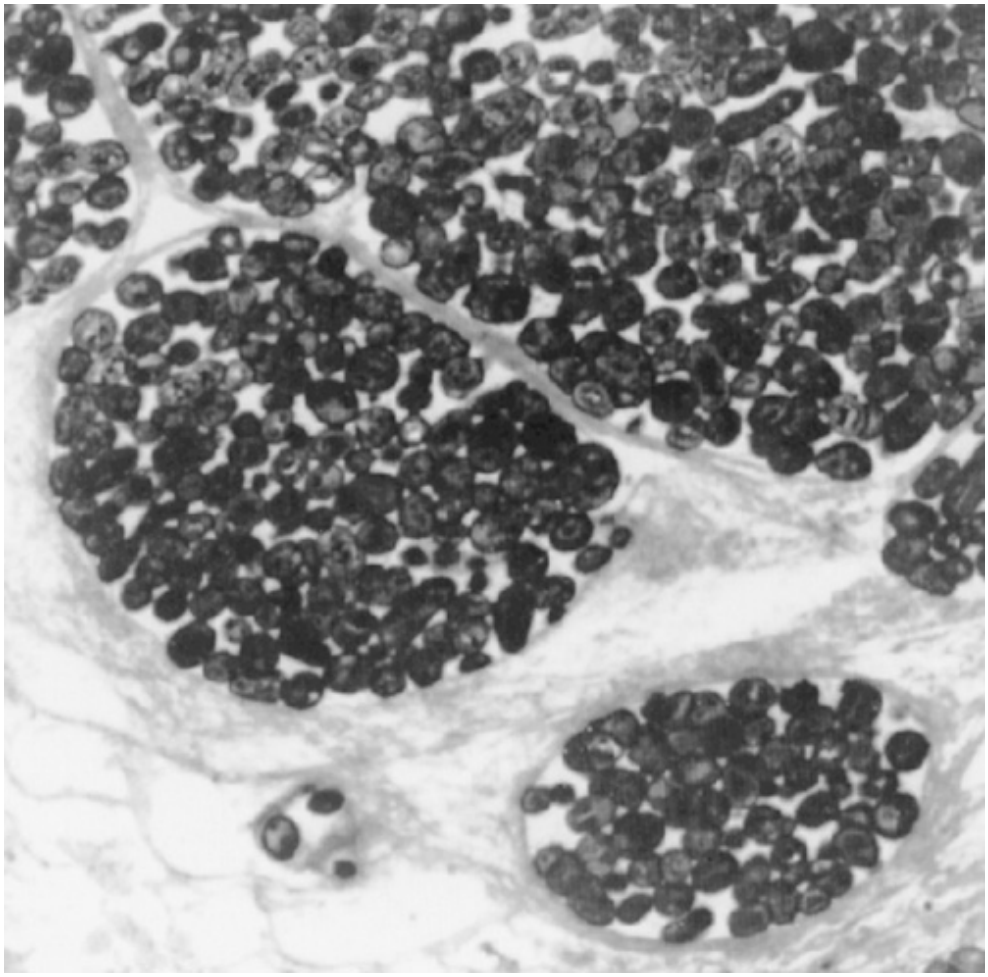

Figure 73-6: Electron micrograph of a vegetation of experimental streptococcal endocarditis (×7800). Note the very large number of cocci in colonies, the protective layers of fibrin, and the absence of leukocytes-all factors that may impede the efficacy of antimicrobial therapy. (From Durack DT. Experimental bacterial endocarditis: 4. Structure and evolution of very early lesions. *J Pathol* 1975; 115:81. Reproduced with permission.)

Development of an abscess is one of the most important complications of valvular infection, and it occurs more frequently with ABE than it does with SBE.[229,231] Abscesses often develop by direct extension of active infection into the fibrous cardiac skeleton-that is, into the rings of supporting connective tissue around the valves. From there, abscesses can extend into the adjacent myocardium and rupture into the pericardium. Hematogenous seeding occasionally leads to development of abscesses elsewhere in the myocardium.

Abscesses are found in the majority of patients who die with active prosthetic valve infection, often spreading around the sewing ring of the prosthesis and causing partial dehiscence of the prosthetic valve.[11,95] Because these valve-ring abscesses are located close to the cardiac conduction system, conduction disturbances commonly result.[233]

Immune Response

Presence of bacteria in endocardial vegetations stimulates the humoral immune system to produce nonspecific antibodies. This can result in a polyclonal increase in gamma globulins, positive rheumatoid factor, and, occasionally, false-positive serologic test results for syphilis.[234] Rheumatoid factor develops in 25 to 50 percent of patients with SBE present for >6 weeks and can provide a useful diagnostic clue; it reverts to negative after eradication of the organisms.[235-237] Antiendocardial and antisarcolemmal antibodies have been detected in 60 to 100 percent of cases;[238] they are more commonly found in SBE than they are in ABE.

Specific antibodies to many of the commensal organisms that cause SBE may be present in low titer before infection. Titers rise during active infection[3] and fall after treatment.

Hemolytic complement levels are low in about 30 percent of patients early in the course of endocarditis, rising later and returning to normal after treatment.[239-245] The lowest levels are found in patients with immune-complex glomerulonephritis.

Circulating immune complexes have been detected in 82 to 97 percent of patients with either ABE or SBE.[244-247] Higher concentrations are correlated with the presence of extracardiac manifestations such as arthritis, splenomegaly, and glomerulonephritis; with longer duration of illness; and with hypocomplementemia. Several studies confirm that glomerulonephritis in patients with endocarditis is mediated by immune complexes.[248,249] It is likely but unproven that arthritis and tenosynovitis-and possibly pericarditis, Osler's nodes, and Roth's spots[244,246,247]-also may represent inflammatory responses involving immune complexes. Antibodies to teichoic acids were found in the serum of 93 percent of patients with *Staph. aureus* endocarditis,[250] but this did not prove to be useful as a routine diagnostic test. Additional relevant information on experimental infective endocarditis is contained in References [251 to 254.]

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Chapter 73: INFECTIVE ENDOCARDITIS

CLINICAL MANIFESTATIONS

Clinical and laboratory manifestations of infective endocarditis can be grouped under three headings (Table 73-6):

- Evidence of a systemic infection
- Evidence of an intravascular lesion
- Evidence of an immunologic reaction to infection

History

The symptoms of subacute endocarditis develop insidiously and with great variability.[3,43,51,116] Fevers, chills, rigors, and night sweats provide evidence of systemic infection. General malaise-with anorexia, fatigue, and weakness-is typical. Weight loss is common, along with headaches and musculoskeletal complaints, including myalgias, arthralgias, and back pains.[255] This symptom complex is often described by the patient or the physician as a "flu-like illness." Evidence of an intravascular lesion is provided by symptoms of left- or right-sided heart failure and by manifestations of embolization, such as focal neurologic injury, chest pain, flank pain, left-upper-quadrant pain, hematuria, or ischemia of an extremity. Symptoms usually persist and worsen intermittently over 4 to 8 weeks before the diagnosis is made.[256,257]

In the acute form of IE, the course is accelerated, and the symptoms are often accentuated in severity. Patients experience hectic fevers, rigors, and prostration, usually leading to hospital admission within a few days.[5,51,103,251,258]

Symptoms of cardiac failure may develop gradually or worsen suddenly in either acute or subacute disease due to mechanical complications such as perforation of a valve leaflet, rupture of one of the chordae tendineae, rupture of a sinus of Valsalva, or development of functional stenosis from obstruction of blood flow by large vegetations.[231,259] Alternatively, heart failure may develop insidiously, or preexisting chronic heart failure may worsen due to progressive damage to the valves or associated structures. Myocarditis or myocardial infarction due to coronary artery embolism may contribute to heart failure.

Physical Examination

The physical exam in IE is a diagnosticians delight since the variety of unique physical findings often allows one to make the diagnosis at the bedside.

Patients with endocarditis may appear acutely or chronically ill. Intermittent chills, rigors, and sweating often provide evidence of a systemic infection. Asthenia and recent weight loss are often notable. Anemia is common,[85] especially in SBE, so many patients are pale. The skin of some patients with long-standing SBE shows the sallow hue of uremia.[3]

VASCULAR PHENOMENA

Patients with endocarditis may exhibit a variety of striking physical findings arising from vascular

abnormalities.

Petechiae

In both SBE and ABE, petechiae are common; they are rare in NBTE. In a few cases, the petechiae have a pale central spot. Most are due to microembolization to small vessels in the skin or mucous membranes. They are commonly found in crops in the conjunctual sac, on the hard palate, behind the ears and over the chest. But all areas of the trunk and extremities may be affected.

Splinter Hemorrhages

Linear subungual hemorrhages, resembling tiny splinters of wood under the nails but not reaching the nail margin, are found in about 20 percent of patients with SBE. They are probably caused by microembolization to linear capillaries under the nail. Because splinter hemorrhages are found in some 5 to 8 percent of patients admitted to the hospital who do not have endocarditis, they are of limited diagnostic value when occuring alone.[260]

Osler's Nodes

These are painful, tender, erythematous nodules in the skin of the extremities, usually in the pulp of the fingers[261] (Fig. 10-17, Plate 34; Fig. 10-18). Occasionally, the center of these pea-sized, red lesions is pale, but necrosis does not occur. Osler's nodes occur in 10 to 20 percent of patients with SBE and in fewer than 10 percent of patients with ABE.[261] They are probably caused by inflammation around the site of lodgment of small, infected emboli in distal arterioles, because the etiologic organism can be recovered from some of the lesions.[262] Inflammation due to focal immunologic reactions probably contributes to formation of Osler's nodes, especially in subacute cases.[247]

Janeway Lesions

Janeway lesions are small (less than 5 mm), flat, nontender red spots, irregular in outline, found on the palms and soles of a few patients with SBE and ABE. Unlike petechiae, they are not hemorrhagic, and they blanch on pressure.[3,44]

Ocular Lesions

Conjunctival petechiae show up as small, bright-red hemorrhages that are easily seen if the upper and lower eyelids are everted. These petechiae are not specific for endocarditis, being found sometimes after cardiac surgery and occasionally in septicemia (Fig. 73-7, Plate 103). Nevertheless, the discovery of conjunctival hemorrhages in a patient with unexplained fever and a heart murmur makes the diagnosis of endocarditis highly likely.

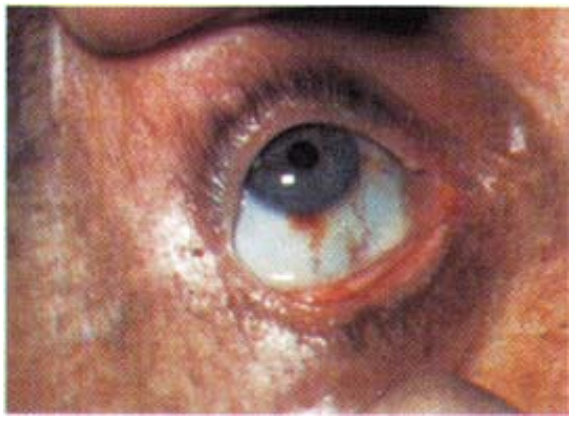

Figure 73-7: (Plate 103) Typical conjunctival petechiae in a patient with subacute bacterial endocarditis due to *Streptococcus sanguis*.

Retinal hemorrhages are found in 10 to 25 percent of cases of both SBE and ABE. They are quite variable in appearance. Some simply represent petechiae in the retina; their round or flame-shaped outline is determined by the layer of the retina in which they develop. Those with a white or yellow center surrounded by a bright-red, irregular halo are known as *Roth's spots*, which probably represent cytoid bodies and associated hemorrhage caused by microinfarction of retinal vessels. Roth's spot are not foci of bacterial infection and are nonspecific to IE.

Loss of vision during the course of endocarditis can occur from embolization to the brain or to the retinal artery, from optic neuritis, or from ophthalmitis. Endophthalmitis may occur in patients with *Candida* endocarditis and/or candidemia. The typical retinal lesions are rounded, white, cotton-like exudates with extension into the vitreous and overlying vitreous haze.[263] Panophthalmitis occurs in some patients with ABE due to hematogenous spread of virulent pathogens.

CLUBBING OF THE FINGERS

Previously common in SBE, finger clubbing is now found in less than 5 percent of cases (Fig. 10-16, Plate 33), presumably because endocarditis is now diagnosed and treated earlier. The pathogenesis of this reaction, which usually resolves after eradication of the infecting organism, is not understood.

SIGNS OF EMBOLIZATION

Decreased or absent arterial pulses in an extremity may signal occlusion of a large artery by a fragment of vegetation. Focal neurologic signs may develop transiently or progress to a completed stroke due to embolization to a cerebral artery (see "Complications," later). Infarctions of the spleen, kidney, or bowel can present with pain and tenderness on palpation of the abdomen, mimicking an acute abdominal event such as bowel obstruction or peritonitis. Myocardial infarction due to obstruction of a coronary artery can cause heart failure or death and is sometimes an unexpected finding at autopsy in patients who die with active disease. These complications are illustrated in Figs. 73-8 to 73-13, Plates 104-109.

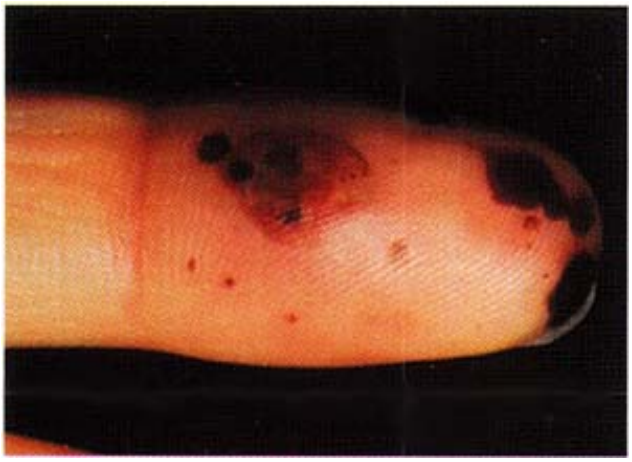

Figure 73-8: (Plate 104) Ischemic, hemorrhagic, and pustular lesions on the extremities in acute *Staphylococcus aureus* endocarditis.

SPLENOMEGALY

Development of splenomegaly is common, occurring in about one-quarter of patients with ABE and one-half of those with SBE. The spleen is usually soft and only slightly tender except in the case of recent embolic infarction, when palpation may be very painful. Radionuclide scanning may reveal infarction or a splenic abscess.

CARDIAC EXAMINATION

The pulse is often rapid as a result of fever or congestive failure. Irregularities of conduction may indicate the presence of an abscess near the conducting system. Underlying or newly developed aortic regurgitation associated with IE may result in a collapsing pulse (Chaps. 10 and 56).

One or more murmurs are present in virtually all patients at some stage of the disease. Even though some of the classic findings of IE are less often seen today than they are formerly, the triad of fever, anemia, and a new murmur should still suggest this disease, provided one remembers that these manifestations are nonspecific. They may be absent initially. *Up to 15 percent of patients do not have a murmur when first seen.*

Only one-third of patients with tricuspid valve endocarditis will demonstrate the typical regurgitant systolic murmur located along the right sternal border that increases with inspiration.[5] Development of a new regurgitation murmur in patients with a prosthetic valve should immediately prompt the suspicion of PVE.

Murmurs present during the course of endocarditis may be due to preexisting cardiac disease, to the infection itself, or to both. Active endocarditis often causes structural damage to the valve, including deformities, tears, perforations, and rupture of chordae tendineae. Since these changes often lead to valvular insufficiency, the murmurs most often heard in association with endocarditis are those of mitral, aortic, or tricuspid regurgitation. IE occurs in association with pure mitral stenosis much less often than it does with mitral regurgitation (with or without associated stenosis) (see Chap. 57). Development of a new aortic regurgitation murmur during a febrile illness strongly suggests the diagnosis of endocarditis, because this finding is seldom associated nonspecifically with increased blood flow due to fever and anemia.

New or changing cardiac murmurs are an important diagnostic finding and are more common in patients with ABE.

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COMPLICATIONS

Heart Failure

Heart failure is the most important complication of infective endocarditis,[51,264-266] because it exerts a critical influence on prognosis. In 1951, Cates and Christie[215] reported a death rate of 37 percent among 314 patients with SBE who had no heart failure and 85 percent death rate among 94 patients who had moderate or severe failure. In the past, congestive heart failure occurred in up to 55 percent of cases, being more common in patients with aortic valve disease (75 percent) than in those with mitral valve (50 percent) or tricuspid valve disease (19 percent).[265] Today, heart failure is less common because of earlier and more effective treatment and valve replacement surgery.

Sudden onset or worsening of left ventricular failure because of perforation or destruction of a valve leaflet or rupture of chordae tendineae is an indication for immediate valve replacement. Intractable left ventricular failure can result from rupture of a sinus of Valsalva due to infection. The right sinus of Valsalva may rupture into the right atrium or right ventricle and the left sinus into the pulmonary artery.[231] This rare condition should be suspected if the severity of heart failure seems out of proportion to the degree of valve dysfunction. Occasionally, bulky vegetations occlude the valve orifice, causing functional stenosis; this phenomenon is most likely to occur during fungal infection of prosthetic valves.[267,268]

Embolization

This important complication is recognized in 12 to 40 percent of patients during the course of SBE and in 40 to 60 percent of those with ABE, but autopsy findings indicate that many other arterial emboli go undetected. Pelletier and Petersdorf[116] reported a 50 percent incidence of major arterial emboli in 125 cases, affecting brain (25 cases), lung (17 cases), coronary artery (8 cases), spleen (8 cases), extremities (8 cases), gut (4 cases), and eye (3 cases). The presence of infection-related antiphospholipid antibodies has been found to be a major risk factor for embolic events.[269]

Conduction Abnormalities

A conduction abnormality is detected during the course of IE in 4 to 16 percent of patients, especially in association with aortic valve infection.[233,259,270] Types of abnormalities observed include first-degree atrioventricular block (45 percent), third-degree atrioventricular block (20 percent), second-degree atrioventricular block (15 percent), and isolated bundle branch blocks (15 percent).[233] *The development of a new, unstable, or changing conduction abnormality is important because it often indicates that a focus of myocardial inflammation has extended near or into the atrioventricular node or the bundle of His and can be associated with a valve-ring abscess. This is associated with a worse prognosis*[266] *and constitutes a strong indication for surgical intervention*. Immediate TEE should be performed in this situation.

Neurologic Manifestations

Involvement of the nervous system during the course of endocarditis is both common and

clinically important.[271-274] Significant neurologic abnormalities occur in 29 to 50 percent of patients with endocarditis.[271,274,275] The initial or presenting complaint involves the nervous system in 10 to 15 percent of patients with endocarditis. A wide range of syndromes occurs, including toxic confusional states, psychiatric symptoms, and minor or major strokes (Fig. 73-13, Plate 00), meningoencephalitis, and cranial or peripheral nerve lesions.[274] (See also Chap. 89.)

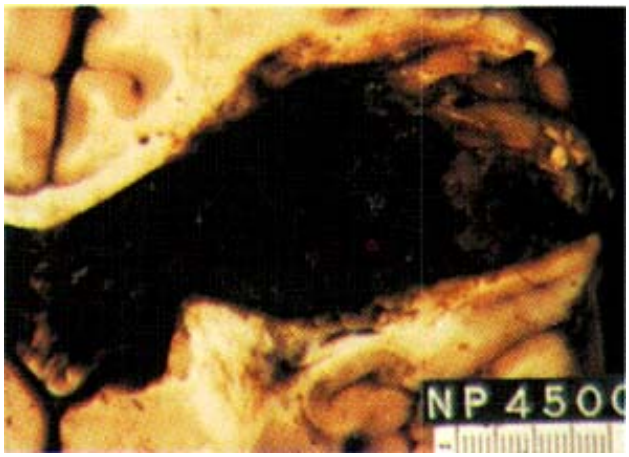

Figure 73-13: (Plate 109) Massive cerebral hemorrhage with intraventricular extension due to rupture of a small, peripheral mycotic aneurysm. The patient had been bacteriologically cured of *Staphylococcus epidermidis* endocarditis several weeks previously. Cultures of the blood, valve, and aneurysm taken at necropsy were negative.

Of 55 patients with cerebrovascular complications of endocarditis, four-fifths suffered infarction and one-fifth hemorrhage.[275] Infarction is usually due to embolism, most often to the middle cerebral arteries. In some series, neurologic complications approach or even surpass heart failure as the leading determinant of mortality.[274] Hemorrhage can be a complication of either emboli or mycotic aneurysms.[116,271-273,276,277]

A meningeal reaction cerebritis occurs in 7 to 15 percent of patients, especially those with staphylococcal ABE.[43,271,273-275] This reaction may be mistakenly diagnosed as acute bacterial meningitis because the cerebrospinal fluid contains polymorphonuclear leukocytes and may have a raised protein concentration. In a minority of such cases (up to 20 percent of those with acute staphylococcal infection) cerebrospinal fluid cultures yield the bacteria causing endocarditis. The glucose level, however, is usually normal; the results of cerebrospinal fluid culture are usually negative; and the abnormalities usually resolve without complications during treatment of the endocarditis. Thus, these cerebrospinal fluid abnormalities more often represent a perivascular cerebritis than true bacterial meningitis.

This cerebritis may develop in brain tissue surrounding small infected emboli lodged in cerebral vessels with associated meningoencephalitis.[274] Computed tomography and magnetic resonance imaging often reveal multiple areas of cerebritis, even in patients with no central nervous system symptoms (Fig. 73-14). In patients with ABE, this inflammatory reaction may progress to form a brain abscess, but more often cerebritis will resolve uneventfully during antibiotic treatment of the underlying disease. Brain abscesses are uncommon in patients with SBE.[274] Bacterial meningitis does occur in some patients with pneumococcal endocarditis.[153]

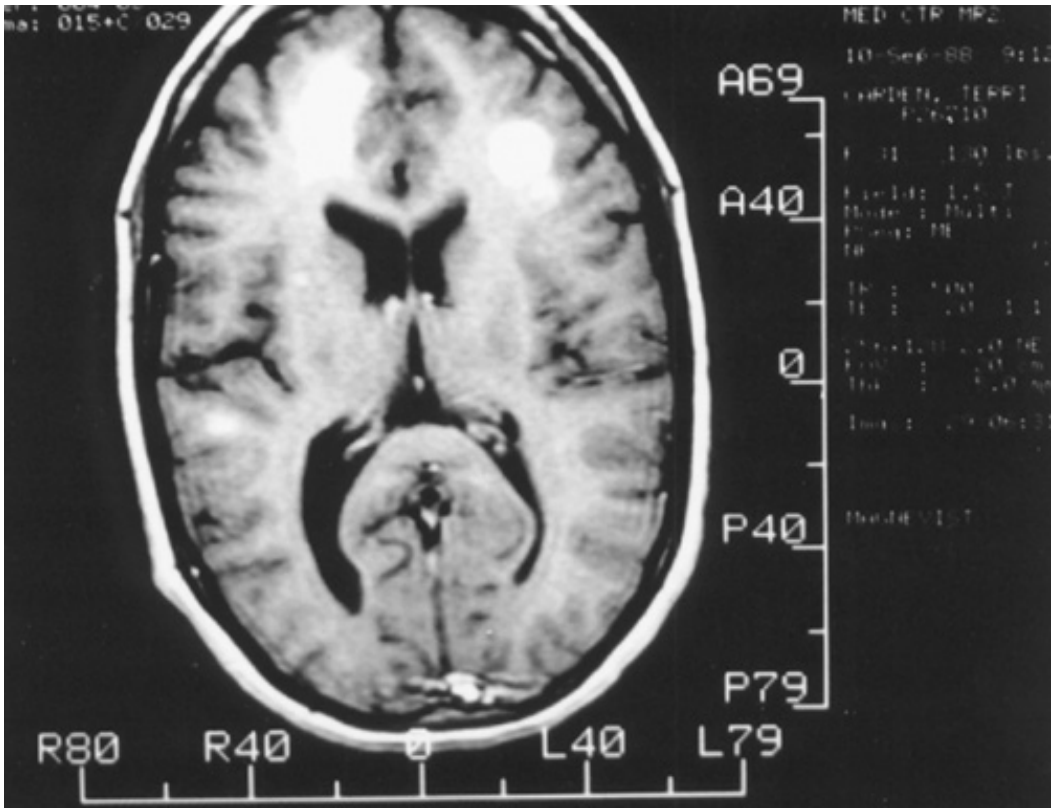

Figure 73-14: Magnetic resonance image of the brain in a patient with acute left-sided *Staphylococcus aureus* endocarditis, showing multiple areas of focal cerebritis. This patient had no focal central nervous system signs and recovered fully with antimicrobial therapy. (MRI by courtesy of the Department of Radiology, Duke University, Durham, NC.)

Mycotic Aneurysm

This complication develops in 3 to 15 percent of patients with IE, and the consequences of expansion and rupture of the aneurysm can be very serious, especially in the brain (Fig. 73-13, Plate 109). In order of frequency, the sites most often involved are the proximal aorta, including the sinuses of Valsalva (25 percent of cases), arteries to the viscera (24 percent), arteries to the extremities (22 percent), and arteries to the brain (15 percent).[276-278] Unfortunately, intracerebral aneurysms are often multiple.[277,278]

Mycotic aneurysms develop when the wall of an artery is damaged by the inflammatory response to microbes.[232,243,279,280] These microbes reach the arterial wall via microemboli to the vasa vasorum or by impaction of a larger infected embolus in the lumen. The arterial wall is apparently an unfavorable culture medium for bacteria because the organisms responsible for weakening the vessel often die out spontaneously, even if untreated. The mycotic aneurysm may continue to enlarge even when living organisms are no longer present, due to the physical effects of arterial blood pressure (Fig. 73-9, Plate 105).[276-278,281]

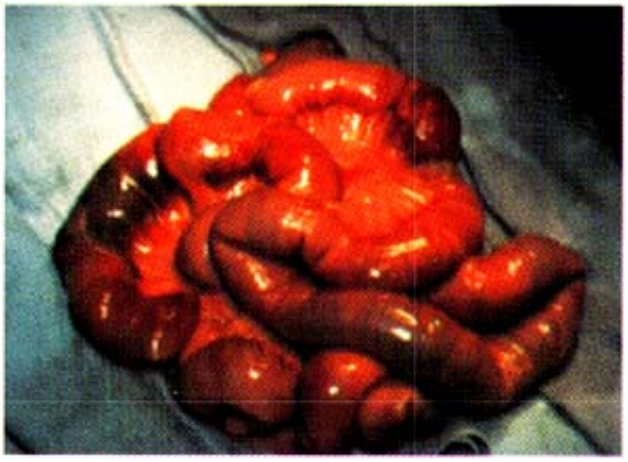

Figure 73-9: (Plate 105) Segmental ischemia and necrosis in the gut, presenting as acute abdomen.

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Chapter 73: INFECTIVE ENDOCARDITIS

DIFFERENTIAL DIAGNOSIS

Because the clinical manifestations of endocarditis are numerous and often nonspecific, the differential diagnosis of this disease is very wide.[3,43,116,282] Of the many conditions that may be considered, only a few leading examples are listed here.

ABE shares many clinical features with nonendocarditic septicemias due to invasive bacterial pathogens such as *Staph. aureus*, *Neisseria*, pneumococci, and gram-negative bacilli. The differential diagnosis for a case of ABE might include sepsis, pneumonia, meningitis, brain abscess, stroke, malaria, acute pericarditis, vasculitis, and disseminated intravascular coagulation.

SBE must be considered during the workup of every patient with fever of unknown origin.[202,282,283] Its manifestations can mimic those of rheumatic fever, osteomyelitis, tuberculosis, meningitis, intraabdominal infections, salmonellosis, brucellosis, glomerulonephritis, myocardial infarction, stroke, endocardial thrombi, atrial myxoma, connective tissue diseases; arthrites of unkown etiology, vasculitis, occult malignancies (especially lymphomas), chronic cardiac failure, pericarditis, and even psychoneurosis.

Diagnostic Criteria

IE can be surprisingly difficult to diagnose with certainty.[202,284] In the course of clinical practice, the diagnosis is suspected much more often than it is confirmed. This is because the presenting symptoms and signs can be highly variable and consistent with many other possible diagnoses. Furthermore, the primary lesion (an endocardial vegetation) is inaccessible to direct inspection except at surgery or autopsy. Major and minor criteria have been defined[202]; they are analogous to the modified Jones criteria[285] (Chap. 55) for diagnosis of acute rheumatic fever[86,202,203] (Tables 73-7 and 73-8). Several diagnostic schemes have been developed to assist the clinician in working through a diagnostic workup, however, it is important to emphasize that while these may be useful guidelines, each patient must be considered on an individual basis. The so-called Duke criteria has received the most attention.[202]

Table 73-7: Criteria for Diagnosis of Infective Endocarditis

Definite Infective Endocarditis
PATHOLOGIC CRITERIA
Microorganisms: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess, *or*
Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
CLINICAL CRITERIA, USING SPECIFIC DEFINITIONS LISTED IN TABLE 73-8
Two major criteria, *or*
One major and three minor criteria, *or*
Five minor criteria
Possible Infective Endocarditis

Findings consistent with infective endocarditis that fall short of 'definite,' but not 'rejected'
Rejected
Firm alternate diagnosis for manifestations of endocarditis,
0x002003 *or*
Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, *or*
No pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy for 4 days or less

SOURCE: From Durack et al.,[202] with permission.

Because the Duke criteria emphasize specificity[203,286] above sensitivity, they should not be used to guide urgent management decisions early in the course of a suspected case. To illustrate: a diagnosis of endocarditis made solely on the basis of presence of fever and a heart murmur would be very sensitive but very nonspecific. These findings alone might make a clinician suspect the diagnosis or begin treatment for endocarditis, but the various diagnostic schemes might guide the clinician to make a final diagnosis, to decide on valve replacement, or to accept the diagnosis for the purpose of epidemiologic studies or clinical trials.

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Chapter 73: INFECTIVE ENDOCARDITIS

LABORATORY INVESTIGATIONS

Routine Laboratory Tests

Anemia usually develops during the course of SBE.[85,287] It is most often mild or moderate in degree and of the hypoproliferative type, with a normochromic, normocytic smear. Anemia occurs less often in ABE and may be due to hemolysis. Chronic low-grade hemolysis associated with a prosthetic valve may confuse interpretation of the blood picture in a patient with PVE. In addition, blood smear may show schistocytes and other red blood cell fragments. Leukocytosis is not a reliable manifestation of SBE.[85] A low-grade, variable elevation of the polymorphonuclear leukocyte count is characteristic, but in some cases the leukocyte count is normal. A high granulocyte count with an increase in band forms is commonly found in patients with ABE. These neutrophils often show toxic granulations. In a few cases of ABE, staphylococci can be identified inside neutrophils on examination of a gram-stained smear of the buffy coat of the peripheral blood.[288] In addition, abnormal histiocytes may be found in smears of peripheral blood in one-third of patients with SBE,[289] but these tests are not in routine use.

The erythrocyte sedimentation rate (ESR) is elevated in about 90 percent of cases of IE. The median ESR on admission is about 65 mm/h, but the range is wide and 10 percent are in the normal range. The median ESR may rise slightly during treatment and does not fall to normal until 3 to 6 months after diagnosis, so it is not useful as evidence of successful antibiotic therapy. The C-reactive protein is usually elevated (96 percent) and falls to normal more quickly than the ESR during successful treatment.[290] Cryoglobulins have also been reported.[291]

Urinalysis shows microscopic hematuria and/or slight proteinuria in >50 percent of cases, even in the absence of specific renal complications.[3,287] Red blood cell casts and heavy proteinuria are found in those patients who develop immune-complex glomerulonephritis, often in association with decreased total serum complement.[248] Gross hematuria suggests that renal infarction has occurred.

Serologic Tests

Nonspecific serologic abnormalities are common during the course of IE. A positive rheumatoid factor is found in >50 percent of cases of SBE,[235-237] with symptoms for longer than 6 weeks.[202] Rheumatoid factor is rarely positive in patients with ABE. A polyclonal increase in gammaglobulins is characteristic of active endocarditis. Occasional false-positive serologic test results for syphilis occur.[234]

Specific serologic tests are important for the diagnosis of IE caused by *Coxiella* (Q fever) and *Bartonella*, both species that are difficult or slow to grow from culture. In these special cases, positive serology (1:800 antiphase 1 IgG antibody titer for Q fever or positive microimmunofluorescence or PCR test for *Bartonella*) or a single positive blood culture may be added as major criteria for diagnosis of IE.[189,292]

Blood Cultures

Isolation of a typical organism or detection of persistent bacteremia constitutes the most important diagnostic test for endocarditis. Blood cultures should be drawn from all patients with undiagnosed fever and a heart murmur. Cultures should also be taken from patients with other symptoms or signs consistent with endocarditis if no other diagnosis has been made.

Bacteremia in SBE is usually continuous.[22] The number of organisms in venous blood varies widely but is usually between 1 and 200 bacteria per mL in subacute cases. Because most blood cultures in untreated patients will be positive, it is seldom necessary to draw more than 3 separate blood specimens to isolate the organism.[293] In one study, the etiologic organism was recovered from cultures taken on the first day of admission to the hospital in 93 percent of patients with culture-positive endocarditis.[294] In other studies, however, the rate of persistently positive blood cultures was lower, in the range of 62 to 68 percent.[116,202] Additional specimens obtained over a longer period may be needed to isolate the etiologic organism from patients who have received recent antibiotic therapy.

A practical approach for investigation of suspected SBE is to draw 3 separate samples of venous blood, each of 16 to 20 mL, on the first day, with at least 1 h between the first and last venipuncture. Half of each sample should be inoculated into an aerobic broth culture medium, and the other half into another broth (usually anaerobic) medium. These media should be capable of supporting growth of fastidious, nutritionally variant bacteria[139,295] and ideally should contain a resin to remove antibiotics. As soon as a culture turns positive, Gram's stain and subculture should be performed. If all 3 samples (6 bottles) are negative by the second or third day but the diagnosis of endocarditis still seems likely, two more samples of venous blood should be drawn for culture. If the patient had received previous antibiotic therapy, several further venous samples may be taken over the following weeks to identify a possible late recrudescence of bacteremia after partial treatment. For ABE, 3 venous blood samples are drawn for culture and empiric antibiotic therapy is begun at once, because in patients with acute endocarditis, treatment should not be delayed until culture results are available. In cases of *Staph. aureus* endocarditis, greater than 95 percent of blood culture would be positive, usually within 24 hours.[5]

Because *Staph.* epidermidis[251] and diphtheroids[296] can cause endocarditis, special care must be taken during venipuncture to avoid contamination of the specimen with these common skin organisms, which could result in diagnostic confusion. Since endocarditis usually produces continuous bacteremia, all cultures are usually positive; when only 1 of 3 grow a *Staph.* epidermidis or diphtheroid, contamination and not true bacteremia should be suspected! If the diagnosis of endocarditis remains likely, and cultures are negative, cultures should be incubated for 3 weeks and Gram's stains made at 5 days, 2 weeks, and 3 weeks even if no growth is apparent on inspection. The HACEK group of organisms, pyridoxyl requiring viridans streptococci, some fungi, *Bartonella*, and some others may take longer than the standard 3 to 5 days to grow.[297] A number of new seralogic and PCR-based techniques are under development and are desperately needed to clarify diagnosis in these culture-negative cases.[298-300]

Electrocardiography

Electrocardiographic studies should be performed initially and repeated at intervals according to progress during treatment. A disturbance of conduction or onset of myocardial irritability [↑ frequency of ventricular premature complexes (VPCs) or atrial premature complexes (APCs)] that develops during the course of endocarditis suggests extension of infection into the myocardium (see earlier). Such extension may be due to focal myocarditis or to an abscess located close to the conduction system.[110] Thus, development of a prolonged PR interval, if due to an abscess, can have major implications: a probable need for valve replacement and a worse prognosis.[87] Electrocardiograms can reveal evidence of silent myocardial infarction due to embolization of a vegetation to a coronary artery. Continuous electrocardiogram monitoring may be appropriate

when conduction or rhythm changes are observed and disease progression is a concern.

Echocardiography

Echocardiographic studies are important in the diagnosis of IE.[301-305] Positive echocardiographic findings, properly defined, constitute an important criteria for the clinical diagnosis of endocarditis and, in the setting of positive blood cultures, essentially establishes the diagnosis of IE.[202] MVP combined with color-flow Doppler imaging (see Chap. 13) provides a wealth of information for both the diagnosis and the management of endocarditis, including the detection of vegetations, valvular perforations[306] and other abnormalities,[307] abscesses, and pericarditis, as well as the assessment of ventricular function (Fig. 73-15*A*-*D*).[302-304] Sensitivity for detection of vegetations, originally in the range of 33 to 63 percent, today is 50 to 75 percent.[307] Sensitivity can be improved to better than 95 percent by use of TEE (see Chap. 14) in selected cases.[270,302] Transesophageal studies also detect abscesses and valve perforation with much greater sensitivity.[304] TEE is markedly better than MVP for evaluation of prosthetic valve endocarditis, especially involving mitral valves.[308,309]

Echocardiography has some limitations.[301] It is not cost-effective as a means of excluding IE in patients with a low pretest probability of having the disease.[310,311] With higher prior probability, a negative study result has useful negative predictive value, especially if transesophageal studies have been performed, but it cannot totally exclude the diagnosis of endocarditis.[170,202,310,311] It is particularly useful in patients with *Staph. aureus* bacteremia. In one study, MVP identified vegetations in 7 of 26 patients with IE, while TEE revealed evidence of vegetations in all (100 percent).[311] These data suggest that a negative TEE allows the clinician to treat for bacteremia alone (usually antibiotic therapy for 2 weeks versus 4 to 6 weeks for IE). Sensitivity for detection of vegetations is somewhat lower on the right side (about 70 percent) than on the left (better than 95 percent).[270,301] The presence of a prosthetic valve sometimes interferes with detection of vegetations, but even in these patients echocardiographic findings are usually informative. Occasionally, the specificity of echocardiography is compromised by falsepositive readings for "vegetations" that do not exist. Such readings are particularly common in patients with myxomatous degeneration of valve leaflets or other preexisting disease with focal pathology. This must be considered when surgery is contemplated.

Sequential echocardiograms performed during treatment can guide decisions on the need and timing for surgery by providing objective assessments of cardiac function. For example, premature mitral valve closure due to elevated end-diastolic pressure is a useful echocardiographic sign indicating severe aortic regurgitation, usually requiring urgent valve replacement (see Chap. 56).[270] Echocardiograms may detect development of an abscess, perforation of a valve, or rupture of an infected sinus of Valsalva,[231] all strong indications for surgical intervention. During successful antimicrobial treatment, vegetations may disappear, decrease in size, or even persist unchanged; therefore, serial echocardiograms should not be used as a "test of cure."[301] Significant enlargement of a vegetation during treatment, however, indicates possible treatment failure and constitutes a relative indication for surgical intervention. The valve of echocardiography to determine risk of embolization and/or death is controversial. A large meta-analysis concluded that the odds ratio for embolization was 2.8 ($p < 0.01$) when vegetations >10 mm were detected but did not predict death.[312] In another study of *Staph. aureus*, IE visualization of vegetation by MVP carried a higher risk of embolization or death (68 percent) than identified only by TEE (16 percent, $p < 0.01$).[313] Therefore, the value of echocardiography as a mechanism for predicting outcome remains unclear.[314,315]

Other Imaging Studies

The most important contribution of the chest x-ray in assessment of endocarditis is to provide evidence of early congestive heart failure, because this complication carries such important implications for both prognosis and management (see "Complications," earlier).

Various other x-ray findings can be helpful in assessing patients with endocarditis. The presence of multiple small, patchy infiltrates in the lungs of an IDU with fever strongly suggests the diagnosis of septic emboli arising from right-sided IE.[65-67] Valvular calcification may identify a previously abnormal valve, thus aiding the localization of presumed intravascular infection. Widening of the aorta may be caused by a mycotic aneurysm. Fluoroscopy can demonstrate abnormal motion of a prosthetic valve, indicating presence of a vegetation or partial dehiscence of the valve from the aortic root. This information often helps to decide whether or not valve replacement is needed during management of PVE.

Computed tomography (Chap. 17) and magnetic resonance imaging (Chap. 18)[274] can be helpful in defining the cause of focal neurologic lesions in patients with endocarditis, especially infarction, hemorrhage from a mycotic aneurysm, and brain abscess. The computed tomography scan is very effective for diagnosis of intracranial complications[316] and infected aortic aneurysms.[133] Magnetic resonance imaging adds additional useful information in some cases (Fig. 73-14).[317] In one study, Magnetic resonance imaging provided evidence of cerebral embolization in 12 patients with IE. Angiographic studies are usually used to demonstrate mycotic aneurysms in the brain or elsewhere.[277,278]

Cardiac Catheterization with Cineangiography

This investigation is usually not necessary for patients who respond well to antimicrobial therapy without developing cardiac failure. When surgical intervention is considered, cardiac catheterization and cineangiography (Chap. 15) can extend and add to information provided by echocardiography. The condition of the coronary arteries should be assessed before valve replacement in adults over 40 years of age, because simultaneous coronary bypass may be indicated if the patient has coronary artery disease. Other relevant anatomic abnormalities such as valvular lesions, congenital defects, asymmetric septal hypertrophy, coarctation of the aorta, or mycotic aneurysm can be better defined. Occasionally, a previously unsuspected diagnosis, such as the presence of a sinus of Valsalva aneurysm, will be made. Physiologic measurements including cardiac output, pressures in the left and right sides of the heart, and the degree of aortic regurgitation may help to decide whether or not valve replacement is indicated and may influence the timing of the operation. Among 35 patients who underwent cardiac catheterization during active endocarditis, the clinical assessment was materially modified by catheterization in 23 patients, the diagnosis of the site of valve involvement was altered in 14, and in 6 valve-ring abscesses were revealed.[318] Surgery was postponed or canceled in 6 patients in whom catheterization revealed only mild hemodynamic abnormalities. There were no serious complications, indicating that catheterization should not be avoided for fear of dislodging emboli when a proper indication exists. In summary, cardiac catheterization and cineangiography should be performed in most adults with IE who are over 40 years of age and in selected younger patients when surgery is considered.

Radionuclide Imaging

Liver-spleen imaging may reveal defects due to splenic infarction, which confirms embolization. In animals, experimental vegetations have been located by scanning for radiolabeled platelets deposited from the bloodstream onto a growing endocardial lesion.[319] Gallium 67 scans have shown increased uptake in the heart in some patients with endocarditis. Scintigraphic studies following injection of indium 111 labeled leukocytes have detected some intracardiac abscesses,[77,320] but no radionuclide imaging technique has sufficient sensitivity and specificity to

justify routine use for detection of vegetations in IE. In selected cases, leukocyte scintigraphy using indium 111 labeled leukocytes can detect mycotic aneurysms and extracardiac foci of infection.[321] Single photon emission computed tomography immunoscintigraphy with antigranulocyte antibody has been described as a nuclear medicine option for diagnosis of IE.

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Chapter 73: INFECTIVE ENDOCARDITIS

TREATMENT

General Principles

Optimal management aims to eradicate the infecting organism as soon as possible, to operate with correct timing if surgical intervention should be required, and to treat complications. Because IE carries a significant risk of death even when well managed, it is important that treatment be continued long enough to ensure that relapse will not occur. In contrast, patients with the more easily cured forms of endocarditis should not be subjected to unnecessarily long, expensive, and potentially toxic treatment in a hospital.[322] This can happen when physicians treat on the basis of outdated rules, such as the one stating that "endocarditis should be treated for 6 weeks." In fact, many patients can be cured in 2[323-325] or 4 weeks,[326] while some require treatment for 6 weeks or longer.

Microbiologic Tests

To choose and regulate antibiotic therapy correctly, certain basic microbiologic information about the infecting organism is required. For group A streptococcal infection, nothing more than positive identification of the organism is necessary, because these organisms, with only rare exceptions, are still sensitive to low concentrations of penicillin. For other species of streptococci, staphylococci, and most other bacteria, the minimal inhibitory concentration (MIC) of relevant antibiotics should be determined. Some of these organisms are resistant to intermediate or high concentrations of penicillin.[327,328] Many strains are tolerant-that is, inhibited but not killed by antibiotic levels achievable in serum.[329,330] Because there is no definitive evidence that tolerance determines treatment outcome in humans, however, it is not necessary to measure minimal bactericidal concentrations (MBC) in most cases.

The serum bactericidal titer (SBT or Schlichter test) has been used frequently to monitor the treatment of endocarditis.[33,331] In this test, the infecting organism is exposed in vitro to the patient's serum, which is drawn while the patient is receiving antibiotic treatment to determine the maximal dilution of serum that will inhibit and kill the organism. On the basis of empirical clinical experience, it was said that the SBT should be 1:8 or higher at intervals during each day of treatment. For streptococcal endocarditis, this can usually be achieved without difficulty; SBTs are often high, in the range of 1:128 to 1:1024. The SBT is technically difficult to perform and to standardize, however, and after years of use, its clinical utility remains unproven.[331,332] Therefore, SBTs are now regarded as obsolete by most experts. Rarely, measurement of the SBT might be informative: in treating unusual organisms, in using unusual antibiotics, in using unusual regimens (such as oral treatment), or when treatment appears to be failing.

Dosage regimens that result in widely fluctuating antibiotic concentrations in serum are traditionally employed for treatment of endocarditis, and they are usually effective. Whether or not the maintenance of continuous serum antibiotic concentrations offers any therapeutic benefit over intermittent dosing regimens is not known; perhaps continuous infusion of antibiotic would be desirable for treatment of some gram-negative organisms, which regrow more rapidly than most gram-positive organisms when antibiotic levels fall below the minimal inhibitory concentration.

Choice of Antibiotics

Bactericidal antibiotics are generally chosen for treatment of endocarditis whenever possible.[33,326] This is not an absolute rule; some patients have been cured with bacteriostatic drugs such as sulfonamides, tetracycline, or chloramphenicol, but the results of treatment with these agents are unreliable.[28,333,334] Bactericidal action is presumably needed because host defense mechanisms are inadequate in the vegetation; relatively few phagocytes are present, and they are hampered by protective layers of fibrin

around the colonies of bacteria (Figs. 73-2 and 73-6). To effect a cure, antibiotic therapy must eradicate organisms completely, without the help of phagocytes to eliminate the subpopulation of microbes that are relatively resistant to antibiotics because they are in the resting phase. In this important respect, IE differs strikingly from bacterial pneumonia in normal hosts, where phagocytes are plentiful and bacteriostatic antibiotics are usually effective. Nevertheless, in treating unusual organisms, it may occasionally be necessary to use a bacteriostatic antibiotic in combination with other drugs to achieve the optimal antibacterial effect. When treatment with unusual combinations of antibiotics is needed, in vitro laboratory tests can be performed to find out whether synergism, indifference, or antagonism exists between them.

For the common forms of bacterial endocarditis caused by gram-positive organisms, specific therapeutic regimens can be recommended with confidence based on extensive published experience.[323,335] Regimens for the more common forms of endocarditis are listed in Table 73-9.

Table 73-9: Treatment Regimens for Infective Endocarditis[a,b]

Organism	Treatment Regimen: Dose and Route	Duration in Weeks	Comments
Fully penicillin-sensitive streptococci: MIC ≤ 0.1 μg/mL viridans (α-hemolytic) streptococci; *Strep. bovis; Strep. pneumoniae; Strep. pyogenes* group A, C, etc.; *Strep. agalactiae* group B	1. Penicillin G 4 million units every 6 h IV alone (4 weeks) *or* 2. Penicillin G 4 million units every 6 h IV with gentamicin (2 weeks) 3. Ceftriaxone 2 g IV or 1 M once daily alone (2 weeks) *or* 4. Ceftriaxone 2 g IV or 1 M once daily or with gentamicin 1 mg/kg twice a day or 3 mg/kg 4 times a day (2 weeks) 5. Vancomycin 15 mg/kg IV every 12 h (4 weeks)[a,b]		
○	4		
○	4		
○	4		
○	Suitable for hospitalized patients but less convenient for outpatient therapy		
○	For patients allergic to penicillins but not cephalosporins or for outpatient therapy in selected patients		
○	For patients allergic to penicillins and cephalosporins		

Relatively penicillin-resistant streptococci: MIC > 0.1 < 1.0 μg/mL, some viridans (α-hemolytic) streptococci; some *Strep. pneumoniae;* etc.	1. Penicillin G 4 million units IV every 4 h *plus* gentamicin 1.0 mg/kg every 12 h IV or IM (for first 2 weeks only)[a] *or* 2. Vancomycin 15 mg/kg IV every 12 h[b]	❍ 4(2) ❍ 4 ❍ For outpatient therapy in selected patients, ceftriaxone 2 g IV once daily may be substituted for penicillin if ceftriaxone MIC ≤ 4 μg/mL, *plus* gentamicin 2.0 mg/kg given once daily ❍ For patients allergic to penicillins
Penicillin-resistant streptococci: MIC ≥ 1.0 μg/mL, *E. faecalis, E. faecium,* other enterococci; some other streptococci	1. Penicillin G 18-30 million units/day IV continuously or in divided doses *plus* gentamicin 1 mg/kg IV or IM every 8 h *or* 2. Ampicillin 12 g/day IV continuously or in divided doses *plus* gentamicin 1.0 mg/kg IV every 8 h, *or* 3. Vancomycin 15 mg/kg IV every 12 h *plus* gentamicin 1.0 mg/kg IV every 8 h[a,b]	❍ 4-6 ❍ 4-6 ❍ 4-6 ❍ Susceptibility testing needed; do not use penicillin- or ampicillin-containing regimen if strain produces β-lactamase. ❍ 4-week regimen recommended for most cases with symptoms for <3 months, otherwise 6 weeks ❍ For patients allergic to

	penicillin; 4 weeks should be adequate for most cases; serum levels should be monitored		
Staphylococci (in the absence of prosthetic material) β-lactam-containing regimens preferred over vancomycin unless patient is definitely hypersensitive to penicillins and cephalosporins; for patients with severe disseminated staphylococcal infection, antimicrobial synergy may be advantageous during early stages of treatment; therefore, gentamicin 1.0 mg/kg IV every 8 h for first 3-5 days only may be added to any of these regimens	Methicillin-susceptible staphylococci: 1. Nafcillin 2 g IV every 4 h IV 4-6 wks *or* 2. Nafcillin 2 g IV every 4 h IV × 4-6 wks plus gentamicin 1.0 mg/kg every 8 h IV × 3-5 days 3. Vancomycin 15 mg/kg IV every 12 h 4-6 wks[b] ○ 4-6 ○ 4-6 ○ 4-6		
In right sided uncomplicated tricus-pid endocarditis	Nafcillin 2 g IV every 4 h and gen-tamicin 1 mg/kg twice a day or 3 mg/kg 4 times a day	2	
	Methicillin-resistant staphylococci: Vancomycin 15 mg/kg IV every 12 h[b]	4-6	
Staphylococci (associated with pros-thetic valve or other prosthetic material)	Methicillin-susceptible staphylo-cocci: Nafcillin 2 g IV every 4 h *plus* gentamicin 1.0 mg/kg IV ev-ery 8 h[a] plus rifampin 600 mg orally 4 times a day	≥6	Cefazolin or vancomycin may be substituted for nafcillin if neces-sary due to drug hypersensitivity
	Methicillin-resistant staphylococci: Vancomycin 15 mg/kg IV every 12 h *plus* gentamicin 1.0 mg/kg IV or IM every 8 h *plus* rifam-pin 300 mg orally every 8 h[a,b]	≥6	

HACEK group organisms: *Haemophilus* species *Actinobacillus actinomycetemcomitans Cardiobacterium hominis Eikenella* species *Kingella kingae*	1. Ceftriaxone 2 g IV or IM once daily *or*	4	Other third-generation cephalospo-rins may be substituted, using ap-propriate dose adjustment
	2. Ampicillin 12 g/day IV continu-ously or in divided doses *plus* gentamicin 1.0 mg/kg every 12 h IV or IM[a]	4	Less convenient for outpatient therapy
Pseudomonas aeruginosa, other gram-negative bacilli	Extended-spectrum penicillin *or* third-generation cephalosporin *or* imipenem *plus* aminoglyco-side	4-6	Combination therapy recom-mended; final choice of antibiotic regimen to be made after sensi-tivity results available
Neisseria species	1. Penicillin G 2 million units IV every 6 h *or* 2. Ceftriaxone 1 g IV or IM once daily	○ 3-4 ○ 3-4	Organisms often highly sensitive to penicillin, but must be tested for β-lactamase production; 3 weeks should be adequate for most patients without complica-tions

[a]All gentamicin- and vancomycin-containing regimens require monitoring for potential toxicity; monitoring of serum concentrations usually will be required.
[b]Vancomycin dose not to exceed 2.0 g per 24 h.

SOURCE: Adapted from Scheld and Sande[50] and from Wilson et al., and The Sanford Guide 2000.[323]

Currently, increasing rates of antibiotic resistance threaten the efficacy of traditional treatment regimens. Penicillin resistance is increasing among viridans streptococci, the majority of which had previously been fully sensitive.[336,337] In 1996, 13 percent of blood culture isolates showed high-level resistance (MIC 4.0 mg/mL or greater) and 42 percent showed intermediate resistance (MIC 0.25 to 2.0 mg/mL).[337] Use of combined antibiotic regimens such as beta-lactam plus aminoglycoside or even vancomycin plus aminoglycoside should be considered for treatment of resistant strains.[336] Synergistic combinations of a beta-lactam and an aminoglycoside have been used successfully to treat enterococci for many years, but increasing resistance among enterococci, especially vancomycin-resistant enterococci, presents new problems for therapy.[338] The most resistant species is *Enterococcus faecium*, which may exhibit high-level resistance to vancomycin as well as intrinsic resistance to beta-lactam antibiotics and imipenem.[94] The optimal treatment for IE caused by these problem strains is not known. Several antibiotic combinations have been tried with some success often with adjunctive surgical valve replacement. These include high-dose ampicillin plus imipenem +/- a fluoroquinolone,[94,339] ampicillin plus imipenem plus vancomycin,[340]

ampicillin plus a fluoroquinolone,[341] and quinupristin/dalfopristin plus doxycycline plus rifampin.[342] Since great variability exists between isolates as to sensitivity and whether drugs are cidal or static, in vitro testing with time-kill experiments and testing various drugs alone and in combination will help with selection. An infectious disease consultation is recommended.[94,339-344]

Staph. epidermidis PVE is difficult to eradicate with antibiotics alone.[166] These staphylococci are frequently resistant to semisynthetic penicillins, cephalosporins, and other antibiotics. A regimen combining vancomycin, rifampin, and an aminoglycoside chosen according to sensitivity tests is most likely to succeed. The organism may develop resistance to rifampin during treatment.

Treatment of endocarditis due to less common organisms must be chosen on the basis of more limited published experience,[50,51,108,326] together with the results of tests performed upon the infecting organism in the microbiology laboratory. Treatment must often be individualized. In general, one of the beta-lactam antibiotics should be included in the regimen whenever possible. Combinations of two or more antibiotics are often employed. The list of potentially useful regimens for these rarer forms of infective endocarditis is too long to detail here.

Empiric Therapy

When the etiologic organism is not known, the choice of empiric therapy should depend on whether the patient has acute or subacute disease. ABE requires broad-spectrum therapy that covers *Staph. aureus* as well as many species of streptococci and gram-negative bacilli. SBE requires a regimen that treats most streptococci, including *E. faecalis.* To meet these requirements, the following suggestions are offered:

- For ABE: nafcillin 2.0 g IV q 4 h plus ampicillin 2.0 g IV q 4 h plus gentamicin 1.5 mg/kg IV q 8 h. If methicillin-resistant *Staph. aureus* is considered likely (for example, in a hospital-acquired case), vancomycin 1.0 g IV q 12 h should be substituted for nafcillin in this regimen until the antibiotic sensitivity is known.
- For SBE: ampicillin 2.0 g IV q 4 h plus gentamicin 1.5 mg/kg IV q 8 h.

Treatment should be adjusted as appropriate when the etiologic organism is identified and again when antibiotic sensitivity is known. In those few cases where empiric therapy is administered as a therapeutic trial to help confirm a diagnosis, treatment should be continued without interruption or unnecessary changes for at least 2 weeks; otherwise, no useful diagnostic information will be gained.

Duration of Therapy

Extensive experience with treatment of the common forms of endocarditis provides the basis for recommendations on duration of therapy (Table 73-9). In the case of *Staph. aureus* endocarditis, the response to appropriate treatment can be variable; some patients recover swiftly without complications, especially young IDUs, who can often be cured within 2 weeks.[70,324] In contrast, some patients remain febrile for 10 to 14 days due to complications such as abscesses or other extracardiac manifestations of disseminated staphylococcal disease. Although 4 weeks of therapy is adequate in most cases, this should not be regarded as a rigid rule, because some patients with *Staph. aureus* endocarditis require treatment for 6 weeks or longer to achieve a cure. For *E. faecalis* endocarditis, 4 weeks of treatment is usually adequate. The relapse rate, however, seems to be higher in patients with mitral valve infection and in those who have had symptoms for more than 3 months,[143] where treatment should continue for 6 weeks.

Parenteral treatment can be completed in the patient's home or in the outpatient clinic in carefully selected cases. Availability of antibiotics with long half-lives, such as vancomycin or ceftriaxone, allows once-daily administration. Supervised parenteral treatment outside the hospital should be fully effective in achieving a microbiologic cure and offers obvious benefits: convenience for the patient and cost containment.[344-346] The risks posed by a possible late complication, such as an embolic stroke or the sudden onset of heart failure, must be balanced against these benefits in selecting candidates for home parenteral therapy. Further trials are needed to refine the criteria and proper applications for outpatient therapy for endocarditis, but current experience indicates that more than one-half of endocarditis patients could receive at least some of their treatment as outpatients.

In general, the less extensive the published experience with a particular organism and treatment regimen, the more one should lean toward prolonging treatment in order to provide a reasonable margin of safety. Guidelines for the duration of treatment of the more common etiologic organisms are listed in Table 73-9. For less common organisms, the optimal duration of treatment required may vary according to individual circumstances.

Role of Surgery

Optimal management of IE requires operative intervention during treatment for about one-third of patients.[87-347] Correct selection of this subgroup of patients and optimal timing of surgery are both critically important.[348]

Major indications for surgery are moderate or severe heart failure not responding to medical treatment, valvular obstruction, periannular or myocardial abscess, prosthetic valve dehiscence, persistent bacteremia despite appropriate antibiotics, and fungal infection. In most such cases, surgery should proceed promptly even if the infection is still active.

Relative indications for surgery include recurrent emboli; staphylococcal and gram-negative bacillary infections, especially involving prosthetic valves; persistent fever despite treatment; and vegetations that enlarge during treatment.[11,110,266,348]

Correct timing is the essence of good surgical management of endocarditis.[347] If surgery is undertaken too soon, the risks of operative mortality and the early and late morbidity associated with valve replacement may be inflicted on the patient unnecessarily, because some patients respond well to medical therapy, allowing surgery to be postponed indefinitely. If surgery can be delayed safely, antibiotic therapy should have eradicated or at least greatly reduced the number of organisms in the vegetation and in any sites of metastatic infection, thus increasing the chance of a successful outcome if surgery becomes necessary. If time is available for the effective treatment of complications such as septicemia, renal failure, pneumonia, myocarditis, and neurologic complications[316] before surgery, the operative risk should be lower. In comparison, if surgery is delayed too long, patients may die suddenly, or their hemodynamic status may deteriorate so seriously that surgery is no longer feasible. This would be a tragic error, because many authors have emphasized that both survival and long-term outcome can be improved by earlier operation for selected patients, even if the endocardial infection is still active.[266,349,350]

Careful, frequent reexamination of the patient, together with repeated echocardiographic studies and sometimes cardiac catheterization to confirm the clinical findings, is indicated in every case where operation might be needed. The decision to operate should also be influenced by knowledge of the natural history of the type of endocarditis being treated. For example, penicillin-sensitive streptococcal endocarditis can almost always be cured bacteriologically (Table 73-10), and the immediate prognosis is good provided that cardiac failure or other major complications do not develop. Therefore, surgery should usually be considered only for those patients with cardiac failure that does not respond well to medical treatment. Similarly, because young IDUs with acute staphylococcal endocarditis have a good prognosis,[5,324] surgery should usually be reserved for those who develop intractable heart failure or definite signs of treatment failure. In contrast, the likelihood that fungal prosthetic valve endocarditis can be eradicated with antifungal drugs alone is negligible (Table 73-10). Such patients should usually undergo valve debridement or replacement early, without waiting to test the remote possibility that antifungal treatment could eradicate the infection.[351] The development of severe aortic regurgitation, especially when accompanied by heart failure, usually requires urgent surgery. Other examples of patients who are highly likely to require operation are those with early-onset PVE, valve-ring abscesses, or gram-negative bacillary infection of prosthetic valves.[11]

Over the past decade, surgical approaches have evolved toward increasingly radical debridement of infected tissue and more extensive use of reconstructive materials.[266,351] For example, an aortic root homograft instead of a standard prosthetic valve is now often inserted after debridement of a valve-ring abscess.[352] The Ross operation, transposing the patient's own pulmonary valve into the aortic position as an autograft after extensive debridement of infected tissue (replacing the pulmonary valve with a homograft) has been

advocated as treatment for patients with complicated aortic root infections.[353,354]

In addition to valve replacement, several other surgical procedures may be available for the treatment of endocarditis.[348] Debridement of vegetations ("vegetectomy"), often combined with valvuloplasty, can cure the infection while sparing the native valve in selected patients.[267,268,355] This can be especially beneficial for young patients, women who wish to bear children, and patients who cannot or will not take anticoagulant therapy reliably.

Early consultation with the surgical service should be sought for most patients with endocarditis, so that an appropriate operation can be performed without delay if necessary. The sudden onset of aortic or mitral regurgitation with consequent acute left ventricular failure can occur without warning, even in the most favorable forms of endocarditis.

Anticoagulant Therapy

Even though the infected vegetation is essentially a thrombotic lesion, there is no evidence that anticoagulation has any useful therapeutic effect on the course of the endocarditis itself. On the contrary, early experience showed that simultaneous treatment with penicillin and heparin carried an increased risk of fatal intracerebral hemorrhage.[356] For this reason, anticoagulation was considered to be strongly contraindicated in patients with endocarditis, until further experience showed that warfarin could usually be given safely during the treatment of patients with prosthetic valve infections.[357-359] However in a series of 21 pH with PVE caused by *Staph. aureus*, 12 had CVS events including 6 intracranial hemorrhages and 5 ischemic strokes that had hemorrhagic transformation. All 11 died, and all had been on oral anticoagulants.[359] Currently available information suggests the following guidelines for patients with IE:

- Avoid use of heparin except for urgent indications, such as treatment of massive pulmonary embolism.
- Discontinue or avoid oral anticoagulants if possible, especially in patients with intracranial complications and if *Staph. aureus* is the cause of IE.
- Anticoagulate with warfarin if there is a clear-cut indication, such as a mechanical prosthetic heart valve, taking care to regulate the prothrombin time between International Normalized Ratio (INR) 2.5 and 3.5.
- Choose an antibiotic treatment regimen that does not require intramuscular injections if anticoagulation is instituted.

Thrombolytic agents theoretically could promote lysis or resolution of vegetations. Adjunctive treatment with recombinant tissue plasminogen activator decreased vegetation size and improved the results of short-term penicillin therapy in rabbits with fresh vegetations.[12] Similarly, aspirin therapy can reduce the size of experimental vegetations and improve rate of sterilization by antibiotics.[360] The potential value of antithrombotic agents, however, has not been demonstrated in human beings; thrombolytic therapy might not work on the older vegetations typical of SBE in human beings and could possibly cause serious hemorrhagic complications.

Management of Complications

HEART FAILURE

The development of moderate or severe cardiac failure due to structural valvular damage indicates the need for **prompt surgical intervention** in most patients with endocarditis, even if the intracardiac infection is still active.[347,349] In patients with mild heart failure, the decision should be individualized, always remembering that lives may be lost unnecessarily if cardiac function suddenly worsens, so that surgery becomes either hazardous or unfeasible.

EMBOLI

The occurrence of one or more significant arterial emboli during the treatment of endocarditis is a relative indication for surgery. The predictable early and long-term mortality and morbidity rates of valve

replacement must be weighed against the highly unpredictable likelihood of further emboli. For this reason, embolization is a weaker indication for valve replacement than is cardiac failure.[348,349] In the author's opinion, operative intervention during antibiotic treatment should seldom be undertaken solely to prevent further emboli unless the patient has suffered more than one or two proved major emboli. Because the frequency of emboli falls rapidly after 1 to 2 weeks of antibiotic therapy,[361] the most logical time to operate for the purpose of preventing emboli would be early, within 1 week of diagnosis.

RENAL FAILURE

In the preantibiotic era, patients with SBE frequently developed chronic renal failure before they died.[3] Subsequently, both the incidence of renal failure and its importance as a cause of death have greatly diminished. In one series, up to one-third of 204 patients with IE developed evidence of acute renal failure, however. Risk factors for renal failure were increased age, hypertension, thrombocytopenia, IE caused by *Staph. aureus*, and PVE. While the earlier diagnosis and antibiotic treatment have forestalled the development of immune-complex glomerulonephritis, in those (about 5 to 10 percent) who still develop this complication of SBE, timely dialysis can maintain the patient until antibiotic treatment results in disappearance of the bacterial antigens that triggered immune-complex nephritis. Renal function usually normalizes smoothly once infection has been controlled, but recovery may take weeks or months. In a few cases, creatinine clearance worsens for a time despite effective antibacterial treatment, perhaps reflecting persistence of bacterial antigen in vegetations after bacteriologic cure. Corticosteroids may have been of value in a small number of cases.[362] Some patients with septicemia, shock, or disseminated intravascular coagulation associated with ABE develop acute renal failure and require dialysis as part of their intensive care.

MYCOTIC ANEURYSM

This complication is diagnosed in less than 5 percent of patients with IE, but the local consequences of aneurysm expansion and rupture can be very serious, especially in the brain (see Chap. 89).[276,278,279] Small aneurysms will often thrombose or resolve spontaneously during or after antibiotic therapy. Once aneurysms exceed 0.5 to 2 cm in diameter, they are likely to enlarge and eventually rupture despite eradication of the etiologic bacteria by antibiotic therapy.[281] Surgery is indicated for accessible aneurysms before this complication occurs.

Intracranial mycotic aneurysms are especially difficult to manage. They may present with headaches, subarachnoid hemorrhage, or stroke, but many are asymptomatic. Even small aneurysms may bleed at any time; they may be multiple and/or located in inaccessible sites. This presents a therapeutic dilemma: whether to treat conservatively with antibiotics and hope for resolution (risking serious or fatal hemorrhage) or to operate (risking neurologic damage and permanent sequelae). Symptoms or signs consistent with an intracranial aneurysm indicate the need for prompt imaging, using computed tomography and/or magnetic resonance imaging. Cerebral angiography may be needed if the findings are inconclusive. In general, large (over 0.5 cm in diameter) or expanding aneurysms or aneurysms that have already leaked or begun to bleed should be clipped if a surgical approach is feasible. An individualized decision must be made on whether or not to operate for smaller aneurysms that have not leaked or ruptured.

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PROGNOSIS

IE is one of the few infectious diseases that are virtually always fatal if untreated. Spontaneous recovery was reported occasionally in the preantibiotic era,[3] but most of these patients probably had illnesses other than IE. The interval between the onset of symptoms and death in patients with untreated subacute disease varied widely, with a median time to death of about 6 months.[3] Almost all patients with acute IE died within less than 4 weeks.

Heart failure is the leading adverse prognostic factor.[264] Other adverse factors include central nervous system complications, renal failure, culture-negative disease, gram-negative bacillary or fungal infection, prosthetic valve infection, and development of abscesses in the valve ring or myocardium.[363] Survival 6 months after PVE in one series was only 54 percent.[364] Six-month survival after early-onset PVE (37 percent) was significantly worse than it was for late-onset PVE (65 percent). Because modern treatment methods, including valve replacement, are effective for treatment of heart failure, central nervous system complications have replaced heart failure as the most important adverse prognostic factor in some case studies.[274]

Favorable prognostic factors include youth, early diagnosis and treatment, infection involving a prolapsing mitral valve, and penicillin-sensitive streptococcal infection. The prognosis is good for young IDUs with *Staph. aureus* infection of the tricuspid valve.[5,335] With earlier diagnosis and appropriate therapy, including surgery, the prognosis for elderly patients can be substantially improved.[90] Eradication of the etiologic organisms (microbiological cure) can be achieved in a high proportion of all patients with bacterial endocarditis.[6,323,344,345] Both early and long-term mortality rates remain significant, however, due to any preexisting disease and added damage caused by endocarditis before the organisms were eradicated. Survival curves after admission with IE show a significant number of late deaths despite microbiologic cure.[9,365]

An analysis of experience over the past 25 years permits a reasonably accurate formulation of the prognosis for microbiologic cure among the various subgroups of patients with IE. Approximate figures are listed in Table 73-10.

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RECURRENT ENDOCARDITIS

Recurrent endocarditis is a general term that includes both relapses and reinfections. The term *relapse* refers to recurrence of infection with the same organism because treatment failed. The frequency of relapse can be predicted from published experience for each of the various forms of IE (Table 73-10). Because relapses occasionally occur even after an optimal treatment regimen has been used, follow-up clinical evaluation should be meticulously performed during the first 2 months after treatment. Any clinical suspicion that relapse might have occurred indicates the need to draw blood cultures. Most relapses occur within a few weeks of ending treatment, but living organisms can persist in seemingly healed vegetations for many months and may occasionally cause late relapse.

The term *reinfection* refers to a new episode of endocarditis occurring after the cure of a previous episode.[366] Usually a different etiologic organism is involved, but if the new isolate appears similar to the initial etiologic organism, molecular typing techniques can be used to determine if the case is a relapse or an infection.

Patients remain permanently at risk of reinfection after cure of IE because of residual valve damage superimposed on the original predisposing lesion (see Tables 73-1 and 73-2). Recurrent episodes are fairly common, being recorded in from 2 to 31 percent of cases.[3,46,48,365,366] This wide variation in reported incidence is partly due to variable duration of follow-up. IDUs and patients with severe periodontitis are at highest risk for reinfection. Occasionally, a patient may suffer three or more separate episodes of IE.[366] Patients who have previously had NVE and have required valve replacement, are at high risk to develop prosthetic valve infection (often with a different organism) for reasons that are not yet understood.[9]

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THE CHALLENGE OF PROPHYLAXIS

Because various invasive procedures induce bacteremias with bacterial species that often cause IE,[367-369] prophylactic antibiotics are frequently given to susceptible patients in an attempt to prevent bacterial endocarditis. Although antibiotics definitely can prevent endocarditis in experimental animals, its effectiveness in human beings has not been proved in prospective randomized clinical trials and likely never will be. Many relevant questions remain unanswered. These include the following:

- Is antibiotic prophylaxis effective?
- Does the prophylactic effect (benefit) outweigh the potential side effect of the drug cost and influence the emergence of drug-resistant bacteria?
- Which operations and diagnostic procedures should be covered?
- Which patients should receive antibiotics?
- What antibiotic regimens will be most effective?

Although the risk of infection has not been quantitated, it is sufficiently low that most of these questions cannot be answered by clinical trials; the number of susceptible patients required to provide significant results would be too large.[55,349]

Less than 15 percent of SBE cases and even fewer of ABE cases follow identifiable medical procedures that cause transient bacteremias[54,367,368,370]; therefore, the proportion of cases that is potentially preventable by antibiotics is vanishingly small.

Because endocarditis causes serious morbidity and mortality, the American Heart Association and the practicing medical community have accepted the practice of using antibiotic prophylaxis without evidence-based studies. It has been accepted that prevention of even a few cases could be worthwhile. For this reason, currently accepted standards of practice require that an antibiotic regimen be administered before certain dental and surgical procedures in patients with known heart lesions that pose a significant risk of endocarditis.

Because several hundred cases of streptococcal endocarditis following dental and genitourinary tract procedures have been recorded, the potential causative role of these procedures is certainly suggested.[367,368] A rather short "incubation period" for endocarditis is typical, in that most of these patients noticed symptoms within 2 weeks of the procedure.[256] It should be emphasized that the link between a case of endocarditis and a recent procedure causing bacteremia cannot be proved, because the infection could have been caused by one of the transient, asymptomatic, low-grade bacteremias that occur very commonly, induced by everyday events such as chewing and cleaning the teeth. In fact, when 273 cases of endocarditis are examined retrospect from 1, 2, and 3 months prior to endocarditis, no correlation to dental procedures were found.[56,367]

In the absence of prospective controlled trials, empirical recommendations[55,370,371] for prophylaxis of bacterial endocarditis have been made on the basis of indirect information. This information includes the reported frequency of bacteremia after various procedures (Table 73-11); the relative risk posed by the patient's cardiac lesion (Table 73-2); case reports of prophylaxis failures[75]; in vitro susceptibility studies on the relevant organisms, especially streptococci; experimental studies in laboratory animals[254,372]; and retrospective studies in human beings.[373-375]

Table 73-11: Representative Rates for Frequency of Bacteremia after Various Dental, Diagnostic, and Therapeutic Procedures

Procedure	% Bacteremia	% Range (if available)
None	0	(0-3)
Oral cavity		
Extraction of teeth	60	(18-85)
Periodontal surgery	88	(60-90)
Brushing teeth or irrigation	40	(7-50)
Tonsillectomy	35	(33-38)
Respiratory tract		
Tracheal intubation	<10	(0-16)
Nasotracheal suctioning	16	
Bronchoscopy (rigid bronchoscope)	15	
Bronchoscopy (flexible bronchoscope)	0	
Genitourinary tract		
Catheter insertion and removal	3	(0-26)
Prostatectomy (sterile urine)	12	(11-13)
Prostatectomy (infected urine)	60	(58-82)
Dilatation of strictures	28	(19-86)
Normal delivery	3	(1-5)
Intrauterine device insertion or removal	0	
Gastrointestinal tract		
Upper gastrointestinal endoscopy	4	(0-8)
Transesophageal echocardiography	1	(0-17)
Endoscopic retrograde cholangiopancreatography	5	(0-6)
Barium enema	10	(5-11)
Colonoscopy	5	(0-5)

Sigmoidoscopy (rigid sigmoidoscope)	5	
Sigmoidoscopy (flexible sigmoidoscope)	0	
Proctoscopy	2	
Hemorrhoidectomy	8	
Esophageal dilatation	45	
Vascular system		
Cardiac catheterization	2	(0-5)
Insufficient data		
Insertion and removal of tympanostomy tubes		
Cesarean section		

SOURCE: From Durack,[370] with permission.

Information from these sources indicates that experimental endocarditis in animals can be prevented by bactericidal antibiotics; that prevention is probably effective in human beings; that only a small proportion of total cases is potentially preventable by use of antibiotics[370,374]; and that the cost per prevented case would be very high.[76,374] Thus, prevention probably would not be cost-effective as a general strategy, but it might be effective for selected individuals (namely patients with previous IE and patients with prosthetic valves), especially for high-risk procedures such as tooth extractions.[370,376]

For the individual patient, the decision to administer prophylaxis should be made by assessing two main factors: the risk posed by the preexisting cardiac lesion and the risk posed by the procedure that might cause bacteremia. For example, if a patient with a prosthetic valve undergoes prostate resection, antibiotic prophylaxis is recommended because both factors present a significant risk of endocarditis. In contrast, if a patient with mitral valve prolapse is scheduled for gastroscopy, prophylaxis is not necessary because the risk for endocarditis in this setting is very low.[369] Such risk assessments may be difficult or inaccurate; in many situations uncertainties will remain. For these, there is no one "correct" answer; the patient's and the physician's attitudes and preferences may influence the decision to use prophylaxis. Updated consensus recommendations by the AHA may be useful in guiding decision making.[79]

These guidelines emphasize the following points:

1. Most cases are not attributable to an invasive procedure.
2. Cardiac conditions should be stratified into light, moderate, and negligible risk categories; these are primarily based on potential outcomes if endocarditis occurs.
3. There are procedures that may cause high grade bacteremia and for which prophylaxis is most likely to be effective.
4. There is an algorithm to use in deciding on prophylaxis in patients with mitral valve prolapse.
5. The initial dose of amoxicillin is reduced to 2 g for oral and dental procedures and a follow-up dose is no longer recommended; clindamycin (not erythromycin) is recommended as an alternative therapy in penicillin-allergic individuals.
6. Prophylactic recommendations in gastrointestinal and genitourinary procedures have been simplified.[79]

Attempted prophylaxis does not always succeed. Of 52 cases of apparent prophylaxis failure in one series, 42 involved patients with heart disease who received oral penicillin or erythromycin, usually to cover dental procedures.[75]

Surprisingly, in one series 12 of 16 patients with known cardiac abnormalities who developed IE with organisms of dental origin and who had a dental procedure within 3 months of onset of IE received prophylactic antibiotics according to AHA guidelines. In fact, only 10 percent of cases of IE in this study would qualify for prophylaxis according to the AHA standards. Even if a prophylaxis was 100 percent effective, it would reduce the incidence of IE by only 2.0 cases per 1,000,000 person-years.

The authors agree with Durack, that on the basis of existing data, it is most reasonable to use prophylaxis prior to dental extractions or gingival surgery including implant placement but not routine dental care, filling of cavities, root canal, cleaning and sealing of teeth, in patients with prosthetic valves or history of prior endocarditis. If any of the four conditions are present, antibiotic prophylaxis seems reasonable.[56]

Common errors in attempted prevention of endocarditis are starting antibiotics too early, continuing for too long, using low doses, covering tooth extractions but not lesser dental procedures, and confusing prevention of rheumatic fever (requiring long-term, low-dose antimicrobial drugs) with prevention of endocarditis (short-term, high-dose).[55]

In the absence of pelvic infection, prophylaxis for endocarditis in patients with heart lesions is not recommended to cover normal delivery, therapeutic abortion, dilation and curettage, and insertion or removal of intrauterine contraceptive devices. Similarly, antibiotics are not recommended before many common procedures, such as cardiac catheterization, insertion of temporary pacemakers, endotracheal intubation, bronchoscopy, endoscopy, or radiographic contrast studies of the upper and lower gastrointestinal tract. In comparison, some physicians choose to cover even these low-risk procedures in patients with prosthetic valves because they are at higher risk for endocarditis than are patients with native valves. Specific regimens suggested for prophylaxis of endocarditis are listed in Table 73-12.

Cardiac surgeons currently administer antibiotics to virtually all patients undergoing cardiac surgery, attempting to prevent both wound infections and endocarditis, although the efficacy of prophylaxis in prevention of endocarditis has not been proved.[55] Current recommendations call for parenteral administration of an antistaphylococcal antibiotic just prior to operation, followed by 1 or 2 further doses (Table 73-12). The regimen may be modified if local experience shows that cases of early PVE caused by *Staph.* epidermidis or gram-negative bacilli have occurred with significant frequency (Table 73-12).

The paradigms that have been proposed by various expert bodies (including the AHA) for the use of antibiotics to prevent IE have developed over time and have been based on indirect evidence derived from studies in animals that demonstrated that prevention was possible, on case reports tying IE to various procedures known to cause bacteremia, and from a concern about the dire consequences of the disease. These recommendations have been accepted as "standard of care" and failure to follow them has taken on medicolegal implications. Various authors have questioned this practice and new information has emerged calling into question the clinical benefit of prophylactic antibiotics in this setting. This is especially important in an era where overuse of antimicrobials is fueling the dangerous epidemic of antibiotic-resistant bacteria. Therefore, it seems prudent for the various expert committees who write such recommendations to carefully weigh the apparent minimal benefits with the downsides of toxicity, cost, and resistance that has come with excessive use of antibiotics.

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NOTE

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Figure 73-14: Magnetic resonance image of the brain in a patient with acute left-sided *Staphylococcus aureus* endocarditis, showing multiple areas of focal cerebritis. This patient had no focal central nervous system signs and recovered fully with antimicrobial therapy. (MRI by courtesy of the Department of Radiology, Duke University, Durham, NC.)

Figure 73-15: *A-D.* Echocardiograms from 4 patients with infective endocarditis showing vegetations located at different sites. *A.* Transesophageal echocardiogram (TEE) showing a large vegetation *(arrow)* on the tricuspid valve (TV). IVC = inferior vena cava; RA = right atrium; AV = aortic valve; RVOT = right ventricular outflow tract. *B.* Large vegetation *(arrowhead)* involving both the atrial and ventricular surfaces of the posterior mitral valve leaflet. LA = left atrium; MV = anterior leaflet of the mitral valve; LVO = left ventricular outflow tract; AV = aortic valve. *C.* TEE showing vegetations on both the mitral *(open arrow)* and aortic valve *(arrow)* in a patient with acute *Staphylococcus aureus* endocarditis. LA = left atrium; LV = left ventricle; VS = ventricular septum. *D.* TEE showing a vegetation on the cusp of a bioprosthetic valve *(arrow)*. LA = left atrium; LV = left ventricle; S = artificial valve struts. (Kindly provided by Dr. B. Khanderia and Dr. J. Steckelberg, Mayo Clinic, Rochester, Minn.)

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